SECTION A - SOLICITATION/CONTRACT FORM

1. Purchase Authority: 42USC201, Public Health Service Act of 1944			Page 1 of 90 Pages
2. Request For Proposal (RFP) Number: NHLBI-HR-06-07	3. Issue Date: November 8, 2005	4. Just In Time: [ ] NO [X] YES See Part IV Section L	5. Set Aside: [X] NO [ ] YES See Part IV Section L

6. TITLE: Long-term Oxygen Treatment Trial (LOTT) – Regional Clinical Centers (RCCs)

7. ISSUED BY:	8. SUBMIT OFFERS TO:
NHLBI Office of Acquisitions National Heart, Lung, and Blood Institute National Institutes of Health Rockledge 2, Room 6114 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 January 24, 2006.** Offers will be valid for 120 days unless a different period is specified by the offeror on "Proposal Summary and Data Record, NIH 2043", Attachment 10.

Proposal Intent Response Sheet, Attachment 2, is due **December 15, 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 FAR CLAUSE 52.215-1(c)(3).

11. In accordance with FAR 4.11, offeror must be registered in the Central Contractor Registry (CCR) prior to award of a contract. http://www.ccr.gov

12. FOR INFORMATION CALL:
NAME: Joanne C. Deshler
PHONE: 301-435-0340 COLLECT CALLS WILL NOT BE ACCEPTED
E-MAIL: deshlerj@nhlbi.nih.gov

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 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

The Long-term Oxygen Treatment Trial (LOTT) contractors will design and conduct a randomized controlled clinical trial to assess the efficacy of around-the-clock, supplemental oxygen therapy in patients with chronic obstructive pulmonary disease (COPD) and moderately severe hypoxemia. This trial is needed to provide a scientific basis for decisions regarding the clinical use of long-term oxygen treatment. The ultimate goal of this project is to improve clinical management of COPD, with increased length and quality of life for patients with COPD.

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

SECTION C—STATEMENT OF WORK/REPORTING REQUIREMENTS

ARTICLE C.1. STATEMENT OF WORK

a. Independently and not as an agent of the Government, the Contractor shall 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 set forth below.

b. The contractor shall deliver the items specified in ARTICLE C.2 to the destinations indicated in ARTICLE F.1.

c. Specifically the Contractor shall:

Phase I (9/30/2006 to 3/31/2007, 6 months)

1. The contractor Principal Investigator (PI) shall provide expertise in clinical management of COPD and clinical trials research. The PI shall participate fully in the activities of the Steering Committee, which shall accomplish the following:

    a. Develop a Protocol for the LOTT that includes a summary of the study; the background and significance; the study design and methods including eligibility requirements, outcome measures, and statistical analyses; a schedule of study interventions; plans for training of staff; plans for recruitment and retention; methods for randomization; plans for monitoring and reporting data quality, subject safety, and compliance; procedures for data management; enrollment targets stratified by race and

ethnicity; plans to conduct analyses, as appropriate, by sex/gender and/or racial/ethnic groups; stopping guidelines; and limitations of the study. The LOTT shall be designed to test the efficacy of essentially continuous O_2 therapy to alter survival and quality of life in patients with COPD, moderately severe hypoxemia, and other characteristics associated with increased risk of mortality.

b. Develop a model informed consent document.

c. Develop patient education materials that address proper management of COPD and adherence to study procedures.

d. Develop tools for advertising the LOTT that can easily be adapted for local use.

e. Assist the DCC in the writing of a Manual of Operations that details the methods, procedures, and operations of the LOTT.

f. Assist the DCC in submitting the Protocol and the model informed consent document for review to a Data and Safety Monitoring Board (DSMB) established by the NHLBI. Make revisions in these documents and in plans for the study as needed to address concerns identified by the NHLBI on the basis of DSMB reviews.

g. Evaluate the scientific merit and feasibility of proposals for substudies recommended by the Substudy Subcommittee.

2. The contractor shall submit the NHLBI-approved LOTT Protocol (or summary thereof) and informed consent document(s) for local IRB approval(s). Approvals shall be requested for each of the performance sites of the RCC. Informed consent documents should be identical to the study-wide model informed consent document or include only minor changes that are dictated by local conditions.

3. If selected for this service, the PI shall participate fully in the activities of the Substudy Subcommittee of the Steering Committee, which shall accomplish the following:

   a. Develop substudy protocols for presentation to the Steering Committee. These shall include a summary of the substudy; the background and significance; the substudy design and methods including eligibility requirements, outcome measures, and statistical analyses; a schedule of study interventions; plans for recruitment and retention; plans for involvement of the LOTT RCCs; methods for randomization; plans for monitoring and reporting data quality, subject safety, and compliance; procedures for data management; enrollment targets stratified by race and ethnicity; and limitations of the study.

   b. Develop a model informed consent document as needed for each substudy.

   c. Assist the DCC in submitting protocols and model informed consent documents approved by the Steering Committee to the Data and Safety Monitoring Board (DSMB) for review. Make revisions in these documents and in plans for the substudies as needed to address concerns identified by the NHLBI on the basis of DSMB reviews.

   d. Assist the DCC in the writing of Manual of Operations chapters that detail the methods, procedures, and operations of substudies approved for implementation by the NHLBI.

4. Assist the Data Coordinating Center (DCC) in the development of forms for the LOTT and approved substudies.

5. The contractor shall not begin work on Phase II activities until the NHLBI has approved the LOTT Protocol, model informed consent document, and Manual of Operations and written approval has been received from the Contracting Officer.

Phase II (4/1/2007 to 9/30/2011, 4 years 6 months)

In accordance with the LOTT Protocol and Manual of Operations the RCC contractor shall:

1. Obtain and maintain IRB approval to perform the LOTT study and approved substudies at each of the performance sites. Provide to the DCC documentation of IRB approvals, copies of all informed consent documents as approved, and marked versions of the informed consent documents that clearly identify any changes from the study-wide model informed consent document.
2. Obtain training and certification of central site staff in the LOTT protocol and procedures.
3. Conduct training on the LOTT protocol and procedures for participating staff at cooperating sites overseen by the contractor at which subjects are screened, enrolled, characterized, educated, or followed. Certify staff who are qualified to conduct LOTT activities and maintain a registry of certified staff.
4. Identify and screen potential study participants. Submit screening data to the DCC. Obtain informed consent from those apparently eligible and willing to participate. Perform additional eligibility testing as described by the Protocol and Manual of Operations.
5. Work with the DCC to make random assignments of subjects to treatment groups.
6. Conduct subject education.
7. Administer baseline questionnaires and perform clinical and laboratory tests.
8. Screen potential subjects. Recruit and enroll the target number of approximately 250 subjects (each RCC).
9. Schedule and conduct follow-up visits to assess outcomes, safety, and compliance.
10. Conduct follow-up telephone interviews to obtain outcome, compliance, and safety data.
11. Obtain follow-up clinical data and vital status from other approved sources.
12. Retain hardcopy originals of data collection forms in a secure archive.
13. Submit screening and study data to the DCC. Assist the DCC with error checking and data editing procedures.
14. Report adverse events in accordance with NHLBI/NIH policies.
15. Assist the DCC and the NHLBI with site visits for performance and data quality control and quality assurance.
16. Participate in telephone conference calls with staff of the DCC and other RCCs (e.g., clinical coordinators) to assure uniformity of study performance, identify problems with study procedures and tools, and develop potential solutions to these problems.
17. The PI shall participate fully in ongoing activities of the Steering Committee, which shall include the following:

    a. Monitor study progress and performance. Identify problems that might compromise the successful completion, scientific integrity, or clinical usefulness of the study. Devise strategies to improve procedures and overcome difficulties. Make recommendations for changes in the study and/or

protocol modifications to address any identified problems. Submit draft changes of the Protocol and the model informed consent document to the DSMB for review.

b. Evaluate the feasibility and merit of proposals for ancillary studies (funded through other sources) proposed by internal or external investigators that would require access to LOTT subjects, specimens, or data.

c. Prepare and submit for publication manuscripts describing study procedures and interim results.

18. The RCC contractor shall not begin Phase III activities until the final study intervention has been completed for all enrolled subjects at the RCC and all data have been submitted to the DCC.

Phase III (10/1/2011 to 9/29/2012, 1 year)

1. Assist the DCC in obtaining any missing data. Assist the DCC with error checking and data editing procedures.

2. The PI shall participate fully in continuing activities of the Steering Committee which shall include the following:

   a. Analyze study data.

   b. Make presentations, write manuscripts, and publish papers to make available the results of the study.

3. Engage in dissemination activities.

ARTICLE C.2. REPORTING REQUIREMENTS

In addition to those reports required by the other terms of this contract, the Contractor shall prepare and submit the following reports in the manner stated below and in accordance with ARTICLE F.1. DELIVERIES of this contract.

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."

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.

Technical Reports

1. **Adverse Event Reports**: These reports shall be submitted in accordance with NHLBI policies found at: http://www.nhlbi.nih.gov/funding/ethics.htm
2. **Semiannual Reports**: Throughout the performance period, the Contractor shall provide semiannual reports of progress and performance. These reports shall also identify problems that hamper or threaten the successful completion of study aims and include proposed measures for dealing with these problems.
3. **Final Report**: This report shall summarize the work performed and results achieved for the entire contract period of performance. The report shall be in sufficient detail to comprehensively describe the results achieved.

Other Deliverables

4. **Abstracts and Papers** shall be submitted 30 calendar days after publication.
5. **Data Collection**: Subject data shall be obtained and submitted in accordance with the LOTT Protocol and Manual of Operations.
6. **Biological Specimens**: Biological specimens obtained from subjects shall be shipped to the DCC repository in accordance with the LOTT Protocol and Manual of Operations.
7. **Informed Consent Documents**: Copies of all informed consent documents as approved by the IRB and marked versions of the informed consent documents that clearly identify any changes from the study-wide model informed consent documents shall be submitted.

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 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 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.

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 52.247-35, F.O.B. Destination, Within Consignees Premises (APRIL 1984), and in accordance with and by the dates specified below:

Item	Description	Deliver to	Delivery Schedule
1	Adverse Event Reports	Contractor's IRB Project Officer DCC	In accordance with NHLBI Policy on Reporting of Adverse Events
2	Semiannual Reports	Project Officer Contracting Officer	On or before: the 15th of May 2006, 2007, 2008, 2009, 2010, 2011 and November 2006, 2007, 2008, 2009, 2010, 2011
3	Final Report	Project Officer Contracting Officer	On or before the contract expiration date
4	Abstracts and Papers	Project Officer	30 calendar days after publication
5	Data Collection	DCC	In accordance with the LOTT Protocol and Manual of Operations
6	Biological Specimens	DCC	In accordance with the LOTT Protocol and Manual of Operations
7	Informed Consent Documents	DCC	On or before: May 1, 2007

Copies of deliverables shall be sent to the following addresses:

Addressee	Item	Quantity
Project Officer National Heart, Lung and Blood Institute Division of Lung Diseases Rockledge Two Building, Room 6701 ROCKLEDGE DR MSC BETHESDA MD 20892-7952	1-4	1
Contracting Officer National Heart, Lung and Blood Institute NHLBI Office of Acquisitions, DEA 6701 ROCKLEDGE DR MSC 7902 BETHESDA MD 20892-7902	2, 3	1

Addressee	Item	Quantity
Data Coordinating Center (To be identified)	1, 5-7	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

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

Name
To be identified

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 of any costs incurred during the performance of this contract; or (5) otherwise change any terms and conditions of this contract. The Government may unilaterally change its Project Officer designation.

