**NATIONAL HEART, LUNG, AND BLOOD INSTITUTE**

**REQUEST FOR PROPOSAL NUMBER NHLBI-HB-06-04**

**AMENDMENT NO. 1**

**DATE OF ISSUANCE: October 27, 2005**

The above numbered solicitation is amended as set forth below. **The hour and the date specified for receipt of Offers remains unchanged.** Offerors must acknowledge receipt of the amendment prior to the hour and the date specified in the solicitation or as amended, by one of the following methods:

1. By acknowledging receipt of this amendment on each copy of the offer submitted. **Please note that this is the preferred method.**

2. By separate letter or telegram, which includes a reference to the solicitation and amendment numbers.

3. By requesting a copy of the Standard Form 30 for this amendment and completing the information requested in items 8 and 15, and returning 1 copy of the amendment; (a hard copy of this amendment, including the Standard Form 30 may be requested from Rick Phillips, Contracting Officer, e-mail: phillipr@nhlbi.nih.gov).

FAILURE OF YOUR ACKNOWLEDGMENT TO BE RECEIVED AT THE PLACE DESIGNATED FOR THE RECEIPT OF OFFERS PRIOR TO THE HOUR AND DATE SPECIFIED MAY RESULT IN REJECTION OF YOUR OFFER. If by virtue of this amendment you desire to change an offer already submitted, such change may be made by letter or telegram, provided each telegram or letter makes reference to the solicitation and this amendment, and is received prior to the opening hour and date specified.

This amendment revises the RFP as stated below:

The purpose of this amendment is to (1) amend the Statement of Work, (2) provide revised pages of the RFP and (3) provide responses to questions received from potential offerors.

PART 1. TECHNICAL QUESTIONS. The following questions and answers are provided for clarification and informational purposes based on inquiries from potential offerors. Each question is followed by the answer in bold text.

1) It is our understanding from reading the statement of work that 100% source verification of the case reports forms is not required. Please confirm.

**This is subject to change by the Steering Committee, but it is very likely the DCC WILL be expected to ensure 100% source verification of the case report forms for all 180 subjects during the main trial and the extension study. This will not be required for the 1,000 subjects to be screened initially for pulmonary hypertension. Source verification will occur during the site visits to clinical centers planned in Phases II and III of the study.**

2) Will the Data Coordinating Center (DCC) be responsible for the medical monitoring and safety reporting aspects of this study?
**Yes. The DCC should include support for a medical consultant to provide independent medical monitoring in real time of adverse events occuring during the study. The DCC will be solely responsible for safety reporting to the Data and Safety Monitoring Board (DSMB), and will be involved, along with the intramural NIH (holder of the IND), in safety reporting to the FDA**.

3) Will the DCC be responsible for managing the sites' IRB approvals for this study? **Yes**

4) Will there be a need under this contract to perform site initiation and close-out monitoring visits?

**Yes**

5) Will there be an Investigator Meeting for this trial or will the central training of study personnel at the NIH campus serve as the Investigator Meeting?
**The first investigator meeting will take place at the same time (i.e. the day before, or the day after) the central training meeting.**

6) Will the DCC be responsible for the selection of the 12 Clinical Centers?
**No. The clinical sites will be awarded by NHLBI under RFP NHLBI-HB-06-06.**

7) Will the DCC be responsible for the selection of the Steering Committee and the DSMB?
**No. Please refer to the Statement of Work.**

8) What are the expectations for the Principal Investigator in terms of clinical or medical experience and qualifications; separate from the Project Director?
**The Principal Investigator of the DCC should have a professional degree (PhD or MD) with experience in the coordination of clinical trials.**

9) The primary analysis model does not seem to consider the intra-patient baseline values. Will the statistical analysis plan cite a more precise method?
**The final decision on the statistical analysis plan will be made by the independent Data and Safety Monitoring Board for this study. Offerors are free to propose a different statistical analysis plan in its proposal**.

10) Could you please further define "other statistical reports" in number 11 of the statement of work?
**The reports would be based on Steering Committee or DSMB recommendations or changes to the protocol.**

11) Will the DCC program statistician be permitted to participate in final protocol review and contribute comments regarding statistical design aspects?
**The NHLBI intends for this protocol to be implemented in a form very similar to the draft protocol included in the RFP. Therefore, significant changes in study design are not anticipated; however, offerors are encouraged to comment on the data analysis plan.**

12) Are protocol design comments expected in the RFP response and will they be part of the scoring for the technical approach?
**No. Please refer to Section M, Technical Evaluation Criteria, for information on proposal scoring.**

13) Could you clarify requirement 8: "develop a system for random assignment...."? Are you expecting a validated tool for use in the execution of the program or the design of such a tool?
**The NHLBI expects the DCC to use a validated tool for patient randomization. Research to develop such a tool is not a part of this program.**

14) Is a core laboratory required for central interpretation of study echocardiograms, or will local quantitative echo measurements only be utilized for trial endpoints? If a core laboratory is required, what costs, if any, associated with the core laboratory should the contractor include in the budget?
**Please refer to the Statement of Work revision in Part 3 of this RFP amendment. Offerors may propose appropriate costs to accomplish the work.**

