SOLICITATION

SECTION A - SOLICITATION/CONTRACT FORM

1. Purchase Authority: Public Law 92-218 as amended

2. **Request For Proposal (RFP) Number**: RFP-NHLBI-06-04	3. **Issue Date**: 10/6/2005	4. **Just In Time**: **[ ]** NO **[x]** YES See Part IV Section L	5. **Set Aside**: **[ ]** NO **[x]** YES See Part IV Section L

6. TITLE: **Phase II/III Trial of Sildenafil for Sickle Cell Disease-Associated Pulmonary Hypertension - Data Coordinating Center**

7. ISSUED BY:	8. SUBMIT OFFERS TO:
Contracts Operations Branch National Heart, Lung, and Blood Institute National Institutes of Health 6701 Rockledge Drive MSC 7902 BETHESDA MD 20892-7902	See Part III, Section J, "Packaging and Delivery of the Proposal," ATTACHMENT 1 of this Solicitation.

9. Proposals for furnishing the supplies and/or services in THE SCHEDULE will be received at the place specified in, and in the number of copies specified in Attachment 1 until **4:00 p.m. local time on 11/21/2005**. Offers will be valid for 120 days unless a different period is specified by the offeror on the Attachment entitled, "Proposal Summary and Data Record, NIH 2043." **All questions should be submitted electronically to the Contracting Officer no later than 4:00 p.m. local time on 10/19/2005. Please complete the Proposal Intent Response Sheet, ATTACHMENT 2, and submit no later that 4:00 p.m. local time 10/26/2005.**

10. THE OFFICIAL POINT OF RECEIPT FOR THE PURPOSE OF DETERMINING TIMELY DELIVERY IS THE ADDRESS PROVIDED FOR THE REVIEW BRANCH AS STATED IN ATTACHMENT 1. IF YOUR PROPOSAL IS NOT RECEIVED AT THE PLACE AND TIME SPECIFIED, THEN IT WILL BE CONSIDERED LATE AND HANDLED IN ACCORDANCE WITH HHSAR CLAUSE 352.215-70, ENTITLED, "LATE PROPOSALS AND REVISIONS" LOCATED IN SECTION L.1. OF THIS SOLICITATION.

11. Offeror must be registered in the Central Contractor Registry (CCR) prior to award of a contract. (http://www.ccr.gov)

12. FOR INFORMATION CALL: Rick Phillips, Contracting Officer
e-mail: phillipr@nhlbi.nih.gov
PHONE: 301-402-6462
COLLECT CALLS WILL NOT BE ACCEPTED.

13. Table of Contents on following page.

DETAILED TABLE OF RFP CONTENTS

PART I - THE SCHEDULE

THE CONTRACT SCHEDULE SET FORTH IN SECTIONS B THROUGH H, HEREIN, CONTAINS CONTRACTUAL INFORMATION PERTINENT TO THIS SOLICITATION. IT IS **NOT** AN EXACT REPRESENTATION OF THE PROPOSED CONTRACT DOCUMENT. CONTRACTUAL PROVISIONS PERTINENT TO THE OFFEROR (I.E., THOSE RELATING TO THE ORGANIZATIONAL STRUCTURE [E.G., NON-PROFIT, COMMERCIAL] AND SPECIFIC COST AUTHORIZATIONS UNIQUE TO THE OFFEROR'S PROPOSAL AND REQUIRING CONTRACTING OFFICER PRIOR APPROVAL) WILL BE DISCUSSED IN THE NEGOTIATION PROCESS AND WILL BE INCLUDED IN THE RESULTANT CONTRACT. HOWEVER, THE ENCLOSED CONTRACT SCHEDULE PROVIDES ALL THE NECESSARY INFORMATION FOR THE OFFEROR TO UNDERSTAND THE TERMS AND CONDITIONS OF THE RESULTANT CONTRACT.

SECTION B - SUPPLIES OR SERVICES AND PRICES/COSTS

ARTICLE B.1. BRIEF DESCRIPTION OF SUPPLIES OR SERVICES

This is a double-blinded, randomized, placebo-controlled clinical trial designed to test the effects of 16 weeks of chronic sildenafil therapy on exercise endurance (six minute walk distance) and pulmonary artery pressure in 180 patients age 14 or older with pulmonary hypertension (PH) and sickle cell disease (SCD). All patients completing the 16-week main protocol will be offered participation in an open-label extension study for up to 1 year. The extension study will be double-blinded for sildenafil dose, allowing a direct comparison of the effects of low (20 mg, three times a day) versus high (80 mg, three times a day) doses on exercise endurance and pulmonary artery pressures. This extension study will end when the last patient enrolled in the main trial has completed 1 year on the extension study, or when the FDA approves sildenafil for clinical use for PH in sickle cell disease, whichever comes first. The contractor shall serve as the Data Coordinating Center (DCC) for the Phase II/III Trial of Sildenafil for Sickle Cell Disease-Associated Pulmonary Hypertension. In addition to the DCC, it is anticipated that up to 12 clinical centers and a pharmacy distribution center will be awarded.

ARTICLE B.2. PRICES/COSTS

The final contract will contain the price/cost provisions agreed upon by the Government and the Offeror.

ARTICLE B.3. PROVISIONS APPLICABLE TO DIRECT COSTS

This article will prohibit or restrict the use of contract funds, unless otherwise approved by the Contracting Officer. The following is a list of items that may be included in the resultant contract as applicable. 1) Acquisition, by purchase or lease, of any interest in real property; 2) Special rearrangement or alteration of facilities; 3) Purchase or lease of any item of general purpose office furniture or office equipment regardless of dollar value; 4) Travel Costs; 5) Consultant Costs; 6) Subcontract Costs; 7) Patient Care Costs; 8) Accountable Government Property; and 9) Research Funding.

ARTICLE B.4. ADVANCE UNDERSTANDINGS

Specific elements of cost, which normally require prior written approval of the Contracting Officer before incurrence of the cost (e.g., foreign travel, consultant fees, subcontracts) will be included in this Article if the Contracting Officer has granted his/her approval prior to contract award.

SECTION C - DESCRIPTION/SPECIFICATIONS/WORK STATEMENT

ARTICLE C.1. STATEMENT OF WORK

Independently and not as an agent of the Government, the Contractor shall be required to furnish all the necessary services, qualified personnel, material, equipment, and facilities, not otherwise provided by the Government, as needed to perform the Statement of Work, Attachment 3, attached hereto and made a part of this Solicitation (See Section J - List of Attachments).

ARTICLE C.2. REPORTING REQUIREMENTS

a. Technical Progress Reports

In addition to the required reports set forth elsewhere in this Schedule, the preparation and submission of regularly recurring Technical Progress Reports will be required in any contract resulting from this solicitation. These reports will require descriptive information about the activities undertaken during the reporting period and will require information about planned activities for future reporting periods. The frequency and specific content of these reports will be determined prior to contract award.

(1) Data Analysis Plan - The contractor shall submit a plan for the analysis of this randomized, double-

blinded, placebo controlled trial within one year of contract award. The plan should include sample size and power calculations, specific statistical tests to be used in the evaluation of the null hypothesis, a discussion of how dropouts will be handled, and any plans for stratification or subgroup analyses. The plan shall demonstrate prioritization of analyses and anticipated methodology to be used.

(2) Monthly Study Status Reports - This report shall include information describing the progress of activities in the study during the reporting period, including the signing of any subcontracts; the finalization of case report forms, protocol, manual of procedures and IRB approval of clinical sites; tabulation of patient enrollment, vital status, and adverse events in the study population, plus such narrative as might be needed to enable an evaluation of progress. The report shall be due within 15 calendar days following the reporting period. A monthly report shall not be required for the period when an annual or final report is due.

(3) Annual Technical Reports - The contractor shall submit an annual report that documents and summarizes the results of that contract year, including recommendations and conclusions based on experience and results obtained. The initial report shall be submitted for the first full twelve months of performance and any fractional part of the initial month. Annual reports thereafter shall be submitted at twelve month intervals. An annual report will not be required for the period when a final report is due.

(4) Steering Committee and Executive Committee Minutes - The contractor shall submit complete and accurate minutes of all Steering Committee meetings and Executive Committee meetings within 30 days following each meeting.

(5) Data and Safety Monitoring Board Reports - The contractor shall submit reports, which detail by clinic and study wide, the quality of data, clinical center performance, forms completion rates, and any adverse events.

(6) Final Technical Report - The contractor shall submit a final report that documents and summarizes the results obtained over the life of the contract due on or before the expiration date of the contract.

(7) Site Visit Reports - Reports for all site visits taken shall be submitted within two weeks of completion of the visit.

b. Summary of Salient Results

The Contractor will be required to prepare and submit, with the final report, a summary (not to exceed 200 words) of salient results achieved during the performance of the contract. This report will be required on or before the expiration date of the contract.

c. Other Reports

1. **Annual Technical Progress Report for Clinical Research Study Populations**

The Contractor shall submit information about the inclusion of women and members of minority groups and their subpopulations for each study being performed under this contract. The contractor shall submit this information in the format indicated in the attachment entitled, "Inclusion Enrollment Report," which is set forth in Section J of this contract. The contractor also shall use this format, modified to indicate that it is a final report, for reporting purposes in the final report. The contractor shall submit the report in accordance with ARTICLE F.1. DELIVERIES of this contract.

In addition, the NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research, Amended, October, 2001 applies. If this contract is for Phase III clinical trials, see II.B of these guidelines. The Guidelines may be found at the following website:

http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm

Include a description of the plans to conduct analyses, as appropriate, by sex/gender and/or racial/ethnic groups in the clinical trial protocol as approved by the IRB, and provide a description of the progress in the conduct of these analyses, as appropriate, in the annual progress report and the final report. If the analysis reveals no subset differences, a brief statement to that effect, indicating the subsets analyzed, will suffice. The Government strongly encourages inclusion of the results of subset

analysis in all publication submissions. In the final report, the contractor shall include all final analyses of the data on sex/gender and race/ethnicity.

2. **Invention Reporting Requirement**

All reports and documentation required by [FAR Clause 52.227-11/FAR Clause 52.227-11 (Deviation)/FAR Clause 52.227-13] including, but not limited to, the invention disclosure report, the confirmatory license, and the government support certification, shall be directed to the Office of Extramural Inventions and Technology Resources Branch, OPERA, NIH, 6705 Rockledge Drive, Room 1040 A, MSC 7980, Bethesda, Maryland 20892-7980 (Telephone: 301-435-1986). In addition, one copy of an annual utilization report, and a copy of the final invention statement, shall be submitted to the Contracting Officer. The final invention statement (see FAR 27.303(a)(2)(ii)) shall be submitted on the expiration date of the contract to the Contracting Officer. The annual utilization report shall be submitted in accordance with ARTICLE F.1. DELIVERIES of this contract. The final invention statement (see FAR 27.303(a)(2)(ii)) shall be submitted on the expiration date of the contract to the following address:

Contracting Officer
National Institutes of Health
National Heart, Lung, and Blood Institute, COB
6701 Rockledge Drive, Room 6132
Bethesda, Maryland 20892 -7902

If no invention is disclosed or no activity has occurred on a previously disclosed invention during the applicable reporting period, a negative report shall be submitted to the Contracting Officer at the address listed above.

To assist contractors in complying with invention reporting requirements of the clause, the NIH has developed "Interagency Edison," an electronic invention reporting system. Use of Interagency Edison is encouraged as it streamlines the reporting process and greatly reduces paperwork. Access to the system is through a secure interactive Web site to ensure that all information submitted is protected. Interagency Edison and information relating to the capabilities of the system can be obtained from the Web (http://www.iedison.gov), or by contacting the Office of Extramural Inventions and Technology Resources Branch, OPERA, NIH.

3. **Use of Interim Study Data**

Legend for Technical Progress Reports Containing Interim Study Data
It is recommended that the contractor incorporate the following legend on the cover of technical progress reports and reports containing study data that are prepared for use by all working committees in their monitoring of the trial. Working committees include but are not limited to the DSMB, Steering Committee and Executive Committee.

> "The data, if any, contained in this report/deliverable are preliminary and may contain unvalidated findings. These data are not intended for public use. Public use of these data could create erroneous conclusions which, if acted upon, could threaten public health or safety."

4. **Limited Access Data**

The National Heart, Lung, and Blood Institute (NHLBI) supports collection of data from participants in numerous clinical trials and epidemiologic studies. These well-characterized population samples represent rare and valuable scientific resources. In order to take full advantage of such resources and maximize their research value, it is important that data collected under NHLBI studies are made available, under appropriate terms and conditions, to the largest possible number of qualified investigators in a timely manner.

Limited access data will be released under this trial or study. Limited access data refers to trial or study data, with certain deletions and recoding that are released to requesting institutions and investigators

for specific purposes and with certain restrictions and conditions. The contractor shall distribute study data in accordance with NHLBI's Policy for Distribution of Data, dated October 1, 2005, and any subsequent revisions. The policy is described at http://www.nhlbi.nih.gov/resources/deca/policy.htm.

Limited access data is a deliverable under the coordinating center contract for this trial or study, as described in Section C.1. Description/Specification/Work Statement and/or Section F.1. Deliveries or Performance of the coordinating center contract.

SECTION D - PACKAGING, MARKING AND SHIPPING

All deliverables required under this contract shall be packaged, marked and shipped in accordance with Government specifications. At a minimum, all deliverables shall be marked with the contract number and contractor name. The Contractor shall guarantee that all required materials shall be delivered in immediate usable and acceptable condition.

SECTION E - INSPECTION AND ACCEPTANCE

a. The Contracting Officer or the duly authorized representative will perform inspection and acceptance of materials and services to be provided.

b. For the purpose of this SECTION, the Project Officer is the authorized representative of the Contracting Officer.

c. Inspection and acceptance will be performed at the National Heart, Lung, and Blood Institute.

Acceptance may be presumed unless otherwise indicated in writing by the Contracting Officer or the duly authorized representative within 30 days of receipt.

d. This contract incorporates the following clause by reference, with the same force and effect as if it were given in full text. Upon request, the Contracting Officer will make its full text available.

FAR Clause **52.246-9, Inspection of Research and Development (Short Form)** (April 1984).

SECTION F - DELIVERIES OR PERFORMANCE

ARTICLE F.1. DELIVERIES

Satisfactory performance of the final contract shall be deemed to occur upon performance of the work described in Article C.1. and upon delivery and acceptance by the Contracting Officer, or the duly authorized representative, of the following items in accordance with the stated delivery schedule:

a. The items specified below as described in SECTION C, ARTICLE C.2. will be required to be delivered F.O.B. Destination as set forth in FAR Clause 52.247-35, F.O.B. Destination, Within Consignees Premises (April 1984), and in accordance with and by the date(s) specified below [and any specifications stated in SECTION D, PACKAGING, MARKING AND SHIPPING, of the contract]:

Item	Description	Quantity	Delivery Schedule
(a)	Data Analysis Plan	11	Within twelve months after contract award
(b)	Monthly Study Status Report	3	Monthly
(c)	Annual Technical Reports	23	Annually
(d)	Minutes of Steering	15	Within 30 days following each

	Committee & Executive Committee meetings		meeting
(e)	Reports requested by the DSMB on patients safety and health status	11	Two weeks prior to DSMB meetings
(f)	Final Technical Report	4	Expiration of Contract
(g)	Edited data tape and documentation	to be determined	Expiration of Contract
(h)	Public Use Data set	in accordance with NHLBI policy	per Public Use Data Clause
(i)	Protocol	15	As necessary
(j)	Manual of Procedures	15	Within 6 months of contract award
(k)	Annual Technical Progress Report for Clinical Research Study Populations	3	Annually with Annual Technical Report
(l)	System Security Plan	1	Within 60 days of contract award
(m)	Site Visit Reports	1	Within 2 weeks of each visit

The items above shall be addressed an delivered to:

Addressee	Deliverable Item #	Quantity
(1) Contracting Officer BDR Contracts Section/Room 6132 Contracts Operations Branch National Heart, Lung, and Blood Institute 6701 Rockledge Drive, MSC 7902 Bethesda, MD 20892-7902	F.1.(a) F.1.(b) F.1.(c) F.1.(d) F.1.(f) F.1.(i) F.1.(j) F.1.(k) F.1.(l)	1 1 1 1 1 1 1 1 1
(2) Project Officer Hemoglobinopathies and Genetics SRG Room 10152 Division of Blood Diseases and Resources National Heart, Lung, and Blood Institute 6701 Rockledge Drive, MSC 7950 Bethesda, MD 20892-7950	F.1.(a) F.1.(b) F.1.(c) F.1.(d) F.1.(e) F.1.(f) F.1.(g) F.1.(h) F.1.(i) F.1.(j) F.1.(k) F.1.(m)	2 1 2 2 3 3 to be determined to be determined 1 1 2 1
(3) 8 DSMB Members (TBN)	F.1.(a) F.1.(b) F.1.(c)	8 1 (chairperson) 8

	F.1.(e)	8
(4) 12 Steering Committee Members (TBN)	F.1.(c) F.1.(d) F.1.(i) F.1.(j)	12 12 12 12
(5) Pharmacy Distribution Center (TBN)	F.1.(i) F.1.(j)	1 1

ARTICLE F.2. CLAUSES INCORPORATED BY REFERENCE, FAR 52.252-2 (FEBRUARY 1998)

This contract incorporates the following clause by reference, with the same force and effect as if it were given in full text. Upon request, the Contracting Officer will make its full text available. Also, the full text of a clause may be accessed electronically at this address: http://www.arnet.gov/far/.

FEDERAL ACQUISITION REGULATION (48 CFR CHAPTER 1) CLAUSE:

52.242-15, Stop Work Order (August 1989) with **Alternate I** (April 1984).

SECTION G - CONTRACT ADMINISTRATION DATA

Any contract awarded from this RFP will contain the following:

ARTICLE G.1. PROJECT OFFICER

The following Project Officer(s) will represent the Government for the purpose of this contract:

[To be specified prior to award]

The Project Officer is responsible for: (1) monitoring the Contractor's technical progress, including the surveillance and assessment of performance and recommending to the Contracting Officer changes in requirements; (2) interpreting the statement of work and any other technical performance requirements; (3) performing technical evaluation as required; (4) performing technical inspections and acceptances required by this contract; and (5) assisting in the resolution of technical problems encountered during performance.

The Contracting Officer is the only person with authority to act as agent of the Government under this contract. Only the Contracting Officer has authority to: (1) direct or negotiate any changes in the statement of work; (2) modify or extend the period of performance; (3) change the delivery schedule; (4) authorize reimbursement to the Contractor any costs incurred during the performance of this contract; or (5) otherwise change any terms and conditions of this contract.

The Contracting Officer hereby delegates the Project Officer as the Contracting Officer's authorized representative responsible for signing software license agreements issued as a result of this contract.

The Government may unilaterally change its Project Officer designation.

ARTICLE G.2. KEY PERSONNEL

Pursuant to the Key Personnel clause incorporated in this contract, the following individual(s) is/are considered to be essential to the work being performed hereunder:

NAME TITLE

[To be specified prior to award]]

ARTICLE G.3 . INVOICE SUBMISSION/CONTRACT FINANCING REQUEST

a. Invoice/Financing Request Instructions for NIH Cost-Reimbursement Type Contracts NIH(RC)-1 are attached and made part of this contract. The instructions and the following directions for the submission of invoices/financing request must be followed to meet the requirements of a "proper" payment request pursuant to FAR 32.9.

(1) Invoices/financing requests shall be submitted as follows:

(a) To be considered a "proper" invoice in accordance with FAR 32.9, Prompt Payment, each invoice shall clearly identify the two contract numbers that appear on the face page of the contract as follows:

Contract No. (This is the 17 digit number that appears in Block 2 of the SF-26, i.e. HHSN268200611000C.)

ADB Contract No. (This is the 10 digit number that appears in the upper left hand corner of the SF-26, i.e. N01-HB-41234.)

(b) An original and two copies to the following designated billing office:

Contracting Officer
Contracts Operations Branch
National Heart, Lung, and Blood Institute, NIH
6701 Rockledge Drive, Room 6132
MSC 7902
BETHESDA MD 20892-7902

(2) Inquiries regarding payment of invoices should be directed to the designated billing office, (301) 402-6462.

ARTICLE G.4. CONTRACT FINANCIAL REPORT

a. Financial reports on the attached Form NIH 2706, Financial Report of Individual Project/Contract, shall be submitted by the Contractor in accordance with the Instructions for Completing Form NIH 2706, which accompany the form, in an original and two copies, not later than the 30th working day after the close of the reporting period. The line entries for subdivisions of work and elements of cost (expenditure categories) which shall be reported within the total contract are listed in paragraph e., below. Subsequent changes and/or additions in the line entries shall be made in writing.

b. Unless otherwise stated in that part of the Instructions for Completing Form NIH 2706, entitled "**PREPARATION INSTRUCTIONS**," all columns A through J, shall be completed for each report submitted.

c. The first financial report shall cover the period consisting of the FIRST FULL THREE CALENDAR MONTHS following the date of the contract, in addition to any fractional part of the initial month. Thereafter, reports will be on a quarterly basis.

d. The Contracting Officer may require the Contractor to submit detailed support for costs contained in one or more interim financial reports. This clause does not supersede the record retention requirements in FAR Part 4.7.

e. The following is a listing of expenditure categories to be reported:

Expenditure Category A	**Percentage of Effort/Hours**
(1) Direct Labor	
(a) Principal Investigator	
(b) Co-Principal Investigator	
(c) Key Personnel	
(I)	
(ii)	
(iii)	
(2) Other Professional Personnel	
(3) Personnel - Other	
(4) Fringe Benefits	
(5) Accountable Personal Property	
(6) Materials/Supplies	
(7) Patient Care Costs	
(8) Travel	
(9) Consultant Costs	
(10) Premium Pay	
(11) Computer Costs	
(12) Subcontract Costs	
(13) Other Direct Costs	
(14) Indirect Costs	
(15) G&A Expense	
(16) Total Cost	
(17) Fee	
(18) Total Cost Plus Fixed Fee	

f. The Government may unilaterally revise the NIH 2706 to reflect the allotment of additional funds.

ARTICLE G.5. INDIRECT COST RATES

In accordance with Federal Acquisition Regulation (FAR) (48 CFR Chapter 1) Clause 52.216-7(d)(2), "Allowable Cost and Payment" incorporated by reference in this contract in Part II, Section I, the cognizant Contracting Officer

representative responsible for negotiating provisional and/or final indirect cost rates is identified as follows:

Director, Division of Financial Advisory Services
Office of Contracts Management
National Institutes of Health
6100 Building, Room 6B05
6100 EXECUTIVE BLVD MSC 7540
BETHESDA MD 20892-7540

These rates are hereby incorporated without further action of the Contracting Officer.

ARTICLE G.6. POST AWARD EVALUATION OF CONTRACTOR PERFORMANCE

a. Contractor Performance Evaluations

Interim and final evaluations of contractor performance will be prepared on this contract in accordance with FAR 42.15. The final performance evaluation will be prepared at the time of completion of work. In addition to the final evaluation, interim evaluations will be prepared annually to coincide with the anniversary date of the contract.

Interim and final evaluations will be provided to the Contractor as soon as practicable after completion of the evaluation. The Contractor will be permitted thirty days to review the document and to submit additional information or a rebutting statement. If agreement cannot be reached between the parties, the matter will be referred to an individual one level above the Contracting Officer, whose decision will be final.

Copies of the evaluations, contractor responses, and review comments, if any, will be retained as part of the contract file, and may be used to support future award decisions.

b. Electronic Access to Contractor Performance Evaluations

Contractors that have Internet capability may access evaluations through a secure Web site for review and comment by completing the registration form that can be obtained at the following address:

http://oamp.od.nih.gov/OD/CPS/cps.asp

The registration process requires the contractor to identify an individual that will serve as a primary contact and who will be authorized access to the evaluation for review and comment. In addition, the contractor will be required to identify an alternate contact who will be responsible for notifying the cognizant contracting official in the event the primary contact is unavailable to process the evaluation within the required 30-day time frame.

SECTION H - SPECIAL CONTRACT REQUIREMENTS

ARTICLE H.1. HUMAN SUBJECTS

Research involving human subjects shall not be conducted under this contract until the protocol developed in Phase I has been approved by the NHLBI Project Officer, written notice of such approval has been provided by the Contracting Officer, and the Contractor has provided to the Contracting Officer a properly completed "Protection of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption", Form OMB No. 0990-0263(formerly Optional Form 310), certifying IRB review and approval of the protocol. The human subject certification can be met by submission of the Contractor's self designated form, provided that it contains the information required by the "Protection of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption", Form OMB No. 0990-0263(formerly Optional Form 310).

ARTICLE H.2. REQUIRED EDUCATION IN THE PROTECTION OF HUMAN RESEARCH PARTICIPANTS

NIH policy requires education on the protection of human subject participants for all investigators receiving NIH

contract awards for research involving human subjects. For a complete description of the NIH Policy announcement on required education in the protection of human subject participants, the contractor should access the NIH Guide for Grants and Contracts Announcement dated June 5, 2000 at the following website: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html. The information below is a summary of the NIH Policy Announcement:

The contractor shall maintain the following information: (1) a list of the names and titles of the principal investigator and any other individuals working under the contract who are responsible for the design and/or conduct of the research; (2) the title of the education program(s) in the protection of human subjects that has been completed for each named personnel and; (3) a one sentence description of the educational program(s) listed in (2) above. This requirement extends to investigators and all individuals responsible for the design and/or conduct of the research who are working as subcontractors or consultants under the contract.

Prior to any substitution of the Principal Investigator or any other individuals responsible for the design and/or conduct of the research under the contract, the contractor shall provide the following written information to the Contracting Officer: the title of the education program and a one sentence description of the program that has been completed by the replacement.

ARTICLE H.3. CONTINUED BAN ON FUNDING OF HUMAN EMBRYO RESEARCH

a. Pursuant to Public Law(s) cited in paragraph b. , below, NIH is prohibited from using appropriated funds to support human embryo research. Contract funds may not be used for (1) the creation of a human embryo or embryos for research purposes; or (2) research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death greater than that allowed for research on fetuses in utero under 45 CFR 46.208(a)(2) and Section 498(b) of the Public Health Service Act (42 U.S.C. 289g(b)). The term "human embryo or embryos" includes any organism, not protected as a human subject under 45 CFR 46 as of the date of the enactment of this Act, that is derived by fertilization, parthenogenesis, cloning, or any other means from one or more human gametes or human diploid cells.

   Additionally, in accordance with a March 4, 1997 Presidential Memorandum, Federal funds may not be used for cloning of human beings.

b. **Public Law and Section No.** **Fiscal Year** **Period Covered**

[Applicable information to be included at award]

ARTICLE H.4. NEEDLE EXCHANGE

a. Pursuant to Public Law(s) cited in paragraph b., below, contract funds shall not be used to carry out any program of distributing sterile needles or syringes for the hypodermic injection of any illegal drug.

b. **Public Law and Section No.** **Fiscal Year** **Period Covered**

[Applicable information to be included at award]

ARTICLE H.5. PRIVACY ACT

This procurement action requires the Contractor to do one or more of the following: design, develop, or operate a system of records on individuals to accomplish an agency function in accordance with the Privacy Act of 1974, Public Law 93-579, December 31, 1974 (5 USC 552a) and applicable agency regulations. Violation of the Act may involve the imposition of criminal penalties.

The Privacy Act System of Records applicable to this project is Number 09-25-0200. This document is incorporated into this contract as Attachment TBD.

ARTICLE H.6. OMB CLEARANCE

In accordance with HHSAR 352.270-7, Paperwork Reduction Act, the Contractor shall not proceed with surveys or interviews until such time as Office of Management and Budget (OMB) Clearance for conducting interviews has been obtained by the Project Officer and the Contracting Officer has issued written approval to proceed.

ARTICLE H.7. SALARY RATE LIMITATION LEGISLATION PROVISIONS

a. Pursuant to the P.L.(s) cited in paragraph b., below, no NIH Fiscal Year funds may be used to pay the direct salary of an individual through this contract at a rate in excess of the applicable amount shown or the applicable Executive Level for the fiscal year covered. Direct salary is exclusive of fringe benefits, overhead and general and administrative expenses (also referred to as "indirect costs" or "facilities and administrative (F&A) costs"). Direct salary has the same meaning as the term "institutional base salary." An individual's direct salary (or institutional base salary) is the annual compensation that the contractor pays for an individual's appointment whether that individual's time is spent on research, teaching, patient care or other activities. Direct salary (or institutional base salary) excludes any income that an individual may be permitted to earn outside of duties to the contractor. The per year salary rate limitation also applies to individuals proposed under subcontracts. It does not apply to fees paid to consultants. If this is a multiple year contract, it may be subject to unilateral modifications by the Government if an individual's salary rate used to establish contract funding exceeds any salary rate limitation subsequently established in future HHS appropriation acts.

b.	**Public Law No.**	**Fiscal Year**	**Dollar Amount of Salary Limitation***

[Applicable information to be included at award]

c. Payment of direct salaries is limited to the Executive Level I rate which was in effect on the date(s) the expense was incurred.

* For the period 10/1/04 - 12/30/04, the Executive Level I rate is $175,700. Effective January 1, 2005, the Executive Level I rate increased to $180,100 and will remain at that rate until it is revised. See the web site listed below for the Executive Schedule rates of pay:

FOR FY05 EXECUTIVE LEVEL SALARIES EFFECTIVE JANUARY 1, 2005:
http://www.opm.gov/oca/05tables/html/ex.asp
(NOTE: This site shows the CY 05 rates. For previous years, click on "salaries and wages" and then scroll down to the bottom of the page and click on the year to locate the desired Executive Level salary rates).

ARTICLE H.8. DATA AND SAFETY MONITORING IN CLINICAL TRIALS AND EPIDEMIOLOGICAL STUDIES

For informational purposes, the contractor is directed to the full text of the NHLBI policies regarding Data and Safety Monitoring Boards, which may be found at the following web sites:

Establishing Data and Safety Monitoring Boards and Observational Study Monitoring Boards
(http://www.nhlbi.nih.gov/funding/policies/dsmb_est.htm)

Guidelines for Data Quality Assurance in Clinical Trials and Observational Studies
(http://www.nhlbi.nih.gov/funding/policies/dataqual.htm)

Responsibilities of DSMBs Appointed by NHLBI
(http://www.nhlbi.nih.gov/funding/policies/dsmb_inst.htm)

ARTICLE H.9 . INFORMATION TECHNOLOGY SYSTEMS SECURITY SPECIFICATIONS

The contractor shall comply with all federal computer and Information Technology (IT) systems security and/or privacy rules, regulations and specifications. Some of the relevant regulations and policies include but are not limited to:

- Computer Security Act of 1987: http://csrc.nist.gov/ispab/csa_87.txt
- OMB A-130, Appendix III, "Security of Federal Automated Information Systems:" http://csrc.nist.gov/policies/appendix_iii.pdf
- DHHS Information Security Program Policy: http://www.hhs.gov/read/irmpolicy/FINALHHSInformationSecurityProgramP.doc
- DHHS Information Security Program Handbook at: http://www.os.dhhs.gov/ohr/manual/pssh.pdf
- OMB Circular A-130 memorandum M-03-22, "OMB Guidance for Implementing the Privacy Provisions of the E-Government Act of 2002:" http://www.whitehouse.gov/omb/memoranda/m03-22.html
- OMB Memorandum M-05-04 (12/04): http://www.whitehouse.gov/omb/memoranda/fy2005/m05-04.pdf

The contractor shall include this provision in any subcontract awarded pursuant to this prime contract. Failure to comply with these requirements shall constitute cause for termination.

The contractor shall protect all information used, gathered, or developed as a result of the Statement of Work (SOW). The contractor shall establish and implement appropriate administrative, technical, and physical safeguards to ensure the security and confidentiality of sensitive Government information, data, and/or equipment.

In addition, during all activities and operations on Government premises, or activities and operations involving government data, computers or networks, the contractor shall comply with all DHHS and National Institutes of Health (NIH), policies and rules of conduct.

a. Required IT Systems Security Training

The contractor shall assure that each employee has completed the NIH Computer Security Awareness Training http://irtsectraining.nih.gov/ prior to performing any work under this contract.