ARTICLE G.3. GOVERNMENT PROPERTY

If this RFP will result in the acquisition or use of Government Property provided by the contracting agency or if the Contracting Officer authorizes in the preaward negotiation process, the acquisition of property (other than real property), this ARTICLE will include applicable provisions and incorporate the DHHS Publication (OS) 686, entitled, **Contractor's Guide for Control of Government Property**, (1990) which can be found at: http://knownet.hhs.gov/log/AgencyPolicy/HHSLogPolicy/contractorsguide.htm.

ARTICLE G.4. 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://ocm.od.nih.gov/cdmp/cps_contractor.htm.

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

Additional special contract requirements other than those listed below shall be determined during negotiations. It is expected that the following Articles will be made part of the resultant contract:

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. 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.

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 coompleted 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. HUMAN MATERIALS

The acquisition and supply of all human specimen material (including fetal material) used under this contract shall be obtained by the Contractor in full compliance with applicable State and Local laws and the provisions of the Uniform Anatomical Gift Act in the United States, and no undue inducements, monetary or otherwise, will be offered to any person to influence their donation of human material.

ARTICLE H.4. 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**	**Fiscal Year**	**Period**
	2006	10/01/2005 to 09/30/2006

[Applicable information to be included at award]

ARTICLE H.5. 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**	**Fiscal Year**	**Period**
	2006	10/01/2005 to 09/30/2006

[Applicable information to be included at award]

ARTICLE H.6. 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, Clinical, Basic and Population-based Research Studies of the National Institutes of Health (NIH), HHS/NIH/OD. The notice can be accessed at: http://oma.od.nih.gov/ms/privacy/pa-files/0200.htm.

ARTICLE H.7. 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.8. 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**	**Fiscal Year**	**Dollar Amount of Salary Limitation**
	2006	Executive Level I

[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.

(NOTE: For previous years salaries go to: http://www.opm.gov/oca/05tables/html/ex.asp *and 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.9. ENERGY STAR REQUIREMENTS

Executive Order 13123, "Greening the Government Through Efficient Energy Management" and FAR 23.203 require that when Federal Agencies acquire energy using products, they select, where life-cycle cost-effective, and available, ENERGY STAR® or other energy efficient products.

Unless the Contracting Officer determines otherwise, all energy-using products acquired under this contract must be either an ENERGY STAR® or other energy efficient product designated by the Department of Energy's Federal Energy Management Program (FEMP).

For more information about ENERGY STAR® see http://www.energystar.gov/

For more information about FEMP see http://www.eere.energy.gov/

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 Cancer Institute, National Institutes of Health, Department of Health and Human Services, under Contract No. .

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**	**Fiscal Year**	**Period**
	2006	10/01/2005 to 09/30/2006

[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**	**Fiscal Year**	**Period**
	2006	10/01/2005 to 09/30/2006

[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. SHARING RESEARCH DATA

The contractor's data sharing plan dated (to be determined at time of award) is hereby incorporated by reference. The contractor agrees to adhere to its plan and shall request prior approval of the Contracting Officer for any changes in its plan.

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 that must be shared with the public and other researchers. 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

NIH recognizes that data sharing may be complicated or limited, in some cases, by institutional policies, local IRB rules, as well as local, state and Federal laws and regulations, including the Privacy Rule (see HHS-published documentation on the Privacy Rule at http://www.hhs.gov/ocr/). The rights and privacy of people who participate in NIH-funded research must be protected at all times; thus, data intended for broader use should be free of identifiers that would permit linkages to individual research participants and variables that could lead to deductive disclosure of the identity of individual subjects.

ARTICLE H.16. 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.17. 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.18. 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 Observational Study Monitoring Boards, which may be found at: http://www.nhlbi.nih.gov/funding/ethics.htm

- Establishing Data and Safety Monitoring Boards and Observational Study Monitoring Boards
- Guidelines for Data Quality Assurance in Clinical Trials and Observational Studies
- Responsibilities of DSMBs Appointed by NHLBI
- Responsibilities of OSMBs Appointed by the NHLBI

ARTICLE H.19. NHLBI LIMITED ACCESS DATA

The National Heart, Lung, and Blood Institute (NHLBI) has supported 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 with public funds be 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 study. Limited access data refers to study data, with certain deletions and recoding, that are released to requesting institutions and investigators for specific purposes and with certain restrictions and conditions. Limited access data will be made available to the public in accordance with the NHLBI Policy for Distribution of Data http://www.nhlbi.nih.gov/resources/deca/policy_new.htm as revised on June 27, 2005. All changes to the policy are hereby incorporated by reference without further amendment to the contract.

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

ARTICLE H.20. 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.21. CONSTITUTION DAY

Each educational institutional institution that receives Federal funds for a fiscal year shall hold an educational program on the United States Constitution on September 17 of such year for the students serviced by the educational institution in accordance with Public Law 108-447.

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 Educational Institutions

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:

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.

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

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

(1) FAR 52.216-15, Predetermined Indirect Cost Rates (APRIL 1998).

(2) FAR 52.219-4, Notice of Price Evaluation Preference for HUBZone Small Business Concerns (JULY 2005).

"(c) Waiver of evaluation preference.....

[ ] Offeror elects to waive the evaluation preference."

(3) FAR 52.219-25, Small Disadvantaged Business Participation Program--Disadvantaged Status and Reporting (OCTOBER 1999).

(4) FAR 52.224-1, Privacy Act Notification (APRIL 1984).

(5) FAR 52.224-2, Privacy Act (APRIL 1984).

(6) FAR 52.227-14, Rights in Data - General (JUNE 1987), Alternate IV (JUNE 1987).

(7) FAR 52.230-5, Cost Accounting Standards - Educational Institution (APRIL 1998).

(8) FAR 52.230-6, Administration of Cost Accounting Standards (APRIL 2005).

(9) FAR 52.242-3, Penalties for Unallowable Costs (MAY 2001).

(10) FAR 52.243-2, Changes—Cost Reimbursement (AUGUST 1987), Alternate V (APRIL 1984).

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 352.270-8, Protection of Human Subjects (MARCH 2005).

Note: The Office for Human Research Protections (OHRP), Office of the Secretary (OS), Department of Health and Human Services (DHHS) is the office responsible for oversight of the Protection of Human subjects and should replace Office for Protection from Research Risks (OPRR), National Institutes of Health (NIH) wherever it appears in this clause.

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).

(2) NIH (RC)-11, Research Patient Care Costs (4/1/84).

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:

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

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

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:	Draft LOTT Protocol	See Attachment Section at the end of this RFP

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

Attachment No.	Title	Location
Attachment 4:	Technical Proposal Cost Summary	http://www.niaid.nih.gov/contract/forms.htm
Attachment 5:	Summary of Related Activities	http://www.niaid.nih.gov/contract/forms.htm
Attachment 6	Government Notice for Handling Proposals	http://www.niaid.nih.gov/contract/forms/form7.pdf
Attachment 7	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 8:	Target Enrollment Table	http://rcb.cancer.gov/rcb-internet/forms/enroll-table.pdf
Attachment 9:	Project Objectives, NIH 1688-1	http://rcb.cancer.gov/rcb-internet/forms/nih1688-1.pdf

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

Attachment No.	Title	Location
Attachment 10:	Proposal Summary and Data Record, NIH-2043	http://www.niaid.nih.gov/contract/forms.htm
Attachment 11:	Breakdown of Proposed Estimated Costs (plus Fee)	Excel Workbook
Attachment 12:	Offeror's Points of Contact	http://www.niaid.nih.gov/contract/forms.htm
Attachment 13:	Certificate of Current Cost or Pricing Data	http://rcb.cancer.gov/rcb-internet/forms/cert-current-cost.pdf
Attachment 14:	Disclosure of Lobbying Activities, OMB Form SF-LLL	http://www.niaid.nih.gov/contract/forms/sf-lll.pdf

INFORMATIONAL ATTACHMENTS: (The following Attachments and Reports are applicable to most contracts resulting from award under this RFP and will become part of any contract selected for award. These documents can be accessed by using the hyperlinks provided below.)

Title	Location
Invoice/Financing Request Instructions--Cost-Reimbursement, NIH(RC)-1	http://rcb.cancer.gov/rcb-internet/forms/rc1.pdf
Invoice/Financing Request and Contract Financial Reporting Instructions--Cost Reimbursement, NIH(RC)-4	http://rcb.cancer.gov/rcb-internet/forms/rc4.pdf
Financial Report of Individual Project/Contract, NIH 2706	http://www.niaid.nih.gov/contract/forms/nih-2706.pdf
Instructions for Completing Form NIH 2706	http://www.niaid.nih.gov/contract/forms/instructions2706.pdf
Procurement of Certain Equipment, NIH(RC)-7	http://www.niaid.nih.gov/contract/forms/NIH-RC-7.pdf
Research Patient Care Costs, NIH(RC)-11	http://www.niaid.nih.gov/contract/forms/nih-rc-11.pdf
Inclusion Enrollment Report	http://rcb.cancer.gov/rcb-internet/forms/inclusion-enrollment.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

Contact the Contracting Officer identified on the cover page of this solicitation if you are unable to access this document.

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
2. Instructions
   a. General Instructions
   b. Technical Proposal Instructions
   c. Business Proposal Instructions

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.

Subcontracting Plan. The offeror's Small Business Subcontracting Plan shall **not** be submitted with the initial business proposal. Only those offerors included in the competitive range will be required to submit **an acceptable** subcontracting plan.

c. **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.

THIS REQUIREMENT IS NOT SET-ASIDE FOR SMALL BUSINESS. However, the Federal Acquisition Regulation (FAR) requires in EVERY solicitation, (except for foreign acquisitions) the inclusion of the North American Industry Classification (NAICS) Code and corresponding size standard which best describes the nature of the requirement in the solicitation.

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

It is anticipated that twenty awards will be made from this solicitation and that the awards 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 six years, and that incremental funding will be used see Section L.2.c. Business Proposal Instructions.

e. **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.

f. **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.

g. **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.

h. **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.

i. **PREPARATION COSTS**

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

j. **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
NHLBI Office of Acquisitions
National Heart, Lung, and Blood Institute, NIH
6701 Rockledge Drive, MSC 7902
Bethesda, Maryland 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.

k. **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.