15) Will an Investigational New Drug (IND) application be submitted to the FDA? If yes, who is expected to hold the IND, and will the IND submission be for monitoring purposes only or for approval of a labeling change for use of sildenafil?
**The NIH holds an active IND in this area. The planned study will be proposed to the FDA as an amendment to this IND. If the trial proves successful, it is anticipated that the labeling of sildenafil will include its use for sickle cell disease-associated pulmonary hypertension.**

16) The RFP indicates that the DCC should budget for the Study Chair's travel to the DSMB but not to the EC/SC meetings. Should this budgeting be consistent, i.e., the DCC pays for Study Chair travel to all meetings, or only the DSMB as specified?
**The DCC should pay for the travel of the Study Chair only to the DSMB meeting. The Study Chair will be the PI of a clinical site, and all of his/her other travel costs (except DSMB) will be included in that clinical site's budget.**

17) The RFP describes the composition of the EC and SC and then says to assume that "16 EC/SC meetings" will be held. Should it be assumed that this is a total of 16 meetings and that the EC will meet the same day as the single-day SC meeting?
**Per the Statement of Work, there will be four in-person meetings of the SC, and up to four in-person meetings of the EC during the course of the project. When it is necessary for the EC to meet in person, the EC will meet after the SC on the same day. In addition to these in-person meetings, there will be up to 16 conference calls total for the SC and EC (combined) over the course of the project.**

18) Site visits are proposed for 1 visit every two years to the clinical centers (24 total visits for 12 clinical centers over 4 years). If this study is being regulated by FDA guidelines, is that sufficient?
**At this time, please propose costs as set forth in the RFP.**

19) In the RFP there are certain requirements specified for human subjects and clinical research studies, that seem to pertain to clinical sites, rather than to this contract for the DCC. Some examples of these requirements include:

- Article C.2.c.1 (pg. 6): Annual Technical Progress Report for Clinical Research Study Populations

- Article H.1 (pg. 13): Human Subjects

- Article H.2 (pg. 13): Required Education in the Protection of Human Research Participants

- Article H.17 (pg. 19): NHLBI Guidelines for Avoiding Conflicts of Interest for Multicenter Clinical Trials

- Article H.18 (pg. 20): Review of Manuscripts

- Section L.2. Subsection a. - General Instructions, item 13 (pg. 40): Institutional Responsibility Regarding Conflicting Interests of Investigators

- Section L.2. Subsection b. - Technical Proposal Instructions, paragraphs 5 through 16 (pgs. 45-55): sections regarding "Human Subjects"

- Section M (Evaluation Factors), Subsection a. - Human Subject Evaluation (pgs. 68 - 71).

Based on the above, please clarify: because the successful contractor under this RFP will not be a clinical site actually conducting the clinical research, are these criteria applicable for this solicitation?

**Yes. Although the DCC will not be a clinical site, it will have access to protected human health information and will play a key role in the execution of this multicenter clinical trial.**

20) Is the DCC required to have a Federal-wide Assurance? **No**

21) Because the DCC is not a clinical site, are the Position Sensitivity Designations and Background Investigations (pgs. 16-17, and pg. 56) applicable? If so, can NHLBI elaborate on these security requirements?

**Yes. Level 5C contractor employees only will need to undergo limited background investigations. The reason is that the DCC will have access to sensitive human health information.**

22) Attachment 3 - Statement of Work, item # 14: RFP states that offerors should assume 24 site visits over the course of the project. For bidding purposes, what location for the sites should be assumed for these travel costs?

**Please assume costs to/from a central location, such as Chicago, Illinois.**

23) Will a central laboratory be used for hematology/biochemistry evaluations? **No**

24) Who/which organization holds the database (i.e., where would contractor post/enter the data)?

**The DCC will hold the database.**

25) Who is responsible for creating/writing the database? Is this a responsibility of the DCC? **Yes**

26) What system is expected/desired for the coding and processing of adverse events and serious adverse events?

**This will ultimately be decided by the Steering Committee after the project starts, but DCC offerors can and should propose what they think is the best way to handle adverse event coding and reporting. Adverse event reporting to the NHLBI, Data and Safety Monitoring Board, and FDA will all be required.**

27) Is the DCC expected to hold a MedDRA license and provide coding personnel?

**This is not formally required at this time.**

28) Under Section M Subsection b. - Evaluation of Data Sharing Plan (pg. 71): It seems that this requirement pertains to the clinical sites, rather than the DCC - please confirm if it is applicable to this RFP. **Yes**

29) Item #12 of the Statement of Work (SOW) states that the DCC shall develop plans for either secure web-based electronic data entry or paper data entry of the CRFs. Would NHLBI prefer that we propose a method for handling data management (eg., electronic data entry) and focus on that method in the technical and business proposal or would the agency prefer that we summarize our abilities both in paper data entry and electronic data entry?
**Please summarize your abilities in both paper data entry and electronic data entry. The final decisions on data entry will be made by the Steering Committee.**