The contractor shall maintain a listing by name and title of each individual working under this contract who has completed the NIH required training. Any additional security training completed by contractor staff shall be included on this listing.

b. Position Sensitivity Designations

(1) The Government has determined that the following position sensitivity designations and associated clearance and investigation requirements apply under this contract:

Level 5C: Moderate Risk (Requires Suitability Determination with NACIC, MBI or LBI). Contractor employees assigned to a Level 5C position with no previous investigation and approval shall undergo a National Agency Check and Inquiry Investigation plus a Credit Check (NACIC), a Minimum Background Investigation (MBI), or possibly a Limited Background Investigation (LBI).

**** (Contractor Position Titles To Be Determined) ****

Level 1C: Non Sensitive (Requires Suitability Determination with an NACI).
Contractor employees assigned to a Level 1C position are subject to a National Agency Check and Inquiry Investigation (NACI).

**** (Contractor Position Titles To Be Determined) ****

(2) The contractor shall submit a roster, by name, position and responsibility, of all IT staff working under the contract. The roster shall be submitted to the Project Officer, with a copy to the

Contracting Officer, within 14 days of the effective date of the contract. The Contracting Officer shall notify the contractor of the appropriate level of background investigations to be performed.

Contractor employees who have had a background investigation conducted by the U.S. Office of Personnel Management (OPM) within the last five years may only require an updated or upgraded investigation.

(3) The Contracting Officer will provide the contractor with a Web site where the contractor may obtain forms needed to complete background investigations. The contractor shall complete the forms and mail them to:

Ms. Rosalin Clipper
Building 31/ Room 5A28
31 Center Drive
MSC 2490
Bethesda, MD 20892

(4) Contractor employees in AIS-related positions shall comply with the DHHS criteria for the assigned position sensitivity designations prior to performing any work under this contract. The following exceptions apply:

Levels 5C, 6C and 1C: Contractor employees may begin work under the contract after the contractor has submitted the name, position and responsibility of the employee to the Project Officer, as described in paragraph b(2) above.

The contract shall perform work under the contract with security oversight by the Project Officer in consultation with the Information Systems Security Officer whenever sensitive data or systems are involved before background investigations are completed and suitability determinations are obtained.

c. Contractor Notification of New and Departing Employees Requiring Background Investigations

(1) The contractor shall notify the contracting officer, the project officer, and the Security Investigation Reviewer when a new employee assumes a position that requires a security clearance or when an employee with a security clearance stops working under the contract. The government will initiate a background investigation on new employees requiring security clearances and will stop pending background investigations for employees that no longer work under the contract.

(2) New employees: provide the name, position title, and security clearance level held by the former incumbent. If the employee is filling a new position, provide a description of the position and the government will determine the appropriate security level.

(3) Departing employees: provide the name, position title, and security clearance level held by or pending for the individual.

d. Commitment to Protect Sensitive Information

(1) Contractor Agreement

The Contractor shall not release, publish, or disclose sensitive information to unauthorized personnel, and shall protect such information in accordance with provisions of the following laws and any other pertinent laws and regulations governing the confidentiality of sensitive information:

-18 U.S.C. 641 (Criminal Code: Public Money, Property or Records)
-18 U.S.C. 1905 (Criminal Code: Disclosure of Confidential Information)
-Public Law 96-511 (Paperwork Reduction Act)

(2) Contractor-Employee Non-Disclosure Agreements

Each contractor employee who may have access to sensitive information under this contract shall complete the attachment entitled, "Commitment To Protect Non-Public Information - Contractor Agreement," which is referenced in Section J of this contract and available at: http://irm.cit.nih.gov/security/Nondisclosure.pdf

A copy of each signed and witnessed Non-Disclosure agreement shall be submitted to the Project Officer prior to performing any work under the contract.

ARTICLE H.10 . PUBLICATION AND PUBLICITY

The contractor shall acknowledge the support of the National Institutes of Health whenever publicizing the work under this contract in any media by including an acknowledgment substantially as follows:

"This project has been funded in whole or in part with Federal funds from the National Heart, Lung, and Blood Institute, National Institutes of Health, Department of Health and Human Services, under Contract No. TBD.

ARTICLE H.11 . PRESS RELEASES

a. Pursuant to Public Law(s) cited in paragraph b., below, the contractor shall clearly state, when issuing statements, press releases, requests for proposals, bid solicitations and other documents describing projects or programs funded in whole or in part with Federal money: (1) the percentage of the total costs of the program or project which will be financed with Federal money; (2) the dollar amount of Federal funds for the project or program; and (3) the percentage and dollar amount of the total costs of the project or program that will be financed by nongovernmental sources.

b. Public Law and Section No. Fiscal Year Period Covered

[Applicable information to be included at award]

ARTICLE H.12 . REPORTING MATTERS INVOLVING FRAUD, WASTE AND ABUSE

Anyone who becomes aware of the existence or apparent existence of fraud, waste and abuse in NIH funded programs is encouraged to report such matters to the HHS Inspector General's Office in writing or on the Inspector General's Hotline. The toll free number is **1-800-HHS-TIPS** (**1-800-447-8477).** All telephone calls will be handled confidentially. The e-mail address is **Htips@os.dhhs.gov** and the mailing address is:

Office of Inspector General
Department of Health and Human Services
TIPS HOTLINE
P.O. Box 23489
Washington, D.C. 20026

ARTICLE H.13 . ANTI -LOBBYING

a. Pursuant to Public Law(s) cited in paragraph c., below, contract funds shall only be used for normal and recognized executive-legislative relationships. Contract funds shall not be used, for publicity or propaganda purposes; or for the preparation, distribution, or use of any kit, pamphlet, booklet, publication, radio, television, or video presentation designed to support or defeat legislation pending before the Congress or any State legislature, except in presentation to the Congress or any State legislature itself.

b. Contract funds shall not be used to pay salary or expenses of the contractor or any agent acting for the contractor, related to any activity designed to influence legislation or appropriations pending before the Congress or any State legislature.

c.	Public Law and Section No.	Fiscal Year	Period Covered

[Applicable information to be included at award]

ARTICLE H.14 . OBTAINING AND DISSEMINATING BIOMEDICAL RESEARCH RESOURCES

Unique research resources arising from NIH-funded research are to be shared with the scientific research community. NIH provides guidance, entitled, "Sharing Biomedical Research Resources: Principles and Guidelines for Recipients of NIH Research Grants and Contracts," (Federal Register Notice, December 23, 1999 [64 FR 72090]), concerning the appropriate terms for disseminating and acquiring these research resources. This guidance, found at : http://ott.od.nih.gov/NewPages/64FR72090.pdf. is intended to help contractors ensure that the conditions they impose and accept on the transfer of research tools will facilitate further biomedical research, consistent with the requirements of the Bayh-Dole Act and NIH funding policy.

Note: For the purposes of this Article, the terms, "research tools," "research materials," and "research resources" are used interchangeably and have the same meaning.

ARTICLE H.15 . HOTEL AND MOTEL FIRE SAFETY ACT OF 1990 (P.L. 101-391)

Pursuant to Public Law 101-391, no Federal funds may be used to sponsor or fund in whole or in part a meeting, convention, conference or training seminar that is conducted in, or that otherwise uses the rooms, facilities, or services of a place of public accommodation that do not meet the requirements of the fire prevention and control guidelines as described in the Public Law. This restriction applies to public accommodations both foreign and domestic.

Public accommodations that meet the requirements can be accessed at:
http://www.usfa.fema.gov/hotel/index.htm

ARTICLE H.16 . NIH POLICY ON ENHANCING PUBLIC ACCESS TO ARCHIVED PUBLICATIONS RESULTING FROM NIH-FUNDED RESEARCH

The Policy requests that beginning May 2, 2005, NIH-funded investigators submit to the NIH National Library of Medicine's (NLM) PubMed Central (PMC) an electronic version of the author's final manuscript, upon acceptance for publication, resulting from research supported in whole or in part with direct costs from NIH. NIH defines the author's final manuscript as the final version accepted for journal publication, and includes all modifications from the publishing peer review process. The PMC archive will preserve permanently these manuscripts for use by the public, health care providers, educators, scientists, and NIH. The Policy directs electronic submissions to the NIH/NLM/PMC: http://www.pubmedcentral.nih.gov.

Additional information is available at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-05-022.html.

ARTICLE H.17. NHLBI GUIDELINES FOR AVOIDING CONFLICTS OF INTEREST FOR MULTICENTER CLINICAL TRIALS

NHLBI Guidelines for Avoiding Conflicts of Interest in Multicenter Clinical Trials (09/06/2000)

In 1995, the Department released its final rule on "Objectivity in Research" (Federal Register, July 11, 1995). Under this rule, an investigator must disclose to an official in his or her institution "any Significant Financial Interests (and those of his/her spouse and dependent children) that would reasonably appear to be affected by the research proposed for funding by the PHS. The institutional official(s) will review those disclosures and determine whether any of the reported financial interests could directly and significantly affect the design, conduct, or reporting of the research and, if so, the institution must, prior to any expenditure of awarded funds, report the existence of such conflicting interests to the PHS Awarding Component and act to protect PHS-funded research from bias due to the conflict of interest."

These are minimum requirements. Individual institutions may interpret them and implement them somewhat

differently, and investigators may decide to go beyond them. Also, in certain circumstances, these rules may need to be adapted to the specific research program. For example, it would be reasonable for investigators in multicenter clinical trials to come up with a study-wide policy on conflict of interest, as different interpretations of the guidelines by different investigators and their institutions may be inappropriate. Certainly, the credibility of the study might depend on all of the investigators having stronger policies for conflict than are mandated by the PHS. Even if one or two of the investigators have financial interests in a drug or device being evaluated in the trial, or in a competitor of the drug or device, questions may arise as to the validity and interpretation of the trial results. An example of this is TIMI-1, where some of the investigators had considerable financial interest in tPA, leading to Congressional investigation.

Most, but not all, clinical trial investigator groups have since developed conflict of interest guidelines. These have ranged from disclosure of interests to prohibition against buying or selling stock in a company manufacturing one of the interventions, to having any equity. In some cases, consulting or giving paid talks for the manufacturers has been discouraged.

Any clinical trial assessing an intervention for which there is or might be an IND (for drugs) or an IDE (for devices) has additional requirements. Details about these requirements may be obtained from the FDA (www.fda.gov/oc/guidance/financialdis.html.) In summary, the integrity of the study must not be compromised by financial interests. To assure that, investigators cannot have financial arrangements that reward a particular study outcome, proprietary interest in the intervention being tested, significant equity in the manufacturer of the intervention, or significant payments of other sorts. Specified financial arrangements must be disclosed. The sponsor of the IND or IDE is responsible for collecting information about financial interests. The NHLBI, even if it is not the sponsor of the IND or IDE, will take an active role in ensuring that these requirements are followed.

It is in the Institute's interest to strongly advise the investigative group to develop guidelines that avoid any perception that the study design, conduct, and data analysis and interpretation might have been biased by investigator conflict. To help investigators comply with the PHS regulations, the Institute Project Officer or Program Scientist and the Principal Investigator(s) must discuss the conflict of interest policy for the study at an early stage in the protocol development process. Although the Institute does not specify exactly what policy a given study should develop, it needs to remind the investigative group that study credibility depends on reasonably strict guidelines. These policies should be clearly spelled out in the protocol. n addition, the Project Officer or Program Scientist should be apprised of conflicts that arise and the corrective actions by the investigator's local institution. As noted in regulations, the Institute "may at any time inquire into the Institutional procedures and actions regarding conflicting financial interests in PHS-funded research, including requirement for submission of, or review on site, all records pertinent to compliance with this subpart."

ARTICLE H.18. REVIEW OF MANUSCRIPTS

In order to balance the oversight responsibility of the National Heart, Lung, and Blood Institute (NHLBI) with the authorization provided the contractor by the Rights in Data clause of this contract, the NHLBI has established a process to review manuscripts produced under this contract. Please note that the NHLBI does not require contractors to seek the Institute's approval of manuscripts.

In order to have sufficient time to conduct a meaningful review, please provide to the Institute's Project Officer and Contracting Officer advance notice of intent to submit a manuscript for publication at least 45 days prior to submission to the publisher. The advance notice should briefly describe the plans for publication of the manuscript. Concurrently or as soon as possible following this notice, please provide the manuscript just to the Project Officer.

Any comments from the NHLBI will be provided in writing within 15 days after receipt of the manuscript by the Project Officer. Comments expressed by the NHLBI about the manuscript shall not be a cause for action under the Disputes clause of the contract by either NHLBI or the contractor, since the NHLBI does not approve manuscripts and draft manuscripts are not contract deliverables.

ARTICLE H.19. USE OF INTERIM STUDY DATA

Interim data used in technical progress reports and other reports developed for the purpose of study monitoring are not intended for public use. Premature release of such data could result in interpretations that prove to be unreliable or invalid once the study is completed and the full context for the data is known. Unreliable or invalid

interpretations can threaten public health and safety by leading the public and medical practitioners to pursue inappropriate measures. In addition, an interpretation of the interim data that is contrary to study protocol could cause participants to drop out of treatment groups. This could prevent completion of the study. A secondary consequence, not in terms of public health and safety, but one that is important in its own right, is that premature release of the data can lead to financial loss to the Government, since any funds spent on a trial that does not answer the questions posed by the study would be devalued.

In consideration of the above, interim data shall be used only for internal study monitoring purposes with the exception of publications and presentations approved in accordance with the programmatic protocol and study procedures.

PART II - CONTRACT CLAUSES

SECTION I - CONTRACT CLAUSES

THE FOLLOWING **ARTICLE I.1 GENERAL CLAUSE LISTING(S)** WILL BE APPLICABLE TO MOST CONTRACTS RESULTING FROM THIS RFP. HOWEVER, THE ORGANIZATIONAL STRUCTURE OF THE SUCCESSFUL OFFEROR(S) WILL DETERMINE THE SPECIFIC GENERAL CLAUSE LISTING TO BE CONTAINED IN THE CONTRACT(S) AWARDED FROM THIS RFP:

General Clauses for a Cost-Reimbursement Research and Development Contract
General Clauses for a Cost-Reimbursement Contract with Non-Profit Organizations Other Than Educational Institutions

The complete listing of these clauses may be accessed at:
http://rcb.cancer.gov/rcb-internet/appl/general-clauses/clauses.jsp

ARTICLE I.2. AUTHORIZED SUBSTITUTIONS OF CLAUSES

Any authorized substitutions and/or modifications other than the General Clauses which will be based on the type of contract/Contractor will be determined during negotiations.

It is expected that the following clause(s) will be made part of the resultant contract:

Alternate IV (October 1997) of FAR Clause **52.215-21, Requirements For Cost Or Pricing Data Or Information Other Than Cost Or Pricing Data--Modifications** (October 1997) is added.

FAR Clauses **52.219-9, Small Business Subcontracting Plan** (July 2005), and **52.219-16, Liquidated Damages--Subcontracting Plan** (January 1999) are deleted in their entirety.

FAR Clause **52.232-20, Limitation Of Cost** (April 1984), is deleted in its entirety and FAR Clause **52.232-22, Limitation Of Funds** (April 1984) is substituted therefor. ***[NOTE: When this contract is fully funded, FAR Clause 52.232-22, LIMITATION OF FUNDS will no longer apply and FAR Clause 52.232-20, LIMITATION OF COST will become applicable.]***

ARTICLE I.3. ADDITIONAL CONTRACT CLAUSES

Additional clauses other than those listed below which are based on the type of contract/Contractor shall be determined during negotiations. Any contract awarded from this solicitation will contain the following:

This contract incorporates the following clauses by reference, (unless otherwise noted), with the same force and effect as if they were given in full text. Upon request, the Contracting Officer will make their full text available.

a. FEDERAL ACQUISITION REGULATION (FAR) (48 CFR CHAPTER 1) CLAUSES

(1) FAR Clause **52.215-17, Waiver of Facilities Capital Cost of Money** (October 1997).

(2) FAR Clause **52.219-6, Notice of Total Small Business Set-Aside** (June 2003).

(3) FAR Clause **52.224-1, Privacy Act Notification** (April 1984).

(4) FAR Clause **52.224-2, Privacy Act** (April 1984).

(5) FAR Clause **52.227-14, Rights in Data - General** (June 1987).

(6) FAR Clause **52.230-6, Administration of Cost Accounting Standards** (April 2005).

(7) FAR Clause **52.242-3, Penalties for Unallowable Costs** (May 2001).

(8) FAR Clause **52.246-23, Limitation of Liability** (February 1997).
AND/OR
(9) FAR Clause **52.246-24, Limitation of Liability - High-Value Items** (February 1997).

b. DEPARTMENT OF HEALTH AND HUMAN SERVICES ACQUISITION REGULATION (HHSAR) (48 CHAPTER 3) CLAUSES:

(1) HHSAR Clause **352.270-1, Accessibility of Meetings, Conferences and Seminars to Persons with Disabilities** (January 2001).

(2) HHSAR Clause **352.270-8, Protection of Human Subjects** (March 2005).

c. NATIONAL INSTITUTES OF HEALTH (NIH) RESEARCH CONTRACTING (RC) CLAUSES:

The following clauses are attached and made a part of this contract:

(1) **NIH (RC)-7, Procurement of Certain Equipment** (April 1984) (OMB Bulletin 81-16).

ARTICLE I.4. ADDITIONAL FAR CONTRACT CLAUSES INCLUDED IN FULL TEXT

Additional clauses other than those listed below which are based on the type of contract/Contractor shall be determined during negotiations. Any contract awarded from this solicitation will contain the following:

This contract incorporates the following clauses in full text.

FEDERAL ACQUISITION REGULATION (FAR)(48 CFR CHAPTER 1) CLAUSES:

a. FAR Clause **52.222-39, Notification Of Employee Rights Concerning Payment Of Union Dues Or Fees** (December 2004)

(a) Definition. As used in this clause--

United States means the 50 States, the District of Columbia, Puerto Rico, the Northern Mariana Islands, American Samoa, Guam, the U.S. Virgin Islands, and Wake Island.

(b) Except as provided in paragraph (e) of this clause, during the term of this contract, the Contractor shall post a notice, in the form of a poster, informing employees of their rights concerning union membership and payment of union dues and fees, in conspicuous places in and about all its plants and offices, including all places where notices to employees are customarily posted. The notice shall include the following information (except that the information pertaining to National Labor Relations Board shall not be included in notices posted in the plants or offices of carriers subject to the Railway Labor Act, as amended (45 U.S.C. 151-188)).

Notice to Employees

Under Federal law, employees cannot be required to join a union or maintain membership in a union in order to retain their jobs. Under certain conditions, the law permits a union and an employer to enter into a union-security agreement requiring employees to pay uniform periodic dues and initiation fees. However, employees who are not union members can object to the use of their payments for certain purposes and can only be required to pay their share of union costs relating to collective

bargaining, contract administration, and grievance adjustment.

If you do not want to pay that portion of dues or fees used to support activities not related to collective bargaining, contract administration, or grievance adjustment, you are entitled to an appropriate reduction in your payment. If you believe that you have been required to pay dues or fees used in part to support activities not related to collective bargaining, contract administration, or grievance adjustment, you may be entitled to a refund and to an appropriate reduction in future payments.

For further information concerning your rights, you may wish to contact the National Labor Relations Board (NLRB) either at one of its Regional offices or at the following address or toll free number:

National Labor Relations Board
Division of Information
1099 14th Street, N.W.
Washington, DC 20570
1-866-667-6572
1-866-316-6572 (TTY)

To locate the nearest NLRB office, see NLRB's website at http://www.nlrb.gov.

(c) The Contractor shall comply with all provisions of Executive Order 13201 of February 17, 2001, and related implementing regulations at 29 CFR part 470, and orders of the Secretary of Labor.

(d) In the event that the Contractor does not comply with any of the requirements set forth in paragraphs (b), (c), or (g), the Secretary may direct that this contract be cancelled, terminated, or suspended in whole or in part, and declare the Contractor ineligible for further Government contracts in accordance with procedures at 29 CFR part 470, Subpart B--Compliance Evaluations, Complaint Investigations and Enforcement Procedures. Such other sanctions or remedies may be imposed as are provided by 29 CFR part 470, which implements Executive Order 13201, or as are otherwise provided by law.

(e) The requirement to post the employee notice in paragraph (b) does not apply to--

(1) Contractors and subcontractors that employ fewer than 15 persons;

(2) Contractor establishments or construction work sites where no union has been formally recognized by the Contractor or certified as the exclusive bargaining representative of the Contractor's employees;

(3) Contractor establishments or construction work sites located in a jurisdiction named in the definition of the United States in which the law of that jurisdiction forbids enforcement of union-security agreements;

(4) Contractor facilities where upon the written request of the Contractor, the Department of Labor Deputy Assistant Secretary for Labor-Management Programs has waived the posting requirements with respect to any of the Contractor's facilities if the Deputy Assistant Secretary finds that the Contractor has demonstrated that--

(I) The facility is in all respects separate and distinct from activities of the Contractor related to the performance of a contract; and
(ii) Such a waiver will not interfere with or impede the effectuation of the Executive order; or

(5) Work outside the United States that does not involve the recruitment or employment of workers within the United States.

(f) The Department of Labor publishes the official employee notice in two variations; one for contractors covered by the Railway Labor Act and a second for all other contractors. The Contractor shall--

(1) Obtain the required employee notice poster from the Division of Interpretations and Standards, Office of Labor-Management Standards, U.S. Department of Labor, 200 Constitution Avenue, NW, Room N-5605, Washington, DC 20210, or from any field office of the Department's Office of Labor-Management Standards or Office of Federal Contract Compliance Programs;

(2) Download a copy of the poster from the Office of Labor-Management Standards website at http://www.olms.dol.gov; or

(3) Reproduce and use exact duplicate copies of the Department of Labor's official poster.

(g) The Contractor shall include the substance of this clause in every subcontract or purchase order that exceeds the simplified acquisition threshold, entered into in connection with this contract, unless exempted by the Department of Labor Deputy Assistant Secretary for Labor-Management Programs on account of special circumstances in the national interest under authority of 29 CFR 470.3(c). For indefinite quantity subcontracts, the Contractor shall include the substance of this clause if the value of orders in any calendar year of the subcontract is expected to exceed the simplified acquisition threshold. Pursuant to 29 CFR part 470, Subpart B--Compliance Evaluations, Complaint Investigations and Enforcement Procedures, the Secretary of Labor may direct the Contractor to take such action in the enforcement of these regulations, including the imposition of sanctions for noncompliance with respect to any such subcontract or purchase order. If the Contractor becomes involved in litigation with a subcontractor or vendor, or is threatened with such involvement, as a result of such direction, the Contractor may request the United States, through the Secretary of Labor, to enter into such litigation to protect the interests of the United States.

PART III - LIST OF DOCUMENTS, EXHIBITS AND OTHER ATTACHMENTS

SECTION J - LIST OF ATTACHMENTS

The following documents are incorporated into this RFP:

SOLICITATION ATTACHMENTS:

Attachment No.	Title	Location
Attachment 1:	Packaging and Delivery of Proposal	See Attachment Section at the end of this RFP
Attachment 2:	Proposal Intent Response Sheet	See Attachment Section at the end of this RFP
Attachment 3:	Statement of Work	See Attachment Section at the end of this RFP
Attachment 4:	Information Technology Systems Security - Prospective Offeror Non-Disclosure Agreement	http://rcb.cancer.gov/rcb-internet/forms/IT-security-nondisclosure.pdf
Attachment 5:	Protocol	See Attachment Section at the end of this RFP

TECHNICAL PROPOSAL ATTACHMENTS: (The following attachments must be completed, where applicable, and submitted with the Technical Proposal.)

Attachment No.	Title	Location
Attachment 6:	Targeted/Planned Enrollment Table	http://rcb.cancer.gov/rcb-internet/forms/enroll-table.pdf
Attachment 7:	Annual Technical Progress Report Format for Each Study	http://rcb.cancer.gov/rcb-internet/forms/atpr.pdf
Attachment 8:	Technical Proposal Cost Summary	http://www.niaid.nih.gov/contract/forms/form5.pdf
Attachment 9:	Summary of Related Activities	http://www.niaid.nih.gov/contract/forms/form6.pdf
Attachment 10:	Government Notice for Handling Proposals	http://www.niaid.nih.gov/contract/forms/form7.pdf
Attachment 11:	Protection of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption, OMB Form No. 0990-0263 (formerly Optional Form 310	http://rcb.cancer.gov/rcb-internet/forms/of310.pdf
Attachment 12:	Project Objectives, NIH 1688-1	http://rcb.cancer.gov/rcb-internet/forms/nih1688-1.pdf

BUSINESS PROPOSAL ATTACHMENTS: (The following attachments must be completed, where applicable, and submitted with the Business Proposal.)

Attachment No.	Title	Location
Attachment 13:	Proposal Summary and Data Record, NIH-2043	http://www.niaid.nih.gov/contract/forms/NIH-2043.pdf

Attachment 14:	Breakdown of Proposed Estimated Costs (plus Fee) with Excel Spreadsheet	http://www.niaid.nih.gov/contract/forms/form2.pdf http://ocm.od.nih.gov/contracts/spsh/spshexcl.xls
Attachment 15:	Offeror's Points of Contact	http://www.niaid.nih.gov/contract/forms/form3.pdf
Attachment 16:	Certificate of Current Cost or Pricing Data	http://rcb.cancer.gov/rcb-internet/forms/cert-current-cost.pdf
Attachment 17:	Disclosure of Lobbying Activities, OMB Form SF-LLL	http://rcb.cancer.gov/rcb-internet/forms/sflllin.pdf

INFORMATIONAL ATTACHMENTS: (The following Attachments and Reports will become part of any contract resulting from this RFP and will be required during contract performance.)

Attachment No.	Title	Location
Attachment 18:	Invoice/Financing Request Instructions--Cost-Reimbursement, NIH(RC)-1	http://rcb.cancer.gov/rcb-internet/forms/rc1.pdf
Attachment 19:	Financial Report of Individual Project/Contract, NIH 2706	http://www.niaid.nih.gov/contract/forms/nih-2706.pdf
Attachment 20:	Instructions for Completing Form NIH 2706	http://www.niaid.nih.gov/contract/forms/instructions2706.pdf
Attachment 21:	Privacy Act System of Records *System of Records No. 09-25-0200 is applicable to this RFP.*	http://oma.od.nih.gov/ms/privacy/pa-files/read02systems.htm
Attachment 22:	Procurement of Certain Equipment, NIH(RC)-7	http://www.niaid.nih.gov/contract/forms/NIH-RC-7.pdf
Attachment 23:	Research Patient Care Costs, NIH(RC)-11	http://www.niaid.nih.gov/contract/forms/nih-rc-11.pdf
Attachment 24:	Inclusion Enrollment Report	http://rcb.cancer.gov/rcb-internet/forms/inclusion-enrollment.pdf
Attachment 25:	Disclosure of Lobbying Activities, OMB Form SF-LLL	http://rcb.cancer.gov/rcb-internet/forms/sflllin.pdf
Attachment 26:	Commitment To Protect Non-Public Information Contractor Agreement	http://irm.cit.nih.gov/security/Nondisclosure.pdf
Attachment 27:	Roster of Employees Requiring Suitability Investigations	http://ais.nci.nih.gov/forms/Suitability-roster.xls
Attachment 28:	Employee Separation Checklist	http://rcb.cancer.gov/rcb-internet/forms/Emp-sep-checklist.pdf

PART IV - REPRESENTATIONS AND INSTRUCTIONS

SECTION K - REPRESENTATIONS, CERTIFICATIONS AND OTHER STATEMENTS OF OFFERORS

SECTION K can be accessed electronically from the INTERNET at the following address:

http://rcb.cancer.gov/rcb-internet/wkf/sectionk.pdf

If you are unable to access this document electronically, you may request a copy from the Contracting Officer identified on the cover page of this solicitation.

IF YOU INTEND TO SUBMIT A PROPOSAL, YOU *MUST* COMPLETE SECTION K AND SUBMIT IT AS PART OF YOUR BUSINESS PROPOSAL.

SECTION L - INSTRUCTIONS, CONDITIONS AND NOTICES TO OFFERORS

1. GENERAL INFORMATION

a. **INSTRUCTIONS TO OFFERORS--COMPETITIVE ACQUISITION** [FAR Provision 52.215-1 (January 2004)]

(a) *Definitions*. As used in this provision--

Discussions are negotiations that occur after establishment of the competitive range that may, at the Contracting Officer's discretion, result in the offeror being allowed to revise its proposal.

"In writing", *"writing"*, or *"written"* means any worded or numbered expression that can be read, reproduced, and later communicated, and includes electronically transmitted and stored information.

"*Proposal modification*" is a change made to a proposal before the solicitation's closing date and time, or made in response to an amendment, or made to correct a mistake at any time before award.

"*Proposal revision*" is a change to a proposal made after the solicitation closing date, at the request of or as allowed by a Contracting Officer as the result of negotiations.

"*Time,*" if stated as a number of days, is calculated using calendar days, unless otherwise specified, and will include Saturdays, Sundays, and legal holidays. However, if the last day falls on a Saturday, Sunday, or legal holiday, then the period shall include the next working day.

(b) *Amendments to solicitations*. If this solicitation is amended, all terms and conditions that are not amended remain unchanged. Offerors shall acknowledge receipt of any amendment to this solicitation by the date and time specified in the amendment(s).

(c) *Submission, modification, revision, and withdrawal of proposals*. (1) Unless other methods (*e.g.*, electronic commerce or facsimile) are permitted in the solicitation, proposals and modifications to proposals shall be submitted in paper media in sealed envelopes or packages (I) addressed to the office specified in the solicitation, and (ii) showing the time and date specified for receipt, the solicitation number, and the name and address of the offeror. Offerors using commercial carriers should ensure that the proposal is marked on the outermost wrapper with the information in paragraphs (c)(1)(I) and (c)(1)(ii) of this provision.

(2) The first page of the proposal must show--
- (I) The solicitation number;
- (ii) The name, address, and telephone and facsimile numbers of the offeror (and electronic address if available);
- (iii) A statement specifying the extent of agreement with all terms, conditions, and provisions included in the solicitation and agreement to furnish any or all items upon which prices are offered at the price set opposite each item;
- (iv) Names, titles, and telephone and facsimile numbers (and electronic addresses if available) of persons authorized to negotiate on the offeror's behalf with the Government in connection with this solicitation; and
- (v) Name, title, and signature of person authorized to sign the proposal. Proposals signed by an agent shall be accompanied by evidence of that agent's authority, unless that evidence has been previously furnished to the issuing office.

(3) *Submission, modification, revision, and withdrawal of proposals*. (I) Offerors are responsible for submitting proposals, and any modifications or revisions, so as to reach the Government office designated in the solicitation by the time specified in the solicitation. If no time is specified in the solicitation, the time for receipt is 4:30 p.m., local time, for the designated Government office on the date that proposal or revision is due.

(ii) (A) Any proposal, modification, or revision received at the Government office designated in the solicitation after the exact time specified for receipt of offers is "late" and will not be considered unless it is received before award is made, the Contracting Officer determines that accepting the late offer would not unduly delay the acquisition; and--

(*1*) If it was transmitted through an electronic commerce method authorized by the solicitation, it was received at the initial point of entry to the Government infrastructure not later than 5:00 p.m. one working day prior to the date specified for receipt of proposals; or

(*2*) There is acceptable evidence to establish that it was received at the Government installation designated for receipt of offers and was under the Government's control prior to the time set for receipt of offers; or

(*3*) It is the only proposal received.

(B) However, a late modification of an otherwise successful proposal that makes its terms more favorable to the Government, will be considered at any time it is received and may be accepted.

(iii) Acceptable evidence to establish the time of receipt at the Government installation includes the time/date stamp of that installation on the proposal wrapper, other documentary evidence of receipt maintained by the installation, or oral testimony or statements of Government personnel.

(iv) If an emergency or unanticipated event interrupts normal Government processes so that proposals cannot be received at the office designated for receipt of proposals by the exact time specified in the solicitation, and urgent Government requirements preclude amendment of the solicitation, the time specified for receipt of proposals will be deemed to be extended to the same time of day specified in the solicitation on the first work day on which normal Government processes resume.