2. INSTRUCTIONS TO OFFERORS

a. General Instructions
b. Technical Proposal Instructions
c. Business Proposal Instructions

a. GENERAL INSTRUCTIONS

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 Business Proposal Instructions). 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.

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.

(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, NIH 2043.)

(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.

(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) **Standards for Privacy of Individually Identifiable Health Information**

The Department of Health and Human Services (DHHS) issued final modifications to the "Standards for Privacy of Individually Identifiable Health Information," the "Privacy Rule," on August 14, 2002. The Privacy Rule is a federal regulation under the Health Insurance Portability and Accountability Act (HIPAA) of 1996 that governs the protection of individually identifiable health information and is administered and enforced by the DHHS Office for Civil Rights (OCR). Those who must comply with the Privacy Rule (classified under the Rule as "covered entities" must do so by April 14, 2003 (with the exception of small health plans which have an extra year to comply.

Decisions about the applicability and implementation of the Privacy Rule reside with the contractor and his/her institution. The OCR Web site (http://www.hhs.gov/ocr/) provides information of the Privacy Rule, including a complete Regulation Text and a set of decision tools on "Am I a covered entity?" Information on the impact of the HIPAA Privacy Rule on NIH processes involving the review, award, and administration of grants, cooperative agreements and contracts can be found at: http://grants1.nih.gov/grants/guide/notice-files/NOT-OD-03-025.html.

(10) **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.

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 no 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.

(11) **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.

(12) **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 will be given an opportunity to submit a written Final Proposal Revision (FPR).

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.

(13) **Small Business Subcontracting Plan**

This document is INCLUDED in the "Just In Time" procedures. Specific instructions for the submission of this document are outlined in SECTION L.1.

If the proposed contract exceeds a total estimated cost of $500,000 for the entire period of performance, the apparent successful offeror shall be required to submit an acceptable subcontracting plan in accordance with the terms of the clause entitled "Small Business Subcontracting Plan," FAR Clause No. 52.219-9, incorporated herein by reference in the Solicitation. A copy of the plan is found at: http://www.niaid.nih.gov/contracts/forms-htm.

a) THIS PROVISION DOES NOT APPLY TO SMALL BUSINESS CONCERNS.

b) The term "subcontract" means any agreement (other than one involving an employer-employee relationship) entered into by a Federal Government prime contractor or subcontractor calling for supplies or services required for the performance of the original contract or subcontract. This includes, but is not limited to, agreements/purchase orders for supplies and services such as equipment purchase, copying services, and travel services.

c) The offeror understands that:

(1) No contract will be awarded unless and until an acceptable plan is negotiated with the Contracting Officer which plan will be incorporated into the contract, as a material part thereof.

(2) An acceptable plan must, in the determination of the Contracting Officer, provide the maximum practicable opportunity for Small Businesses, Small Disadvantaged Businesses, Women-Owned Small businesses, HubZone Small Businesses, Veteran-Owned Small Businesses, and Service Disabled Veteran-Owned Small Businesses to participate in the performance of the contract.

(3) If a subcontracting plan acceptable to the Contracting Officer is not negotiated within the time limits prescribed by the contracting activity and such failure arises out of causes within the control and with the fault or negligence of the offeror, the offeror shall be ineligible for an award. The Contracting Officer shall notify the Contractor in writing of the reasons for determining a subcontracting plan unacceptable early enough in the negotiation process to allow the Contractor to modify the plan within the time limits prescribed.

(4) Prior compliance of the offeror with other such subcontracting plans under previous contracts will be considered by the Contracting Officer in determining the responsibility of the offeror for award of the contract.

(5) It is the offeror's responsibility to develop a satisfactory subcontracting plan with respect to Small Business Concerns, Small Disadvantaged Business Concerns, Women-Owned Small Business Concerns, HubZone Small Business Concerns, Veteran-Owned Small Business Concerns, and Service Disabled Veteran-Owned Small Business Concerns that each such aspect of the offeror's plan will be judged independent of the other.

(6) The offeror will submit, as required by the Contracting Officer, subcontracting reports in accordance with the instructions thereon, and as further directed by the Contracting Officer. Subcontractors will also submit these reports to the Government's Contracting Officer or as otherwise directed, with a copy to the prime Contractor's designated small and disadvantaged business liaison.

d) Each plan must contain the following:

(1) Goals, expressed in terms of percentages of total planned subcontracting dollars, for the use of Small, Small Disadvantaged, Women-Owned, HUBZone, Veteran-Owned, and Service Disabled Veteran-Owned Small Business Concerns as subcontractors.

(2) A statement of total dollars planned to be subcontracted. A statement of total dollars to be subcontracted to each of the following type of small business concerns: Small, Small Disadvantaged, Women-Owned, HUBZone, Veteran-Owned, and Service Disabled Veteran-Owned Small Businesses.

(3) A description of the principal types of supplies and services to be subcontracted with an identification of which supplies and services are expected to be subcontracted to Small, Small Disadvantaged, Women-Owned, HUBZone, Veteran-Owned, and/or Service Disabled Veteran-Owned Small Business Concerns.

(4) A description of the method used to develop the subcontracting goals.

(5) A description of the method used to identify potential sources for solicitation purposes.

(6) A statement as to whether or not indirect costs were included in establishing subcontracting goals. If they were, a description of the method used to determine the proportionate share of indirect costs to be incurred with Small, Small Disadvantaged, Women-Owned, HUBZone, Veteran-Owned, and Service Disabled Veteran-Owned Small Businesses.

(7) The name of the individual employed by the offeror who will administer the offeror's subcontracting program and a description of his/her duties.

(8) A description of the efforts the offeror will make to assure that Small, Small Disadvantaged, Women-Owned, HUBZone, Veteran-Owned, and Service Disabled Veteran-Owned Small Businesses have an equitable chance to compete for subcontracts.

(9) Assurances that the offeror will include in all subcontracts the contract clause "Utilization of Small Business Concerns." Assure that all subcontractors, other than small businesses, in excess of $500,000 adopt a plan similar to the plan agreed upon by the offeror.

(10) Assurances that the offeror (and any required subcontractors) will cooperate in studies or surveys as required and submit required reports (SF 294 and SF 295) to the Government.

(11) List the types of records the offeror will maintain to demonstrate procedures that have been adopted to comply with the requirement and goals in the plan, including establishing source lists. Also, the offeror shall describe its efforts to locate Small, Small Disadvantaged, Women-Owned, HUBZone, Veteran-Owned, and Service Disabled Veteran-Owned Small Businesses and award subcontracts to them.

For additional information about each of the above elements required to be contained the subcontracting plan, see FAR Clause 52.219-9, Small Business Subcontracting Plan, and the Sample Subcontracting Plan which is provided as an attachment to this RFP in SECTION J.

HHS expects each procuring activity to establish minimum subcontracting goals for all procurements. The anticipated minimum goals for this RFP are as follows:

[specify %] for Small Business; % for Small Disadvantaged Business; % for Women-Owned Small Business; ___% for HUBZone Small Business; and ___% for Veteran-Owned Small Business and Service-Disabled Veteran-Owned Small Business.

(14) **HUBZone Small Business Concerns**

Small Business offerors located in underutilized business zones, called "HUBZones," will be evaluated in accordance with FAR Clause 52.219-4, NOTICE OF PRICE EVALUATION PREFERENCE FOR HUBZONE SMALL BUSINESS CONCERNS, which is incorporated by reference in ARTICLE I.3. of this solicitation. Qualified HUBZone firms are identified in the Small Business Administration website at: http://www.sba.gov/hubzone.

(15) **Extent of Small Disadvantaged Business Participation**

In accordance with FAR Subpart 15.304(c)(4), the extent of participation of Small Disadvantaged Business (SDB) concerns in performance of the contract in the authorized NAICS Subsectors shall be evaluated in unrestricted competitive acquisitions expected to exceed $500,000 ($1,000,000 for construction) subject to certain limitations (see FAR 19.1202-1 and 19.1202-2(b). The dollar amounts cited above include any option years/option quantities that may be included in this solicitation. The definition of a "small disadvantaged business" is cited in FAR 19.001.

The factor entitled “Extent of Small Disadvantaged Business Participation” as set forth under the Evaluation Criteria in Section M shall be used for evaluation purposes.

The Department of Commerce determines, on an annual basis, by Subsectors, as contained in the North American Industry Classification System (NAICS) code, and region, if any, the authorized SDB procurement mechanisms and applicable factors (percentages). The NAICS codes can be found at: http://www.sba.gov/size

The Department of Commerce website for the annual determination for NAICS codes* is: http://www.arnet.gov/References/sdbadjustments.htm.

**Note: Public Law 103-355 which authorized the SDB Price Evaluation Adjustment (PEA) and associated percentages/factors expired on December 9, 2004, therefore, the percentages shown at this website are no longer applicable.*

Offerors shall include with their offers, SDB targets, expressed as dollars and percentages of total contract value, in each of the applicable, authorized NAICS Subsector(s). The applicable authorized NAICS Subsector(s) for this project is (are) identified elsewhere in this RFP. A total target for SDB participation by the prime contractor, that includes any joint ventures and team members, shall be provided as well as a total target for SDB participation by subcontractors. In addition, offerors must provide information that describes their plans for meeting the targets set forth in their proposal. **This information shall be provided in one clearly marked section of the Business Proposal, which shall describe the extent of participation of SDB concerns in the performance of the contract.**

If the evaluation factor in this solicitation includes an SDB evaluation factor or subfactor that considers the extent to which SDB concerns are specifically identified, the SDB concerns considered in the evaluation shall be listed in any resultant contract. Offerors should note that addressing the extent of small disadvantaged business participation **is not in any way intended to be a substitute** for submission of the subcontracting plan. An example of the type of information that might be given (in addition to the narrative describing the plan for meeting the targets) follows:

EXAMPLE

Targets for SDB Participation - NAICS Subsector 223

	SDB Percentage of Total Contract Value	**SDB Dollars**
Total Contract Value- $1,000,000	25%	$250,000
SDB Participation by Prime (Includes joint venture partners and team arrangements)*	10%	$100,000
SDB Participation by subcontractors	15%	$150,000

*Note: FAR Subpart 9.6 defines "Contractor team arrangements" to include two or more companies forming a partnership or joint venture to act as a potential prime contractor, or a potential prime contractor who agrees with one or more companies to have them act as its subcontractors on a specific contract or acquisition program. For purposes of evaluation of the SDB participation factor, FAR 19.1202-4 requires that SDB joint ventures and teaming arrangements at the prime level be presented separately from SDB participation by subcontractors.

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

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.

h) Institutional Management of Conflicting Interests

1. 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.

2. 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.

(17) **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.

(18) **Electronic and Information Technology Accessibility**

Section 508 of the Rehabilitation Act of 1973 (29 U.S.C. 794d), as amended by P.L.105-220 under Title IV (Rehabilitation Act Amendments of 1998) and the Architectural and Transportation

Barriers Compliance Board Electronic and Information Technology (EIT) Accessibility Standards (36 CFR part 1194) require that all EIT acquired must ensure that:

a. Federal employees with disabilities have access to and use of information and data that is comparable to the access and use by Federal employees who are not individuals with disabilities; and

b. Members of the public with disabilities seeking information or services from an agency have access to and use of information and data that is comparable to the access to and use of information and data by members of the public who are not individuals with disabilities.