(v) Proposals may be withdrawn by written notice received at any time before award. Oral proposals in response to oral solicitations may be withdrawn orally. If the solicitation authorizes facsimile proposals, proposals may be withdrawn via facsimile received at any time before award, subject to the conditions specified in the provision at 52.215-5, Facsimile Proposals. Proposals may be withdrawn in person by an offeror or an authorized representative, if the identity of the person requesting withdrawal is established and the person signs a receipt for the proposal before award.

(4) Unless otherwise specified in the solicitation, the offeror may propose to provide any item or combination of items.

(5) Offerors shall submit proposals in response to this solicitation in English, unless otherwise permitted by the solicitation, and in U.S. dollars, unless the provision at FAR 52.225-17, Evaluation of Foreign Currency Offers, is included in the solicitation.

(6) Offerors may submit modifications to their proposals at any time before the solicitation closing date and time, and may submit modifications in response to an amendment, or to correct a mistake at any time before award.

(7) Offerors may submit revised proposals only if requested or allowed by the Contracting Officer.

(8) Proposals may be withdrawn at any time before award. Withdrawals are effective upon receipt of notice by the Contracting Officer.

(d) *Offer expiration date*. Proposals in response to this solicitation will be valid for the number of days specified on the solicitation cover sheet (unless a different period is proposed by the offeror).

(e) *Restriction on disclosure and use of data.* (1) The proposal submitted in response to this request may contain data (trade secrets; business data, e.g., commercial information, financial information, and cost and pricing data; and technical data) which the offeror, including its prospective subcontractor(s), does not want used or disclosed for any purpose other than for evaluation of the proposal. The use and disclosure of any data may be so restricted; provided, that the Government determines that the data is not required to be disclosed under the Freedom of Information Act, 5 U.S.C. 552, as amended, and the offeror marks the cover sheet of the proposal with the following legend, specifying the particular portions of the proposal which are to be restricted in accordance with the conditions of the legend. The Government's determination

to withhold or disclose a record will be based upon the particular circumstances involving the record in question and whether the record may be exempted from disclosure under the Freedom of Information Act. The legend reads:

> Unless disclosure is required by the Freedom of Information Act, 5 U.S.C. 552, as amended, (the Act) as determined by Freedom of Information (FOI) officials of the Department of Health and Human Services, data contained in the portions of this proposal which have been specifically identified by page number, paragraph, etc. by the offeror as containing restricted information shall not be used or disclosed except for evaluation purposes.
>
> The offeror acknowledges that the Department may not be able to withhold a record (data, document, etc.) nor deny access to a record requested pursuant to the Act and that the Department's FOI officials must make that determination. The offeror hereby agrees that the Government is not liable for disclosure if the Department has determined that disclosure is required by the Act.
>
> If a contract is awarded to the offeror as a result of, or in connection with, the submission of this proposal, the Government shall have right to use or disclose the data to the extent provided in the contract. Proposals not resulting in a contract remain subject to the Act.
>
> The offeror also agrees that the Government is not liable for disclosure or use of unmarked data and may use or disclose the data for any purpose, including the release of the information pursuant to requests under the Act. The data subject to this restriction are contained in pages (insert page numbers, paragraph designations, etc. or other identification).

(2) In addition, the offeror should mark each page of data it wishes to restrict with the following statement:

> "Use or disclosure of data contained on this page is subject to the restriction on the cover sheet of this proposal or quotation."

(3) Offerors are cautioned that proposals submitted with restrictive legends or statements differing in substance from the above legend may not be considered for award. The Government reserves the right to reject any proposal submitted with a nonconforming legend.

(f) *Contract award*. (1) The Government intends to award a contract or contracts resulting from this solicitation to the responsible offeror(s) whose proposal(s) represents the best value after evaluation in accordance with the factors and subfactors in the solicitation.

(2) The Government may reject any or all proposals if such action is in the Government's interest.

(3) The Government may waive informalities and minor irregularities in proposals received.

(4) The Government intends to evaluate proposals and award a contract without discussions with offerors (except clarifications as described in FAR 15.306(a)). Therefore, the offeror's initial proposal should contain the offeror's best terms from a cost or price and technical standpoint. The Government reserves the right to conduct discussions if the Contracting Officer later determines them to be necessary. If the Contracting Officer determines that the number of proposals that would otherwise be in the competitive range exceeds the number at which an efficient competition can be conducted, the Contracting Officer may limit the number of proposals in the competitive range to the greatest number that will permit an efficient competition among the most highly rated proposals.

(5) The Government reserves the right to make an award on any item for a quantity less than the quantity offered, at the unit cost or prices offered, unless the offeror specifies otherwise in the proposal.

(6) The Government reserves the right to make multiple awards if, after considering the additional administrative costs, it is in the Government's best interest to do so.

(7) Exchanges with offerors after receipt of a proposal do not constitute a rejection or counteroffer by the Government.

(8) The Government may determine that a proposal is unacceptable if the prices proposed are materially unbalanced between line items or subline items. Unbalanced pricing exists when, despite an acceptable total evaluated price, the price of one or more contract line items is significantly overstated or understated as indicated by the application of cost or price analysis techniques. A proposal may be rejected if the Contracting Officer determines that the lack of balance poses an unacceptable risk to the Government.

(9) If a cost realism analysis is performed, cost realism may be considered by the source selection authority in evaluating performance or schedule risk.

(10) A written award or acceptance of proposal mailed or otherwise furnished to the successful offeror within the time specified in the proposal shall result in a binding contract without further action by either party.

(11) If a post-award debriefing is given to requesting offerors, the Government shall disclose the following information, if applicable:

(I) The agency's evaluation of the significant weak or deficient factors in the debriefed offeror's offer.
(ii) The overall evaluated cost or price and technical rating of the successful and debriefed offeror and past performance information on the debriefed offeror.
(iii) The overall ranking of all offerors, when any ranking was developed by the agency during source selection;
(iv) A summary of the rationale for award.
(v) For acquisitions of commercial items, the make and model of the item to be delivered by the successful offeror.
(vi) Reasonable responses to relevant questions posed by the debriefed offeror as to whether source-selection procedures set forth in the solicitation, applicable regulations, and other applicable authorities were followed by the agency.

(End of Provision)

Alternate I (October 1997). As prescribed in 15.209(a)(1), substitute the following paragraph (f)(4) for paragraph (f)(4) of the basic provision:

(f) (4) The Government intends to evaluate proposals and award a contract after conducting discussions with offerors whose proposals have been determined to be within the competitive range. If the Contracting Officer determines that the number of proposals that would otherwise be in the competitive range exceeds the number at which an efficient competition can be conducted, the Contracting Officer may limit the number of proposals in the competitive range to the greatest number that will permit an efficient competition among the most highly rated proposals. Therefore, the offeror's initial proposal should contain the offeror's best terms from a price and technical standpoint.

b. "**JUST IN TIME**"

This RFP contains special procedures for the submission of business management proposals. These special procedures are designed to reduce the administrative burden on offerors without compromising the information during the initial evaluation of proposals. Certain documents will not longer be required to be submitted with initial proposals, but will be requested at a later stage in the competitive process. Specifically, the travel policy, the annual financial statement, the total compensation plan, the subcontracting plan, and certain types of cost/pricing information will only be required to be submitted from those offerors included in the competitive range, or the apparent successful offeror. The special procedures for submission of this documentation are set

forth in detail below:

Travel Policy. The offeror's (and any proposed subcontractor's) written travel policy shall **not** be submitted with the initial business proposal. All offerors included in the competitive range will be required to submit a travel policy as a part of their final proposal revision.

Annual Report. The offeror's most recent annual report shall **not** be submitted with the initial business proposal. All offerors included in the competitive range will be required submit a copy of their most recent annual report as a part of their final proposal revision.

Total Compensation Plan. The offeror's total compensation plan shall **not** be submitted with the initial business proposal. All offerors included in the competitive range will be required submit a total compensation plan as a part of their final proposal revision.

Cost/Pricing Information. The offeror's business proposal shall include the basic cost/pricing information specified in Section L.2.c.(1) of this RFP. In addition, the Government may require offerors included in the competitive range to submit additional information substantiating their proposed costs or prices. This additional cost/pricing information will be requested after establishment of the competitive range, and potentially includes payroll documentation, vendor quotes, invoice prices, and/or any other information deemed necessary by the contracting officer to evaluate the reasonableness of the price or to determine cost realism. [The information may also include submission and certification of cost or pricing data.]

c. **NOTICE OF SMALL BUSINESS SET-ASIDE**

(1) **General**. Bids or proposals under this procurement are solicited only from small business concerns. The procurement is to be awarded only to one or more such concerns, organizations, or individuals. This action is based on a determination by the Contracting Officer, alone or in conjunction with a representative of the Small Business Administration, that it is in the interest of maintaining or mobilizing the Nation's full productive capacity, or in the interest of war or national defense programs, or in the interest of assuring that a fair proportion of Government procurement is placed with small business concerns. Bids or proposals received from others will be considered non-responsive.

(2) **Definitions**. The term "small business concern" means a concern, including its affiliates, which is independently owned and operated, is not dominant in the field of operation in which it is bidding on Government contracts, and can further qualify under the criteria set forth in the regulations of the Small Business Administration (13 CFR 121.3-8). In addition to meeting these criteria, a manufacturer or a regular dealer submitting bids or proposals in his own name must agree to furnish in the performance of the contract end items manufactured or produced in the United States, its territories and possessions, Commonwealth of Puerto Rico, the Trust Territory of the Pacific Islands, and the District of Columbia, by small business concerns. Provided, that this additional requirement does not apply in connection with construction or service contracts.

d. **NAICS CODE AND SIZE STANDARD**

Note: The following information is to be used by the offeror in preparing its Representations and Certifications (See Section K of this RFP), specifically in completing the provision entitled, SMALL BUSINESS PROGRAM REPRESENTATION, FAR Clause 52.219-1.

(1) The North American Industry Classification System (NAICS) code for this acquisition is 541710.
(2) The small business size standard is 500.

e. **TYPE OF CONTRACT AND NUMBER OF AWARD(S)**

It is anticipated that One Award will be made from this solicitation and that the award will be made on/about September 30, 2006.

It is anticipated that the award from this solicitation will be a multiple-year, cost reimbursement type contract

(completion) with a period of performance of four years, and that incremental funding will be used [see Section L.2.c. Business Proposal Instructions].

f. **PERFORMANCE BASED ACQUISITION**

The Government intends to use a Performance Based Acquisition method in the evaluation and award of any contract resulting from this RFP.

The Performance Based contract is designed to motivate the contractor to perform at a higher standard. Outstanding performance is rewarded through an incentive defined in the contract. The following performance incentive will be used in any contract awarded from this RFP:

Cost-Plus-Award-Fee (CPAF): The CPAF contract includes an estimated cost and an award fee amount that is paid based upon periodic evaluations of contractor performance. The Quality Assurance Surveillance Plan (QASP), which will be negotiated prior to contract award, sets forth all the elements required for evaluation and determination of the award fee amount. The award fee determination is made unilaterally by the Government and is not subject to Disputes clause procedures.

g. **ESTIMATE OF EFFORT**

It is expected that a completion type contract will be awarded as a result of this RFP. The level of effort devoted to this project must be compatible with the scientific and technical approach proposed to cover the activities in the Statement of Work. Professional, technical and support staff should have experience pertinent to that required for the Data Coordinating Center approved in the Statement of Work.

The following staffing patterns are to be considered broad guidelines and are not inclusive of all staffing positions. This information is provided for the offeror's information only and is not to be considered restrictive for proposal purposes.. The staffing guidelines are based on the amount of work that will be required during the planning phase, the amount of data that will be generated during active patient follow-up in Phase II, and the amount of data analysis and manuscript writing that will occur during Phase III. All staffing levels should be accompanied by specific justifications as to the type and hours of work expected to be performed by all personnel. The categories and levels of effort presented are offered as information only and are not to be considered restrictive for proposal purposes. If a consultant(s) is proposed, a letter of commitment shall be provided.

Position - Data Coordinating Center	Level of Effort		
	Phase I	Phase II	Phase III
Principal Investigator	20%	20%	20%
Project Director	50%	100%	50%
Statistician (Ph.D.)	20%	20%	50%
Data Manager	20%	100%	50%
Data Clerk	50%	100%	50%
Clinical Monitor	0%	7%	16%
Web Developer	50%	25%	0%
Statistical Programmer	20%	10%	0%
Research Administrative Assistant	50%	100%	50%

h. **COMMITMENT OF PUBLIC FUNDS**

The Contracting Officer is the only individual who can legally commit the Government to the expenditure of public funds in connection with the proposed procurement. Any other commitment, either explicit or implied, is invalid.

i. **COMMUNICATIONS PRIOR TO CONTRACT AWARD**

Offerors shall direct all communications to the attention of the Contract Specialist or Contracting Officer cited on the face page of this RFP. Communications with other officials may compromise the competitiveness of this acquisition and result in cancellation of the requirement.

j. **RELEASE OF INFORMATION**

Contract selection and award information will be disclosed to offerors in accordance with regulations applicable to negotiated acquisition. Prompt written notice will be given to unsuccessful offerors as they are eliminated from the competition, and to all offerors following award.

k. **COMPARATIVE IMPORTANCE OF PROPOSALS**

You are advised that paramount consideration shall be given to the evaluation of technical proposals. All evaluation factors other than cost or price, when combined, are significantly more important than cost or price. The relative importance of the evaluation factors are specified in SECTION M of this solicitation. However, the Government reserves the right to make an award to the best advantage of the Government, cost and other factors considered.

l. **PREPARATION COSTS**

This RFP does not commit the Government to pay for the preparation and submission of a proposal.

m. **SERVICE OF PROTEST** (AUGUST 1996) - FAR 52.233-2

(a) Protests, as defined in section 33.101 of the Federal Acquisition Regulation, that are filed directly with an agency, and copies of any protests that are filed with the General Accounting Office (GAO), shall be served on the Contracting Officer (addressed as follows) by obtaining written and dated acknowledgment of receipt from:

Contracting Officer
Contracts Operations Branch
National Heart, Lung, and Blood Institute
6701 ROCKLEDGE DRIVE/ Room 6132
MSC 7902
BETHESDA MD 20892-7902

(b) The copy of any protest shall be received in the office designated above within one day of filing a protest with the GAO.

(End of Provision)

n. **LATE PROPOSALS AND REVISIONS**, HHSAR 352.215-70

Notwithstanding the procedures contained in FAR 52.215-1(c)(3) of the provision of this solicitation entitled Instructions to Offerors-Competitive Acquisition, a proposal received after the date specified for receipt may be considered if it offers significant cost or technical advantages to the Government; and it was received before proposals were distributed for evaluation, or within five calendar days after the exact time specified for receipt, whichever is earlier.

(End of provision)

2. INSTRUCTIONS TO OFFERORS

a. GENERAL INSTRUCTIONS

INTRODUCTION

The following instructions will establish the acceptable minimum requirements for the format and contents of proposals. Special attention is directed to the requirements for technical and business proposals to be submitted in accordance with these instructions.

(1) **Contract Type and General Clauses**

It is contemplated that a cost-reimbursement (completion) type contract will be awarded. (See General Information) Any resultant contract shall include the clauses applicable to the selected offeror's organization and type of contract awarded as required by Public Law, Executive Order, or acquisition regulations in effect at the time of execution of the proposed contract.

(2) **Authorized Official and Submission of Proposal**

The proposal must be signed by an official authorized to bind your organization and must stipulate that it is predicated upon all the terms and conditions of this RFP. Your proposal shall be submitted in the number of copies, to the addresses, and marked as indicated in the Attachment entitled, PACKAGING AND DELIVERY OF PROPOSAL, Part III, Section J hereof. Proposals will be typewritten, paginated, reproduced on letter size paper and will be legible in all required copies. To expedite the proposal evaluation, all documents required for responding to the RFP should be placed in the following order:

I. COVER PAGE

Include RFP title, number, name of organization, DUNS No., identification of the proposal part, and indicate whether the proposal is an original or a copy.

II. TECHNICAL PROPOSAL

It is recommended that the technical proposal consist of a cover page, a table of contents, and the information requested in the Technical Proposal Instructions and as specified in SECTION J, List of Attachments.

III. BUSINESS PROPOSAL

It is recommended that the business proposal consist of a cover page, a table of contents, and the information requested in the Business Proposal Instructions and as specified in SECTION J, List of Attachments.

(3) **Proposal Summary and Data Record (NIH-2043)**

The Offeror must complete the Form NIH-2043, attached, with particular attention to the length of time the proposal is firm and the designation of those personnel authorized to conduct negotiations. (See Section J, Attachment entitled, PROPOSAL SUMMARY AND DATA RECORD.)

(4) **Separation of Technical and Business Proposals**

The proposal must be prepared in two parts: a "Technical Proposal" and a "Business Proposal." Each of the parts shall be separate and complete in itself so that evaluation of one may be accomplished independently of, and concurrently with, evaluation of the other. The technical proposal must include direct cost and resources information, such as labor-hours and categories and applicable rates, materials, subcontracts, travel, etc., and associated costs so that the offeror's understanding of the project may be evaluated (See Attachment entitled, TECHNICAL PROPOSAL COST INFORMATION/SUMMARY OF LABOR AND DIRECT COSTS). However, the technical proposal should **not** include pricing data relating to individual salary information, indirect cost rates or amounts, fee amounts (if any), and total costs. The

technical proposal should disclose your technical approach in as much detail as possible, including, but not limited to, the requirements of the technical proposal instructions.

(5) **Alternate Proposals**

You may, at your discretion, submit alternate proposals, or proposals which deviate from the requirements; provided, that you also submit a proposal for performance of the work as specified in the statement of work. Such proposals may be considered if overall performance would be improved or not compromised and if they are in the best interests of the Government. Alternative proposals, or deviations from any requirements of this RFP, shall be clearly identified.

(6) **Evaluation of Proposals**

The Government will evaluate technical proposals in accordance with the criteria set forth in Part IV, Section M of this RFP.

(7) **Potential Award Without Discussions**

The Government reserves the right to award a contract without discussions if the Contracting Officer determines that the initial prices are fair and reasonable and that discussions are not necessary.

(8) **Use of the Metric System of Measurement**

It is the policy of the Department of Health and Human Services to support the Federal transition to the metric system and to use the metric system of measurement in all procurement, grants, and other business related activities unless such use is impracticable or is likely to cause significant inefficiencies.

The offeror is encouraged to prepare their proposal using either "Hard Metric," "Soft Metric," or "Dual Systems" of measurement. The following definitions are provided for your information:

Hard Metric - The replacement of a standard inch-pound size with an accepted metric size for a particular purpose. An example of size substitution might be: selling or packaging liquids by the liter instead of by the pint or quart (as for soft drinks), or instead of by the gallon (as for gasoline).

Soft Metric - The result of a mathematical conversion of inch-pound measurements to metric equivalents for a particular purpose. The physical characteristics are not changed.

Dual Systems - The use of both inch-pound and metric systems. For example, an item is designed, produced, and described in inch-pound values with soft metric values also shown for information or comparison purposes.

(9) **Obtaining and Disseminating Biomedical Research Resources**

As a public sponsor of biomedical research, the National Institutes of Health (NIH) has a dual interest in accelerating scientific discovery and facilitating product development. Intellectual property restrictions can stifle the broad dissemination of new discoveries and limit future avenues of research and product development. At the same time, reasonable restrictions on the dissemination of research tools are sometimes necessary to protect legitimate proprietary interests and to preserve incentives for commercial development. To assist NIH contractors achieve an appropriate balance, the NIH has provided guidance in the form of a two-part document, consisting of Principles setting forth the fundamental concepts and Guidelines that provide specific information to patent and license professionals and sponsored research administrators for implementation.

The purpose of these Principles and Guidelines is to assist NIH funding recipients in determining: 1) Reasonable terms and conditions for making NIH-funded research resources available to scientists in other institutions in the public and private sectors (disseminating research tools); and 2) Restrictions to accept as a condition of receiving access to research tools for use in NIH-funded research (acquiring research tools). The intent is to help recipients ensure that the conditions they impose and accept on the transfer of research tools will facilitate further biomedical research, consistent with the requirements of the Bayh-

Dole Act and NIH funding policy.

This policy, entitled, "Sharing Biomedical Research Resources: Principles and Guidelines for Recipients of NIH Research Grants and Contracts," (Federal Register Notice, December 23, 1999 [64 FR 72090] will be included in any contract awarded from this solicitation. It can be found at the following website: http://ott.od.nih.gov/NewPages/64FR72090.pdf.

(a) **Sharing Research Data**

[Note: The NIH Guide announcement referenced below states that this policy is applicable to "all investigator-initiated applications with direct costs greater than $500,000 in any single year." This is an overall grant policy which requires that an applicant must seek agreement by NIH to accept assignment of their application in advance of the submission date. As such, this policy has not correlation to the contract process, therefore, the threshold is not applicable to contracts. Thus, this article applies to ***any*** *contract that may generate research data.]*

The NIH endorses the sharing of final research data to expedite the translation of research results into knowledge, products, and procedures to improve human health. This contract is expected to generate research data. Therefore, the offeror must submit a plan for data sharing or state why data sharing is not possible. If data sharing is limited, the offeror should explain such limitations in its data sharing plan. NIH's data sharing policy may be found at the following Web site:

http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-032.html

[If the resultant contract is part of a collaborative program involving multiple sites, the data sharing will be governed by a dissemination plan to be developed jointly following award. Offerors must include in their proposals a statement of willingness to work collaboratively after award with the other funded sites to prepare a joint dissemination plan. Coordinating Center proposals should describe methods to coordinate the dissemination planning and implementation. The Coordinating Center must include a budget and justification for any additional costs of this collaborative effort.]

(10) **Privacy Act - Treatment of Proposal Information**

The Privacy Act of 1974 (P.L. 93-579) requires that a Federal agency advise each individual whom it asks to supply information, the authority which authorizes the solicitation, whether disclosure is voluntary or mandatory, the principal purpose or purposes for which the information is intended to be used, the uses outside the agency which may be made of the information, and the effects on the individual, if any, of not providing all or any part of the requested information.

The NIH is requesting the information called for in this RFP pursuant to the authority provided by Sec. 301(a)(7) of the Public Health Service Act, as amended, and P.L. 92-218, as amended.

Providing the information requested is entirely voluntary. The collection of this information is for the purpose of conducting an accurate, fair, and adequate review prior to a discussion as to whether to award a contract.

Failure to provide any or all of the requested information may result in a less than adequate review.

In addition, the Privacy Act of 1974 (P.L. 93-579, Section 7) requires that the following information be provided when individuals are requested to disclose their social security number.

Provision of the social security number is voluntary. Social security numbers are requested for the purpose of accurate and efficient identification, referral, review and management of NIH contracting programs. Authority for requesting this information is provided by Section 301 and Title IV of the PHS Act, as amended.

The information provided by you may be routinely disclosed for the following purposes:

- to the cognizant audit agency and the General Accounting Office for auditing.

- to the Department of Justice as required for litigation.
- to respond to congressional inquiries.
- to qualified experts, not within the definition of Department employees, for opinions as a part of the review process.

(11) **Selection of Offerors**

a) The acceptability of the [scientific and] technical portion of each [research] contract proposal will be evaluated by a technical review committee. The committee will evaluate each proposal in strict conformity with the evaluation criteria of the RFP, utilizing point scores and written critiques. The committee may suggest that the Contracting Officer request clarifying information from an offeror.

b) The business portion of each contract proposal will be subjected to a cost and price analysis, management analysis, etc.

c) If award will be made without conducting discussions, offerors may be given the opportunity to clarify certain aspects of their proposal (e.g., the relevance of an offeror's past performance information and adverse past performance information to which the offeror has not previously had an opportunity to respond) or to resolve minor or clerical errors.

d) If the Government intends to conduct discussions prior to awarding a contract-

(1) Communications will be held with offerors whose past performance information is the determining factor preventing them from being placed within the competitive range. Such communications shall address adverse past performance information to which an offeror has not had a prior opportunity to respond. Also, communications may be held with any other offerors whose exclusion from, or inclusion in, the competitive range is uncertain.

Such communications shall not be used to cure proposal deficiencies or omissions that alter the technical or cost elements of the proposal, and/or otherwise revise the proposal, but may be considered in rating proposals for the purpose of establishing the competitive range.

(2) The Contracting Officer will, in concert with program staff, decide which proposals are in the competitive range. The competitive range will be comprised of all of the most highly rated proposals. Oral or written discussions will be conducted with all offerors in the competitive range.

While it is NHLBI's policy to conduct discussions with all offerors in the competitive range, NHLBI reserves the right, in special circumstances, to limit the number of proposals included in the competitive range to the greatest number that will permit an efficient competition. All aspects of the proposals are subject to discussions, including cost, technical approach, past performance, and contractual terms and conditions. At the conclusion of discussions, each offeror still in the competitive range shall be given an opportunity to submit a written Final Proposal Revision (FPR) with the reservation of the right to conduct finalization of details with the selected source in accordance with HHSAR 315.370.

e) The process described in FAR 15.101-1 will be employed, which permits the Government to make tradeoffs among cost or price and non-cost factors and to consider award to other than the lowest price offeror or other than the highest technically rated offeror. This process will take into consideration the results of the technical evaluation, the past performance evaluation (if applicable) and the cost analysis.

f) The NHLBI reserves the right to make a single award, multiple awards, or no award at all to the RFP. In addition, the RFP may be amended or canceled as necessary to meet NHLBI requirements.

(12) **Salary Rate Limitation in Fiscal Year 2005**

Offerors are advised that pursuant to P.L. 108-447, no NIH Fiscal Year 2005 (October 1, 2004 - September 30, 2005) funds may be used to pay the direct annual salary of an individual through

anycontract awarded as a result of this solicitation at a rate in excess of the Executive Schedule, Level I* (direct salary is exclusive of Overhead, Fringe Benefits and General and Administrative expenses, also referred to as "indirect cost" or "facilities and administrative (F&A) costs"). Direct salary has the same meaning as the term "institutional base salary." An individual's direct salary (or institutional base salary) is the annual compensation that the contractor pays for an individual's appointment whether that individual's time is spent on research, teaching, patient care or other activities. Direct salary (or institutional base salary) excludes any income that an individual may be permitted to earn outside of duties to the contractor.

This does not preclude the offeror from absorbing that portion of an employee's annual salary (plus the dollar amount for fringe benefits and associated indirect costs) that exceeds a rate of the Executive Schedule, Level I*. The salary rate limitation set by P.L. 108-447 applies only to Fiscal Year 2005 funds, however, salary rate ceilings for subsequent years may be included in future DHHS appropriation acts. Multi-year contracts awarded pursuant to this solicitation may be subject to unilateral modifications by the Government if an individual's annual salary exceeds any salary rate ceiling established in future appropriations acts. The Executive Schedule, Level I* annual salary rate limit also applies to individuals proposed under subcontracts, however it does not apply to consultants. P.L. 108-447 states in pertinent part:

"None of the funds appropriated in this Act for the National Institutes of Health, the Agency for Healthcare Research and Quality, and the Substance Abuse, and Mental Health Services Administration shall be used to pay the salary of an individual through a grant or extramural mechanism at a rate in excess of Executive Level I*."

LINK TO EXECUTIVE SCHEDULE SALARIES: http://www.opm.gov/oca/05tables/html/ex.asp

Note to Offerors: *The current Fiscal Year Executive Level I Salary Rate should be adhered to in the preparation of your proposal. All costs associated with any resultant contract award will be required to be in compliance with the current Fiscal Year 2005 Executive Level I Salary rates.*

(13) **Institutional Responsibility Regarding Conflicting Interests of Investigators**

EACH INSTITUTION MUST:

(a) Maintain an appropriate written, enforced policy on conflict of interest that complies with 42 CFR Part 50 Subpart F and/or 45 CFR Part 94 as appropriate and inform each investigator of the Institution's policy, the Investigator's reporting responsibilities, and the applicable regulations. If the Institution carries out the NIH funded research through subgrantees, contractors or collaborators, the Institution must take reasonable steps to ensure that Investigators working for such entities comply with the regulations, either by requiring those investigators to comply with the Institution's policy or by requiring the entities to provide assurances to the Institution that will enable the Institution to comply with the regulations.

(b) Designate an Institutional official(s) to solicit and review financial disclosure statements from each Investigator who is planning to participate in NIH-funded research.

(c) Require that by the time an application/proposal is submitted to the NIH each investigator who is planning to participate in the NIH-funded research has submitted to the designated official(s) a listing of his/her known Significant Financial Interests (and those of his/her spouse and dependent children): (I) that would reasonably appear to be affected by the research for which the NIH funding is sought; and (ii) in entities whose financial interests would reasonably appear to be affected by the research. All financial disclosures must be updated during the period of the award, either on an annual basis or as new reportable Significant Financial Interests are obtained.

(d) Provide guidelines consistent with the regulations for the designated official(s) to identify conflicting interests and take such actions as necessary to ensure that such conflicting interests will be managed, reduced, or eliminated.

(e) Maintain records, identifiable to each award, of all financial disclosures and all actions taken by the

institution with respect to each conflicting interest for: (1) in the case of grants, at least three years from the date of submission of the final expenditures report or, where applicable, from other dates specified in 45 CFR Part 74.53(b) and (2) in the case of contracts, 3 years after final payment or, where applicable, for the other time period specified in 48 CFR Part 4 Subpart 4.7, Contract Records Retention.

(f) Establish adequate enforcement mechanisms and provide for sanctions where appropriate.

(g) Certify, in each application/proposal for funding to which the regulations applies, that:

1) there is in effect at the Institution a written and enforced administrative process to identify and manage, reduce or eliminate conflicting interests with respect to all research projects for which funding is sought from the NIH;

2) prior to the Institution's expenditure of any funds under the award, the Institution will report to the awarding component the existence of a conflicting interest (but not the nature of the interest or other details) found by the Institution and assure that the interest has been managed, reduced or eliminated in accord with the regulations; and for any interest that the Institution identifies as conflicting subsequent to the expenditure of funds after award, the report will be made and the conflicting interest managed, reduced, or eliminated, at least on a temporary basis within sixty days of that identification;

3) the Institution agrees to make information available, upon request, to the awarding component regarding all conflicting interests identified by the Institution and how those interested have been managed, reduced, or eliminated to protect the research from bias; and

4) the Institution will otherwise comply with the regulations.

Institutional Management of Conflicting Interests

(a) The designated official(s) must: (1) review all financial disclosures; and (2) determine whether conflict of interest exists, and if so, determine what actions should be taken by the Institution to manage, reduce or eliminate such conflict of interest. **A conflict of interest exists when the designated official(s) reasonably determines that a Significant Financial Interest could directly and significantly affect the design, conduct, or reporting of the NIH-funded research**.

Examples of conditions or restrictions that might be imposed to manage actual or potential conflicts of interests include, but are not limited to:

(I) public disclosure of significant financial interests;
(ii) monitoring of research by independent reviewers;
(iii) modification of the research plan;
(iv) disqualification of the Investigator(s) from participation in all or a portion of the research funded by the awarding component;
(v) divestiture of significant financial interests; or
(vi) severance of relationships that create actual or potential conflicts of interests.

(b) An Institution may require the management of other conflicting financial interests in addition to those described in paragraph (a) of this section, as the Institution deems appropriate.

(14) **ROTC Access and Federal Military Recruiting on Campus**

Section 514 of the FY 1997 Appropriations Act prohibits NIH from providing contract funds to educational institutions that the Secretary of Defense determines have a policy or practice (regardless of when implemented) that either prohibits, or in effect prevents (1) the maintaining, establishing, or operation of a unit of the Senior Reserve Officer Training Corps at the covered education entity; or (2) a student at the covered educational entity from enrolling in a unit of the Senior Reserve Officer Training Corps at another institution of higher education.

Further, contract funds may not be provided to educational institutions that have a policy or practice that prohibits or prevents (1) entry to campuses, or access to students (who are 17 years of age or older) on campuses, for purposes of Federal military recruiting; or (2) access by military recruiters for purposes of Federal military recruiting to information pertaining to students (who are 17 years of age or older) enrolled at the covered educational entity.

(15) **Solicitation Provisions Incorporated by Reference, FAR 52.252-1 (February 1998)**

This Solicitation incorporates one or more solicitation provisions by reference, with the same force and effect as if they were given in full text. Upon request, the Contracting Officer will make their full text available. The offeror is cautioned that the listed provisions may include blocks that must be completed by the offeror and submitted with its quotation or offer. In lieu of submitting the full text provisions, the offeror may identify the provision by paragraph identifier and provide the appropriate information with its quotation or offer. Also, the full text of a solicitation provision may be accessed electronically at this address: http://www.arnet.gov/far/.

FEDERAL ACQUISITION REGULATION (48 CFR CHAPTER 1):

a) Data Universal Numbering System (DUNS) Number, FAR Clause 52.204-6 (October 2003).

b) Facilities Capital Cost of Money, FAR Clause 52.215-16, (October 1997).

c) Order of Precedence-Uniform Contract Format, FAR Clause 52.215-8, (October 1997).

d) Preaward On-Site Equal Opportunity Compliance Evaluation, (Over $10,000,000), FAR Clause 52.222-24, (February 1999).

(16) **Uniform Resource Locators (URLs) in Contract Proposals**

All proposals must be self-contained within the specific page limitations cited elsewhere in this solicitation. Unless otherwise specified, URLs/Internet addresses shall not be used to provide information necessary to the review because reviewers are under no obligation to review the Internet sites.

(17) **Page and Formatting Limitations**

The Technical Plan (objectives, approach, methods and procedures, and schedule) of the Technical Proposal shall not exceed 50 single-sided pages or 25 double-sided pages. This page limitation does not apply to the cover sheet, abstract, table of contents, personnel, facilities, equipment and resources, other considerations, other support, cost information, and literature cited. Appendices shall be limited to 100 single-sided pages or 50 double-sided pages. Pages in excess of this will be deleted and will be neither read nor evaluated. Each page of the Technical Proposal must be numbered sequentially. Offerors are encouraged to limit the overall size of the Technical Proposal, inclusive of appendices, attachments, etc. Note that although no page limit has been placed on the Business Proposal, offerors are encouraged to limit its content to only those documents necessary to provide adequate support for the proposed costs.

Type density and size must be 10 to 12 points. If constant spacing is used, 15 cpi (characters per inch) or fewer shall be used, whereas proportional spacing should provide an average of no more than 15 cpi. There must be no more than six lines of text within a vertical inch. Margins must be set to 1 inch around.

b. TECHNICAL PROPOSAL INSTRUCTIONS

A detailed work plan must be submitted indicating how each aspect of the statement of work is to be accomplished. Your technical approach should be in as much detail as you consider necessary to fully explain your proposed technical approach or method. The technical proposal should reflect a clear understanding of the nature of the work being undertaken. The technical proposal must include information on how the project is to be organized, staffed, and managed. Information should be provided which will demonstrate your understanding and management of important events or tasks.

(1) **Technical Discussions**

The technical discussion included in the technical proposal should respond to the items set forth below:

a) **Project Objectives, NIH-1688-1**

The offeror shall insert a completed NIH Form 1688-1, Project Objective, as provided in Section J, Attachments, behind the Title Page of each copy of the proposal, along with the "Government Notice for Handling Proposals." The NIH Form 1688-1 is to be completed as follows:

- For an **Institution of Higher Education:** The form MUST be completed in its entirety.
- For **OTHER** than an Institution of Higher Education: The starred items (Department, Service, Laboratory or Equivalent, and Major Subdivision) should be left blank.

The information required under the "Summary of Objectives" portion of the form MUST meet the requirements set forth in the section of the form entitled, **"INSTRUCTIONS:"**

b) **Statement of Work**

(1) Objectives

State the overall objectives and the specific accomplishments you hope to achieve. Indicate the rationale for your plan, and relation to comparable work in progress elsewhere. Review pertinent work already published which is relevant to this project and your proposed approach. This should support the scope of the project as you perceive it.

(2) Approach

Use as many subparagraphs, appropriately titled, as needed to clearly outline the general plan of work. Discuss phasing of research and, if appropriate, include experimental design and possible or probable outcome of approaches proposed.

(3) Methods

Describe in detail the methodologies you will use for the project, indicating your level of experience with each, areas of anticipated difficulties, and any unusual expenses you anticipate.

(4) Schedule

Provide a schedule for completion of the work and delivery of items specified in the statement of work. Performance or delivery schedules shall be indicated for phases or segments, as applicable, as well as for the overall program. Schedules shall be shown in terms of calendar months from the date of authorization to proceed or, where applicable, from the date of a stated event, as for example, receipt of a required approval by the Contracting Officer. Unless the request for proposal indicates that the stipulated schedules are mandatory, they shall be treated as desired or recommended schedules. In this event, proposals based upon the offeror's best alternative schedule, involving no overtime, extra shift or other premium, will be accepted for consideration.

c) **Personnel**

Describe the experience and qualifications of personnel who will be assigned for direct work on this program. Information is required which will show the composition of the task or work group, its general qualifications, and recent experience with similar equipment or programs. Special mention shall be made of direct technical supervisors and key technical personnel, and the approximate percentage of the total time each will be available for this program.

OFFERORS SHOULD ASSURE THAT THE PRINCIPAL INVESTIGATOR, AND ALL OTHER PERSONNEL PROPOSED, SHALL NOT BE COMMITTED ON FEDERAL GRANTS AND CONTRACTS FOR MORE THAN A TOTAL OF 100% OF THEIR TIME. IF THE SITUATION ARISES WHERE IT IS DETERMINED THAT A PROPOSED EMPLOYEE IS COMMITTED FOR MORE THAN 100% OF HIS OR HER TIME, THE GOVERNMENT WILL REQUIRE ACTION ON THE PART OF THE OFFEROR TO CORRECT THE TIME COMMITMENT.

(1) Principal Investigator/Project Director

List the name of the Principal Investigator/Project Director responsible for overall implementation of the contract and key contact for technical aspects of the project. Even though there may be co-investigators, identify the Principal Investigator/Project Director who will be responsible for the overall implementation of any awarded contract. Discuss the qualifications, experience, and accomplishments of the Principal Investigator/Project Director. State the estimated time to be spent on the project, his/her proposed duties, and the areas or phases for which he/she will be responsible.

(2) Other Investigators

List all other investigators/professional personnel who will be participating in the project. Discuss the qualifications, experience, and accomplishments. State the estimated time each will spend on the project, proposed duties on the project, and the areas or phases for which each will be responsible.

(3) Additional Personnel

List names, titles, and proposed duties of additional personnel, if any, who will be required for full-time employment, or on a subcontract or consultant basis. The technical areas, character, and extent of subcontract or consultant activity will be indicated and the anticipated sources will be specified and qualified. For all proposed personnel who are not currently members of the offeror's staff, a letter of commitment or other evidence of availability is required. A resume does not meet this requirement. Commitment letters for use of consultants and other personnel to be hired must include:

-The specific items or expertise they will provide.

-Their availability to the project and the amount of time anticipated.

-Willingness to act as a consultant.

-How rights to publications and patents will be handled.

(4) Resumes

Resumes of all key personnel are required. Each must indicate educational background, recent experience, specific or technical accomplishments, and a listing of relevant publications.

(2) **Technical Evaluation**

Proposals will be technically evaluated in accordance with the factors, weights, and order of relative

importance as described in the Technical Evaluation Criteria (Section M, hereof).

(3) **Additional Technical Proposal Information**

a) Proposals which merely offer to conduct a program in accordance with the requirements of the Government's scope of work will not be eligible for award. The offeror must submit an explanation of the proposed technical approach in conjunction with the tasks to be performed in achieving the project objectives.

b) The technical evaluation is conducted in accordance with the weighted technical evaluation criteria by an initial review panel. This evaluation produces a numerical score (points) which is based upon the information contained in the offeror's proposal only.

(4) **Other Considerations**

Record and discuss specific factors not included elsewhere which support your proposal. Using specifically titled subparagraphs, items may include:

a) Any agreements and/or arrangements with subcontractor(s). Provide as much detail as necessary to explain how the statement of work will be accomplished within this working relationship.

b) Unique arrangements, equipment, etc., which none or very few organizations are likely to have which is advantageous for effective implementation of this project.

c) Equipment and unusual operating procedures established to protect personnel from hazards associated with this project.

d) Other factors you feel are important and support your proposed research.

e) Recommendations for changing reporting requirements if such changes would be more compatible with the offeror's proposed schedules.

IMPORTANT NOTE TO OFFERORS: The following 12 paragraphs [(5) through (16)] shall be addressed in a SEPARATE SECTION of the Technical Proposal entitled, "HUMAN SUBJECTS."

(5) **Human Subjects**

The following notice is applicable when contract performance is expected to involve risk to human subjects:

Notice to Offerors of Requirements of 45 CFR Part 46, Protection of Human Subjects (MARCH 2005)

(a) Copies of the Department of Health and Human Services (Department) regulations for the protection of human subjects, 45 CFR Part 46, are available from the Office for Human Research Protections (OHRP), Bethesda, Maryland 20892. The regulations provide a systematic means, based on established ethical principles, to safeguard the rights and welfare of individuals who participate as subjects in research activities supported or conducted by the Department.

(b) The regulations define a human subject as a living individual about whom an investigator (whether professional or student) conducting research obtains data through intervention or interaction with the individual, or identifiable private information. The regulations extend to the use of human organs, tissue, and body fluids from individually identifiable human subjects as well as to graphic, written, or recorded information derived from individually identifiable human subjects. The use of autopsy materials is governed by applicable State and local law and is not directly regulated by 45 CFR Part 46.

(c) Activities in which the only involvement of human subjects will be in one or more of the categories set forth in 45 CFR 46.101(b)(1-6) are exempt from coverage.

(d) Inappropriate designations of the noninvolvement of human subjects or of exempt categories of research in a project may result in delays in the review of a proposal. The OpDiv will make a final determination of whether the proposed activities are covered by the regulations or are in an exempt category, based on the information provided in the proposal. In doubtful cases, prior consultation with OHRP, (telephone: 301-496-7005), is recommended.

(e) In accordance with 45 CFR Part 46, prospective Contractors being considered for award shall be required to file with OHRP an acceptable Assurance of Compliance with the regulations, specifying review procedures and assigning responsibilities for the protection of human subjects. The initial and continuing review of a research project by an institutional review board shall assure that the rights and welfare of the human subjects involved are adequately protected, that the risks to the subjects are reasonable in relation to the potential benefits, if any, to the subjects and the importance of the knowledge to be gained, and that informed consent will be obtained by methods that are adequate and appropriate. The contracting officer will direct the offeror/contractor to the OHRP IRB Registration and Assurance Filing website, found at http://www.hhs.gov/ohrp/ or to the physical address if the offeror/contractor cannot access the Internet. HHS regulations for the protection of human subjects may be found at:

http://www.access.gpo.gov/nara/cfr/waisidx_01/45cfr46_01.html

(f) It is recommended that OHRP be consulted for advice or guidance concerning either regulatory requirements or ethical issues pertaining to research involving human subjects.

(End of provision)

(6) **Instructions to Offerors Regarding Protection of Human Subjects**

Offerors must address the following human subjects protections issues if this contract will be for research involving human subjects (note: under each of the following points below, the offeror should indicate whether the information provided relates to the primary research site, or to a collaborating performance site(s), or to all sites:

(a) Risks to the subjects

Human Subjects Involvement and Characteristics:

- Describe the proposed involvement of human subjects in response to the solicitation.

- Describe the characteristics of the subject population, including their anticipated number, age range, and health status.

- Identify the criteria for inclusion or exclusion of any subpopulation. Explain the rationale for the involvement of special classes of subjects, such as fetuses, pregnant women, children, prisoners, institutionalized individuals, or others who are likely to be vulnerable populations.

Sources of Materials:

- Identify the sources of research material obtained from individually identifiable living human subjects in the form of specimens, records, or data. Indicate whether the material or data will be obtained specifically for research purposes or whether use will be made of existing specimens, records, or data.

Potential Risks:

- Describe the potential risks to subjects (physical, psychological, social, legal, or other) and assess their likelihood and seriousness to the subjects.

- Describe alternative treatments and procedures, including the risks and benefits of the alternative treatments and procedures, to participants in the proposed research, where appropriate.

(b) Adequacy of Protection Against Risks

Recruitment and Informed Consent:

- Describe plans for the recruitment of subjects and the procedures for obtaining informed consent. Include a description of the circumstances under which consent will be sought and obtained, who will seek it, the nature of the information to be provided to prospective subjects, and the method of documenting consent. The informed consent document for the contractor and any collaborating sites should be submitted only if requested elsewhere in the solicitation. Be aware that an IRB-approved informed consent document for the contractor and any participating collaborative sites must be provided to the Government prior to patient accrual or participant enrollment.

Protection Against Risk:

- Describe the procedures for protecting against or minimizing potential risks, including risks to confidentiality, and assess their likely effectiveness.

- Discuss provisions for ensuring necessary medical or professional intervention in the event of adverse effects to the subjects where appropriate.

- In studies that involve interventions, describe the provisions for data and safety monitoring of the research to ensure the safety of subjects.

(c) Potential Benefits of the Proposed Research to the Subjects and Others

- Discuss the potential benefits of the research to the subjects and others.

- Discuss why the risks to subjects are reasonable in relation to the anticipated benefits to subjects and others.

- Describe treatments and procedures that are alternatives to those provided to the participants by the proposed research, where appropriate.

(d) Importance of the Knowledge to be Gained

- Discuss the importance of the knowledge gained or to be gained as a result of the proposed research.

- Discuss why the risks to subjects are reasonable in relation to the importance of the knowledge that may reasonably be expected to result.

Note: If a test article (investigational new drug, device, or biologic) is involved, name the test article and state whether the 30-day interval between submission of offeror's certification to the Food and Drug Administration (FDA) and its response has elapsed or has been waived and/or whether the FDA has withheld or restricted use of the test article.

Collaborating Site(s)

When research involving human subjects will take place at collaborating site(s) or other performance site(s), the offeror must provide in this section of its proposal a list of the collaborating sites and their assurance numbers. Further, if you are awarded a contract, you must obtain in writing, and keep on file, an assurance from each site that the previous points have been adequately addressed at a level of attention that is at least as high as that documented at your organization. Site(s) added after an award is made must also adhere to the above requirements.

(7) **Required Education in the Protection of Human Research Participants**

NIH policy requires education on the protection of human subject participants for all investigators submitting NIH proposals for contracts for research involving human subjects. This policy announcement is found in the **NIH Guide for Grants and Contracts** Announcement dated June 5, 2000 at the following website: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html. Offerors should review the policy announcement prior to submission of their offers. The following is a summary of the Policy Announcement:

For any solicitation for research involving human subjects, the offeror shall provide in its technical proposal the following information: (1) a list of the names of the principal investigator and any other individuals proposed under the contract who are responsible for the design and/or conduct of the research; (2) the title of the education program completed (or to be completed prior to the award of the contract) for each named personnel; (3) a one sentence description of the program(s) listed in (2) above. This requirement extends to investigators and all individuals responsible for the design and/or conduct of the research who are working as subcontractors or consultants under the contract.

Curricula that are readily available and meet the educational requirement include the NIH on-line tutorial, titled "Protection of Human Research Subjects: Computer-Based Training for Researchers," available at http://ohsr.od.nih.gov/cbt/. You may download the information at this site at no cost and modify it, if desired. The University of Rochester has made its training program available for individual investigators. Completion of this program will also satisfy the educational requirement. The University of Rochester manual can be obtained through Centerwatch, Inc. at

http://www.centerwatch.com/order/pubs_profs_protect.html.

In addition, the NCI sponsors an online training course at:

http://cme.cancer.gov/clinicaltrials/learning/humanparticipant-protections.asp.

If an institution already has developed educational programs on the protection of research participants, completion of these programs also will satisfy the educational requirement.

In addition, prior to the substitution of the principal investigator or any other individuals responsible for the design and/or conduct of the research under the contract, the contractor shall provide the contracting officer with the title of the education program and a one sentence description of the program that the replacement has completed.

(8) **Inclusion of Women and Minorities in Research Involving Human Subjects**

It is NIH policy that women and members of minority groups and their sub-populations must be included in all NIH-supported clinical research projects involving human subjects, unless a clear and compelling rationale and justification establishes to the satisfaction of the relevant Institute/Center Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. The Director, NIH, may determine that exclusion under other circumstances is acceptable, upon the recommendation of an Institute/Center Director, based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. This policy results from the NIH Revitalization Act of 1993 (Section 492B of Public Law 103-43), ***and applies to research subjects of all ages***.

All investigators proposing research involving human subjects should read the UPDATED "NIH Policy and

Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research, Amended October 2001," published in the NIH Guide for Grants and Contracts on October 9, 2001 at the following web site:

http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm

These guidelines contain a definition of **clinical research** adopted in June 2001, as: "(1) Patient-oriented research. Research conducted with human subjects (or on material of human origin such as tissues, specimens and cognitive phenomena) for which an investigator (or colleague) directly interacts with human subjects. Excluded from this definition are in vitro studies that utilize human tissues that cannot be linked to a living individual. Patient-oriented research includes (a) mechanisms of human disease, (b) therapeutic interventions, (c) clinical trials, and (d) development of new technologies; (2) Epidemiologic and behavioral studies; and (3) Outcomes research and health services research," at:
(http://www.nih.gov/news/crp/97report/execsum.htm).

Information Required for ALL Clinical Research Proposals

This solicitation contains a review criterion addressing the adequacy of: (1) the offeror's plans for inclusion of women and minorities in the research proposed; or (2) the offeror's justification(s) for exclusion of one or both groups from the research proposed.

Provide information on the composition of the proposed study population in terms of sex/gender and racial/ethnic groups and provide a rationale for selection of such subjects in response to the requirements of the solicitation. The description may include (but is not limited to) information on the population characteristics of the disease or condition being studied in the planned research, and/or described in the statement of work, national and local demography, knowledge of the racial/ethnic/cultural characteristics of the population, prior experience and collaborations in recruitment and retention of the populations and subpopulations to be studied, and the plans, arrangements and letters of commitment from relevant community groups and organizations for the planned research.

The proposal must include the following information:

- A description of the subject selection criteria
- The proposed dates of enrollment (beginning and end)
- A description of the proposed outreach programs for recruiting women and minorities as subjects
- A compelling rationale for proposed exclusion of any sex/gender or racial/ethnic group
- The proposed sample composition using the "Targeted/Planned Enrollment Table"(see Section J, Attachments)

NOTE 1: *For all proposals, use the ethnic and racial categories and complete the "Targeted/Planned Enrollment Table in accordance with the Office of Management and Budget (OMB) Directive No. 15, which may be found at: http://www.whitehouse.gov/OMB/fedreg/ombdir15.html.*

NOTE 2: *If this is an Indefinite Delivery, Indefinite Quantity (IDIQ) or Requirements contract as defined in FAR 16.5, the proposal should describe in general terms how it will comply with each bulleted item above for each task order. When the Government issues a task order request for proposal, each of the bulleted information items must be fully and specifically addressed in the proposal.*

Standards for Collecting Data. When you, as a contractor, are planning data collection items on race and ethnicity, you shall use, at a minimum, the categories identified in OMB Directive No. 15. The collection of greater detail is encouraged. However, you should design any additional, more detailed items so that they can be aggregated into these required categories. Self-reporting or self-identification using two separate questions is the preferred method for collecting data on race and ethnicity. When you collect race and ethnicity separately, you must collect ethnicity first. You shall offer respondents the option of selecting one or more racial designations. When you collect data on race and ethnicity separately, you shall also make provisions to report the number of respondents in each racial category who are Hispanic or Latino. When you present aggregate data, you shall provide the number of respondents who selected only one category,

for each of the five racial categories. If you collapse data on multiple responses, you shall make available, at a minimum, the total number of respondents reporting "more than one race." Federal agencies shall not present data on detailed categories if doing so would compromise data quality or confidentiality standards.

In addition to the above requirements, solicitations for **NIH defined Phase III clinical trials**[1] require that*:* a) all proposals and/or protocols provide a description of plans to conduct analyses, as appropriate, to detect significant differences in intervention effect (see NIH Guide: http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm, Definitions - Significant Difference), by sex/gender, racial/ethnic groups, and relevant subpopulations, if applicable; and b) all contractors to report annually cumulative subject accrual, and progress in conducting analyses for sex/gender and race/ethnicity differences.

Offerors may obtain copies of the Updated Guidelines from the sources above or from the contact person listed in the solicitation.

Also, the proposal must include one of the following plans:

- Plans to conduct valid analysis to detect significant differences in intervention effect among sex/gender and/or racial/ethnic subgroups when prior studies strongly support these significant differences among subgroups, OR

- Plans to include and analyze sex/gender and/or racial/ethnic subgroups when prior studies strongly support no significant differences in intervention effect between subgroups, OR

- Plans to conduct valid analyses of the intervention effect in sex/gender and/or racial/ethnic subgroups (without requiring high statistical power for each subgroup) when the prior studies neither support nor negate significant differences in intervention effect between subgroups.

Use the form entitled, "Targeted/Planned Enrollment Table," when preparing your response to the solicitation requirements for inclusion of women and minorities. (See Section J-List of Documents, Exhibits and Other Attachments of the RFP)

Unless otherwise specified in this solicitation, the Government has determined that the work required by this solicitation does not involve a sex/gender specific study or a single or limited number of minority population groups. Therefore, the NIH believes that the inclusion of women and minority populations is appropriate for this project. (See Section M of this RFP for more information about evaluation factors for award.)

Use the form entitled, "Inclusion Enrollment Report," for reporting in the resultant contract.

(9) **Inclusion of Children in Research Involving Human Subjects**

It is NIH policy that children (defined below) must be included in all human subjects research, including, but not limited to, clinical trials, conducted under a contract funded by the NIH, unless there are *clear and compelling* reasons not to include them. (See examples of Justifications for Exclusion of Children below). For the purposes of this policy, contracts involving human subjects include categories that would otherwise be exempt from the DHHS Policy for Protection of Human Research Subjects (sections 101(b) and 401(b) of 45 CFR 46), such as surveys, evaluation of educational interventions, and studies of existing data or specimens that should include children as participants. This policy applies to both domestic and foreign research contracts.

For purposes of this policy, a child is defined as an individual under the age of 21 years.

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[1] See NIH Guide http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm, for the Definition of an "NIH-Defined Phase III clinical trial.

All offerors proposing research involving human subjects should read the "NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects" which was published in the NIH Guide for Grants and Contracts on March 6, 1998 and is available at the following URL address:

http://www.nih.gov/grants/guide/notice-files/not98-024.html

Offerors also may obtain copies from the contact person listed in the RFP.

Inclusion of children as participants in research must be in compliance with all applicable subparts of 45 CFR 46 as well as other pertinent laws and regulations whether or not such research is otherwise exempted from 45 CFR 46. Therefore, any proposals must include a description of plans for including children, unless the offeror presents clear and convincing justification for an exclusion. The "Human Subjects" section of your technical proposal should provide either a description of the plans to include children and a rationale for selecting or excluding a specific age range of child, or an explanation of the reason(s) for excluding children as participants in the research. This solicitation contains a review criterion addressing the adequacy of: (1) the plans for including children as appropriate for the scientific goals of the research; and/or (2) the justification of exclusion of children or exclusion of a specific age range of children.

When children are included, the plan also must include a description of: (1) the expertise of the investigative team for dealing with children at the ages included; (2) the appropriateness of the available facilities to accommodate the children; and, (3) the inclusion of a sufficient number of children to contribute to a meaningful analysis relative to the purpose/objective of the solicitation.

Justifications for Exclusion of Children

It is expected that children will be included in all research involving human subjects unless one or more of the following exclusionary circumstances can be fully justified:

- The objective of the solicitation is not relevant to children.

    - There are laws or regulations barring the inclusion of children in the research to be conducted under the solicitation.

    - The knowledge being sought in the research is already available for children or will be obtained from another ongoing study, and an additional study will be redundant. You should provide documentation of other studies justifying the exclusion.

        - A separate, age-specific study in children is warranted and preferable. Examples include:
        - The relative rarity of the condition in children, as compared with adults (in that extraordinary effort would be needed to include children); or
        - The number of children is limited because the majority are already accessed by a nationwide pediatric disease research network; or
        - Issues of study design preclude direct applicability of hypotheses and/or interventions to both adults and children (including different cognitive, developmental, or disease stages of different age-related metabolic processes); or
        - Insufficient data are available in adults to judge potential risk in children (in which case one of the research objectives could be to obtain sufficient adult data to make this judgment). While children usually should not be the initial group to be involved in research studies, in some instances, the nature and seriousness of the illness may warrant their participation earlier based on careful risk and benefit analysis; or
        - Study designs aimed at collecting additional data on pre-enrolled adult study subjects (e.g., longitudinal follow-up studies that did not include data on children);
        - Other special cases justified by the offeror and found acceptable to the review group and the Institute Director

Definition of a Child

For the purpose of this solicitation, a child is defined as an individual under the age of 21 years. The definition of child described above will pertain to this solicitation (notwithstanding the FDA definition of a child as an individual from infancy to 16 years of age, and varying definitions employed by some states). Generally, State laws define what constitutes a "child," and such definitions dictate whether or not a person can legally consent to participate in a research study. However, State laws vary, and many do not address when a child can consent to participate in research. Federal Regulations (45 CFR 46, subpart D, Sec.401-409) address DHHS protections for children who participate in research, and rely on State definitions of "child" for consent purposes. Consequently, the children included in this policy (persons under the age of 21) may differ in the age at which their own consent is required and sufficient to participate in research under State law. For example, some states consider a person age 18 to be an adult and therefore one who can provide consent without parental permission.

(10) **Data and Safety Monitoring in Clinical Trials**

For informational purposes, the contractor is directed to the full text of the NHLBI policies regarding Data and Safety Monitoring Boards, which may be found at the following web sites:

- **Establishing Data and Safety Monitoring Boards and Observational Study Monitoring Boards** (http://www.nhlbi.nih.gov/funding/policies/dsmb_est.htm)
- **Guidelines for Data Quality Assurance in Clinical Trials and Observational Studies** (http://www.nhlbi.nih.gov/funding/policies/dataqual.htm)
- **Responsibilities of DSMBs Appointed by NHLBI** (http://www.nhlbi.nih.gov/funding/policies/dsmb_inst.htm)

(11) **Research Involving Human Fetal Tissue**

Human Fetal Tissue means tissue or cells obtained from a dead human fetus, including human embryonic stem cells, human pluripotent stem cells and human embryonic germ cells.

The governing federal statute is the Public Health Service Act, 42 U.S.C. 289g-1 and 289g-2. Implementing regulations and guidance for conducting research on human fetal tissue may be found at 45 CFR 46, Subpart B and http://grants1.nih.gov/grants/guide/notice-files/not93-235.html and any subsequent revisions to this NIH Guide to Grants and Contracts ("Guide") Notice.

By signing the face page of the proposal, the offeror (authorized institutional official) certifies that researchers using human fetal tissue are in compliance with 42 USC 289g-2. This statute specifically prohibits any person from knowingly acquiring, receiving, or transferring any human fetal tissue for valuable consideration. "Valuable consideration" is a concept similar to profit, and does not include reasonable payment for costs associated with the collection processing, preservation, storage, quality control or transportation of these tissues.

Research involving the transplantation of human fetal tissue must be conducted in accordance with applicable Federal, State and local law.

(12) **Research Involving Prisoners as Subjects**

a. HHS Regulations at 45 CFR Part 46, Subpart C provide additional protections pertaining to biomedical and behavioral research involving prisoners or those individuals who, during the period of the contract become prisoners, as subjects. These regulations also set forth the duties of the Institutional Review Board (IRB) where prisoners are involved in the research. HHS-funded research involving prisoners as subjects may not proceed until the Office for Human Research Protections (OHRP) issues approval, in writing, as required by 45 CFR 46.306(a)(2). In addition, OHRP Guidance on the Involvement of Prisoners in Research may be found at:
http://www.hhs.gov/ohrp/humansubjects/guidance/prisoner.htm

b. HHS Waiver for Epidemiological Research Involving Prisoners as Subjects

On June 20, 2003 the Secretary of HHS waived the applicability of certain provisions of Subpart C of 45 CFR Part 46, (Additional DHHS Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects) to specific types of epidemiological research involving prisoners as subjects.

The applicability of 45 CFR 46.305(a)(1) and 46.306(a)(2) for certain epidemiological research conducted or funded by DHHS is waived when:

1. The sole purposes are:

   a) to describe the prevalence or incidence of a disease by identifying all cases, or
   b) to study potential risk factor associations for a disease, and

2. The Institution responsible for the conduct of the research certifies to the OHRP that the Institutional Review Board (IRB) approved the research and fulfilled its duties under 45 CFR 46.305(a)(2-7) and determined and documented that:

   a) the research presents no more than minimal risk, and
   b) no more than inconvenience to the prisoner-subjects, and
   c) prisoners are not a particular focus of the research.

For more information about this Waiver see http://www.hhs.gov/ohrp/special/prisoners/Prisoner waiver 6-20-03.pdf

(13) **Research Involving Recombinant DNA Molecules (including Human Gene Transfer Research)**

Recombinant DNA Molecules are either 1) molecules that are constructed outside of living cells by joining natural or synthetic DNA segments to DNA molecules that can replicate in a living cell, or 2) DNA molecules that result from the replication of those described in 1).

The NIH Guidelines for Research Involving Recombinant DNA Molecules (http://www4.od.nih.gov/oba/rac/guidelines/guidelines.html and the May 28, 2002 Notice, Compliance with the NIH Guidelines for Research Involving Recombinant DNA Molecules, at:
(http://grants1.nih.gov/grants/guide/notice-files/NOT-OD-02-052.html)
and any subsequent revisions to the Guide Notice) stipulates biosafety and containment measures for recombinant DNA research and delineates critical, ethical principles and key safety reporting requirements for human gene transfer research (See Appendix M of the NIH Guidelines). These guidelines apply to both basic and clinical research studies.

The Recombinant DNA Advisory Committee (RAC) is charged with the safety of manipulation of genetic material through the use of recombinant DNA techniques. Prior to beginning any clinical trials involving the transfer of recombinant DNA to humans, the trial must be registered with the RAC. If this contract involves new protocols that contain unique and//or novel issues, the RAC must discuss them in a public forum and then the Institutional Biosafety Committee (IBC), the Institutional Review Board (IRB), and the project officer and contracting officer must approve the protocol prior to the start of the research.

Failure to comply with these requirements may result in suspension, limitation, or termination of NIH funding for any work related to Recombinant DNA Research or a requirement for the contracting officer's prior approval of any or all Recombinant DNA projects under any contract awarded from this solicitation. This includes the requirements of the Standing Institutional Biosafety Committee (IBC) (See http://www4.od.nih.gov/oba/IBC/IBCindexpg.htm).

As specified in Appendix M-1-C-4 of the NIH Guidelines, any serious adverse event must be reported

immediately to the IRB, the IBC, the Office for Human Research Protections (if applicable), and the NIH Office for Biotechnology Activities (OBA), followed by the filing of a written report with each office/group and copies to the project officer and contracting officer.
(http://www4.od.nih.gov/oba/rac/guidelines_02/Appendix_M.htm#_Toc7255836)

(14) **Human Embryonic Germ Cell (HEGC) Research**

1. Guidelines.

Research use of human embryonic germ cells derived from fetal tissue with Federal funds requires review of compliance with the NIH Guidelines for Research Using Human Pluripotent Stem Cells (http://stemcells.nih.gov/policy/guidelines.asp) (only the information regarding human embryonic germ cells is relevant). Embryonic germ cells are pluripotent stem cells derived from human embryos. See NIH Guide for Grants and Contracts Notice NOT-OD-02-049, requiring that offerors/contractors submit certain documents to the Human Pluripotent Stem Cell Review Group (HPSCRG), which will be reviewed in a public meeting. Research using human embryonic germ cells may not be performed prior to approval by the HPSCRG.

All offerors should read the "NIH Guidelines" (http://stemcells.nih.gov/policy/guidelines.asp) if they either: (1) propose to respond to the Statement of Work requirements by conducting research that uses human embryonic germ cells or, (2) are responding to a Statement of Work that requires the use of human embryonic germ cells.

Offerors may obtain copies of these Guidelines from the website above or from the contact person listed in this solicitation.

2. Procedure for Required Review by Human Pluripotent Stem Cell Review Group (HPSCRG)

If the offeror intends to fulfill the requirements of the Statement of Work by performing research using human embryonic germ cells, it must so state in its proposal.