This requirement includes the development, maintenance, and/or use of EIT products/services, therefore, any proposal submitted in response to this solicitation must demonstrate compliance with the established EIT Accessibility Standards.

Further information about Section 508 is available via the Internet at http://www.section508.gov .

(19) **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):

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

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

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

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

b. TECHNICAL PROPOSAL INSTRUCTIONS

A detailed work plan must be submitted indicating how each aspect of the statement of work is to be accomplished. 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 Discussion**

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.

Note: *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) **Page and Formatting Limitations**

The Technical Plan (objectives, approach, methods and procedures, and substudy proposal) of the technical proposal shall not exceed 30 single-sided pages or 15 double-sided pages. This page limitation does not include the cover sheet, abstract, table of contents, personnel, facilities, equipment and resources, other considerations, schedule, other support, cost information, and literature cited. The substudy proposal section of the Technical Plan (included within the 30 page limit) shall not exceed 8 single-sided or 4 double-sided pages. Appendices shall not exceed a total of 50 single-sided pages or 25 double-sided pages. Pages in excess of the limitation 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. 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 no less than ½ inch around, exclusive of headers and footers.

(3) **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).

(4) **Additional Technical Proposal Information**

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.

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.

(5) **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 paragraphs shall be addressed in a SEPARATE SECTION of the Technical Proposal entitled, "HUMAN SUBJECTS."

(6) **Human Subjects**

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

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

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.

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.

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.

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.

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

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)

b. 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.

c. 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.

d. 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.

e. 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.

f. 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.*

g. 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 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.

h. 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.)

i. 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.

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.

j. 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

k. 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.

l. 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.

m. 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://ohrp.osophs.dhhs.gov/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

n. 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)

o. Human Embryonic Germ Cell (HEGC) Research

a. 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.

b. 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 or option period(s). During Option Period(s)/Phase(s) 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.

p. 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:

a. 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;

b. 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;

c. The stem cells must have been derived from an embryo that was created for reproductive purposes;

d. The embryo was no longer needed for these purposes;

e. Informed consent must have been obtained for the donation of the embryo;

f. 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.

(7) **General Description/Background Information**

General Description

The LOTT will consist of one DCC and approximately 20 regional clinical centers (RCCs). The DCC will be awarded under RFP NHLBI-HR-06-08. The LOTT will test the efficacy of supplemental oxygen treatment in subjects with COPD, moderately severe hypoxemia, and other risk factors for premature death such as severe dyspnea, exercise limitation, low body mass, or frequent exacerbations. The trial will be designed to detect a difference in mortality between two groups randomized to receive long-term oxygen treatment or usual care with periodic monitoring of hypoxemic status. The trial will also test for possible differences in quality of life. Contractors will design and carry out the clinical trial, monitor and report adverse events, analyze the study data, submit results of the study and substudies for publication in peer-reviewed scientific journals, and engage in other dissemination activities. The RCCs will organize and manage a network of cooperating sites (such as hospitals, clinics, pulmonary rehabilitation centers, and physician offices) to assist in subject enrollment, characterization, and follow up. It is expected that a total of approximately 5000 subjects will be enrolled over a 3 - 3½ year period and that subjects will be followed for an additional year after the end of the enrollment period.

Background Information

Severe COPD is often fatal, but long-term treatment with supplemental oxygen (LTO) improves survival in patients with COPD and severe resting hypoxemia. However, it is not known if LTO prolongs life in those with less-than-severe hypoxemia. Given the paucity of alternative treatments, many physicians prescribe oxygen for patients with severe COPD even when their hypoxemia is not reproducibly severe, despite the lack of a scientific basis for this practice. In fact, usage of LTO in patients with sporadic or moderate hypoxemia may represent the majority of the 1 million patients in the U.S. who receive LTO and the majority of the $2 billion in annual costs to Medicare for provision of LTO.

Uncertainty regarding indications for LTO is a problem of particular importance because of the possibility that LTO may actually do harm. Retrospective analysis of National Emphysema Treatment Trial data showed that subjects without severe hypoxemia who were prescribed oxygen died at a higher rate than those who were not -- despite similar severity of COPD in the two groups by spirometry and a measure of dyspnea. Oxygen toxicity is a plausible explanation since oxidative stress contributes to the pathogenesis of COPD, and oxygen treatment might hasten the progression of COPD. Oxygen inhalation has been shown to increase biomarkers of oxidative stress and airway inflammation in subjects with COPD. Furthermore, use of oxygen is inconvenient and limits mobility, activity, and social functioning. On the other hand, it is possible that moderately hypoxemic patients with COPD would live longer and better quality lives if treated with oxygen.

Arterial oxygen concentration was the primary criterion for inclusion of subjects in early clinical trials of oxygen, and related measures remain the primary basis for insurance coverage. This singular focus on arterial oxygen levels may not be ideal. It is likely that LTO does more than simply improve peripheral oxygenation. Oxygen may also modulate systemic inflammatory mediators, decrease pulmonary hypertension, alter gene expression, and promote remodeling of the lung. Hence, factors such as comorbid systemic vascular or heart disease, pulmonary vascular tone, lung inflammatory status, or antioxidant genotypes may strongly influence therapeutic responsiveness. In fact, overall health may be a better indicator of need for LTO than a point measure of arterial oxygen since it can reflect a broad range of pathophysiological problems related to respiratory insufficiency. Anecdotally, physician prescribing behavior is often influenced by the presence of other systemic factors that

portend a poor prognosis in COPD, such as severe dyspnea, poor exercise capability, or low body mass. It may be appropriate for an oxygen trial to consider evidence of systemic illness, in addition to arterial oxygenation, in the selection of subjects.

Based on advice provided by a Working Group on "Long-term Oxygen Treatment in COPD" convened by the NHLBI in Bethesda, Maryland on May 10-11, 2004 (see summary at http://www.nhlbi.nih.gov/meetings/workshops/oxygen-rx.htm), the NHLBI anticipates that the LOTT will be a large, randomized controlled trial with a primary outcome measure of survival and secondary outcomes that may include quality of life, physical activity, exercise capability, rate of hospitalizations, and cognitive function. It is expected that subjects will be enrolled who have COPD, moderately severe hypoxemia, and evidence of systemic disease such as severe dyspnea, exercise limitation, or low body mass. Substudies may examine baseline predictors of therapeutic responsiveness (such as clinical characteristics, physiological measures, biomarkers, or specific genotypes) or intermediate outcomes predictive of therapeutic responsiveness (such as oxygen utilization or short term improvements in transcutaneous oximetry, activity, dyspnea, or quality of life). The detailed design of the LOTT will be proposed by the contractors and approved by the NHLBI during Phase 1.

(8) **Capitation**

A capitation reimbursement system will be developed during Phase I for the participating RCCs. Capitation rates will be based on cost elements identified for performance of Protocol procedures. Reimbursement of capitated costs will only be made after the DCC has verified to the Contracting Officer that data for the particular subject meet study standards for completeness and quality.

(9) **Medical Insurance Coverage for Patient Care Costs**

The LOTT will not provide payment for patient care costs associated with participation in the trial. Patient care costs (paid by the participant or by his/her medical insurer or health care system) will include the costs of oxygen equipment and supplies as well as routine clinical laboratory testing. The Center for Medicare and Medicaid Services (CMS) will cover the costs of items and services that are otherwise generally available to Medicare beneficiaries (i.e., there exists a benefit category, it is not statutorily excluded, and there is not a national non-coverage decision). Hence, it is anticipated that the RCCs will recruit primarily from the Medicare-eligible population. Subjects or their secondary insurers will be responsible for payments of copays and deductibles associated with patient care costs. Offerors who propose to recruit a substantial number of subjects from a Medicare-ineligible population (e.g., foreign offerors) must demonstrate that economic burden will not impair subject enrollment at their site. For example, such an offeror might document an agreement by the predominant health care payor(s) at that site to cover those costs that would normally be covered in the Medicare-eligible population.

(10) **Level of Effort**

The Government considers the types of personnel and estimated levels of effort identified below to be necessary for completion of the RCC objectives. The effort required for some tasks in Phase II (e.g., administration of questionnaires) will be directly related to the number of subjects enrolled in the study at the RCC, and a capitation system will be developed for reimbursement of these costs. Hence, Government estimates of the required level of effort include both Core support and Capitation, expressed as a percentage of FTE (full-time equivalent) labor. The personnel and levels of effort listed below were formulated by NHLBI staff experienced in the conduct of multi-center trials, utilizing recent experience. These estimates are for information only and are not to be considered restrictive for proposal purposes.

Phase	Labor Category	Core (% FTE)	Capitated (% FTE)
I	Principal Investigator	30	-
	Co-Investigator	10	-
	Clinical Coordinator	50	-
	Clinical Research Assistant	-	-
II	Principal Investigator	15	-
	Co-Investigator	10	-
	Clinical Coordinator	25	64 [1]
	Clinical Research Assistant	-	122 [2]
III	Principal Investigator	15	-
	Co-Investigator	10	-
	Clinical Coordinator	25	-
	Clinical Research Assistant	-	-

[1] Represents 75% FTE for the first 3½ years and 25% FTE for the final year of Phase 2.

[2] Represents 150% FTE for the first 3½ years and 25% FTE for the final year of Phase 2. Effort listed for Clinical Research Assistant may be distributed among several individuals.

Note: Offerors shall ensure that all personnel are 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 individual is committed for more than 100% of his or her time, the Government will require action on the part of the offeror to adjust the time commitment.

(11) **Phasing**

Phase I (6 months): During this phase LOTT investigators will meet to develop the Protocol(s), model informed consent document(s), Manual of Operations, and study forms. The Steering Committee will develop procedures and tools for training of staff, randomization of subjects, data management, and quality assurance/quality control of study activities and data. Staff will assist the DCC in the development and review of study forms.

Phase II (4 years 6 months): This phase will include training of staff, subject screening and recruitment, interventions, and follow-up at the RCCs and data collection and monitoring at the DCC. Phase II will conclude when all subjects have been enrolled and their follow-up assessments completed.

Phase III (1 year): The final phase will include data analysis and reporting.

(12) **Travel**

During Phase I, the PI and one co-investigator will attend 5 meetings of the Steering Committee. These meetings will take place in Bethesda, MD and each will last 2 days.

Early in Phase II, contractor staff will attend a meeting for training in study operations. For proposal purposes, offerors may assume that 5 staff will attend a 2 day training session in Chicago, IL. During Phase II, the PI, one co-investigator, and the clinical coordinator will attend quarterly meetings of the Steering Committee in Bethesda, MD each lasting 1 day. The PI will also participate in site visits to other RCCs as needed during this phase. For the purposes of estimating costs, the offeror should assume that the PI will attend 1 site visit as a reviewer in a major U.S. city 300-1000 miles distant from the RCC during year 2.