If the offeror's proposal includes research using human embryonic germ cells and it receives a contract award, the contractor may not perform any research using these human embryonic germ cells until the Human Pluripotent Stem Cell Review Group (HPSCRG) has reviewed and approved the documentation furnished as prescribed in "Procedures for Submission of Compliance Documents to the Human Pluripotent Stem Cell Review Group (HPSCRG) for the Research Use of Human Embryonic Germ Cells" (http://grants2.nih.gov/grants/guide/notice-files/NOT-OD-02-049.html) and the contracting officer has notified the contractor of the approval in writing.

The resultant contract will be divided into discrete phases. During Phase I of the contract, the contractor shall submit the original and two copies of the required documentation and assurances that address the areas covered in "Procedures for Submission of Compliance Documents to the Human Pluripotent Stem Cell Review Group (HPSCRG) for the Research Use of Human Embryonic Germ Cells," at:
(http://grants2.nih.gov/grants/guide/notice-files/NOT-OD-02-049.html)
to the contracting officer. This documentation will be forwarded for review and approval to the HPSCRG.

If the HPSCRG disapproves the documentation presented by the contractor, the Contracting Officer may elect to either terminate the contract in accordance with the Termination for Convenience clause of the contract OR determine not to exercise subsequent option(s) as appropriate based the terms of the specific contract. Otherwise, when the HPSCRG approves the documentation, the contracting officer will notify the contractor in writing that research using the human embryonic germ cells may commence.

Research involving the use of human embryonic germ cells shall not be conducted under the contract until the HPSCRG review and approval have been obtained, and the contracting officer has provided

written notice of such approval to the contractor.

(15) **Human Embryonic Stem Cell (HESC) Research**

On August 9, 2001, the President announced the criteria that must be met for Federal funds to be used for research on existing human embryonic stem cell lines. These criteria were subsequently published by the NIH at: http://grants1.nih.gov/grants/guide/notice-files/NOT-OD-02-005.html. The following eligibility criteria must be met:

1. The derivation process (which commences with the removal of the inner cell mass from the blastocyst) must have already been initiated prior to August 9, 2001;
2. Prior to August 9, 2001, the embryo from which the stem cell line was derived no longer had the possibility of development as a human being;
3. The stem cells must have been derived from an embryo that was created for reproductive purposes;
4. The embryo was no longer needed for these purposes;
5. Informed consent must have been obtained for the donation of the embryo;
6. No financial inducements were provided for the donation of the embryo.

To facilitate research using human embryonic stem cells, the NIH has established a Human Embryonic Stem Cell Registry ("the NIH Registry") that lists the human embryonic stem cells that meet the eligibility criteria. This registry is available at: http://stemcells.nih.gov/registry/.

Research involving the derivation of new stem cells from human embryos or the use of human embryonic stem cells that are not listed on the NIH Human Embryonic Stem Cell Registry may not be conducted with Federal funding.

If a particular human embryonic stem cell line has not been required by the Statement of Work, an offeror proposing research involving human embryonic stem cells must cite a human embryonic stem cell line that is listed in the NIH Registry in its proposal.

(16) **HIV Antiretroviral Treatment Trials**

The NIH is committed to conducting HIV/AIDS research in an effort to improve the health of people living with this disease, particularly people in countries most affected by the epidemic. It is important that individuals who volunteer to participate in NIH-funded HIV antiretroviral trials be given the option to continue to receive antiretroviral treatment following their completion of the trial. In order to accomplish this, the contractor must work with the host countries' authorities and other stakeholders to identify sources available, if any, in the country for the provision of such treatment. It is noted that NIH cannot provide this treatment following the completion of the research. See NIH Guide Notice, "Guidance for Addressing the Provision of Antiretroviral Treatment for Trial Participants Following Their Completion of NIH-Funded HIV Antiretroviral Treatment Trials in Developing Countries," located at:
http://grants.nih.gov/grants/guide/notice-files/NOT-OD-05-038.html.

The offeror's proposal must address a plan that describes the following:

- A description of available sources, if any (e.g., name of source, location, contact person of facility/organization) for the provision of antiretroviral treatment and care following the completion of the trial;
- A summary of the offeror's interaction with the providers;
- Documents, if any, from available sources/ providers regarding plans for implementation;
- A description of how this information will be conveyed to the trial participants.

If there are no sources for antiretroviral treatment in or available to the country in which the treatment trials will take place, the offeror must provide:

- A statement confirming that at the time of the offer, no sources of antiretroviral treatment could be identified;

- A description of how this information will be conveyed to the trial participants;
- A commitment to continue to explore potential sources as the trial proceeds.

This plan or the documentation provided regarding the lack of available sources of antiretroviral treatment will be evaluated by the Project Officer as a part of the overall review of the proposal. While an offeror's documentation of the lack of available sources for antiretroviral treatment will not, of itself, constitute denial of a contract award, priority for contract awards may be given to those offerors who identify sources for the provision of antiretroviral treatment following the completion of the trial.

(17) **Information Technology Systems Security,** is applicable to this solicitation and the following information is provided to supplement this item to assist in proposal preparation.

(a) **Sensitivity and Security Level Designations.**

The Statement of Work (SOW) requires the successful offeror to develop or access a Federal Automated Information System (AIS). Based upon the security guidelines contained in the *Department of Health and Human Services (DHHS) Security Program Policy,* the Government has determined that the following apply:

(1) Category of Safeguarded Information

The safeguarded agency information that the successful offeror will develop or access is categorized as:

[ ] Non Sensitive Information
[x] Sensitive Information

(2) Security Level Designations

The information that the successful offeror will develop or access is designated as follows:

Level high 3 applies to the sensitivity of the data.
Level medium 2 applies to the operational criticality of the data.
The overall Security Level designation for this requirement is **Level high 3** .

(3) Position Sensitivity Designations

Prior to award, the Government will determine the position sensitivity designation for each contractor employee that the successful offeror proposes to work under the contract. For proposal preparation purposes, the following designations apply:

[ ] Level 6C: Sensitive - High Risk (Requires Suitability Determination with a BI). Contractor employees assigned to a Level 6C position are subject to a Background Investigation (BI).

[x] Level 5C: Moderate Risk (Requires Suitability Determination with NACIC, MBI or LBI). Contractor employees assigned to a Level 5C position with no previous investigation and approval shall undergo a National Agency Check and Inquiry Investigation plus a Credit Check (NACIC), a Minimum Background Investigation (MBI), or possibly a Limited Background Investigation (LBI).

[ ] Level 1C: Non Sensitive (Requires Suitability Determination with an NACI). Contractor employees assigned to a Level 1C position are subject to a National Agency Check and Inquiry Investigation (NACI).

written notice of such approval to the contractor.

(15) **Human Embryonic Stem Cell (HESC) Research**

On August 9, 2001, the President announced the criteria that must be met for Federal funds to be used for research on existing human embryonic stem cell lines. These criteria were subsequently published by the NIH at: http://grants1.nih.gov/grants/guide/notice-files/NOT-OD-02-005.html. The following eligibility criteria must be met:

1. The derivation process (which commences with the removal of the inner cell mass from the blastocyst) must have already been initiated prior to August 9, 2001;
2. Prior to August 9, 2001, the embryo from which the stem cell line was derived no longer had the possibility of development as a human being;
3. The stem cells must have been derived from an embryo that was created for reproductive purposes;
4. The embryo was no longer needed for these purposes;
5. Informed consent must have been obtained for the donation of the embryo;
6. No financial inducements were provided for the donation of the embryo.

To facilitate research using human embryonic stem cells, the NIH has established a Human Embryonic Stem Cell Registry ("the NIH Registry") that lists the human embryonic stem cells that meet the eligibility criteria. This registry is available at: http://stemcells.nih.gov/registry/.

Research involving the derivation of new stem cells from human embryos or the use of human embryonic stem cells that are not listed on the NIH Human Embryonic Stem Cell Registry may not be conducted with Federal funding.

If a particular human embryonic stem cell line has not been required by the Statement of Work, an offeror proposing research involving human embryonic stem cells must cite a human embryonic stem cell line that is listed in the NIH Registry in its proposal.

(16) **HIV Antiretroviral Treatment Trials**

The NIH is committed to conducting HIV/AIDS research in an effort to improve the health of people living with this disease, particularly people in countries most affected by the epidemic. It is important that individuals who volunteer to participate in NIH-funded HIV antiretroviral trials be given the option to continue to receive antiretroviral treatment following their completion of the trial. In order to accomplish this, the contractor must work with the host countries' authorities and other stakeholders to identify sources available, if any, in the country for the provision of such treatment. It is noted that NIH cannot provide this treatment following the completion of the research. See NIH Guide Notice, "Guidance for Addressing the Provision of Antiretroviral Treatment for Trial Participants Following Their Completion of NIH-Funded HIV Antiretroviral Treatment Trials in Developing Countries," located at:
http://grants.nih.gov/grants/guide/notice-files/NOT-OD-05-038.html.

The offeror's proposal must address a plan that describes the following:

- A description of available sources, if any (e.g., name of source, location, contact person of facility/organization) for the provision of antiretroviral treatment and care following the completion of the trial;
- A summary of the offeror's interaction with the providers;
- Documents, if any, from available sources/ providers regarding plans for implementation;
- A description of how this information will be conveyed to the trial participants.

If there are no sources for antiretroviral treatment in or available to the country in which the treatment trials will take place, the offeror must provide:

- A statement confirming that at the time of the offer, no sources of antiretroviral treatment could be identified;

to potential offerors.

(d) **References**

The following documents are electronically accessible:

(1) OMB Circular A-130, Appendix III:
http://www.whitehouse.gov/omb/circulars/a130/a130appendix_iii.html
(2) DHHS Personnel Security/Suitability Handbook: http://www.hhs.gov/ohr/manual/pssh.pdf
(3) DHHS Information Security Program Policy:
http://www.hhs.gov/read/irmpolicy/FINALHHSInformationSecurityProgramP.doc
(4) NIH Applications/Systems Security Template: http://irm.cit.nih.gov/security/secplantemp.doc
(5) NIH Security Plan Outline: http://irm.cit.nih.gov/nihsecurity/Security_Plan_Outline.doc
(6) NIST Special Publication 800-16, "Information Technology Security Training Requirements:"
http://csrc.nist.gov/publications/nistpubs/800-16/800-16.pdf
Appendix A-D: http://csrc.nist.gov/publications/nistpubs/800-16/AppendixA-D.pdf
(7) NIH CIT-Policies, Guidelines and Regulations:
Table 1 - Categories of Safeguarded Agency Information:
http://irm.cit.nih.gov/security/table1.htm
Table 2 - Security Level Designations for Agency Information:
http://irm.cit.nih.gov/security/table2.htm
Table 3 - Positions Sensitivity Designations for Individuals Accessing Agency Information:
http://irm.cit.nih.gov/security/table3.htm
(8) NCI Information Technology Security Policies, Forms and Procedures for Contracts:
http://ais.nci.nih.gov/

c. BUSINESS PROPOSAL INSTRUCTIONS

(1) Basic Cost/Price Information

The business proposal must contain sufficient information to allow the Government to perform a basic analysis of the proposed cost or price of the work. This information shall include the amounts of the basic elements of the proposed cost or price. These elements will include, as applicable, direct labor, fringe benefits, travel, materials, subcontracts, purchased parts, shipping, indirect costs and rate, fee, and profit. **Note: Proposed costs should be submitted using the Excel spreadsheet found in Section J, Attachment 14, and be broken down as follows:**

Phase I - 9 months: 09/30/06-06/29/07
Phase II - 30 months: 06/30/07-06/29/08
06/30/08-06/29/09
06/30/09-12/29/09
Phase III - 9 months 12/30/09-09/29/10

(2) Information Other than Cost or Pricing Data

a) The information submitted shall consist of data to permit the Contracting Officer and authorized representatives to determine price reasonableness or cost realism, e.g., information to support an analysis of material costs (when sufficient information on labor and overhead rates is already available), or information on prices and quantities at which the offeror has previously sold the same or similar items.

Any information submitted must support the price proposed. Include sufficient detail or cross references to clearly establish the relationship of the information provided to the price proposed. Support any information provided by explanations or supporting rational as needed to permit the Contracting Officer and authorized representative to evaluate the documentation.

[Unless otherwise stated in this solicitation, the information may be submitted in the offeror's own format.]

(3) Cost and Pricing Data

[Note: This document is INCLUDED in the "Just In Time" procedures. Specific instructions for the submission of this document are outlined in SECTION L.1.a. of this RFP.]

1. General Instructions

A. You must provide the following information on the first page of your pricing proposal:

(1) Solicitation, contract, and/or modification number;
(2) Name and address of offeror;
(3) Name and telephone number of point of contact;
(4) Name of contract administration office (if available);
(5) Type of contract action (that is, new contract, change order, price revision/redetermination, letter contract, unpriced order, or other);
(6) Proposed cost; profit or fee; and total;
(7) Whether you will require the use of Government property in the performance of the contract, and, if so, what property;
(8) Whether your organization is subject to cost accounting standards; whether your organization has submitted a CASB Disclosure Statement, and if it has been determined adequate; whether you have been notified that you are or may be in noncompliance with your Disclosure Statement or CAS, and, if yes, an explanation; whether any aspect of this proposal is inconsistent with your disclosed practices or applicable CAS, and, if so, an explanation; and whether the proposal is consistent with

your established estimating and accounting principles and procedures and FAR Part 31, Cost Principles, and, if not, an explanation;

(9) The following statement: This proposal reflects our estimates and/or actual costs as of this date and conforms with the instructions in FAR 15.403-5(b)(1) and Table 15-2. By submitting this proposal, we grant the Contracting Officer and authorized representative(s) the right to examine, at any time before award, those records, which include books, documents, accounting procedures and practices, and other data, regardless of type and form or whether such supporting information is specifically referenced or included in the proposal as the basis for pricing, that will permit an adequate evaluation of the proposed price;

(10) Date of submission; and

(11) Name, title and signature of authorized representative.

B. In submitting your proposal, you must include an index, appropriately referenced, of all the cost or pricing data and information accompanying or identified in the proposal. In addition, you must annotate any future additions and/or revisions, up to the date of agreement on price, or an earlier date agreed upon by the parties, on a supplemental index.

C. As part of the specific information required, you must submit, with your proposal, cost or pricing data (that is, data that are verifiable and factual and otherwise as defined at FAR 15.401). You must clearly identify on your cover sheet that cost or pricing data are included as part of the proposal. In addition, you must submit with your proposal any information reasonably required to explain your estimating process, including--

(1) The judgmental factors applied and the mathematical or other methods used in the estimate, including those used in projecting from known data; and

(2) The nature and amount of any contingencies included in the proposed price.

D. You must show the relationship between contract line item prices and the total contract price. You must attach cost-element breakdowns for each proposed line item, using the appropriate format prescribed in the "Formats for Submission of Line Item Summaries" section of this table. You must furnish supporting breakdowns for each cost element, consistent with your cost accounting system.

E. When more than one contract line item is proposed, you must also provide summary total amounts covering all line items for each element of cost.

F. Whenever you have incurred costs for work performed before submission of a proposal, you must identify those costs in your cost/price proposal.

G. If you have reached an agreement with Government representatives on use of forward pricing rates/factors, identify the agreement, include a copy, and describe its nature.

H. As soon as practicable after final agreement on price or an earlier date agreed to by the parties, but before the award resulting from the proposal, you must, under the conditions stated in FAR 15.406-2, submit a Certificate of Current Cost or Pricing Data.

2. **Cost Elements**

Depending on your system, you must provide breakdowns for the following basic cost elements, as applicable:

A. **Materials and services**. Provide a consolidated priced summary of individual material quantities included in the various tasks, orders, or contract line items being proposed and the basis for pricing (vendor quotes, invoice prices, etc.). Include raw materials, parts, components, assemblies, and services to be produced or performed by others. For all items proposed, identify the item and show the source, quantity, and price. Conduct price

analyses of all subcontractor proposals. Conduct cost analyses for all subcontracts when cost or pricing data are submitted by the subcontractor. Include these analyses as part of your own cost or pricing data submissions for subcontracts expected to exceed the appropriate threshold in FAR 15.403-4. Submit the subcontractor cost or pricing data as part of your own cost or pricing data as required in paragraph 2.A(2) of this table. These requirements also apply to all subcontractors if required to submit cost or pricing data.

(1) *Adequate Price Competition*. Provide data showing the degree of competition and the basis for establishing the source and reasonableness of price for those acquisitions (such as subcontracts, purchase orders, material order, etc.) exceeding, or expected to exceed, the appropriate threshold set forth at FAR 15.403-4 priced on the basis of adequate price competition. For interorganizational transfers priced at other than the cost of comparable competitive commercial work of the division, subsidiary, or affiliate of the contractor, explain the pricing method (see FAR 31.205-26(e)).

(2) *All Other*. Obtain cost or pricing data from prospective sources for those acquisitions (such as subcontracts, purchase orders, material order, etc.) exceeding the threshold set forth in FAR 15.403-4 and not otherwise exempt, in accordance with FAR 15.403-1(b) (i.e., adequate price competition, commercial items, prices set by law or regulation or waiver). Also provide data showing the basis for establishing source and reasonableness of price. In addition, provide a summary of your cost analysis and a copy of cost or pricing data submitted by the prospective source in support of each subcontract, or purchase order that is the lower of either $10,000,000 or more, or both more than the pertinent cost or pricing data threshold and more than 10 percent of the prime contractor's proposed price. The Contracting Officer may require you to submit cost or pricing data in support of proposals in lower amounts. Subcontractor cost or pricing data must be accurate, complete and current as of the date of final price agreement, or an earlier date agreed upon by the parties, given on the prime contractor's Certificate of Current Cost or Pricing Data. The prime contractor is responsible for updating a prospective subcontractor's data. For standard commercial items fabricated by the offeror that are generally stocked in inventory, provide a separate cost breakdown, if priced based on cost. For interorganizational transfers priced at cost, provide a separate breakdown of cost elements. Analyze the cost or pricing data and submit the results of your analysis of the prospective source's proposal. When submission of a prospective source's cost or pricing data is required as described in this paragraph, it must be included along with your own cost or pricing data submission, as part of your own cost or pricing data. You must also submit any other cost or pricing data obtained from a subcontractor, either actually or by specific identification, along with the results of any analysis performed on that data.

B. **Direct Labor**. Provide a time-phased (e.g., monthly, quarterly, etc.) breakdown of labor hours, rates, and cost by appropriate category, and furnish bases for estimates.

C. **Indirect Costs**. Indicate how you have computed and applied your indirect costs, including cost breakdowns. Show trends and budgetary data to provide a basis for evaluating the reasonableness of proposed rates. Indicate the rates used and provide an appropriate explanation.

D. **Other Costs**. List all other costs not otherwise included in the categories described above (e.g., special tooling, travel, computer and consultant services, preservation, packaging and packing, spoilage and rework, and Federal excise tax on finished articles) and provide bases for pricing.

E. **Royalties**. If royalties exceed $1,500, you must provide the following information on a separate page for each separate royalty or license fee:

(1) Name and address of licensor.

(2) Date of license agreement.
(3) Patent numbers.
(4) Patent application serial numbers, or other basis on which the royalty is payable.
(5) Brief description (including any part or model numbers of each contract item or component on which the royalty is payable).
(6) Percentage or dollar rate of royalty per unit.
(7) Unit price of contract item.
(8) Number of units.
(9) Total dollar amount of royalties.
(10) If specifically requested by the Contracting Officer, a copy of the current license agreement and identification of applicable claims of specific patents (see FAR 27.204 and 31.205-37).

F. **Facilities Capital Cost of Money**. When you elect to claim facilities capital cost of money as an allowable cost, you must submit Form CASB-CMF and show the calculation of the proposed amount (see FAR 31.205-10).

3. **Formats for Submission of Line Item Summaries**

The detailed breakdown shall be in the format as shown on the form **Breakdown of Proposed Estimated Cost (plus fee) and Labor Hours** (Section J, List of Attachments). For each separate cost estimate, the offeror must furnish a breakdown by cost element as indicated above. In addition, summary total amounts shall be furnished. In the event the RFP cites specific line items, by number, a cost breakdown for each line item must be furnished.

4. There is a clear distinction between submitting cost or pricing data and merely making available books, records, and other documents without identification. The requirement for submission of cost or pricing data is met when all accurate cost or pricing data reasonably available to the offeror have been submitted, either actually or by specific identification, to the Contracting Officer or an authorized representative. As later information comes into your possession, it should be submitted promptly to the Contracting Officer in a manner that clearly shows how the information relates to the offeror's price proposal. The requirement for submission of cost or pricing data continues up to the time of agreement on price, or an earlier date agreed upon between the parties if applicable.

5. By submitting your proposal, you grant the Contracting Officer or an authorized representative the right to examine records that formed the basis for the pricing proposal. That examination can take place at any time before award. It may include those books, records, documents, and other types of factual information (regardless of form or whether the information is specifically referenced or included in the proposal as the basis for pricing) that will permit an adequate evaluation of the proposed price.

[NOTE: Data substantiating the costs or prices proposed (i.e. payroll documentation, vendor quotes, invoice price, etc.) shall not be submitted with the initial proposal. This information will be requested from the offeror during the negotiation process. The initial proposal need only indicate from what source the proposed costs and prices are substantiated.]

(4) **Requirements for Cost or Pricing Data or Information Other than Cost and Pricing Data** [FAR Clause 52.215-20 (October 1997)]

(a) Exceptions from cost or pricing data.

(1) In lieu of submitting cost or pricing data, offerors may submit a written request for exception by submitting the information described in the following subparagraphs. The Contracting Officer may require additional supporting information, but only to the extent necessary to determine whether an exception should be granted, and whether the price is fair and

reasonable.

(I) Identification of the law or regulation establishing the price offered. If the price is controlled under law by periodic rulings, reviews, or similar actions of a governmental body, attach a copy of the controlling document, unless it was previously submitted to the contracting office.

(ii) Commercial item exception. For a commercial item exception, the offeror shall submit, at a minimum, information on prices at which the same item or similar items have previously been sold in the commercial market that is adequate for evaluating the reasonableness of the price for this acquisition. Such information may include--

(A) For catalog items, a copy of or identification of the catalog and its date, or the appropriate pages for the offered items, or a statement that the catalog is on file in the buying office to which the proposal is being submitted. Provide a copy or describe current discount policies and price lists (published or unpublished), e.g., wholesale, original equipment manufacturer, or reseller. Also explain the basis of each offered price and its relationship to the established catalog price, including how the proposed price relates to the price of recent sales in quantities similar to the proposed quantities;

(B) For market-priced items, the source and date or period of the market quotation or other basis for market price, the base amount, and applicable discounts. In addition, describe the nature of the market;

(C) For items included on an active Federal Supply Service Multiple Award Schedule contract, proof that an exception has been granted for the schedule item.

(2) The offeror grants the Contracting Officer or an authorized representative the right to examine, at any time before award, books, records, documents, or other directly pertinent records to verify any request for an exception under this provision, and the reasonableness of price. For items priced using catalog or market prices, or law or regulation, access does not extend to cost or profit information or other data relevant solely to the offeror's determination of the prices to be offered in the catalog or marketplace.

(b) Requirements for cost or pricing data. If the offeror is not granted an exception from the requirement to submit cost or pricing data, the following applies:

(1) The offeror shall prepare and submit cost or pricing data and supporting attachments in accordance with Table 15-2 of FAR 15.408.

(2) As soon as practicable after agreement on price, but before contract award (except for unpriced actions such as letter contracts), the offeror shall submit a Certificate of Current Cost or Pricing Data, as prescribed by FAR 15.406-2.

(End of provision)

Alternate I (October 1997). As prescribed in 15.408(l), substitute the following paragraph (b)(1) for paragraph (b)(1) of the basic provision:

(b)(1) The offeror shall submit cost or pricing data and supporting attachments in the following format:

The format specified in paragraph L.2.c.(4) Cost and Pricing Data, subparagraph 3. Formats for Submission of Line Item Summaries shall be used for the submission cost information. Submission of all other cost or pricing data shall be in accordance with Table 15-2 in FAR 15.408.

(5) **Qualifications of the Offeror**

You are requested to submit a summary of your "General Experience, Organizational Experience Related to this RFP, Performance History and Pertinent Contracts."

a) **General Experience**

General experience is defined as general background, experience and qualifications of the offeror. A discussion of proposed facilities which can be devoted to the project may be appropriate.

b) **Organizational Experience Related to the RFP**

Organizational experience is defined as the accomplishment of work, either past or on-going, which is comparable or related to the effort required by this RFP. This includes overall offeror or corporate experience, **but not** the experience and/or past performance of individuals who are proposed as personnel involved with the Statement of Work in this RFP.

c) **Performance History**

Performance history is defined as meeting contract objectives within delivery and cost schedules on efforts, either past or on-going, which is comparable or related to the effort required by this RFP.

d) **Pertinent Contracts**

Pertinent contracts is defined as a listing of each related contract completed within the last three years or currently in process. The listing should include: 1) the contract number; 2) contracting agency; 3) contract dollar value; 4) dates contract began and ended (or ends); 5) description of contract work; 6) explanation of relevance of work to this RFP; 7) actual delivery and cost performance versus delivery and cost agreed to in the contract(s). For award fee contracts, separately state in dollars the base fee and award fee available and the award fee actually received. The same type of organizational experience and past performance data should be submitted.

e) **Pertinent Grants**

List grants supported by the Government that involved similar or related work to that called for in this RFP. Include the grant number, involved agency, names of the grant specialist and the Science Administrator, identification of the work, and when performed.

You are cautioned that omission or an inadequate or inaccurate response to this very important RFP requirement could have a negative effect on the overall selection process.

(6) **Other Administrative Data**

a) **Property**

(1) It is DHHS policy that Contractors will provide all equipment and facilities necessary for performance of contracts. Exception may be granted to furnish Government-owned property, or to authorize purchase with contract funds, only when approved by the Contracting Officer. If the offeror is proposing that the Government provide any equipment, other than that specified under Government Furnished Property in the RFP, the proposal must include comprehensive justification which includes:

(a) An explanation that the item is for a special use essential to the direct performance of the contract and the item will be used exclusively for the purpose. Office equipment such as desks, office machines, etc., will not be provided under a contract except under very exceptional circumstances.

(b) No practical or economical alternative exists (e.g., rental, capital investment) that can be used to perform the work.

(2) The offeror shall identify Government-owned property in its possession and/or Contractor titled property acquired from Federal funds, which it proposes to use in the performance of the prospective contract.

(3) The management and control of any Government property shall be in accordance with DHHS Publication (OS) 686 entitled, "Contractor's Guide for Control of Government Property (1990)," a copy of which will be provided upon request.

c) **Submission of Electronic Funds Transfer Information with Offer, FAR Clause 52.232-38**, (May 1999)

The offeror shall provide, with its offer, the following information that is required to make payment by electronic funds transfer (EFT) under any contract that results from this solicitation. This submission satisfies the requirement to provide EFT information under paragraphs (b)(1) and (j) of the clause at 52.232-34, Payment by Electronic Funds Transfer--Other than Central Contractor Registration.

(1) The solicitation number (or other procurement identification number).
(2) The offeror's name and remittance address, as stated in the offer.
(3) The signature (manual or electronic, as appropriate), title, and telephone number of the offeror's official authorized to provide this information.
(4) The name, address, and 9-digit Routing Transit Number of the offeror's financial agent.
(5) The offeror's account number and the type of account (checking, savings, or lockbox).
(6) If applicable, the Fedwire Transfer System telegraphic abbreviation of the offeror's financial agent.
(7) If applicable, the offeror shall also provide the name, address, telegraphic abbreviation, and 9-digit Routing Transit Number of the correspondent financial institution receiving the wire transfer payment if the offeror's financial agent is not directly on-line to the Fedwire and, therefore, not the receiver of the wire transfer payment.

d) **Financial Capacity**

The offeror shall indicate if it has the necessary financial capacity, working capital, and other resources to perform the contract without assistance from any outside source. If not, indicate the amount required and the anticipated source.

e) **Incremental Funding**

An incrementally funded cost-reimbursement contract is a contract in which the total work effort is to be performed over a multiple year period and funds are allotted, as they become available, to cover discernible phases or increments of performance. The incremental funding technique allows for contracts to be awarded for periods in excess of one year even though the total estimated amount of funds expected to be obligated for the contract are not available at the time of the contract award. If this requirement is specified elsewhere in this RFP, the offeror shall submit a cost proposal for each year. In addition, the following provisions are applicable:

HHSAR 352.232-75, Incremental Funding (January 2001)

(a) It is the Government's intention to negotiate and award a contract using the incremental funding concepts described in the clause entitled Limitation of Funds. Under the clause, which will be included in the resultant contract, initial funds will be obligated under the contract to cover the first year of performance. Additional funds are intended to be allotted to the contract by contract modification, up to and including the full estimated cost of the contract, to accomplish the entire project. While it is the Government's intention to

progressively fund this contract over the entire period of performance up to and including the full estimated cost, the Government will not be obligated to reimburse the Contractor for costs incurred in excess of the periodic allotments, nor will the Contractor be obligated to perform in excess of the amount allotted.

(b) The Limitation of Funds clause to be included in the resultant contract shall supersede the Limitation of Cost clause found in the General Provisions.

(End of provision)

f) **Facilities Capital Cost of Money**, FAR 52.215-16, (June 2003)

(This is applicable if you are a commercial organization.)

(a) Facilities capital cost of money will be an allowable cost under the contemplated contract, if the criteria for allowability in FAR 31.205-10(b) are met. One of the allowability criteria requires the prospective Contractor to propose facilities capital cost of money in its offer.

(b) If the prospective Contractor does not propose this cost, the resulting contract will include the clause Waiver of Facilities Capital Cost of Money.

(End of Provision)

If the offeror elects to claim this cost, the offeror shall specifically identify or propose it in the cost proposal for the contract by checking the appropriate box below.

[ ] The prospective Contractor has specifically identified or proposed facilities capital cost of money in its cost proposal and elects to claim this cost as an allowable cost under the contract. Submit Form CASB-CMF (see FAR 31.205-10).

[ ] The prospective Contractor has not specifically identified or proposed facilities capital cost of money in its proposal and elects not to claim it as an allowable cost under the contract.

(7) **Subcontractors**

If subcontractors are proposed, please include a commitment letter from the subcontractor detailing:

a) Willingness to perform as a subcontractor for specific duties (list duties).

b) What priority the work will be given and how it will relate to other work.

c) The amount of time and facilities available to this project.

d) Information on their cognizant field audit offices.

e) How rights to publications and patents are to be handled.

f) A complete cost proposal in the same format as the offeror's cost proposal.

Note: Organizations that plan to enter into a subcontract with an educational concern under a contract awarded under this RFP should refer to the following Web Site for a listing of clauses that are required to be incorporated in Research & Development (R&D) subcontracts with educational institutions: http://ocm.od.nih.gov/contracts/rfps/FDP/FDPclausecover.htm

(8) **Proposer's Annual Financial Report**

[NOTE: This document is INCLUDED in the "Just In Time" procedures. Specific instructions for the submission of this document are outlined in SECTION L.1.a. of this RFP.]

All offerors included in the competitive range will be required to submit a copy of the organization's most recent annual financial report.

(9) **Representations and Certifications**

One copy of the Representations and Certifications attached as Section K shall be completed and be signed by an official authorized to bind your organization. Additionally, a completed copy of the Representations and Certifications shall be submitted from any proposed subcontractor.

(10) **Travel Costs/Travel Policy**

a) **Travel Costs - Commercial**

Costs for lodging, meals, and incidental expenses incurred by Contractor personnel shall be considered to be reasonable and allowable to the extent they do not exceed on a daily basis the per diem rates set forth in the Federal Travel Regulations, General Services Administration (GSA). Therefore, if travel costs are applicable and proposed by offerors, please be advised that they shall be calculated using the per diem rate schedule as established by GSA. Reimbursement of travel costs under any contract awarded from this RFP shall be in accordance with FAR 31.205-46.

b) **Travel Policy**

[NOTE: This document is INCLUDED in the "Just In Time" procedures. Specific instructions for the submission of this document are outlined in SECTION L.1.a. of this RFP.]

All offerors included within the competitive range will be required to submit one copy of their written travel policy. A written travel policy for any proposed subcontractors shall also be submitted at that time. If an offeror (or any proposed subcontractor) does not have a written travel policy, the offeror shall so state.