During Phase III, the PI and one co-investigator will attend quarterly meetings of the Steering Committee in Bethesda, MD each lasting 1 day. To disseminate the results of the study, the PI and one co-investigator will also attend 1 national scientific meeting. For proposal purposes the offeror should assume that this meeting will be held in Atlanta, GA and will last 1 day.

(13) **Study Committees**

The Steering Committee will consist of a study Chairperson selected by the NHLBI, PI's from each RCC, the PI of the DCC, a representative of CMS, and the NHLBI Project Officer. This committee will work during Phase I to develop the LOTT study Protocol, Manual of Operations, and study forms. The committee will also prioritize and recommend substudies developed by the Substudy Subcommittee (see below). During Phase I the Steering Committee will meet approximately monthly and hold additional telephone conference calls. The Steering Committee will monitor study progress during Phase II and make recommendations for changes in study procedures as appropriate. During Phase III this committee or a delegated subcommittee will analyze the data and report the study findings. During Phases II and III the Steering Committee will meet twice a year and hold monthly telephone conference calls. Each contractor will have one vote on issues pertaining to the LOTT. Subcommittees of the Steering Committee will be established as needed for specific purposes (e.g., Executive and Publications Subcommittees).

The Substudy Subcommittee of the Steering Committee will consist of the study Chairperson, the PI of the DCC, 6-8 of the RCC PI's, a representative of CMS, and the NHLBI Project Officer. The Substudy Subcommittee will provide recommendations to the Steering Committee regarding selection and design of substudies.

A Data and Safety Monitoring Board (DSMB) will be established to 1) evaluate the parent study and substudy protocols and the model informed consent documents recommended by the Steering Committee and 2) monitor overall study progress and performance, data quality, and subject safety. The Board will periodically evaluate study procedures, review reports for adverse events, and perform interim assessments of study outcomes. The Board will meet once during Phase I, twice per year during Phases II and III, and conduct teleconferences as needed. This Board is advisory to the NHLBI.

(14) **Clinical Research/Human Subjects**

Research involving the collection, processing, and use of clinical data and biological specimens from humans will be proposed in response to this solicitation. The Government intends for the representation of women and members of minority groups in the LOTT study population to approximate the proportion of these groups in the U.S. population afflicted with severe COPD. Because COPD is generally a disease of older adults, no children are expected to participate in the trial. The following guidelines and policies, which can be viewed at http://www.nhlbi.nih.gov/funding/policies, may be applicable to this solicitation.

- NHLBI Guidelines for Implementation of the Policy on Inclusion of Minorities and Women in Study Populations
- Terms and Conditions for Accrual of Research Subjects in Research Supported by NHLBI
- Establishing Data and Safety Monitoring Boards and Observational Study Monitoring Boards
- Responsibilities of DSMBs Appointed by NHLBI
- Guidelines for Data Quality Assurance in Clinical Trials and Observational Studies
- Avoiding Conflicts of Interest in Multi-Center Clinical Trials—Guidelines
- NHLBI Guidance on Reporting Adverse Events to Institutional Review Boards for NIH-Supported Multi-Center Clinical Trials

- Medicare Coverage of Clinical Trials
- Human Tissue Repositories—Guidelines
- Tissue Sharing in Informed Consent—Guidance

(15) **Offerors Must Address**

1. The offeror shall provide the names, degrees, training, qualifications, role in project, and effort for each individual proposed.
2. The PI shall be a board-certified adult pulmonary specialist with experience in the design and conduct of clinical trials. Proposals shall document prior participation of the PI and any co-investigator(s) in multi-center clinical trials related to the treatment of COPD and prior research experience as evidenced by external support and publications.
3. The Clinical Coordinator and other support staff shall be experienced in clinical research and provide expertise in the telephone screening of potential participants, administration of questionnaires, medical chart review, education of subjects, blood drawing, clinical testing related to pulmonary medicine, electronic data entry and transmission with error checking and correction, adverse event reporting, record keeping, and methods for maintaining the confidentiality of personal data. Proposals shall document prior participation of the Clinical Coordinator and other support staff in clinical trials related to chronic diseases of older adults, especially COPD, prior participation of the Clinical Coordinator and other support staff in multi-center trials involving electronic transmission of data to a data coordinating center, and prior experience of the Clinical Coordinator in the development of study forms.
4. The offeror shall document the availability to this study of all facilities, equipment, and laboratory personnel that may be required for clinical laboratory characterization of LOTT participants, including arterial blood gas determination, transcutaneous measurement of hemoglobin oxygen saturation, pulmonary function testing, and exercise testing using the six minute walk test. Proposals shall document prior experience in performing these tests according to defined protocols in research studies with evaluation of the testing by quality control and quality assurance procedures of those studies.
5. The offeror shall describe in detail a proposed regional network of cooperating sites that will assist the RCC in identifying potential participants, determining their eligibility, enrolling them in the study, performing baseline testing, and ascertaining outcomes. Cooperating sites may include hospitals, medical clinics, health maintenance organizations, pulmonary rehabilitation clinics, pulmonary and primary care physician offices, and other medical facilities with appropriate facilities and staff. The offeror shall identify the designated IRB for each cooperating site. As illustrated in the Sample Protocol for Proposal Purposes (Attachment 2), the offeror shall identify which tasks and procedures will be performed in the cooperating sites and which will be performed centrally in the RCC itself. The offeror shall identify specific individuals at the cooperating sites who will perform the assigned tasks and document their capabilities to perform these functions. The offeror shall describe in detail plans for training and certifying personnel of the cooperating sites in study procedures, for providing oversight of these sites, and for accomplishing the secure transfer of study data as needed to the RCC. The offeror shall describe quality control and quality assurance procedures for the cooperating sites. The offeror shall provide, in an Appendix, letters from responsible individuals at each proposed cooperating site stating their willingness to cooperate in the study, the number of eligible patients that are expected to be seen at the site during the enrollment period (based on the eligibility criteria in the Sample

Protocol for Proposal Purposes), and the estimated, capitated, total cost for performing the procedures proposed for the cooperating sites, excluding patient care costs that would normally be covered by Medicare insurance if medically indicated. Proposals shall describe the geographic area covered by the network of cooperating sites as well as the number of potential participants with whom they have contact. Proposals shall document prior involvement of the cooperating sites in subject recruitment for clinical trials and previous research collaborations between the RCC (or PI) and the network of cooperating sites.

6. Provide a plan for recruitment of an adequate number of eligible subjects. Describe the planned procedures for initiating contact with potential participants; the size and clinical characteristics of the populations from which subjects will be recruited; the anticipated rate at which subjects will be screened; and the proportion of individuals that would likely remain eligible after screening, after Visit 1, and after the eligibility testing of Visit 2 as described in the Sample Protocol for Proposal Purposes (Attachment 2). Describe alternative approaches for recruitment that will be employed if the rate of enrollment falls below what would be needed for timely completion of the trial. Provide evidence that the populations that will be targeted for enrollment are largely Medicare-eligible or have alternative means for payment of study-related patient care costs. If a large proportion of the targeted population is not Medicare-eligible, provide documentation of an alternative mechanism for payment of patient care costs that will allow subjects to participate in the trial without incurring a significant economic burden.

7. The offeror shall propose one substudy for the LOTT that will utilize subjects and data of the parent trial and enhance the scientific value of the parent trial. The substudy proposal may involve all or only a subset of the LOTT RCCs. Appropriate general aims of the substudy include, but are not limited to, identification of responsive or non-responsive subpopulations, identification of toxicities or subpopulations at risk of toxicity, validation of alternate outcome measures for future trials of oxygen therapy, and cost effectiveness analyses. The substudy proposal must address a clinically important question that is relevant to oxygen treatment in COPD patients. For example, a substudy proposal whose aim was to identify pathogenetic mechanisms in COPD would not be considered responsive to this requirement. The substudy proposal should include the specific aim, the scientific rationale, a literature review, the study design and methods, a schedule of substudy interventions and assessments, an estimate of the number of subjects required, an estimate of the total cost of the substudy, and literature cited. The substudy portion of the Technical Proposal, excluding literature citations, shall not exceed eight single-sided pages in length. A detailed budget for the substudy is not required in the proposal, but the total cost of the proposed substudy, at all participating sites and including facilities and administrative charges, should not exceed $900,000. Costs for the proposed substudy must not be included in the offeror's Cost Proposal.

(16) **Technical Proposal Table of Contents**

A. Technical Plan

The Technical Plan (Objectives, Approach, Methods and Procedures) shall not exceed 30 single-sided pages or 15 double-sided pages. Pages in excess of the limitation will be deleted and will be neither read nor evaluated.

(1) Objectives . . . . . Page #

(2) Approach . . . . . Page #

(3) Methods . . . . . Page #

(4) Procedures . . . . . Page #

(5) Schedule . . . . . Page #

B. Personnel

(1) List of All Personnel in the Project Including Subcontractors, Consultants/collaborators, by Name, Title, Department and Organization . . . . . Page #

Provide Narrative For:

(2) Principal Investigator/project Director . . . . . Page #

(3) Other Investigators . . . . . Page #

(4) Additional Personnel . . . . . Page #

[Note: for Personnel, Include a Two-page Biosketch under Appendices Below.]

C. Facilities, Equipment, and Other Resources . . . . . Page #

List/describe all facilities, equipment and other resources available for this project.

D. Other Considerations . . . . . Page #

E. Substudies . . . . . Page #

The substudy proposal section shall not exceed 8 single-sided or 4 double-sided pages. For additional guidance on substudies, see Instructions to Offerors, Technical Proposal Instructions, item 7.

6. Summary of Related Activities (Attachment 5) . . . . . Page #

7. Technical Proposal Cost Summary (Attachment 4) . . . . . Page #

8. Human Subjects . . . . . Page #

This section should be completed in accordance with Instructions to Offerors, Technical Proposal Instructions, item 6. Include a copy of OMB Form 0990-0263, Attachment 7, and Target Enrollment Table, Attachment 8.

9. Appendices . . . . . Page #

Appendices shall be limited to 50 single-sided pages or 25 double-sided pages.

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.

(2) **Cost and Pricing Data**

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 submitted using the **Excel Workbook,** Attachment 11, posted with this RFP. 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.

**** ***(Please note that 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.)*** ****

(3) **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) The Contracting Officer's phone number, 4) contract dollar value; 5) dates contract began and ended (or ends); 6) description of contract work; 7) explanation of relevance of work to this RFP; 8) 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. Experience and past performance are factors which are relevant to the ability of the offerors to perform and are considered in the source selection process.

(4) **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.

b. **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.

c. **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.

d. **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)

e. **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.

(5) **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

(6) **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 .]

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

(7) **Representations and Certifications**

In accordance with Section K, Representations and Certifications can be accessed electronically at: http://rcb.cancer.gov/rcb-internet/wkf/sectionk.pdf

(8) **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. .