SECTION M - EVALUATION FACTORS FOR AWARD

The technical proposal will receive paramount consideration in the selection of the Contractor for this acquisition. All evaluation factors, other that cost or price, when combined are significantly more important than cost or price. However, cost/price may become a critical factor in source selection in the event that two or more offerors are determined to be essentially equal following the evaluation of all factors other than cost or price. Past performance is not an evaluation factor but will be considered in determining an offeror's responsibility in accordance with FAR 9.104-3(b). The trade-off process described in FAR 15.101-1 will be employed. This process permits tradeoffs among cost/price and non-cost factors and allows the Government to consider award to other than the lowest priced or highest technically rated offeror. In any event, the Government reserves the right to make an award to that offeror whose proposal provides the best overall value to the Government.

The evaluation will be based on the demonstrated capabilities of the prospective Contractors in relation to the needs of the project as set forth in the RFP. The merits of each proposal will be evaluated carefully. Each proposal must document the feasibility of successful implementation of the requirements of the RFP. Offerors must submit information sufficient to evaluate their proposals based on the detailed criteria listed below.

a. **HUMAN SUBJECT EVALUATION**

This research project involves human subjects. NIH Policy requires:

(a) **Protection of Human Subjects from Research Risks**

The offeror's proposal must address the involvement of human subjects and protections from research risk relating to their participation in the proposed research plan, or provide sufficient information on the research subjects to allow a determination by NCI that a designated exemption is appropriate.

If you claim that this research should be considered exempt from coverage by the Federal Regulations at 45 CFR 46, the proposal should address why you believe it is exempt, and under which exemption it applies.

The reviewers will evaluate the proposal with regard to four issues: Risks to Human Subjects, Adequacy of Protection Against Risks, Potential Benefits of the Proposed Research to the Subjects and Others, and Importance of the Knowledge to be Gained. See Section L for a complete discussion of what is required to be addressed for each of these issues. Based on the response to this criterion, this section of the proposal may be rated "unacceptable" (i.e., concerns are identified as to the protections described against risk to human subjects or no discussion is found regarding protections against risk to human subjects) or "acceptable." If the reviewers find that this portion of the proposal is "unacceptable" they will provide a narrative supporting their finding.

If the Government includes your proposal in the competitive range (for competitive proposals), or if the Government holds discussions with the selected source (for sole source acquisitions), you will be afforded the opportunity to address the concerns raised by the reviewers. You will be able to further discuss and/or clarify your position until submission of your Final Proposal Revision (FPR). Once discussions are closed with the submission of your FPR, if your proposed plan for the protection of human subjects from research risks is still found to be unacceptable, then your proposal may not be considered further for award.

(b) **Data and Safety Monitoring**

The offeror's proposal must include a general description of the Data and Safety Monitoring Plan for all clinical trials. The principles of data and safety monitoring require that all biomedical and behavioral clinical trails be monitored to ensure the safe and effective conduct of human subjects research, and to recommend conclusion of the trial when significant benefits or risks are identified or if it is unlikely that the trial can be concluded successfully. Risks associated with participation in research must be

minimized to the extent practical and the method and degree of monitoring should be commensurate with risk. Additionally, all plans must include procedures for adverse event reporting. Finally, generally, for Phase III clinical trials, the establishment of a Data and Safety Monitoring Board (DSMB) is required, whereas for Phase I and II clinical trials, the establishment of a DSMB is optional. The reviewers will rely on the Statement of Work and Section L in the solicitation, as well as any further technical evaluation criteria in this Section M, as applicable, for the solicitation's specific requirements for data and safety monitoring.

As a part of the evaluation for proposals, the reviewers will consider the acceptability of the proposed data and safety monitoring plan with respect to the potential risks to human participants, complexity of study design, and methods for data analysis. Based on the evaluation of the response to this criterion, this section of the proposal may be rated “unacceptable” (i.e., concerns are identified as to the adequacy of the monitoring plan or no discussion can be found regarding the proposed monitoring plans) or “acceptable.” If the reviewers find that this portion of the proposal is "unacceptable" they will provide a narrative supporting their finding.

If the Government includes your proposal in the competitive range (for competitive proposals), or if the Government holds discussions with the selected source (for sole source acquisitions), you will be afforded the opportunity to address the concerns raised by the reviewers. You will be able to further discuss and/or clarify your position until submission of your Final Proposal Revision (FPR). Once discussions are closed with the submission of your FPR, if your proposed plan for data and safety monitoring is still found to be unacceptable, then your proposal may not be considered further for award.

(c) **Women and Minorities**

Women and members of minority groups and their subpopulations must be included in the study population of research involving human subjects, unless a clear and compelling rationale and justification are provided indicating that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. In addition, for NIH-Defined Phase III clinical trials, all proposals and/or protocols must provide a description of plans to conduct analyses, as appropriate, to detect significant differences in intervention effect (see NIH Guide http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm, Definitions - Significant Difference) by sex/gender, racial/ethnic groups, and relevant subpopulations, if applicable, unless the Government has specified that this solicitation involves a sex/gender specific study or a single or limited number of minority population groups. The proposal also must include one of the following plans:

- Plans to conduct valid analysis to detect significant differences in intervention effect among sex/gender and/or racial/ethnic subgroups when prior studies strongly support these significant differences among subgroups, OR

- Plans to include and analyze sex/gender and/or racial/ethnic subgroups when prior studies strongly support no significant differences in intervention effect between subgroups (representation of sex/gender and/or racial/ethnic groups as subject selection criterion is not required; however, inclusion and analyses are encouraged), OR

- Plans to conduct valid analyses of the intervention effect in sex/gender and/or racial/ethnic subgroups (without requiring high statistical power for each subgroup) when the prior studies neither support nor negate significant differences in intervention effect between subgroups.

Also, the proposal must address the proposed outreach programs for recruiting women and minorities as participants.

Reviewers will consider the areas covered here and in Section L of the solicitation in narrative form in their evaluation. Some of the issues they will evaluate include:

- whether the plan proposed includes minorities and both genders in adequate representation
- how the offeror addresses the inclusion of women and members of minority groups and their subpopulations in the development of a proposal that is appropriate to the scientific objectives of the solicitation
- the description of the proposed study populations in terms of sex/gender and racial/ethnic groups and the rationale for selection of such subjects
- if exclusion is proposed, that the rationale is appropriate with respect to the health of the subjects and/or to the purpose of the research.
- In addition, for gender exclusion, the reviewers will examine the rationale to determine if it is because:

    - the purpose of the research constrains the offeror's selection of study participants by gender (e.g., uniquely valuable stored specimens or existing datasets are single gender; very small numbers of subjects are involved; or
    - overriding factors dictate selection of subjects); or
    - gender representation of specimens or existing datasets cannot be accurately determined, and this does not compromise the scientific objectives of the research.

- For minority group exclusion, the reviewers will examine the rationale to determine if those minority groups are excluded because:

    - inclusion of those groups would be inappropriate with respect to their health,;or
    - inclusion of those groups would be inappropriate with respect to the purpose of the research.

- For NIH-defined Phase III clinical trials, reviewers will also consider whether there is an adequate description of plans to conduct analyses to detect significant differences of clinical or public health importance in intervention effect(s) by sex/gender and/or racial ethnic subgroups when the intervention effect(s) is expected in the primary analyses, or if there is an adequate description of plans to conduct valid analyses of the intervention effect in subgroups when the intervention effect(s) is not expected in the primary analyses.

If you determine that inclusion of women and minority populations is not feasible, you must submit a detailed rationale and justification for exclusion of one or both groups from the study population with the technical proposal. The Government will review the rationale to determine if it is appropriate with respect to the health of the subjects and/or the purpose of the research

Based on the evaluation of the response to this criterion, this section of the proposal may be rated "unacceptable" (i.e., no discussion can be found regarding the proposed gender/minority inclusion plans, or concerns are identified as to the gender or minority representation, or the proposal does not adequately address limited representation of one gender or minority; or the plan is not in accordance with NIH policy guidelines) or "acceptable." See Section L of the solicitation for the requirements of women/minorities inclusion. If the reviewers find that this portion of the proposal is "unacceptable" they will provide a narrative supporting their finding.

If the Government includes your proposal in the competitive range (for competitive proposals), or if the Government holds discussions with the selected source (for sole source acquisitions), you will be afforded the opportunity to address the concerns raised by the reviewers. You will be able to further discuss and/or clarify your position until submission of your Final Proposal Revision (FPR). Once discussions are closed with the submission of your FPR, if your proposed plan for the inclusion/exclusion of women and minorities is still found to be unacceptable, then your proposal may not be considered further for award.

(d) **Children**

Children (i.e. individuals under the age of 21) must be included in all human subject research unless there are clear and compelling reasons not to include them.

Your proposal must include a description of plans for including children. If you plan to exclude children from the required research, your proposal must present an acceptable justification for the exclusion. If you determine that exclusion of a specific age range of child is appropriate, your proposal must also address the rationale for such exclusion. Also, the plan must include a description of the expertise of the investigative team for dealing with children at the ages included, of the appropriateness of the available facilities to accommodate the children, and the inclusion of a sufficient number of children to contribute to a meaningful analysis relative to the purpose/objective of the solicitation. Also, see Section L of the solicitation for further specific requirements on inclusion of children.

Based on the reviewers' evaluation of the offeror's response, this section of the proposal may be rated "unacceptable" (i.e., no discussion can be found regarding the proposed inclusion plans for children; or concerns are identified as to the offeror's response regarding the inclusion of children; or the plan is not in accordance wit h NIH policy guidelines) or "acceptable." If the reviewers find that this portion of the proposal is "unacceptable" they will provide a narrative supporting their finding.

If the Government includes your proposal in the competitive range (for competitive proposals), or if the Government holds discussions with the selected source (for sole source acquisitions), you will be afforded the opportunity to address the concerns raised by the reviewers. You will be able to further discuss and/or clarify your position until submission of your Final Proposal Revision (FPR). Once discussions are closed with the submission of your FPR, if your proposed plan for the inclusion of children is still found to be unacceptable, then your proposal may not be considered further for award.

If the information provided in your proposal about the inclusion of children is rated "unacceptable" and the Government includes your proposal in the competitive range (for competitive proposals), or if the Government holds discussions with the selected source (for sole source acquisitions), you will be afforded the opportunity to further discuss, clarify or modify your plan during discussions and in your Final Proposal Revision (FPR). If your plan for inclusion of children is still considered "unacceptable" by the Government after discussions, your proposal may not be considered further for award.

(e) **HIV Antiviral Treatment Trials**

The offeror's proposal must address a plan to have host countries authorities and/or other stakeholders identify sources available, if any, to provide antiretroviral treatment to HIV-affected populations that have participated in the contract-funded HIV antiretroviral treatment trial, OR describe why the offeror believes that there are no such sources available. The information provided must be in accordance with Section L.

The Project Officer will evaluate the documentation provided. While an offeror's documentation of the lack of available sources for antiretroviral treatment will not, of itself, constitute denial of a contract award, priority for contract awards may be given to those offerors who identify sources for the provision of antiretroviral treatment following the completion of the trial.

b. **EVALUATION OF DATA SHARING PLAN**

The offeror's plan for the sharing of final research data shall be assessed for appropriateness and adequacy. If your proposal does not include a plan or if the plan in your proposal is considered "unacceptable," and the Government includes your proposal in the competitive range (for competitive proposals), or if the Government holds discussions with the selected source (for sole source acquisitions), you will be afforded the opportunity to further discuss, clarify or modify your data sharing plan during discussions and in your Final Proposal Revision (FPR). If your data sharing plan is still considered "unacceptable" by the Government after discussions, your proposal may not be considered further for award.

c. **TECHNICAL EVALUATION CRITERIA**

The evaluation criteria are used by the technical evaluation committee when reviewing the technical proposals. The criteria below are listed in the order of relative importance with weights assigned for

evaluation purposes.

Technical Approach 40%

Adequacy of technical approach to coordinate and manage a multi-center randomized clinical trial. The approach must include suitable plans for data management, data analysis, and for fulfilling Data Coordinating Center functions; including methods for coordinating, monitoring, and managing all activities required for the collaborative development of the study protocol and for the conduct of activities as described in the study protocol. These activities include plans for the randomization of patients, intervention approaches, preparation and updating the Manual of Operations, oversight of standardization and quality control of data collection, and assistance in archiving samples for repository placement. Adequacy of plans for managing the data derived from this study, including plans for assessing the reliability and validity of the data collected.

Personnel Qualifications 30%

Documented experience, expertise and availability of key personnel relevant to the operation of a coordinating center for a complex multi-center randomized clinical trial. Personnel should have experience in sickle cell disease clinical research, drug treatment distribution, quality control, tracking of adverse reactions to drug therapy, as well as experience in data collection, monitoring, standardization, and preparation of scientific reports and manuscripts.

Institutional Experience and Administrative Structure 20%

Adequacy of the organizational and administrative structure to participate in a complex multi-center randomized clinical trial. Prior successful experience in studies, both in the collection of data from multiple clinical sites, as well as experience in monitoring the quality and timeliness of data. Documented institutional commitment to the program.

Facilities and Equipment 10%

Availability of adequate facilities, equipment, and resources necessary to support the technical objectives. Adequacy of computer systems and appropriate software for the input and maintenance of data files and of proposed measures taken to assure security of the data.

SOLICITATION ATTACHMENTS INCLUDED WITH THE RFP

The following pages include Attachments applicable to this RFP as specified in SECTION J - List of Attachments

PACKAGING AND DELIVERY OF THE PROPOSAL

Your proposal shall be organized as specified in Section L.2., "Instructions to Offerors" - General Instructions. Shipment and marking shall be as indicated below.

EXTERNAL PACKAGE MARKING: In addition to the address cited below, mark each package as follows:

"**RFP NO. NHLBI-HB-06-04 Phase II/III Trial of Sildenafil for Sickle Cell Disease-Associated Pulmonary Hypertension - Data Coordinating Center TO BE OPENED BY AUTHORIZED GOVERNMENT PERSONNEL ONLY"**

NUMBER OF COPIES

Technical Proposal: Original* and 35 copies
Business Proposal: Original* and 10 copies

If hand-delivered or delivery service

Review Branch, Division of Extramural Activities
National Heart, Lung, and Blood Institute
Rockledge 2, Room 7091
6701 ROCKLEDGE DRIVE MSC 7924
BETHESDA, MD 20817

If using U.S. Postal Service

Review Branch, Division of Extramural Activities
National Heart, Lung, and Blood Institute
Rockledge 2, Room 7091
6701 ROCKLEDGE DRIVE MSC 7924
BETHESDA, MD 20892-7924

*THE ORIGINALS MUST BE READILY ACCESSIBLE FOR DATE STAMPING PURPOSES.

ATTACHMENT 2

PROPOSAL INTENT RESPONSE SHEET

RFP No. NHLBI-HB-06-04

TITLE: Phase II/III Trial of Sildenafil for Sickle Cell Disease-Associated Pulmonary Hypertension- Data Coordinating Center

PLEASE REVIEW THE REQUEST FOR PROPOSAL. FURNISH THE INFORMATION REQUESTED BELOW AND SUBMIT NO LATER THAT 4:00 P.M. LOCAL TIME 10/26/2005. IF YOU KNOW THE IDENTITIES OF ANY PERSONNEL TO BE PROPOSED, PLEASE PROVIDE THAT INFORMATION AT THIS TIME . YOUR EXPRESSION OF INTENT IS NOT BINDING BUT WILL GREATLY ASSIST US IN PLANNING FOR PROPOSAL EVALUATION.

[ ] DO INTEND TO SUBMIT A PROPOSAL

[ ] DO NOT INTEND TO SUBMIT A PROPOSAL FOR THE FOLLOWING REASONS:

COMPANY/INSTITUTION NAME:

ADDRESS:

PROJECT DIRECTOR'S NAME:

TITLE:

TELEPHONE NUMBER:

E-MAIL ADDRESS:

NAMES OF COLLABORATING INSTITUTIONS AND INVESTIGATORS
(include Subcontractors and Consultants):

AUTHORIZED SIGNATURE:

TYPED NAME AND TITLE:

DATE:

RETURN TO: Rick Phillips, Contracting Officer
phillipr@nhlbi.nih.gov

National Institutes of Health
National Heart, Lung and Blood Institute
6701 Rockledge Drive/Room 6132
Bethesda MD 20892-7902

PHONE: 301-402-6462/FAX: 301-480-3432

STATEMENT OF WORK

The study schedule is estimated to be as follows:

Phase I - Protocol development and planning - 9 months
Phase II - Patient enrollment and follow-up - 30 months
Phase III - Data Analysis - 9 months

Specifically, the Contractor shall serve as the Data Coordinating Center and perform the following project requirements:

1. Participate as a member of the Steering Committee (SC) and Executive Committee (EC). Arrange for and schedule Steering and Executive Committee meetings. Maintain a central website with a repository of minutes and materials relating to the functioning of the various committees. Arrange for and participate in subcommittee meetings and generate minutes as necessary, by conference call or in person. The EC shall be comprised of the Chair of the SC, the NHLBI Project Officer, and the Principal Investigator of the DCC. The Steering Committee will be comprised of the clinical site PI's, the NHLBI Project Officer, and a chairperson that will be determined by NHLBI. **For solicitation purposes, assume 3 DCC staff will attend 4 one-day meetings to be held on the NIH campus over the course of the project. Assume costs for 16 conference calls of the SC and EC.**

2. Prepare statistical reports as needed to monitor study progress, quality of data, participating center performance, etc. for use by the Data and Safety Monitoring Board (DSMB). Attend the open portion of DSMB meetings. **For solicitation purposes, assume travel expenses for 2 DCC staff and the Chair of the SC for 4 one-day meetings to be held on the NIH campus over the course of the project. Assume costs for 4 conference calls. The DCC will not be responsible for travel expenses or honoraria for DSMB members.**

3. Participate in the development and finalization of the protocol as a member of the Steering Committee. Reproduce and distribute the protocol and study forms to the clinical centers. The draft protocol entitled, "Phase II/III Trial of Sildenafil for Sickle Cell Disease-Associated Pulmonary Hypertension" (see Attachment 5) is hereby made part of the contract. It is mutually agreed that future revisions of this protocol are considered to be incorporated by reference into this contract without further contract modification. The final protocol shall be approved by the NHLBI.

4. Coordinate the development, writing, and distribution of the Manual of Procedures (MOP). The DCC shall work with the NHLBI Project Officer and all Steering Committee members to develop, write, refine, reproduce and distribute the official MOP for this study. The MOP shall describe, in detail, the proper collection of data and coordination of the study. The final version shall be due to the NHLBI Project Officer within 6 months of contract award. Upon its completion, the MOP is made part of the contract by reference.

5. Develop and Distribute Case Report Forms. The DCC shall work with the NHLBI Project Officer and clinical site principal investigators to develop the official case report forms for this study. Both the main trial (with patients on study for 16 weeks) and the extension study (with patients on study for 1 full year in addition to the 16 weeks) shall be included in the Case Report Form. The DCC shall distribute these forms to all clinical sites.

6. Conduct central training of study personnel. The DCC shall organize, coordinate and conduct one central training session for all clinical sites supported under this study. The purpose of this training shall be to instruct all clinical site personnel on the standard operating procedures for conduct of this trial. **For solicitation purposes, assume 3 DCC staff will conduct a 1-day training to be held on the NIH campus, the day after or before the first in-person SC meeting.**

7. Oversee a Pharmacy Distribution Center (PDC). The function of the PDC is to distribute study medications to the clinical sites in a timely and efficient manner. The DCC shall work with the PDC to prepare for study initiation. The DCC shall coordinate bulk shipments of sildenafil and placebo from the drug source; provide instructions to the PDC for drug repackaging and distribution to clinical sites, including package size, pill size, and schedule; and collect regular progress reports from the PDC. **For solicitation purposes, the DCC shall not be responsible for selecting or paying the PDC. The DCC shall be notified of the PDC identity and the source of the study drug after contract award.**

8. Develop a system for random assignment to each treatment arm for each patient enrolled in the trial. Implement the process for communicating random assignments to the individual clinical sites.

9. Collect, tabulate, and make available to the Project Officer patient accrual targets for each clinical site.

10. Monitor patient entry at all sites. Collect, tabulate, and make available to the Project Officer patient enrollment data for each clinical site on a monthly basis. Advise the Project Officer on the progress of the study with monthly status reports to insure that the participating clinical sites meet study requirements in an accurate and timely fashion.

11. Prepare other statistical reports as needed to monitor study progress and quality of data for use by the Project Officer.

12. Develop plans for either secure web-based electronic data entry, or paper data entry, by clinical sites using official Case Report Forms. The DCC shall maintain a secure database with all study data and shall make provisions for computer backup systems in the event of primary system failure. The database shall also contain bar coding information for tracking of blood and plasma samples (from all patients) to be sent from clinical sites to the NHLBI Blood Specimen Repository. **For solicitation purposes, assume no shipping costs.**

13. Centrally monitor data entry on case report forms (on web pages or paper forms) in accordance with the final study protocol. Monitor and inform the clinical sites of erroneous, missing, delayed, or incomplete data.

14. Conduct site visits in conjunction with NHLBI staff to check on data quality/integrity, consent forms, protocol violations, compliance with inclusion and exclusion criteria, etc. **For solicitation purposes, assume 24 site visits by 2 DCC personnel over the course of the project.**

15. Generate and distribute to individual clinical sites appropriate calendars, patient lists, etc., to assist in their specific data collection.

16. Provide coordination and leadership in the resolution of operational problems for the entire study.

17. If necessary, as determined by the Project Officer and Contracting Officer, subcontract with additional clinical sites as to achieve the timely recruitment of patients needed for this trial.

18. Analyze the study data collected. Participate with the clinical site investigators in the analysis and writing of trial manuscripts and reports for publication and presentation. Prepare and analyze data that shall be used for specific manuscript preparation. A data analysis plan shall be prepared by the Contractor and submitted to the NHLBI by the end of the first year of the contract for approval. Analysis shall involve data from all centers. **[Note to offerors: All publications of data from this study shall be overseen and coordinated by the Steering Committee or its subcommittees, which are advisory to the NHLBI].**

ATTACHMENT 5

A RANDOMIZED TRIAL OF SILDENAFIL IN PULMONARY ARTERIAL HYPERTENSION SECONDARY TO SICKLE CELL DISEASE:

BACKGROUND

Pulmonary hypertension, diagnosed by Doppler echocardiography, is common in adults with sickle cell disease. It appears to be a complication of chronic hemolysis, is resistant to hydroxyurea therapy, and confers a high risk of death (rate ratio, 10.1; 95 percent confidence interval, 2.2 to 47.0; $P<0.001$). Preliminary, open label phase I/II data from the intramural NIH demonstrate safety and efficacy of Sildenafil in the treatment of pulmonary hypertension in this population. Therapeutic trials targeting this population of patients are indicated.

INCLUSION CRITERIA

1. Males or females, 14 years of age or older.
2. Diagnosis of sickle cell disease (electrophoretic documentation of SS, SC, or Sβ° thalassemia genotype is required).
3. At least mild pulmonary hypertension with TR jet velocity $\geq$ 2.5 m/s by echocardiogram. And for patients undergoing right heart catheterization, mean pulmonary artery pressure at rest greater than 25 mmHg or greater than 30 mmHg during exercise with pulmonary capillary wedge pressure less than 28 mmHg.
4. Ability to walk at least 150 meters and less than 450 meters during six-minute walk test.

EXCLUSION CRITERIA

1. Current pregnancy or lactation.
2. Any of the following medical conditions:
   A) Severe renal insufficiency (patient on hemodialysis or serum creatinine > 2.5 mg/dl).
   B) Stroke within the last six weeks.
   C) New diagnosis of pulmonary embolism within the last three months.
   D) History of retinal detachment or retinal hemorrhage in the last 2 years.
   E) History of sustained priapism requiring medical or surgical treatment, unless currently impotent within the last two years.

3. Patients taking, nitrate-based vasodilators, prostacyclin (inhaled, subcutaneous or intravenous) or endothelin antagonists. Patients taking calcium channel blockers will be allowed to participate provided they are on a stable dose for ≥ one month.
4. Patients who are in other research studies for the treatment of pulmonary hypertension or who are on treatment specific for pulmonary hypertension.

STUDY DESIGN

Screening

Each center will receive funding to screen 84 subjects with sickle cell disease. Patients will have a Doppler-echocardiogram with specific and detailed assessment of the tricuspid regurgitant jet velocity, diastolic function (e.g E/A ratio deceleration time), valvular and systolic function. History and physical exam will be performed, and blood will be collected for preparation and storage of DNA and plasma, to be stored at the NHLBI Biological Specimen Repository.

Main trial

All subjects with TR jet velocity ≥ 2.5 m/s will undergo screening with complete history, physical examination and baseline laboratory testing including documentation of SS, SC, or $S\beta^0$ thalassemia hemoglobin genotype, pulmonary function studies, and a echocardiogram with documentation of tricuspid regurgitant jet velocity for estimation of right ventricular systolic pressure, six-minute walk test for baseline exercise capacity, and assessment of NYHA/WHO functional class.

This trial is designed to test the effects of 16 weeks of chronic sildenafil therapy on exercise endurance (six minute walk distance) and pulmonary artery pressure in patients with pulmonary hypertension and sickle cell disease. In a double blind placebo control fashion, patients with TR jet velocity ≥ 2.5 m/s will be randomized to receive sildenafil 20 mg three times a day or placebo on an outpatient basis for six weeks with the dosage increased to 40 mg TID for four weeks and then increased to 80 mg PO TID for six weeks. Patients enrolled in the trial with TR jet velocity ≥ 2.9 m/s (at least moderate pulmonary hypertension) will also undergo right heart catheterization (using standard techniques) with exercise, at baseline and after 16 weeks of treatment. Randomization of patients meeting inclusion criteria will be stratified in two subgroups according to TR jet velocity (TRV < 2.9 m/s and TRV ≥ 2.9 m/s).

Study of the acute hemodynamic effects of sildenafil

In patients undergoing right heart catheterization the acute hemodynamic effects of three escalating doses of intravenous sildenafil will be assessed at rest and during exercise (peak dose). These measurements will be performed at baseline.

Extension trial

After completion of the main 16 week trial, patients will be invited to continue in a one- year, double-blinded extension study. Individuals in the active drug arm of the main trial will be offered the option to continue treatment with sildenafil 80 mg TID and those who were on the placebo arm will receive sildenafil 20 mg TID. During the extension phase the effects of treatment (six minute walk test and TR jet velocity measurement) will be assessed at 6, 12, and18 weeks, and every 12 weeks thereafter.

PRIMARY ENDPOINT (MAIN TRIAL)

Change in 6-minute walk distance on sildenafil vs. placebo after 16 weeks of therapy

SECONDARY ENDPOINTS (MAIN TRIAL AND EXTENSION STUDY)

A) Hemodynamic parameters (mean PA pressure, PVR, CVP, cardiac output)
B) Change in TR jet velocity
C) Time to clinical deterioration (as defined by a 15% decrease in six-minute walk distance on two-successive measurements plus deterioration in NYHA/WHO functional class or need for additional PAH specific therapy)
D) Incidence of vaso-occlusive crises (ER visits, hospitalizations, blood transfusions, acute chest syndrome)
E) NYHA/WHO functional class
F) Borg dyspnea scale
G) Quality of life (measured by the SF-36 and EQ-5d scales)
H) Change in six minute walk distance on sildenafil 20 mg vs. 40mg and 80 mg in the group receiving active drug during the placebo controlled study
I) Change in six minute walk distance on sildenafil 20 mg vs. 80 mg in the extension study

SAMPLE SIZE

Primary endpoint

Using a difference of 40 meters (m) for drug and 0 for placebo, and a standard deviation of 67 m in both groups, 5% two-sided significance level, and 95% power, then n = 74 patients per group. In order to account for a potential 20% dropout rate during the trial, 180 patients will be enrolled in the study.

Secondary hemodynamic endpoint

Using the hemodynamic data from the 80 mg arm of the SUPER-1 trial with 5% two-sided significance level and 80 % power, the n for mean PA pressure is 32 patients per group, for pulmonary vascular resistance the n is 25 patients per group. Assuming that half of the patients enrolled in the trial will have moderate to severe pulmonary hypertension and meet hemodynamic criteria, the study will be adequately powered to ascertain the hemodynamic effects of sildenafil.

DISCONTINUATION RULES AND DOSE ADJUSTMENTS FOR ADVERSE EFFECTS

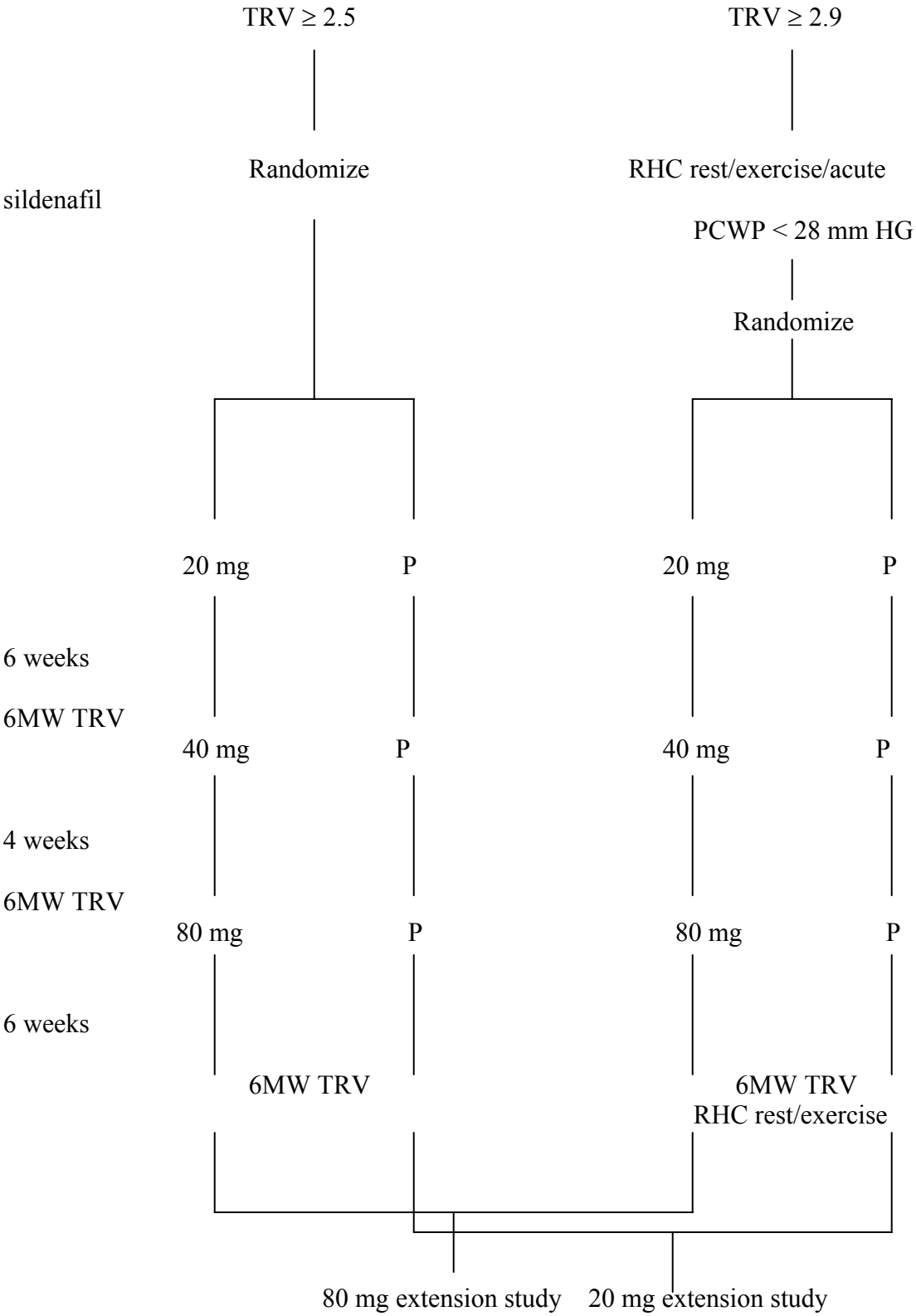
Triggers for Discontinuation

1. Priapism
2. Retinal hemorrhage
3. CVA
4. Clinical worsening

Dose Adjustment for Symptomatic Headache or Facial/Skin Edema Sufficient to Warrant Discontinuation of the Drug

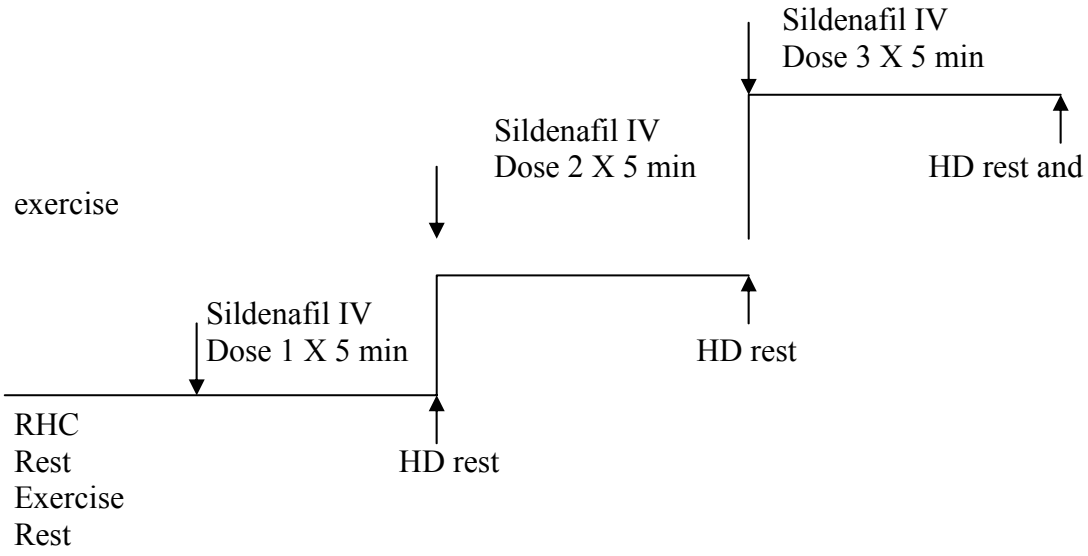
1. If present during initial dose (20 mg) hold for one week and rechallenge. If symptoms occur upon rechallenge, discontinue drug and patient from study.
2. If present during dose escalation (40 or 80 mg) hold drug for one day and restart at previously tolerated dose for one week. If symptoms recur, patient should be discontinued. If tolerated for one week, increase dose to desired level as dictated by protocol. If symptoms recur upon second increase, hold drug for one day and drop dose to previously tolerated dose.