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.

(9) **Business Proposal Table of Contents**

Note: Certain items do not need to be submitted at this time. All offerors included in the competitive range will be required to submit the following items: Travel Policy, Annual Report, Total Compensation Plan, Subcontracting Plan, Data Substantiating the Costs or Prices Proposed (i.e. payroll documentation, vendor quotes, invoice price, etc.).

SECTION M - EVALUATION FACTORS FOR AWARD

GENERAL

Selection of offerors for contract awards will be based on evaluation of proposals against the following factors in order of importance: technical (which encompasses experience and past performance), cost/price, small disadvantaged business (SDB) participation, female and minority representation in the anticipated subject population, and geographic proximity to other RCC sites (see Geographic and Other Considerations below). The technical proposal will receive paramount consideration in the selection of contractors for this acquisition. Evaluation of SDB participation and female and minority representation will be performed only on those offers being considered for award. SDB participation will not be scored, but the government's conclusions about overall commitment and realism of the offeror's SDB Participation Plan will be considered in determining the relative merits of the offerors' proposals. All evaluation factors other than cost/price, when combined, are significantly more important that cost/price. The trade-off process described in FAR 15.101-1 will be employed. This process permits trade-offs between price and non-cost factors and allows the Government to make awards for other than the lowest priced or highest technically rated proposal. In any event, the Government reserves the right to make an award to the offeror whose proposal offers the best value to the government.

EXTENT OF SMALL DISADVANTAGED BUSINESS PARTICIPATION

SDB participation will not be scored, but the Government's conclusions about overall commitment and realism of the offeror's SDB Participation targets will be used in determining the relative merits of the offeror's proposal and in selecting the offeror whose proposal is considered to offer the best value to the Government.

The extent of the offeror's Small Disadvantaged Business Participation Targets will be evaluated before determination of the competitive range. Evaluation of SDB participation will be assessed based on consideration of the information presented in the offeror's proposal. The Government is seeking to determine whether the offeror has demonstrated a commitment to use SDB concerns for the work that it intends to perform.

Offers will be evaluated on the following sub-factors:

(a) Extent to which SDB concerns are specifically identified
(b) Extent of commitment to use SDB concerns
(c) Realism of the proposal
(d) Past performance of offerors in complying with subcontracting plan goals for SDB concerns and monetary targets for SDB participation

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, 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), 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), 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 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), 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.

GEOGRAPHIC AND OTHER CONSIDERATIONS

Because a subject can participate in the LOTT through only one RCC, the Government expects to make an award to no more than one offeror in any particular metropolitan statistical area or division, as defined by the Office of Management and Budget (http://www.census.gov/population/www/estimates/metroarea.html). This approach will promote widespread local access of potential participants to the LOTT and successful enrollment of the total required number of subjects. More than one RCC in a single metropolitan statistical area or division will be considered only if those centers will enroll subjects from distinct populations (for example, from different health care systems).

Location will not be considered in the scoring of technical merit by the technical evaluation committee. Geographic location will be considered by the Government in determining the relative merit of proposals that are within the competitive range.

TECHNICAL EVALUATION CRITERIA

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

No.		Weights
1	**Capabilities of and Plan for Management of Cooperating Sites.** Capabilities of the proposed network of cooperating sites for the identification, screening, enrollment, and follow-up of subjects. Appropriateness of plans for the training and oversight of personnel at these sites. Adequacy of plans for quality control/quality assurance of cooperating site operations. Documentation of the willingness of personnel at these sites to perform the prescribed functions.	30
2	**Personnel.** Qualifications, expertise, and experience of the Principal Investigator as related to the design and conduct of a multi-center clinical trial of oxygen therapy in COPD. Qualifications, expertise, and experience of the Clinical Coordinator and other staff in the conduct of similar multi-center research studies.	30

3	**Scientific Merit of Proposed Substudy.** Significance, design, feasibility, efficiency, and clinical importance of the proposed substudy.	30
4	**Facilities and Equipment.** Adequacy of the offeror's facilities and the infrastructure for support of a large trial involving patients with COPD.	10

SOLICITATION ATTACHMENTS INCLUDED WITH THE RFP

The following pages include Attachments 1-3, applicable to this RFP as specified in SECTION J - LIST OF ATTACHMENTS

PACKAGING AND DELIVERY OF THE PROPOSAL

DUE DATE: 4:00 p.m. local time on January 24, 2006

Proposals not received at the place and time specified in the solicitation will be considered late and will handled in accordance with FAR clause 52.215-1(c)(3). Your proposal shall be organized as specified in Section L.2., "Instructions to Offerors". 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-HR-06-07, Long-term Oxygen Treatment Trial (LOTT): Regional Clinical Centers (RCCs) TO BE OPENED BY AUTHORIZED GOVERNMENT PERSONNEL ONLY"

NUMBER OF COPIES:

Technical Proposal: Original and Forty Five (**45**) Copies

Business Proposal: Original and Four (**4**) Copies

IF HAND-DELIVERED/DELIVERY SERVICE:

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

IF USING U.S. POSTAL SERVICE:

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

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

PROPOSAL INTENT RESPONSE SHEET

RFP No.: NHLBI-HR-06-07

TITLE OF RFP: Long-term Oxygen Treatment Trial (LOTT): Regional Clinical Centers (RCCs)

If you intend to submit a proposal, please furnish the information requested below and return this page by **December 15, 2005**. Your expression of intent is not binding but will assist us in planning for proposal evaluation.

COMPANY/INSTITUTION NAME:

ADDRESS:

PROJECT DIRECTOR'S/PRINCIPAL INVESTIGATOR'S NAME:

PROJECT DIRECTOR'S/PRINCIPAL INVESTIGATOR'S TITLE:

TELEPHONE NUMBER:

COLLABORATING INSTITUTIONS AND INVESTIGATORS:

(For each subcontractor or consultant provide the name of the institution, project director's name, and title)

RETURN TO:

Review Branch
NIH, NHLBI
Attention: Valerie Pregner **FAX (301) 480-0730**
6701 ROCKLEDGE DR MSC 7924
BETHESDA MD 20892-7924

Attachment 2

SAMPLE PROTOCOL FOR PROPOSAL PURPOSES

Note: The LOTT Protocol will be developed by the Steering Committee after contract awards and may differ in significant ways from this sample protocol. The Sample Protocol for Proposal Purposes is intended for information purposes only and is not prescriptive. It is provided to assist offerors in estimating the facilities, resources, and personnel that may be required for the RCCs and to provide a tangible and uniform basis for the business proposals.

a. Summary

The Long-term Oxygen Treatment Trial (LOTT) will be a randomized, controlled trial of supplemental oxygen therapy in subjects with chronic obstructive pulmonary disease (COPD), moderate hypoxemia, and increased risk of mortality. Approximately 5142 subjects will be randomized to receive round-the-clock oxygen or usual care with periodic retesting of hypoxemic status. Subjects will be followed for 1 to 4 years (average follow-up 2.5 years). The primary endpoint will be survival, using an intent-to-treat analysis. Secondary endpoints will include quality of life, exercise capability, number of hospitalizations, and cognitive function.

b. Background and Significance

The ability of the lungs to oxygenate blood is often impaired in COPD as a result of alveolar destruction and small airway narrowing. Long-term O_2 treatment, which increases the O_2 content of inspired air and partially compensates for this impairment, has been shown in clinical trials to substantially decrease mortality among subjects with COPD and severe, resting hypoxemia. The most notable studies are the Nocturnal Oxygen Therapy Trial (NOTT) and the Medical Research Council (MRC) study, which used similar eligibility criteria: clinical diagnosis of COPD; $FEV_1/FVC < 70\%$ predicted; TLC $\geq$ 70% predicted; age > 35 years; and severe hypoxemia at rest ($PaO_2 \leq 55$ mm Hg or ≤ 59 mm Hg in the presence of edema, hematocrit $\geq$ 55%, or P pulmonale on ECG).[1,2] Eligibility required demonstration of hypoxemia on at least two occasions more than 1 week apart during a 3 week period of disease stability. Each study found a survival advantage in those randomized to receive a longer daily duration of O_2 treatment. The median survival for those using O_2 an average of 18 hours per day was approximately 2-fold longer than for those receiving no O_2.

In contrast to the NOTT and MRC studies, trials reported by Górecka *et al.* and Chaouat *et al.* found no effect of long-term O_2 treatment on survival in subjects with less severe hypoxemia.[3,4] Although neither of these studies was of sufficient size or duration to statistically prove the absence of a meaningful effect on survival, the striking similarity of results between treated and untreated groups suggests that individuals with less severe COPD do not, as a group, derive any survival benefit from supplemental O_2. However, benefit with O_2 remains a possibility, especially for those at high risk of mortality.

The four trials referenced above represent the only randomized trials of O_2 efficacy to date that have measured survival. These involved a total of only 501 subjects, few participants were women, and the studies were performed over a thirty year period in which the demographics of COPD and methods for managing the disease were evolving. Given the disparate results, methodological differences among the studies, and the great heterogeneity of COPD, it is very often unclear to physicians and insurers which of these previous studies applies to their individual patients. This is particularly true for patients who are found to have severe hypoxemia at a single point in time or those whose hypoxemia occurs sporadically during exercise or sleep. Characteristics other than arterial oxygen content may also be relevant to O_2 responsiveness, but few data are available on this topic. COPD has many different manifestations and comorbidities; there can be substantial variation in clinical status over time; and laboratory measurements of arterial oxygenation are poorly

reproducible. Overall, the optimal indications for long-term O_2 supplementation and how patients should be assessed remain unclear.

There is similar uncertainty with regard to the optimal manner for administering O_2. Giving supplemental O_2 only during times in which there is severe hypoxemia might yield the full benefit, minimize costs, and avoid a theoretical risk of toxicity from oxidative stress. On the other hand, continuous use may be more effective in inducing protective antioxidant mechanisms and enhancing possible intrapulmonary effects of treatment related to regulation of pulmonary blood flow and modulation of lung gene expression and cellular phenotype.[5-8] Data on continuous *vs.* sporadic use of O_2 are inconclusive, but aggregate analysis of NOTT and MRC data suggests that survival is directly related to the daily hours of oxygen use. If this is true in general, the absence of an effect of supplemental O_2 on survival in the studies by Górecka *et al.* and Chaouat *et al.* might be due to the short daily duration of O_2 use in those studies (averaging 13.5 and 8.9 hrs/day, respectively).[3,4]

Another area of uncertainty is whether there are important benefits to O_2 other than increased survival. Some relatively small and/or short-term studies have shown improvements with O_2 treatment in other outcome measures; including depression, cognitive function, quality of life, exercise capability, and frequency of hospitalizations.[9-17] Evidence for sustained functional and clinical improvements in patients with COPD might warrant prescription of therapeutic O_2 even in the absence of a survival benefit. Further research is needed to verify O_2 efficacy for outcomes other than survival and to clarify which patients are most likely to derive these benefits.