Trial schema



6MW TRV at 6,12 and 18 weeks the q12 weeks thereafter

Acute sildenafil challenge



Protocol Title: Sildenafil Therapy in Patients with Sickle Cell Disease and Pulmonary Hypertension

Abbreviated Title: NO Based Therapy in SCD PHT

Identifying words: PDE inhibitors, sickle cell, pulmonary hypertension

Principal Authors: Roberto Machado, MD
Mark T. Gladwin, MD

Table of Contents

1. Precis

Sickle cell anemia is an autosomal recessive disorder and the most common genetic disease affecting African-Americans. Approximately 0.15% of African-Americans are homozygous for sickle cell disease, and 8% have sickle cell trait. Acute pain crisis, acute chest syndrome (ACS), and pulmonary hypertension are common complications of sickle cell anemia. Pulmonary hypertension has now been identified as a marker of mortality in adults with sickle cell disease. Sildenafil has been proven beneficial in pulmonary arterial hypertension and recent phase I/II studies from the intramural NIH suggest it is well tolerated and efficacious in the sickle cell disease population. Furthermore, a number of recent studies have suggested that NO based therapies may have a favorable impact on sickle red cells at the molecular level and could improve the abnormal microvascular perfusion that is characteristic of sickle cell anemia.

The project is designed in three stages:

1. Screening: 1000 subjects with sickle cell disease will be screened with historical and laboratory data and Doppler echocardiography. Plasma and DNA will be obtained.
2. Main study: randomized, placebo-controlled trial designed to determine the effects of 16 weeks of Sildenafil therapy versus placebo on exercise endurance, cardiopulmonary hemodynamic parameters, and symptoms in this patient population.
3. Extension study: after completion of the main 16 week trial, patients will be invited to continue in a one-year, double-blinded extension study comparing two different doses of sildenafil.

4. Introduction

2.1 Sickle Cell Anemia and Pulmonary Hypertension

Sickle cell disease occurs in individuals who are homozygous for a single nucleotide substitution in the β-globin gene that ultimately renders their hemoglobin (HbS) much less soluble than normal hemoglobin (HbA) when deoxygenated. This insolubility causes aggregation (or polymerization) of HbS inside sickle erythrocytes as they traverse the microcirculation. The severity of sickle cell anemia has been described by models that emphasize either the intracellular kinetics of polymer formation (and cell sickling) or the extent of polymerization (and cell rigidity) at the reduced oxygen saturation values of various tissues and organs. The pathogenesis of sickle cell anemia is also thought to be affected by adhesion of the sickle erythrocytes to the microvascular endothelium. Increased expression of adhesion molecules on erythrocytes ($\alpha 4\beta 1$, CD36) and endothelial cells (VCAM-1, CD36), interaction with leukocytes, increased levels of circulating inflammatory cytokines, enhanced microvascular thrombosis, and endothelial damage are all thought to contribute to obstruction of the arterioles by polymer-containing sickle erythrocytes. Factors that increase the intracellular concentration of hemoglobin (red blood cell dehydration), increase time spent in the microcirculation (increased expression of adhesion molecules endothelial VCAM-1 and erythrocyte $\alpha 4\beta 1$), or increase deoxygenation of hemoglobin, all contribute to increased HbS polymerization.

Pulmonary hypertension, a disorder characterized by an elevated pulmonary artery pressure and pulmonary vascular resistance, is an increasingly recognized observation in sickle cell anemia(1-7). Pulmonary hypertension has been defined by the 1981 NHLBI/NIH national registry as a mean pulmonary artery pressure (MPAP) ≥ 25 mm Hg at rest or ≥ 30 mm Hg with exercise (8). Echocardiographic studies performed at tertiary care sickle cell centers have reported that 20-30% of screened patients have pulmonary hypertension (mean pulmonary artery pressures (PAP) ≥ 25 mm Hg) (1, 2). Furthermore, sickle cell patients with pulmonary hypertension have a significantly increased mortality rate compared with patients without pulmonary hypertension. Sutton and colleagues reported a 40% mortality rate at 22 months with an odds ratio for death of 7.86 (2.63-23.4)(2). Powars and colleagues reported a mean 2.5 year survival in sickle cell patients with chronic lung disease with pulmonary hypertension (9). Data presented at the 1999 American Thoracic Society by investigators at Wayne State University revealed a 30% prevalence of pulmonary hypertension in their sickle cell clinic population and a 30% two-month mortality rate. Castro and colleagues (10) reported a 50% two year mortality rate

in patients with sickle cell disease with pulmonary hypertension confirmed by right heart catheterization. It is clear that this disease, similar to idiopathic pulmonary arterial hypertension (formerly primary pulmonary hypertension) and pulmonary hypertension associated with other conditions, e.g. scleroderma, HIV, carries an unacceptably high morbidity and mortality rate. The variability in 6 to12 month prognoses is likely attributable to the variability in the pulmonary hypertension in the patients studied.

These data are consistent with the results of an NIH pulmonary hypertension screening study (11). 195 adult patients with sickle cell disease were recruited from the greater Washington DC region. All patients were screened with transthoracic echocardiograms and the tricuspid regurgitant jet velocity (TRV) was used to estimate the pulmonary artery systolic pressure. Pulmonary hypertension was prospectively defined by a TRV $\geq$ 2.5 m/sec and moderate-to-severe pulmonary hypertension defined by a TRV $\geq$ 3.0 m/sec. Right heart catheterization was performed in consenting patients with TRV $\geq$ 2.8 m/sec. This study revealed that 32% of patients with sickle cell disease had elevated pulmonary artery systolic pressure (TRV $\geq$ 2.5 m/sec) and 9% had at least moderately elevated pressures. Multiple logistic regression analysis identified a history of renal or cardiovascular complications, increased systemic systolic blood pressure, markers of hemolysis (LDH), elevated alkaline phosphatase, and low transferrin levels as independent predictors of pulmonary hypertension. More importantly, TRV of at least 2.5 m/sec, as compared to a velocity of less than 2.5 m/sec, was associated with an increased risk of death (RR 10.1; 95% CI, 22. 47; $P < 0.001$) and remained so after adjustment for other possible risk-factors in proportional hazards regression analysis. The 18 month mortality approached 20% for patients with a tricuspid regurgitant jet velocity of greater than or equal to 2.5 m/sec. In another recent prospective study of 60 patients systematically sampled at a comprehensive sickle cell treatment center, the prevalence of pulmonary hypertension (defined by an age and body-mass index adjusted nomogram) was 30 % (12). In addition, a study by De Castro and colleagues presented at the most recent meeting of the American Society of Hematology reported a similar prevalence of pulmonary hypertension and a remarkably similar 17% mortality rate for patients with pulmonary hypertension over 2 years compared with approximately 2% for subjects without pulmonary hypertension (13).

Therapeutic trials targeting pulmonary hypertension in this high risk population are indicated.

2.2. Decreased NO Bioavailability in Hemolytic Disorders Provide Rationale for NO Based Therapies of Pulmonary Hypertension

As a result of hemolysis, hemoglobin is released into plasma where it reacts with and destroys nitric oxide, resulting in abnormally high NO consumption. Consequently, smooth muscle guanylyl cyclase is not activated and vasodilation is inhibited. Plasma from patients with sickle-cell disease contains cell-free ferrous hemoglobin, which stoichiometrically consumes micromolar quantities of nitric oxide and abrogates forearm blood flow responses to nitric oxide donor infusions, and that hemoglobin oxidation by NO inhalation restores NO bioavailability(14, 15). As such, plasma hemoglobin and oxygen free radical-mediated consumption of nitric oxide produces a state of resistance to nitric oxide in patients with sickle cell disease (16-23)NO destruction by hemoglobin can also cause further impairment in vascular endothelial function via transcription derepression of adhesion molecules, including VCAM-1 and E-selectin, and vasoconstrictor/growth factors such as endothelin-1(24, 25). In addition to haemoglobin decompartmentalization, hemolysis releases erythrocyte arginase, which converts L-arginine, the substrate for NO synthesis, to ornithine (26-29), Morris *et al* 2004; JAMA manuscript in press). Consistent with this observation, in patients with sickle cell disease, the arginine-to-ornithine ratio decreases significantly as pulmonary pressures increase (11).

These alterations in NO bioavailability are likely to be involved in the pathogenesis of the secondary pulmonary hypertension associated with sickle cell disease and other chronic hemolytic disorders. As such, therapeutic interventions that enhance nitric oxide effects or act as NO donors are of potential benefit and may alter the progression of the disorder. The sub-population of patients with sickle cell disease who have pulmonary hypertension suffer the highest morbidity and mortality and are most likely to respond to these therapies.

2.3. Sildenafil Therapy in Hemolysis Associated Pulmonary Hypertension

Endothelial nitric oxide activates the enzyme guanylate cyclase, which results in increased levels of cyclic guanosine monophosphate (cGMP), producing smooth muscle relaxation. Sildenafil has no direct relaxant effect, but enhances the effect of NO by inhibiting phosphodiesterase type 5 (PDE5), which is responsible for degradation of cGMP. Studies *in vitro* have shown that sildenafil is selective for PDE5. Its effect is more

potent on PDE5 than on other known phosphodiesterases (>80-fold for PDE1, >1,000-fold for PDE2, PDE3, and PDE4).

In addition to human corpus cavernosum smooth muscle, PDE5 is also found in lower concentrations in other tissues including platelets, vascular and visceral smooth muscle, and skeletal muscle. The inhibition of PDE5 in these tissues by sildenafil may be the basis for the enhanced platelet anti-aggregatory activity of NO observed *in vitro*, an inhibition of platelet thrombus formation *in vivo* and peripheral arterial-venous dilatation *in vivo*. Recent studies now suggest that PDE5 is also present in greater abundance in the pulmonary vasculature. Sildenafil has thus been found to promote relatively selective pulmonary vasodilation in different subgroups of patients with pulmonary hypertension and is being utilized as an alternative therapeutic agent (30-42).

Acute administration of a single oral dose of sildenafil (50-75 mg) causes a significant decrease in mean pulmonary arterial pressure, pulmonary vascular resistance with minimal or no effects on mean systemic arterial pressure. The effect peaks at 60 minutes and lasts as long as 4 hours(30, 31, 33, 35, 37). The magnitude of the effect in the pulmonary circulation is comparable to that of inhaled NO, iloprost and epoprostenol (33, 35). Synergistic effects with inhaled NO and inhaled iloprost have also been demonstrated (41).

Case series have also documented a favorable effect of chronic sildenafil administration in patients with pulmonary hypertension. Ghofrani et al (42) treated 12 patients with inoperable chronic thromboembolic disease and pulmonary hypertension. After 6 months of sildenafil therapy (50 mg three times/day) mean pulmonary arterial pressure decreased from 53 to 45 mmHg (P = 0.03) and six-minute walk distance increased from 312 to 366 m (P = 0.02). Three months of sildenafil therapy added to standard of care was also associated with improvements in functional class, walking distance, pulmonary artery pressure and right ventricular mass in five individuals with pulmonary arterial hypertension (40). In another group of 14 patients with pulmonary arterial hypertension failing iloprost therapy, the addition of sildenafil for up to 12 months was also associated improvements in pulmonary hemodynamics and exercise capacity (41). The cumulative published experience from case series involving more than two patients is summarized in table 1. A recently completed phase III study of sildenafil for pulmonary arterial hypertension confirmed these observations. In this trial 277 patients were randomized to receive placebo or sildenafil 20mg, 40mg or 80mg three times daily. All three sildenafil treatment groups demonstrated a significant improvement in exercise capacity when

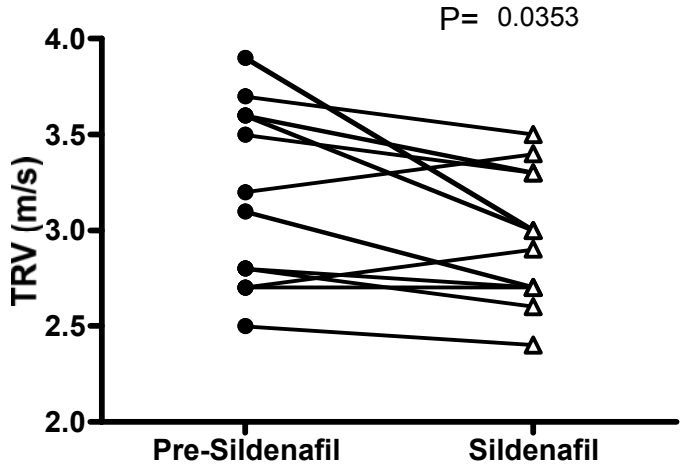
compared to placebo with placebo corrected effects on six-minute walk distance ranging from 45 to 50 m, but without a dose related response. Sildenafil treatment significantly decreased mean PA pressure and pulmonary vascular resistance and increased cardiac output and mixed venous oxygen saturation.

Over the last three years we have treated 22 patients with sickle cell disease and pulmonary hypertension with sildenafil under protocols 03-CC-0127 and 01-H-0223. These limited experiences suggest that sildenafil is well tolerated in this population (see section 9.3.2) and appears to effectively lower pulmonary artery pressures and increase exercise capacity (figure 1). While the observed effects are comparable to inhaled NO gas the oral modality of sildenafil therapy offers substantial advantages. Based on these data we hypothesize that chronic Sildenafil therapy in patients with pulmonary hypertension associated with sickle cell disease will result in improvements in exercise capacity and pulmonary hemodynamics.

Table 1

Reference	Number of Patients	Dose	Duration	Main Results
Lepore (35)	9	50 mg X1	Single dose	Significant decrease in mean pulmonary arterial pressure
Michelakis (37)	13	75 mg X1	Single dose	Significant 27% decrease in mean pulmonary arterial pressure
Ghofrani (30)	8	50 mg	Single dose	Significant 32.5 % decrease in pulmonary vascular resistance index
Michelakis (40)	5	50 mg TID	3 months	Significant improvement in NYHA functional class, 6-minute walk distance, mean pulmonary arterial pressure and pulmonary vascular resistance
Ghofrani (41)	14	25 mg TID- 50 mg TID	9-12 months	Significant improvement in NYHA functional class, 6-minute walk distance, mean pulmonary arterial pressure and pulmonary vascular resistance
Ghofrani (42)	12	50 mg TID	6 months	Significant improvement in 6-minute walk distance, mean pulmonary arterial pressure and pulmonary vascular resistance

A)



B)

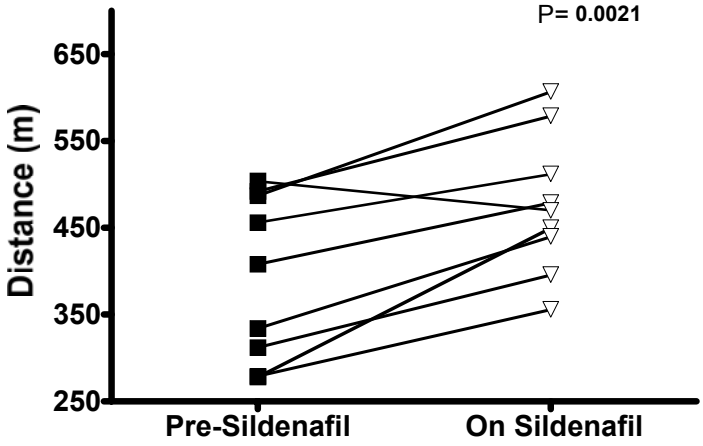


Figure 1- Effects of Sildenafil on (A) pulmonary pressures and (B) functional capacity, measured by six minute walk distance, in patients with pulmonary hypertension and sickle cell disease.

3. Objectives

Our study has the following major objectives:

1) Screening, to identify patients with sickle cell disease who have pulmonary hypertension and to create a cohort with an established cardiovascular phenotype and a plasma/DNA repository.
2) In a randomized, double-blinded, placebo-controlled phase II/III trial, to determine the safety and efficacy of 16 weeks of sildenafil therapy on exercise capacity (six-minute walk distance), symptoms, and hemodynamic parameters including pulmonary artery pressure in patients with sickle cell disease and pulmonary hypertension. In patients undergoing right heart catheterization, determine the acute hemodynamic effects of three escalating doses of intravenous sildenafil at rest and during exercise (peak dose).
3) In a one-year, double-blinded extension study, determine the efficacy of sildenafil therapy on exercise capacity, symptoms, pulmonary pressures estimated by echocardiogram.

The study's primary endpoint will be change in 6-minute walk distance on sildenafil vs. placebo after 16 weeks of therapy.

4. Study Design and Methods

Overview: Upon screening, if a patient is found to have a TR jet velocity of $\geq$ 2.5 m/s they will be invited to participate in the protocol. Upon repeat echocardiogram if the patient has a TR jet velocity of $\geq$ 2.5 m/s and no exclusion criteria, they will be enrolled in the trial. Patients will be enrolled in a randomized, double-blind, placebo-controlled trial of sildenafil or placebo for 16 weeks. All patients who complete the 16-week study will be offered enrollment in a blinded extension study of sildenafil 20 mg vs. 80 mg. Patients with TR jet velocity $\geq$ 2.9 m/s will be also evaluated with right heart catheterization (RHC). Patients will be stratified and randomized in the following two groups: TR jet velocity 2.5-2.8 m/sec (no RHC) and TR jet velocity $\geq$ 2.9 m/s (RHC).

4.1 Screening Study

Each center will receive funding to screen 84 subjects with sickle cell disease. Patients will have a Doppler-echocardiogram with specific and detailed assessment of the tricuspid regurgitant jet velocity, diastolic function (e.g E/A ratio deceleration time), valvular and systolic function. History and physical exam will be performed, and blood will be collected for DNA and plasma.

4.2 Main Trial

All subjects with TR jet velocity $\geq$ 2.5 m/s will undergo screening with complete history, physical examination and baseline laboratory testing including documentation of SS, SC, or Sβ^0 thalassemia hemoglobin genotype, pulmonary function studies, and a echocardiogram with documentation of tricuspid regurgitant jet velocity for estimation of right ventricular systolic pressure, 6-minute walk test for baseline exercise capacity, and assessment of NYHA/WHO functional class.

The main trial is designed to test the efficacy of 16 weeks of chronic sildenafil therapy on exercise endurance (six minute walk distance) and pulmonary artery pressure in patients with pulmonary hypertension and sickle cell disease (appendix A). In a double-blinded, placebo-controlled fashion, patients with TR jet velocity ≥ 2.5 m/s will be randomized to receive sildenafil 20 mg three times a day or placebo (matching in pill color and size) on an outpatient basis for six weeks with the dosage increased to 40 mg TID for four weeks and then increased to 80 mg PO TID for six weeks. Patients enrolled in the trial with TR jet velocity ≥ 2.9 m/s (at least moderate pulmonary hypertension) will also undergo right heart catheterization (using standard techniques) with exercise, at baseline and after 16 weeks of treatment. Randomization of patients meeting inclusion criteria will be stratified in two subgroups according to TR jet velocity (TRV 2.5-2.8 m/s and TRV ≥ 2.9 m/s) and an equal number of individuals will be enrolled in each arm.

Patients enrolled in the trial with TR jet velocity ≥ 2.9 (at least moderate pulmonary hypertension) will also undergo right heart catheterization (using standard techniques) at baseline and after 16 weeks. Following premedication, right heart catheterization is performed under local anesthesia with a heparin-bonded thermodilution Swan-Ganz catheter inserted percutaneously into the right internal jugular or a femoral vein depending on anatomic landmarks. Catheter is positioned in the pulmonary artery with

pressure monitoring. Catheter tip position will be evaluated by fluoroscopy or chest radiography. Fluoroscopy may be used according to standard clinical practice. A 20-gauge heparin-bonded cannula is inserted percutaneously into a radial, brachial or femoral artery for blood sampling and monitoring of systemic arterial pressure. Mean vascular pressure levels are determined by electronic integration of the pressure signals. Heart rate and vascular pressures are monitored continuously. Cardiac output is measured in triplicate by thermodilution and by the Fick method. Systemic and pulmonary vascular resistances are calculated using the mean cardiac index and mean vascular pressures.

In patients undergoing right heart catheterization the acute hemodynamic effects of three escalating doses of intravenous sildenafil will be assessed at rest and during exercise (peak dose) (appendix B). These measurements will be performed at baseline.

The exercise protocol will consist of upper extremity exercise with 1 liter saline bags for five minutes with hemodynamic measurements at 1,3 and 5 minutes.

Male patients will start therapy as inpatients for clinical observation for one day of sildenafil (three doses) to evaluate for potential priapism. Prior to enrollment patients will have a type and cross match for red blood cells obtained for possible exchange transfusion should refractory priapism occur (defined as priapism of greater than 2 hours duration).

Clinical follow-up will occur at 6 ± 1, 10 ±1 and 16 ± 1 weeks. At these visits venous blood will be obtained for BNP and standard chemistries. Total weekly symptoms, emergency room visits, hospital admissions, and narcotic use will be recorded. Six-minute walk (with assessment of Borg dyspnea index, and NYHA/WHO functional class) and echocardiogram with assessment of TR jet velocity will be repeated at these intervals until the completion of the study. In the event of vaso-occlusive crises end-point assessment will be performed one week after resolution of the acute event. In patients with TR jet velocity $\geq$ 2.9m/s a second right heart catheterization will be performed at 16 weeks.

4.3 Double Blinded Extension Trial

After completion of the main 16 week trial patients will be invited to continue in a one year double blinded extension study. Individuals on active drug will be continued on sildenafil

80 mg TID (or the highest tolerated dose) and those who were on the placebo arm will receive sildenafil 20 mg TID. During the extension phase the effects of treatment (six minute walk test and TR jet velocity measurement) will be assessed at 6, 12, 18 weeks and every 12 weeks thereafter. If this study shows clinical benefit, after this year patients will be encouraged to seek medical insurance to cover chronic sildenafil use.

4.4 Alternative Therapies

Upon enrollment in the study, all patients will be evaluated for intensification of sickle cell disease therapy according to clinical standards of practice. Treatments that will be considered (at the discretion of primary providers) include hydroxyurea 15 mg/kg or exchange transfusion therapy in patients with sickle cell disease, oxygen supplementation in case of significant daytime and/or nighttime hypoxemia, and anticoagulation in patients with at least moderate pulmonary hypertension (mean PAP **≥** 40 mmHg).

5. Special Clinical and Laboratory Methods

5.1 Echocardiography

Transthoracic echocardiography will be performed according to the guidelines of the American Society of Echocardiography. Transmitral flow, Doppler determinations of the severity of valvular regurgitation, and left ventricular stroke volume will assessed and graded. Peak velocities of the E wave and A wave, the ratio of the E wave to the A wave, and the deceleration time will be measured. Isovolumic relaxation time will be measured as the time from aortic valve closure to the start of mitral inflow.

Tricuspid regurgitation will be assessed in the parasternal right ventricular inflow, parasternal short-axis, and apical four-chamber views, and a minimum of five sequential complexes will be recorded. Continuous-wave Doppler sampling of the peak regurgitant jet velocity will be used to estimate the right-ventricular-to-right-atrial systolic pressure gradient with the use of the modified Bernoulliequation (4 x [tricuspid regurgitant jet velocity]^2). Pulmonary-artery systolic pressure will be quantitated by adding the Bernoulli-derived pressure gradient to the estimated mean right atrial pressure.
The mean right atrial pressure will be calculated according to the degree of collapse of the inferior vena cava with inspiration: 5 mm Hg for a collapse of at least 50 percent and 15 mm Hg for a collapse of less than 50 percent.

5.2 Right Heart Catheterization

The pulmonary artery catheter is a triple lumen central venous catheter with two lumens devoted to the pressure transduction functions. The distal port will transduce pressure from the pulmonary artery and from the left atrium, when in the "wedge" position. The central venous port transduces right atrial pressures. During catheter placement, right ventricular pressures are transduced. Warmed coils on the catheter and a thermister at the catheter tip allows for continuous thermal dilution cardiac output measurements which complement mixed venous blood saturation for cardiac output calculation by the Fick method. Pulmonary artery systolic and diastolic pressures, right atrial pressure, pulmonary capillary wedge pressure, systemic artery systolic and diastolic pressures, cardiac output, and calculated systemic and pulmonary vascular resistances will be obtained using this methodology.

5.3 6 Minute Walk

The 6-minute walk will be performed in accordance with standard practice (33, 43-45). Briefly, patients will be asked to walk with a trained exercise technician for six minutes along a pre-measured path. A practice walk will be performed first (45). Distance walked, Borg dyspnea index, NYHA functional class, and oxygen saturation will be determined.

6. Subject Accrual

6.1 Eligibility

All volunteer subjects must be at least 14 years of age and must be able to provide informed, written consent for participation in this study. Eligibility in the study is determined prior to enrollment on the basis of the following inclusion and exclusion criteria.

6.2 Inclusion criteria

5. Males or females, 14 years of age or older.
6. Diagnosis of sickle cell disease (electrophoretic documentation of SS, SC, SD, or $S\beta^{o/+}$ thalassemia phenotype is required).

7. At least mild pulmonary hypertension with TR jet velocity ≥ 2.5 m/s by echocardiogram. And for patients undergoing right heart catheterization, pulmonary capillary wedge pressure less than 28 mmHg.
8. Ability to walk at least 150 meters and less than 450 meters during six-minute walk test.

6.3 Exclusion criteria

5. Current pregnancy or lactation.
6. Any of the following medical conditions:

    - Severe renal insufficiency (patient on hemodialysis or serum creatinine > 2.5 mg/dl).
    - Stroke within the last six weeks.
    - New diagnosis of pulmonary embolism within the last three months
    - History of retinal detachment or retinal hemorrhage in the last 6 months.
    - History of sustained priapism requiring medical or surgical treatment, unless currently impotent within the last two years.

7. Patients taking nitrate-based vasodilators, prostacyclin (inhaled, subcutaneous or intravenous) or endothelin antagonists. Patients taking calcium channel blockers will be allowed to participate provided they are on a stable dose for ≥ one month.
8. Patients who are in other research studies with investigational drugs with the exception of hydroxyurea.

7. Monitoring Of Subjects and Criteria For Discontinuation Of Subjects

Men with sickle cell disease will start therapy as inpatients for clinical observation for one day of sildenafil (three doses) to evaluate for potential priapism. Prior to enrollment patients will be typed and crossed for red blood cells for possible simple or exchange transfusion should refractory priapism occur (defined as priapism of greater than 2 hours duration). Patients will also be specifically monitored for incidence of priapism. Patients will be instructed to contact a member of the study team at the onset of any degree of priapism and will be admitted for immediate evaluation and treatment, including exchange transfusions and urologic evaluation if necessary.

Therapy will be discontinued for the following reasons:

1) Major bleeding complication including intracerebral hemorrhage or stroke, GI hemorrhage, need for major surgery.

2) One episode of severe priapism defined as priapism lasting for more than 2 hours or requiring transfusion or surgical therapy.

3) Positive quantitative blood HCG or pregnancy

4) New retinal detachment or hemorrhage

In patients presenting with evidence of clinical deterioration due to worsening pulmonary hypertension (defined as a 15% decrease in six-minute walk distance on two successive evaluations while not in vaso-occlusive crisis, plus deterioration in NYHA/WHO functional class or need for additional PAH specific therapy), the study drug should be discontinued. In addition, the patients should be unblinded to enter open-label sildenafil therapy or an alternate agent.

7.1 Dose adjustment for symptomatic/dose limiting headache or facial/skin edema sufficient to warrant discontinuation of the drug (only for symptoms that are severe enough as described by patient or physician to warrant holding the drug)

3. If present during initial dose (20 mg), hold for one week and rechallenge. If symptoms occur upon rechallenge, discontinue drug and discontinue patient from study.
4. If present during dose escalation (40 or 80 mg), hold drug for one day and restart at previously tolerated dose for one week. If symptoms recur, the patient should be discontinuned. If tolerated for one week, increase dose to desired level as dictated by protocol. If symptoms recur upon second increase, hold drug for one day and drop dose to previously tolerated dose for the duration of the main trial (and extension study).

7.2 Stopping Rules

Recommended criteria for stopping are:

1. Four excess unexpected, possibly associated deaths (5% of treatment group), or 2 highly probably associated death in the investigational treatment arm, as compared to the placebo arm.

   OR

2. ≥ 9 excess subjects (10% of one treatment arm) requiring discontinuation of therapy for safety in the investigational treatment arm, as compared to the placebo arm:
   - Priapism sustained for more that 2 hours and requiring hospital admission with medical or surgical intervention.
   - Any serious adverse event thought to be probably or highly probably related to the medication.
   - Clinically significant hypotension (requiring fluid or vsopressor resuscitation).
   - Major bleeding complication including intracerebral hemorrhage or stroke, GI bleed, need for major surgery.
   - Retinal detachment or hemorrhage.

8. Analysis of the Study

8.1 Analysis

Primary endpoint:

Change in 6 minute walk distance on sildenafil vs. placebo after 16 weeks of therapy.

We plan to analyze six-minute walk distance by a unpaired t-test, on the change from baseline (i.e., 6 minute walk distance at 16 weeks – 6 minute walk distance at baseline). The statistical null hypothesis tested is that there is no change in mean change of six-minute walk distance when sildenafil therapy is compared to placebo. Longitudinal methods (generalized linear models and their general estimating equation models) will be applied to incorporate intermediate measurements into the analysis. For patients not completing 16 weeks of therapy, data from the last 6-minute walk obtained prior to withdrawal from the study will be utilized for analysis. Data for the blinded extension study will be analyzed using similar methods.

Other hemodynamic variables, including mean pulmonary artery pressure, pulmonary vascular resistance (PVR) and cardiac output (CO) will be analyzed in the same way as 6-minute walk distance.

An interim analysis is planned after 120 patients completed the study (90 % power). The study can be terminated only for lack of efficacy (futility) for change in six-minute walk distance or safety reasons. The required continuation is to ensure appropriate power for hemodynamic and sickle cell related and toxicity related secondary endpoints.