A Working Group entitled "Long-term Oxygen Treatment in COPD" was convened by the NHLBI and CMS on May 10-11, 2004 to review the state of science related to oxygen therapy and to make recommendations regarding future research. The Working Group identified serious gaps in knowledge and recommended that four clinical trials be performed, including the present study, which was considered to have very high priority. Design features considered by the Working Group to be important were: 1) using both mortality and quality of life as outcome measures, 2) including subjects with less severe hypoxemia than was required for the NOTT, 3) limiting eligibility to subjects with clinical characteristics associated with a high risk of premature death, 4) excluding subjects who meet the eligibility criteria of the NOTT (and should receive supplemental O_2), and 5) targeting continuous use of O_2 in the treatment group.

The clinical management decisions that will be informed by this study affect a large number of patients, may significantly influence the length and quality of life for these patients, and are associated with substantial expenditures for health care costs. Annual mortality in the U.S. due to COPD is approximately 125,000. COPD affects over 15 million Americans, and approximately 1 million of these patients receive supplemental oxygen each year. Total Medicare reimbursements for costs related to O_2 exceed $2 billion per year and are increasing at an annual rate of 12-13% (unpublished data; CMS).

The present trial may have important implications for clinical management of COPD regardless of the outcome. Greater mortality among subjects not receiving O_2 would support the identification and treatment of patients with COPD, moderate hypoxemia, and other eligibility criteria. At present there are inadequate data to justify O_2 treatment in this group, and clinical practice guidelines do not recommend it.[18,19] Such patients may number in the hundreds of thousands in the U.S. On the other hand, greater mortality among those treated with O_2 would suggest that round-the-clock O_2 supplementation should be restricted to those with severe resting hypoxemia. This outcome remains a possibility since retrospective analysis of National Emphysema Treatment Trial (NETT) data showed greater mortality among control subjects receiving oxygen than in controls with similar FEV_1's who were not receiving O_2 (unpublished data). Hundreds of thousands of COPD patients could

benefit from knowledge of such a result, since anecdotal reports and some studies indicate that a large fraction of patients currently receiving long-term O_2 treatment do not meet the rigorous inclusion criteria of the NOTT and MRC study.[20] Finally, the LOTT will provide data on the effects of long-term O_2 treatment on quality of life and other outcomes that should inform prescribing behavior should there be no different in mortality between the two treatment groups.

In addition to addressing the specific goals of the LOTT, this study will provide valuable data on clinical phenotypes and outcomes in patients with advanced COPD. The LOTT will be the largest ever study of subjects at high risk of dying as a result of COPD, and it is expected to yield new insights into current medical practices, predictors of mortality, and the natural history of severe COPD.

c. Research Design and Methods

1. Overview of Trial Design

The LOTT will be a randomized controlled, prospective trial with two parallel, equal sized treatment groups. Alternative management strategies will be applied in these two groups throughout the follow up period. Enrollment will occur over a period of approximately 3 years, and all subjects will be followed until 1 year after the last randomization.

2. Eligibility Criteria

Screening Criteria (by self report; all are required)

a) Age ≥ 40 years

b) Physician diagnosis of COPD, emphysema, or chronic bronchitis; No physician diagnosis of asthma.

c) No use of O_2 from a stationary source within the past 2 months

d) Shortness of breath (walking on a level path for 5 minutes)

e) No hospitalization or change in oral medications for COPD in the past 30 days

f) Willingness to consider participation in a long-term research project that involves selection of therapy by chance

Inclusion Criteria (all are required)

a) Presence of COPD, GOLD Stage II or greater
   - Appropriate clinical setting,
   - Postbronchodilator $FEV_1/FVC \leq 0.7$, and
   - Postbronchodilator $FEV_1 \leq 80\%$ predicted.

b) Moderate oxyhemoglobin desaturation
   - O_2 saturation ≤ 90% at rest or for at least 2 minutes during a 6 minute walk test.

c) Increased risk of mortality as indicated by a BODE Index ≥ 5, calculated as sum of

Body-mass index (BMI)	1 pt	if ≤ 21
FEV1 (% pred)	1, 2, or 3 pts	if 50-64, 36-49, or ≤ 35, respectively
MMRC dyspnea scale	1, 2, or 3 pts	if 2, 3, or 4, respectively
6 min walk distance (m)	1, 2, or 3 pts	if 250-349, 150-249, or ≤ 149, resp.

Exclusion Criteria (any)

a) Unable or unwilling to give informed consent
b) Unable to perform the required laboratory procedures, including a 6 minute walk test
c) Clinical diagnosis of asthma (judgement of investigator)
d) Recent exacerbation
   - Hospitalization, antibiotic use, or increased corticosteroid use (oral or inhaled) for increased symptoms of COPD within 30 days prior to either Visit 1 or Visit 2.
e) Severe resting hypoxemia
   - Resting O_2 saturation $\leq$ 88% (or = 89% if edema, hematocrit $\geq$ 55%, or P pulmonale is present) at Visit 1, and
   - Resting $P_aO_2 \leq$ 55 mm Hg (or $\leq$ 59 mm Hg if edema, hematocrit $\geq$ 55%, or P pulmonale is present) at Visit 2.

3. Statistical Design and Sample Size

Eligible subjects will be assigned to two treatment groups at random and with equal probability. To minimize effects of possible geographic variations in population and health care systems, randomization will be stratified by RCC. The main analysis of the primary outcome (all cause mortality) will be by survival analysis according to the intention-to-treat principle without consideration of covariates. Secondary analyses will also be performed using a Cox proportional hazards model to investigate contributions of pre-randomization factors such as age, gender, lung function, severity of hypoxemia, and exercise capability.

Celli *et al.* observed a mortality rate of 60% after 52 months in subjects with BODE scores in the range 5-10, as will be required for inclusion in this trial.[21] Based on this we conservatively estimate that death will occur among subjects in the control arm at a rate of 15% per year, equivalent to a median survival of 4.3 years.

The magnitude of the effect of long-term O_2 treatment on mortality in this population is not known. However, we estimate that an absolute change in mortality rate of at least 4% (i.e., a hazard ratio $\geq$ 1.297) would be considered by patients and physicians as sufficient cause to use or to refrain from using supplemental O_2. With further assumptions of a 3 year accrual period and an additional 1 year follow up period, the sample sizes required for 85% power to detect a difference with a 2-sided significance level of 0.05 are:

Crossover Rate	Corrected Hazard Ratio	Sample Size Required
0	1.297	1826
5%	1.263	2237
10%	1.231	2792
15%	1.199	3618
20%	1.168	4885
25%	1.138	6971

The sample sizes given above are not corrected for subject withdrawals or losses to follow up. Such losses should be small (perhaps 5%) since adverse events that would require withdrawal are not expected, and vital status/date of death can be ascertained for virtually all willing participants through the National Death Index. Hence, we estimate a required sample size of 5142 (= 4885 ÷ 0.95), assuming 20% crossover from each group and 5% other losses.

We anticipate that the DSMB will carry out sequential analyses with interim looks at efficacy data at approximately 6 month intervals. This will result in a slight decrease in the power of the study. Precise plans for interim analyses and specific stopping criteria will be developed based on monitoring plans of the DSMB.

4. Outcome Measures

Primary: All cause mortality

Secondary:
a) Disease-specific quality of life (change in St. George's RQ)
b) Dyspnea (change in MMRC dyspnea scale)
c) Cognitive function (change in Trail Making Test)
d) Rate of hospitalizations (by self report)
e) Exercise capability (change in 6 minute walk test distance)
f) Time till onset of persistent, severe resting hypoxemia

Serum and DNA will be archived for future biomarker and genetics studies.

d. Schedule of Study Interventions

Study Timetable

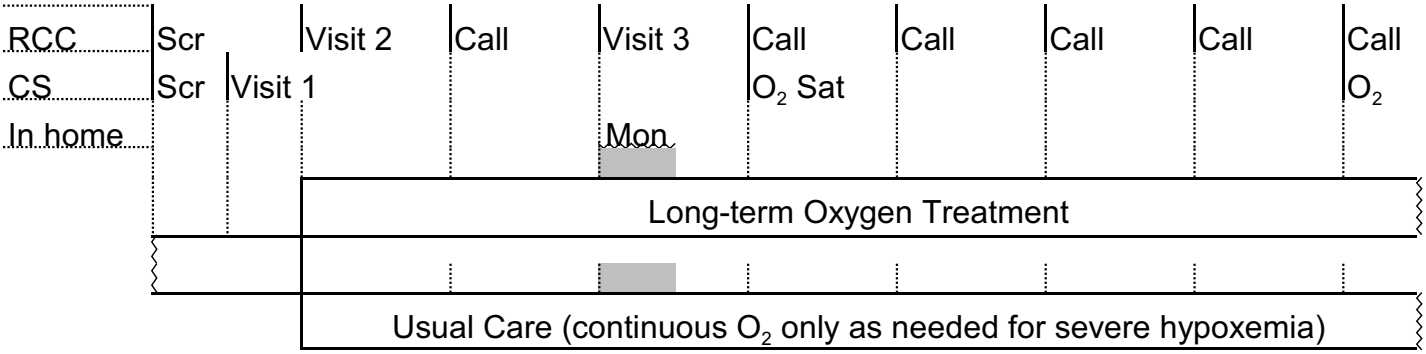
6 mo.	3 years 6 mo.	1 year	1 year
Protocol Design	Enrollment and Follow-up	Additional Follow-up	Data Analysis and Reporting

Schedule of LOTT Interventions

Time	Event	Site	Interventions
	Screening	Telephone or any	Screening questionnaire
-2 wks	Visit 1	Cooperating Site	Informed consent Height and weight Recent medical history Spirometry w/ bronchodilator Electrocardiogram O_2 saturation Modified Medical Research Council dypnea Trail Making Test St. George's respiratory questionnaire 6 minute walk test
0	Visit 2	RCC	Review informed consent Medical history Physical examination Arterial blood gas measurement – RANDOMIZATION – Venous blood for hct, serum, and DNA Subject education
6 wks	Follow up	Telephone	Recent medical history Self-reported O_2 utilization Adverse events

12 wks	Visit 3	RCC	Recent medical history Self-reported O_2 utilization Adverse events Review subject education
12 - 16 wks	Continuous assessments	In home	Monitoring of stationary and portable O_2 usage and of activity by 3-D accelerometry
18 wks and q 6 wks for duration	Follow up	Telephone	Recent medical history Self-reported O_2 utilization Adverse events
6 mo. and q 6 mo. for duration	Hypoxemia assessment	Cooperating Site	O_2 saturation 6 minute walk test Modified Medical Research Council dypnea Trail Making Test St. George's respiratory questionnaire

Timing of LOTT Interventions (Initial Six Months)



CS = cooperating site; Scr = screening; Mon = in home monitoring of activity and O_2 usage

e. Recruitment and Retention

Subjects will be recruited through a variety of methods including national and local advertising, a study website, mailings to primary care and pulmonary physicians, and direct contact with patients by physicians, nurses, and respiratory therapists, in accordance with HIPAA regulations. Study-wide materials will be developed, but the methods and materials for initial contact will be chosen by the individual RCCs and tailored to their regional environment.