Specific secondary endpoints will be as follows:

J) Hemodynamic parameters (mean PA pressure, PVR, CVP, cardiac output)
K) Change in TR jet velocity
L) Time to clinical deterioration (as defined by a 15% decrease in six-minute walk distance on two-successive measurements plus deterioration in NYHA/WHO functional class or need for additional PAH specific therapy)
M) Incidence of vaso-occlusive crises (ER visits, hospitalizations, blood transfusions, acute chest syndrome)
N) NYHA/WHO functional class
O) Borg dyspnea scale
P) Quality of life (measured by the SF-36 and EQ-5d scales)
Q) Change in six minute walk distance on sildenafil 20 mg vs. 40mg and 80 mg in the group receiving active drug during the placebo controlled study
R) Change in six minute walk distance on sildenafil 20 mg vs. 80 mg in the extension study

Missing data at the week-16 assessment will be derived from predefined replacement rules. Patients without an assessment at week 16 will have their last 6-min walking distance, Borg dyspnea index, and WHO functional class carried forward, but are excluded from the hemodynamic analysis. Discontinuation of study medication because of clinical worsening or death will be analyzed with the patient's assessment at the time of premature withdrawal. If no assessment is recorded, these patients will be assigned the worst rank value—0 m for the 6-min walk test; a score of 10 for the Borg dyspnea index; class IV for WHO functional class; the highest pulmonary artery pressure recorded in the same patient population, the highest pulmonary capillary wedge pressure, the highest right atrial pressure, the highest pulmonary vascular resistance, and the greatest decrease from baseline cardiac index to week 16 from the same group.

8.2 Sample Size

In order to estimate the trial sample size we utilized six-minute walk distance derived from Ghofrani's evaluation the effects of sildenafill in patients with chronic thromboembolic pulmonary hypertension (42). Assuming a 16-week change of 40m in six-minute walk distance in patients on sildenafil and no change in patients on placebo (i.e. a 16-week effect size of 40m between the two treatment groups) with a standard deviation of 67m for the 16-week change in each of the treatment groups, a sample of n=74 patients per group will be required to maintain 95% power at a 5% significance level with a two-sided test.

Now we show that the sample size calculated for the primary endpoint is appropriate for detecting significance in the secondary hemodynamic endpoint using data from the recently completed SUPER-1 trial, a randomized placebo control trial evaluating the effects of 20 mg, 40 mg or 80 mg TID of sildenafil in patients with pulmonary arterial hypertension. Using the hemodynamic data from the 80 mg arm of the SUPER-1 trial with 5% two-sided significance level and 80 % power, the n for mean PA pressure is 32 patients per group, for pulmonary vascular resistance the n is 25 patients per group. Assuming that half of the patients enrolled in the trial will have moderate to severe pulmonary hypertension and meet hemodynamic criteria the study will be adequately powered to ascertain the hemodynamic effects of 80 mg sildenafil.

In order to account for a potential 20% dropout rate during the trial we will enroll 180 patients in the study. Assuming a 30 % incidence of pulmonary hypertension in adults with sickle cell disease approximately 1000 patients will have to be screened for eligibility to ensure a sufficient number of patients with TR jet velocity $\geq$ 2.9 m/sec. An equal number of subjects will be enrolled in each ***TR jet velocity stratum and treatment arm (2.5-2.8 m/s and ≥2.9 m/s)***

9. Human Subject Protection

9.1 Rationale for Subject Selection

Subjects of both genders will be considered for inclusion in this study. Because sickle cell anemia is primarily a disease affecting African Americans, most if not all of the patients will be African American. Cognitively impaired and institutionalized persons will

not participate in this study. Subjects will be recruited through advertisement at contract-supported clinical sites. Criteria for exclusion or discontinuation from the study are based on the presence of other disease processes that may interfere with the interpretation of our results or situations that may be harmful to the healthy subjects.

9.2 Participation of Children

Children younger than 14 will not be considered for inclusion in this study because of uncertainty about the prevalence and associated mortality of pulmonary hypertension in this age group.

9.3 Evaluation of Benefits and Risks/Discomforts

9.3.1 Risks/Discomforts of Procedures

Arterial and venous angiocatheters. With intra-arterial puncture there is a small potential for local hematoma (less than 5%). A very remote risk for thrombosis and laceration of arteries and veins has been reported in the literature; however, in the NHLBI experience (approximately 1000 arterial punctures with infusion studies in more than 10 years), these complications have never occurred. In our experience in protocols #98-CC-0129 and # 00-H-0031 we have performed arterial catheterizations in more than 50 individuals during NO breathing without complication and in more than 20 studies involving individuals with sickle cell anemia.

Central venous catheter (CVC) introducer. To minimize discomfort and complications all catheters will be placed under sonographic guidance by the most experienced operators. Complications of internal jugular venous catheter placement include pneumothorax (< 0.5%), catheter tip malposition requiring fluoroscopy to reposition (<5%), arterial puncture (<1%), and regional hematoma. Very rare complications include brachial plexus injury, mediastinal hematoma, significant bleeding, and catheter malposition outside of the vasculature system (46). The risk of infection after 24-48 hours of catheter placement is minimal.

Pulmonary Artery Catheter. Of 187 patients undergoing cardiac catheterization in the NHLBI/NIH national prospective study, there were only four adverse effects of the catheterization (arterial puncture, over sedation, and one pneumothorax)(8). Rare complications include nonsustained and sustained atrial and ventricular arrhythmia, right

bundle branch block, and catheter malposition. Many of these complications could be very serious and theoretically lead to death if the treatments of these complications are not effective. We have never had a death related to a pulmonary artery placement in the 10D ICU over the last 10 years with greater than 100 PA catheter placements per year. Very rare complications include pulmonary artery laceration during catheter balloon insufflation, which could lead to death (this has never occurred at our facility and has only been reported in the literature as case reports). We have performed greater than 40 right heart catheterizations in patients with sickle cell disease with only one complication. One patient developed a delayed thrombosis and phlebitis of her right internal jugular vein one week after PA catheter placement in that vein.

Fluoroscopy. According to dosimetry estimates calculated by Dr. James Vucich of the Clinical Center Nuclear Medicine Department, this exposure to x-ray will result in 0.315 rem to skin, 0.0312 rem to the left lung, 0.0036 rem to the right lung, 0.0102 rem to the breast, 0.0006 rem to the right kidney, 0.0024 rem to the left kidney, and 0.0366 rem to the heart for both studies.

9.3.2 Risks/Discomforts of Medications

Sildenafil:

Systolic Blood Pressure, Healthy Volunteers.

Effects of sildenafil on Cardiac Parameters: Single oral doses of sildenafil up to 100 mg produced no clinically relevant changes in the electrocardiograms of normal male volunteers.

Studies have produced relevant data on the effects of sildenafil on cardiac output. In one small, open-label, uncontrolled, pilot study, eight patients with stable ischemic heart disease underwent right heart catheterization. A total dose of 40 mg sildenafil was administered by four intravenous infusions.

The results from this pilot study demonstrated that the mean resting systolic and diastolic blood pressures decreased by 7% and 10% compared to baseline in these patients. Mean resting values for right atrial pressure, pulmonary artery pressure, pulmonary capillary wedge pressure and cardiac output decreased by 28%, 28%, 20% and 7%, respectively. Even though this total dosage produced plasma sildenafil concentrations, which were approximately two to five times higher than the mean maximum plasma concentrations following a single oral dose of 100 mg in healthy male volunteers, the hemodynamic response to exercise was preserved in these patients.

Effects of sildenafil on Vision: At single oral doses of 100 mg and 200 mg, transient dose-related impairment of color discrimination (blue/green) was detected using the Farnsworth-Munsell 100-hue test, with peak effects near the time of peak plasma levels. This finding is consistent with the inhibition of PDE6, which is involved in phototransduction in the retina. An evaluation of visual function at doses up to twice the maximum recommended dose revealed no effects of sildenafil on visual acuity, intraocular pressure, or pupillometry.

Adverse Reactions

Pre-marketing Experience:

Sildenafil was administered to over 3700 patients (aged 19-87 years) during clinical trials worldwide. Over 550 patients were treated for longer than one year.

In placebo-controlled clinical studies, the discontinuation rate due to adverse events for sildenafil (2.5%) was not significantly different from placebo (2.3%). The adverse events were generally transient and mild to moderate in nature.

In trials of all designs, adverse events reported by patients receiving sildenafil were generally similar. In fixed-dose studies, the incidence of some adverse events increased with dose. The nature of the adverse events in flexible-dose studies, which more closely reflect the recommended dosage regimen, was similar to that for fixed-dose studies.

When sildenafil was taken as recommended (on an as-needed basis) in flexible-dose, placebo-controlled clinical trials, the following adverse events were reported:

TABLE 2.

Adverse Events Reported By 2% Of Patients Treated With sildenafil And More Frequent On Drug Than Placebo In PRN Flexible-Dose Phase II/III Studies

Percentage of Patients Reporting Event	
SILDENAFIL	**PLACEBO**
N=734	**N=725**
Headache	
16%	4%
Flushing	
10%	1%
Dyspepsia	
7%	2%
Nasal Congestion	
4%	2%
Urinary Tract Infection	
3%	2%
Abnormal Vision†	
3%	0%
Diarrhea	
3%	1%
Dizziness	
2%	1%
Rash	
2%	1%

†Abnormal Vision: Mild and transient, predominantly color tinge to vision, but also increased sensitivity to light or blurred vision. In these studies, only one patient discontinued due to abnormal vision. Other adverse reactions occurred at a rate of >2%, but equally common on placebo: respiratory tract infection, back pain, flu-like syndrome, and arthralgia. In fixed-dose studies, dyspepsia (17%) and abnormal vision (11%) were more common at 100 mg than at lower doses. At doses above the recommended dose range, adverse events were similar to those detailed above but generally were reported more frequently.

Post-Marketing Experience:

Cardiovascular

Serious cardiovascular events, including myocardial infarction, sudden cardiac death, ventricular arrhythmia, cerebrovascular hemorrhage, transient ischemic attack and hypertension, have been reported post-marketing in temporal association with the use of sildenafil. Most, but not all, of these patients had preexisting cardiovascular risk factors. Many of these events were reported to occur during or shortly after sexual activity, and a few were reported to occur shortly after the use of sildenafil without sexual activity. Others were reported to have occurred hours to days after the use of sildenafil and sexual activity. It is not possible to determine whether these events are related directly to sildenafil, to sexual activity, to the patient's underlying cardiovascular disease, to a combination of these factors, or to other factors (see WARNINGS for further important cardiovascular information).

Other events

Other events reported post-marketing to have been observed in temporal association with sildenafil and not listed in the pre-marketing adverse reactions section above include:

Nervous: seizure and anxiety.

Urogenital: prolonged erection, priapism and hematuria.

Ocular: diplopia, temporary vision loss/decreased vision, ocular redness or bloodshot appearance, ocular burning, ocular swelling/pressure, increased intraocular pressure, retinal vascular disease or bleeding, vitreous detachment/traction and paramacular edema.

A number of studies evaluating both acute dosing (12.5-100 mg)(30, 31, 35, 37, 47) and chronic dosing (25-100 mg TID) (34, 36, 48-50) have been performed. These studies report no serious adverse events with only mild headache, dyspepsia, and flushing reported (see Table 3).

TABLE 3: Sildenafil Trials in Men and Women with Pulmonary Hypertension with Published Adverse Events

Reference	Number of Patients	Dose	Duration	Adverse Event
Zimmerman (39)	1	50 mg TID 50 mg QID	30 weeks	Transient headache Mild dyspepsia and flushing
Jackson (34)	2	50 mg TID	6 months	None
Lepore (35)	9	50 mg X1	Single dose	None (MAP stable)
Littera (36)	1 (patient with β-thalassemia intermedia	50 mg BID	15 months	Nasal congestion
Michelakis (37)	13 (9 women)	75 mg X1	Single dose	1 patient with headache (no change in MAP)
Watanabe (51)	2	25 – 50 mg PO BID	3 months	None
Singh (38)	2	25 mg TID – 100 mg QID	5 months	None
Abrams (52)	1 (4 year old girl)	2mg/kg QID	3 months	None
Ghofrani (30)	8	50 mg	Single dose	None
Michelakis(40)	5	50 mg TID	3 months	None
Ghofrani(41)	14	25 mg TID- 50 mg TID	9-12 months	None
Ghofrani(42)	12	50 mg TID	6 months	None
SUPER-1	207 on active drug	20 mg, 40 mg, 80 mg TID	12 week	Headache Dyspepsia Flushing Back Pain

Sildenafil and Sickle Cell Disease:

Overall we have treated 22 patients with sickle cell disease and pulmonary hypertension with sildenafil. The drug is well tolerated and only 2 patients required drug discontinuation due to headaches. We have also observed the presence of eyelid edema in three sickle cell patients at either sildenafil initiation

or dose escalation. This phenomenon was not reported in the literature, is transient in nature even with continuation of the drug and was not associated with any impairment in visual function.

Sildenafil in Men with Sickle Cell Disease

Up to 45 % of patients with sickle cell disease (HbSS) will develop one episode of priapism, and patients with the disease are advised to use sildenafil with caution. There have been no cases of priapism reported in clinical trials, and no case reports of sildenafil-induced priapism in sickle cell disease. However, there has been one case of an individual with sickle cell trait (HbAS) presenting with priapism after a 50 mg dose of sildenafil. In contrast to that report, Bialecki and Bridges (53) describe resolution of recalcitrant priapism with acute administration of sildenafil in three patients with sickle cell disease. Interestingly, in the two patients who were offered outpatient therapy, the use of sildenafil at the onset of priapism resulted in resolution of the episode. At the intramural NIH we have treated with sildenafil eleven males with sickle cell disease and pulmonary hypertension. One developed an episode of mild priapism that spontaneously resolved in two hours without any clinical sequelae.

9.3.3 Benefits

Sildenafil Therapy: The study will be a safety and efficacy trial and, therefore, the treatment may prove beneficial, harmful or to have no effect. We believe that the information obtained from this study will be important for better understanding the therapeutic efficacy of sildenafil for sickle cell patients with lung disease.

9.4 Protocol Consent Processes and Documents

Each subject will receive an oral and written explanation of the purposes, procedures, and risks of this study in language appropriate for the individual's level of understanding. A copy of the signed consent form will be placed in the medical record. A member of the protocol team will be available to answer questions about the study to be performed.

10. Adverse Event Reporting

Each patient/subject will be assessed for any new or continuing adverse events by the clinical investigator and the study coordinator. An adverse event is defined as any untoward medical occurrence in a patient/subject of a clinical investigation that involves the administration of a pharmaceutical product. The event need not have a causal relationship with the treatment. This includes any events that are not seen at baseline or, if present at baseline, have worsened in severity. These adverse events will only be collected during study treatment time. The severity and drug relationship will be determined, and any management required will be recorded. The investigator will review the clinical laboratory test results in a timely fashion. Only those results qualifying as adverse events, as defined above, will be recorded as an adverse event.

10.1 Study Drug Relationship

Clinical site investigators will be responsible for assessing the causal relationship between any events and the study treatment. Additionally, the investigator is responsible for providing appropriate treatment for the event and for adequately following the event until resolution. The clinical investigator should determine the study drug relationship using the following definitions:

Not Related
The event is clearly related to other factors such as the patient's/subject's clinical state, therapeutic interventions, or concomitant drugs administered to the patient/subject.

Remote
The event was most likely produced by other factors such as the patient's/subject's clinical state, therapeutic interventions or concomitant drugs administered to the patient/subject, and does not follow a known response pattern to the study drug.

Possible
The event follows a reasonable temporal sequence from the time of drug administration and/or follows a known response pattern to the study drug, but could have been produced by other factors such as the patient's/subject's clinical state, therapeutic interventions or concomitant drugs administered to the patient/subject.

Probable
The event follows a reasonable temporal sequence from the time of drug administration and follows a known response pattern to the study drug and cannot be reasonably

explained by other factors such as the patient's/subject's clinical state, therapeutic interventions or concomitant drugs administered to the patient/subject.

Highly Probable

The event follows a reasonable temporal sequence from the time of drug administration and follows a known response pattern to the study drug and cannot be reasonably explained by other factors such as the patient's/subject's clinical state, therapeutic interventions or concomitant drugs administered to the patient/subject and either occurs immediately following study drug administration, or improves on stopping the drug, or reappears on repeat exposure, or there is a positive reaction at the application site.

Temporal sequence is defined as an association between the suspect drug and the observed reaction or event in which the suspect drug was present prior to the reaction or event as defined by history or blood level of drug.

Study drug(s) includes the drug(s) under evaluation, the reference drug(s), placebo, or any other drug(s) required by the protocol.

Severity of an adverse event will be defined from the qualitative assessment of the degree of intensity of the event as determined by the investigator or as reported to him/her by the patient/subject. The assessment of severity is made irrespective of drug relationship or seriousness of the event and should be evaluated according to the following scales:

1 = **Mild** - awareness of the symptom but easily tolerated
2 = **Moderate** - discomfort enough to interfere with normal activities
3 = **Severe** - Incapacitating with the inability to perform normal activities

10.2 Guidelines Serious Adverse Events Reporting

A serious adverse event is defined as any event that at any dose: results in death, is life-threatening, results in persistent or significant disability / incapacity, requires or prolongs inpatient hospitalization, or is a congenital anomaly. Important medical events that without medical or surgical intervention would also have resulted in one of the outcomes listed above are also considered a serious adverse event.

The patient/subject must be monitored carefully until the condition disappears, reaches a clinically stable endpoint and/or the etiology is identified. The initial telephone contact will

be followed by detailed descriptions of the event and supported as needed with written copies of hospital case reports, autopsy reports, and other documents when applicable.

All patient/subject deaths will be reported independent of the temporal relationship to the patient's/subject's study participation and treatment (i.e. test drug, placebo).

All serious and unexpected adverse events must be reported to the IRB in writing. All serious adverse events will also be distributed to the Data and Safety Monitoring Board (DSMB) and other investigative sites within the same timeframe required for IRB reporting of SAEs.

10.3 Adverse Events

The following expected outcomes will be listed in the protocol and the consent approved by IRB and not be reported to IRB.

Cardiology

- Vasovagal symptoms during placement of intravascular or arterial catheters or during blood draw.
- Cardiovascular symptoms occurring more than 24 hours after administration of pharmacologic agents (e.g. prostacyclin, nitric oxide, oxygen) during cardiac catheterization studies.

Pulmonary Artery Catheterization

- Transient arrhythmia
- Chest or extremity discomfort
- Vasovagal reaction
- Non-sustained hypotension
- Hematoma
- Arterial puncture

6 Minute Walk

- Shortness of breath
- Dizziness
- Headache

- Transient arrhythmia
- Accidental injury sustained from falling not requiring medical evaluation
- Chest or extremity discomfort
- Vasovagal reaction
- Non-sustained hypotension

Pulmonary Function Testing

- Chest and/or abdominal discomfort
- Vasovagal reaction
- Non-sustained hypotension
- Headache

Hematology (Sickle Cell Anemia)

- Anemia and its complications; simple transfusion for anemia
- Transfusion reactions
- Treatable infections from bacteria, viruses, protozoa and fungi.
- Mild vaso-occlusive crisis requiring oral narcotic analgesia

Sildenafil

- Transient minor headache
- Nasal congestion
- Dyspepsia
- Transient visual abnormalities including eyelid edema
- Asymptomatic hypotension

The following expected outcomes would not be reported to IRB at each occurrence. The PI will incorporate these events into the protocol and consent as appropriate. They will be responsible for reporting them in summary form bi-yearly at the DSMB, at the time of continuing review and at termination of the protocol.

Pulmonary Artery Catheterization

- Conduction abnormalities or atrial/ventricular arrhythmias occurring cardiac catheterization study not requiring pacing or cardioversion/defibrillation.
- Hematoma with pseudoaneurysm following the catheterization.
- Pericardial effusion following diagnostic/research cardiac catheterization study not requiring treatment.
- Pneumothorax following diagnostic/research cardiac catheterization (left ventricular puncture) not requiring treatment.

6 Minute Walk

- Atrial/ventricular arrhythmias occurring during study not requiring pacing or cardioversion/defibrillation.
- Accidental injury sustained from falling that requires medical evaluation
- Chest or extremity discomfort requiring treatment
- Sustained hypotension requiring treatment

Hematology (Sickle Cell Anemia)

- Acute chest syndrome/pneumonia requiring simple or exchange transfusion, admission and antibiotic therapy (not mechanical ventilation)
- Treatable infections from bacteria, viruses, protozoa and fungi requiring hospital admission
- Vaso-occlusive crisis requiring hospital admission
- Avascular necrosis of the femoral head
- Bleeding requiring transfusion
- Sustained anemia, thrombocytopenia, or neutropenia
- New leg ulcers
- All hospitalizations for medical indications

Pulmonary Function Testing

- Sustained bronchospasm or chest tightness

Sildenafil

- Hypotension requiring admission or fluid resuscitation
- Visual changes requiring discontinuation of therapy or ophthalmologic evaluation

The following serious adverse events will be listed in the protocol and consent and reported to IRB within 7 days of a death or 15 days of any other serious adverse events as outlined in the Interim Guidelines for Adverse Event Reporting.

Pulmonary Artery Catheterization

- Conduction abnormalities or atrial/ventricular arrhythmias occurring during cardiac catheterization requiring pacing or cardioversion/defibrillation.
- Injury to coronary artery, myocardium, or great vessel during diagnostic or research cardiac catheterization that requires further treatment; interventionally, surgically or pharmacologically.
- Pericardial effusion following diagnostic/research cardiac catheterization study requiring more intensive monitoring, or treatment such as a pericardial tap.
- Pneumothorax following diagnostic/research cardiac catheterization (left ventricular puncture) requiring more intensive monitoring or insertion of a chest tube.
- Apnea requiring airway management during conscious sedation for diagnostic cardiac catheterization.
- Myocardial infarction/neurological event during or following (within 24 hours) diagnostic/research cardiac catheterization.

Hematology (Sickle Cell Anemia)

- Acute chest syndrome/pneumonia requiring mechanical ventilation
- Priapism requiring medical or surgical intervention
- Infections from bacteria, viruses, protozoa and fungi requiring vasopressor support
- Avascular necrosis of the femoral head requiring surgical intervention
- Major bleeding complication including intracerebral hemorrhage, stroke or GI bleed
- Sustained anemia, thrombocytopenia, or neutropenia resulting in infectious complications
- New leg ulcers requiring surgical intervention
- Greater than two admissions for vaso-occlusive crisis per week for two sequential weeks
- Retinal detachment or vitreous bleeding
- Pulmonary embolism

Pulmonary Function Testing

- Sustained bronchospasm or chest tightness resulting in mechanical ventilation

Sildenafil

- Hypotension that requires vasopressor support
- Priapism requiring exchange transfusion or surgical intervention

11. Data and Safety Monitoring.

Because secondary pulmonary hypertension in patients with sickle cell anemia is a severe disease with high morbidity and mortality rates, it is expected that patients on therapy will develop vaso-occlusive crisis, acute chest syndrome, and other complications consistent with the natural history of the disease, including death. Two year mortality for patients with sickle cell disease and secondary pulmonary hypertension is assumed to be 20-40%, based on retrospective and our prospective studies performed at tertiary care centers in various parts of the U.S (1, 10, 11). Although the adverse event profile of sildenafil has been well characterized, all possible risks cannot be predicted with certainty. To ensure the well being of patients enrolled in the trial, a DSMB will be convened by the National Heart, Lung, and Blood Institute to review specific safety parameters in an ongoing fashion. Specifically, the DSMB will review the protocol and consent form template before the study starts, and will review all adverse events and all discontinuations from therapy. Withdrawal criteria have been established to ensure patient safety during treatment (see section above on **Monitoring of Subjects and Criteria for Discontinuation of Subjects).** The DSMB will have access to the randomization codes, and may choose to interpret adverse events in full knowledge of the treatment. The committee may recommend to the Steering Committee at any time that the study be modified or terminated for safety concerns based on pre-specified criteria. The committee will review data for safety after targeted enrollment has been completed for 25, 50, 100, 150 and 180 subjects and/or with successive patient enrollment, and will have full access to data at any point during the trial.

Adverse events will be reported to the DSMB and the IRB as outlined in section 10 above and provided every 6 months.

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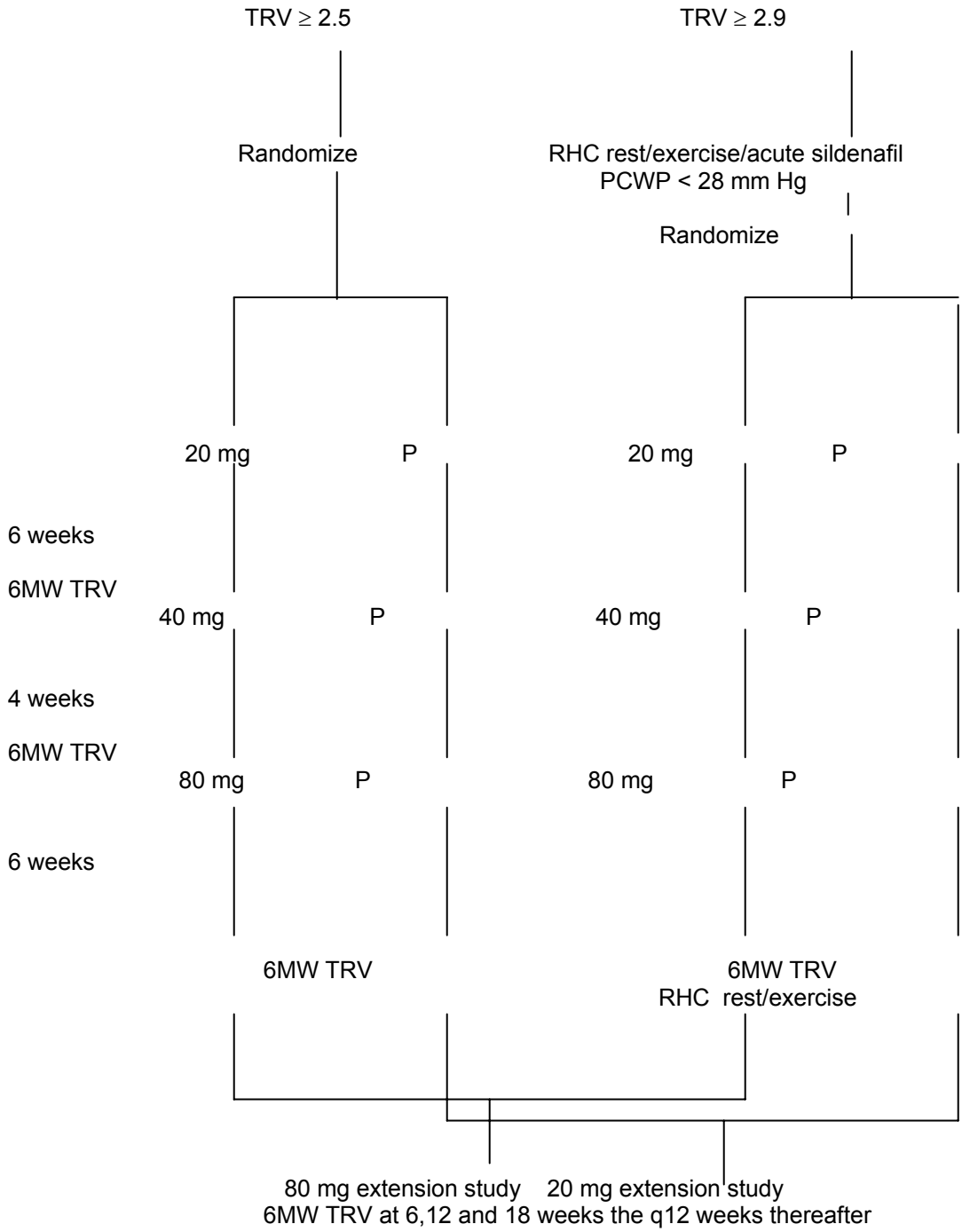
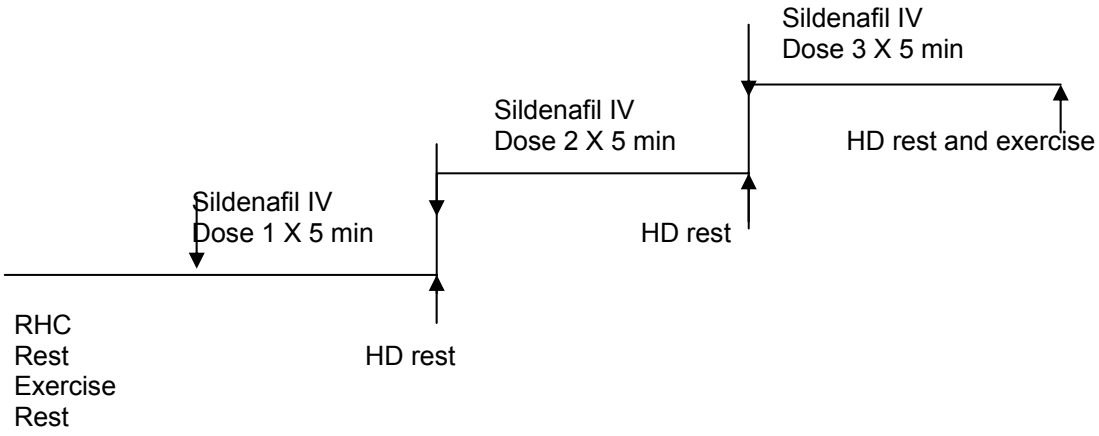
Appendix A –Trial schema



Appendix B - Acute sildenafil challenge



Appendix B – Six Minute Walk Test

The **unencouraged** 6-minute walk test will be used. The test should be administered by the same tester throughout the study. The timing for all walk tests should be within ± 1 hr of the Baseline timing for conducting the test. The test should be conducted in a corridor on a course with a predetermined length, e.g. 30 m and at least 6-10 feet in width. The area should be well ventilated with temperature controlled at 20-23 °C (68-76 °F). If the subject was using oxygen for his Baseline walk test, subsequent walk tests should be performed under the same conditions.

The tester may be at the starting end of the corridor or at the midpoint of the corridor with a stop-watch. Intermittent rest periods are allowed if the subject can no longer continue. If the subject needs to rest briefly, he may stand or sit and then begin walking again when sufficiently rested; the clock will continue to run.

Subjects will be instructed that the preceding meal should be light. They will be told to wear comfortable clothing and shoes. The person administering the test will use the following exact dialogue with the subject: “The purpose of this test is to find out how far you can walk in six minutes. You will start from this point and follow the hallway to the marker at the end, turn around, and walk back. When you arrive back at the starting point, you will go back and forth again. However, the most important thing about the test is that you cover as much ground as you possibly can during the 6 minutes. I will tell you the time, and I will let you know when 6 minutes are up. When I say STOP, please stand right where you are.”

After these instructions are given, the tester will then ask: “Do you have any questions about the test? Please explain what you are going to do.”

The tester will then start the test by saying the following: “Are you ready? Start when I say GO”. The tester will tell the subject the time at 2 and 4 minutes by saying, “You have completed 2 minutes” and “You have completed 4 minutes.” **No other instruction or encouragement should be given during the test**. Eye contact with the subject should be avoided during the test. At the end of 6 minutes, the tester will call “stop” while simultaneously stopping the watch; the distance walked will be measured. The Borg dyspnea score will then be recorded (Appendix 3) by asking,

“Please grade your level of the greatest degree of shortness of breath that you experienced at any time during the 6-minute walk test, using this scale.”

Modified NYHA Functional Classification

Class I Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope.

Class II Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.

Class III Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.

Class IV Patients with pulmonary hypertension resulting in the inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea and/or fatigue may be present at rest, and discomfort is increased by any physical activity.

Borg dyspnea score

SCALE	SEVERITY OF BREATHLESSNESS
0	Nothing At All
0.5	Very Very Slight (Just Noticeable)
1	Very Slight
2	Slight
3	Moderate
4	Somewhat Severe
5	Severe
6	
7	Very Severe
8	
9	Very Very Severe (Almost Maximum)
10	Maximum

Borg GA. Psychophysical bases of perceived exertion. *Med Sci Sports Exerc* 1982; 14:377–381.