Subjects will typically be enrolled at satellite sites of the RCC. These cooperating sites may be hospitals, medical clinics, physician offices, or other medical facilities. Those excluded because of recent exacerbation may be reconsidered at a later time. Randomization will occur during a visit to the RCC central site, and education provided during that visit will include the important of continuing in the study till completion and

complying with study protocols. Retention of subjects will also be reinforced through regular follow up telephone calls, which will take place at six week intervals following the early study visits.

f. Treatment Groups

The long-term O_2 treatment group will be provided stationary and light weight portable O_2 sources and will be encouraged to use supplemental O_2 as continuously as is practical. The prescribed stationary source flow rate will be the minimum required to obtain an O_2 saturation of 94% at rest. The portable source prescription will target an O_2 saturation of 94% during level walking at the maximum comfortable speed for the subject. Retesting and adjustments of the O_2 prescriptions will be made as needed for changes in symptoms and at 6 month intervals. No other aspects of medical care for these subjects will be dictated by protocol.

The control group will receive medical care from their usual providers with no restrictions other than with regard to the use of O_2. Ambulatory O_2 supplementation, for use during physical activity and for a total time not exceeding 8 hours per day, will be allowed if recommended by the subject's physician. However, the equipment, supplies, and O_2 required will not be provided by the study. Control subjects will have O_2 saturation at rest retested at 6 month intervals. Interim testing may also be done outside the study for increased respiratory symptoms. If severe resting hypoxemia (O_2 saturation $\leq$ 88% or = 89% if edema, hematocrit $\geq$ 55%, or P pulmonale is present) is found in either case, the subject will, by protocol, be started on round-the-clock O_2 supplementation. If the subject's history indicates a current or recent (past 30 days) COPD exacerbation, the measurement of O_2 saturation will be repeated after 1 month of disease stability, and if > 88% (and > 89% if edema, hematocrit $\geq$ 55%, or P pulmonale is present) at that time the continuous O_2 supplementation will be discontinued. If severe resting hypoxemia is found with no current or recent exacerbation, round-the-clock O_2 supplementation will be provided for 1 month at which time arterial O_2 content will be measured. If resting $P_aO_2 \leq$ 55 mm Hg (or $\leq$ 59 mm Hg if edema, hematocrit $\geq$ 55%, or P pulmonale is present) the control subject will be placed on round-the-clock O2 supplementation, equivalent to that provided in the O_2 treatment arm, for the duration of the study. If the measurement of P_aO_2 does not indicate severe resting hypoxemia, round-the-clock O_2 supplementation will be discontinued at that time.

g. Concomitant Therapy

There are no limitations on concomitant therapy. In particular, subjects randomized to the control arm will be permitted to receive supplemental O_2 during exercise from a portable source if it is prescribed by the subject's physician.

h. Masking

The study will not be masked. Masking is considered unfeasible since subjects in the control arm are likely to require O_2 supplementation during exacerbations.

i. Data Management

An in-person training session will be held for RCC staff after approval of the protocol and study forms and before enrollment of subjects. This training will include the rationale and objectives of the study; characteristics of anticipated subjects; methods of advertising, screening, and enrollment; informed consent and ethics of human subjects research; study schedule; forms and their completion; procedures for data entry and editing; script for telephone follow up; process for withdrawal from the study; and technical procedures for subject characterization. RCC staff will in turn conduct training sessions for staff of the cooperating sites.

Data will be collected at the RCC on paper forms, which will be kept in a secure archive at that site. Study data, without readily identifiable personal information, will be transferred to the DCC using a password-protected,

web-based, distributed data entry system developed and maintained by the DCC. The data entry system will check for out-of-range and other implausible data entries and immediately prompt the RCC staff to confirm or correct the entry.

Data collected at the cooperating sites will be sent to the RCC on paper forms and transferred to the DCC by RCC staff according to the same procedures used to enter data collected at the RCC. Data from the cooperating sites will be stored in a secure archive at the RCC.

Study data will be maintained in a secure computer system at the DCC with monthly off-site backup. DCC staff will regularly monitor data quality and completeness by automatic and manual audits and will communicate with RCC staff to obtain missing data and to correct apparent entry errors. Error rates for each RCC will be assessed by manual reentry of a randomly selected subset of forms by DCC staff. Remedial training and site visits will be conducted as needed to assure data quality.

Serious unexpected adverse events will be reported by the RCCs to the DCC by express courier or secure email. The DCC will establish an email / secure website system that will allow expedited reviews of serious unexpected adverse event reports by the DSMB.

j. Limitations of the Study

1. Feasibility. The major threat to successful completion of this trial is the need to enroll approximately 5000 subjects. This potential problem has been addressed by creating a large and widespread infrastructure for recruitment, using relatively inclusive eligibility criteria, and reducing subject burden by minimizing interventions after the first 4 months of participation. Enrollment will be monitored at monthly intervals by the DCC and the NHLBI, and remedial actions will be taken as needed. These may include enhancement of advertising, expansion of outreach to local physicians and the public, and dedicated meetings of RCC PI's to discuss recruitment issues and share successful approaches and strategies.
2. Compliance. An inevitable limitation of this trial is treatment noncompliance, particularly, the failure of O_2-treated subjects to use O_2 around-the-clock or at all. This situation may be aggravated by the inconvenience of O_2 use and the obligation of the investigators to accurately communicate the state of scientific equipoise regarding O_2 efficacy. The design choice to enroll subjects with relatively severe systemic disease (BODE score $\geq$ 5) may serve to limit this problem. The extent of noncompliance will be assessed in a subset of subjects by electronic, in-home monitoring. Conversely, given the morbidity in this population and the paucity of other effective treatments, out-of-protocol use of O_2 by control subjects will no doubt occur. This may be minimized by the protocol's liberal allowance of O_2 supplementation during exacerbations or ambulation. Compliance issues weaken the power of the study to demonstrate efficacy of O_2 and substantially increase the number of subjects required, but these limitations will not diminish the policy implications of a positive trial result since similar behaviors exist in clinical practice.
3. Generalizability and Clinical Translation of Results. The heterogeneity of the study population and the necessity for complex eligibility criteria will limit the confidence with which study results can be applied to individual patients. Only a subset of those included may actually benefit from O_2 supplementation, and the study is not designed to statistically test whether any particular phenotypic characteristic is an important determinant of responsiveness. Nonetheless, the eligibility criteria selected are sufficiently rational and objective to be useful for policy and insurance coverage decisions. Furthermore, the LOTT

will allow *post hoc* analyses of clinical characteristics and ancillary biomarker and genetics studies that may suggest testable hypotheses regarding more personalized indications for supplemental O_2.

4. Uniform Protocol Implementation. The protocol's reliance on standard clinical tests for characterizing subjects and the study's use of simple outcome measures will enhance the uniformity of procedures across the RCCs. In addition, extensive training, certification of staff, and vigorous monitoring of study activities by the DCC will assure consistent implementation of the LOTT protocol. However, certain criteria for eligibility and treatment are necessarily subjective. These include the clinical diagnoses of COPD (inclusion) and of asthma (exclusion) and the presence or absence of a recent exacerbation (control arm management). Because it would be counterproductive to define these conditions in a purely objective way, the study will rely on the clinical judgement of the investigators. To promote uniformity across the study, the investigators will discuss these issues in advance and will be encouraged to use standard diagnostic criteria. Also, during the trial, unusual cases will be discussed in detail by the Steering Committee to promote the refinement of uniform standards.

k. Human Subjects Issues

1. Risks to Subjects

The only recognized risk of long-term O_2 treatment is burns due to enhanced combustion of existing fires.[22] These events are probably rare but can be catastrophic. Of particular concern is the possibility of burns to the face and hands if a subject lights a cigarette while using O_2. To allow generalizability of study findings, the LOTT will not exclude smokers. All smokers will be advised to enter a smoking cessation program, and staff will strongly encourage subjects never to smoke while using O_2 or in the same room as an O_2 source. Subjects will be asked about the occurrence of burns during each follow up visit or telephone call.

2. Informed Consent

Verbal consent for screening will be obtained upon initial contact with prospective subjects. No personal identifying information will be collected during screening. Those apparently eligible, based on the screening questionnaire, will be scheduled for a study visit. Informed consent will be obtained at that visit prior to any study interventions. The informed consent process and documents will conform to federal regulations and NIH policies and will be approved by the local IRB. Study personnel who obtain consent will receive training in research ethics, O_2 treatment of COPD, and study aims and procedures. In the second study visit, conducted at the central site of the RCC, study staff will review the informed consent document with the subject to ensure comprehension and continued willingness to participate in the study.

3. Adverse Events

High morbidity and mortality are anticipated in both treatment groups of this study. Deaths, exacerbations of COPD, and hospitalizations for any cause are outcome measures of the trial and will not be reported as adverse events. These outcomes will be monitored by the DCC and the DSMB for differential rates of occurrence. In accordance with policies of the NHLBI, other serious events, including severe injuries and new diagnoses of potentially fatal or disabling medical conditions will be reported as serious adverse events of the study to the local IRB, the DCC, the DSMB, and the NHLBI.

4. Study Monitoring

Monitoring will be performed by a Medical Monitor on the staff of the DCC and by an independent Data and Safety Monitoring Board (DSMB) established by the NHLBI. The DCC will provide relevant data on center performance, data quality, adherence to protocol, adverse events, and study outcomes to the DSMB, which will make recommendations to the NHLBI Director regarding changes in protocol or early termination of the study. NHLBI staff will provide oversight of the monitoring process in accordance with NIH policies.

5. Population Demographics

The LOTT intends to enroll as subjects women and members of minority groups in proportion to their representation in the U.S. population that would be eligible for participation in the study. Because increased risk of death is a primary inclusion criterion, we estimate the demographics of the eligible population based on COPD-attributable mortality data from the National Vital Statistics System. Data reported by the Centers for Disease Control for the year 2000 indicate that 93% of deaths due to COPD occurred among whites and 50% among women.[23] Based on this and data from the U.S. Census Bureau, the LOTT study population is expected to have the demographics described in the table below. Because COPD is a disease of adults, no children will be enrolled in the LOTT.

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
	Sex/Gender		
Ethnic Category	Females	Males	Total
Hispanic or Latino	83	83	166
Not Hispanic or Latino	2,300	2,300	4,600
Ethnic Category: Total of All Subjects *	2,383	2,383	4,766
Racial Categories			
American Indian/Alaska Native	10	10	20
Asian	24	24	48
Native Hawaiian or Other Pacific Islander	1	1	2
Black or African American	86	86	172
White	2,262	2,262	4,524
Racial Categories: Total of All Subjects ^	2,383	2,383	4,766

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