30) Will there be an NDA associated with this study? If so, does the DCC have any responsibility for providing data support for the submission?
**No. This drug is already licensed for primary pulmonary hypertension (unrelated to sickle cell disease).**

31) Will the DCC be responsible for the SAE collection and reporting to the FDA?
**The DCC will be responsible for all SAE collection in this study. It will be solely responsible for safety reporting to the Data and Safety Monitoring Board (DSMB). The DCC, together with the intramural NIH, will be responsible for safety reporting to the FDA.**

32) Will the DCC be responsible for any monitoring to ensure compliance with GCP?
**No. However, the DCC should provide independent medical monitoring in real time of adverse events occuring during the study.**

33) Regarding item# 17 of the SOW, we assume that if subcontracts with additional clinical sites are needed, the agency would provide additional funding via a contract modification. Does the agency expect us in our proposed budget to address this potential contractual need? **No**

**PART 2. BUSINESS QUESTIONS. The following questions and answers are provided for clarification and informational purposes based on inquiries from potential offerors.**

1) Section L, 1.g. ESTIMATE OF EFFORT (Page 34): What is the FTE number of hours that the level of effort is based upon? **2080**

2) Section L 2. c. (7) f) Subcontractors (Page 66): Is a complete cost proposal in the same format as the offeror's cost proposal required if the subcontractor uses commercial unit pricing and a unit price justification letter from the subcontractor is included in the offeror's proposal?
**Not at this time.**

3) Section L 2. c. (9) Representations and Certifications (Page 67): Is a copy still required if the contractor is currently registered on-line via the ORCA (Online Representations and Certifications Application)?
**Yes**

4) It is clear from the RFP that the contractor should not include shipping costs for specimens. However, should the contractor include the cost of specimen collection kits or will this cost be paid under separate contract with the NHLBI Blood Specimen Repository?

**This cost will be paid under separate contract with the NHLBI Biological Specimen Repository.**

5) Section L.2. Subsection c. - Business Proposal Instructions (pg. 59), Item 1 states that proposal costs should be "broken down as follows" (then the 3 Phases are listed, along with their anticipated periods of performance). For Phase II, does NHLBI also desire a cost breakdown for each of the 3 sub-periods as well (i.e. 6/30/07- 6/29/08, 6/30/08 - 6/29/09, 6/30/09 - 12/29/09)? **Yes**

**Part 3. REVISION TO STATEMENT OF WORK.** The statement of work is revised to include the additional tasks listed below.

19) The DCC shall coordinate central reading of all echocardiograms (following an initial local reading) for the screening, main trial, and extension stages of this project. The DCC shall collect copies of echocardiogram data sets (in digital or magnetic tape form) from all clinical centers during Phase II, will pay charges for shipping batches of echocardiogram data sent to the DCC from clinical centers, and will distribute copies of the data sets for central review. The DCC will coordinate the timely (on a schedule set by the Steering Committee) secondary review of all echocardiogram data, including collection of the results on paper or web-based case report forms. **[For solicitation purposes, the DCC will not be responsible for identifying the site(s) for centralized reading, nor their costs].**

20) The DCC shall provide an independent medical monitor for this project. The medical monitor shall be responsible for rapid initial review of all adverse event reports arising in this project, and will assist the DCC with adverse event reporting to the DSMB, NHLBI, and FDA.

**Part 4. REVISION TO RFP. Pages 55-58 of the RFP are incorrect. The text below represents the correct wording of these pages.**

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

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

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

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

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

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

(16) **HIV Antiretroviral Treatment Trials**

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

http://grants.nih.gov/grants/guide/notice-files/NOT-OD-05-038.html.

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

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

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

- A statement confirming that at the time of the offer, no sources of antiretroviral treatment could be identified;
- A description of how this information will be conveyed to the trial participants;
- A commitment to continue to explore potential sources as the trial proceeds.

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

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

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

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

(1) Category of Safeguarded Information

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

**[ ]** Non Sensitive Information

**[x ]** Sensitive Information

(2) Security Level Designations

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

**Level high 3** applies to the sensitivity of the data.

**Level medium 2** applies to the operational criticality of the data.

The overall Security Level designation for this requirement is

**Level high 3** .

(3) Position Sensitivity Designations

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

**[ ]** **Level 6C: Sensitive - High Risk (Requires Suitability Determination with a BI).**

Contractor employees assigned to a Level 6C position are subject to a Background Investigation (BI).

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

**[ ]** **Level 1C: Non Sensitive (Requires Suitability Determination with an NACI).**

Contractor employees assigned to a Level 1C position are subject to a National Agency Check and Inquiry Investigation (NACI).

Upon award, the contractor will be required to submit a roster of all IT staff working under the contract. The Government will determine the appropriate level of suitability investigation required for each staff member.

Contractor employees who have met investigative requirements within the past five years may only require an updated or upgraded investigation.

(b) **Information Technology (IT) System Security Program**

The offeror's proposal must:

(1) The offeror's SSP shall provide detail commensurate with the size and complexity of the requirements of the Statement of Work. The minimum areas to be addressed shall include, but are not limited to administrative, technical, and physical security as follows:

(I) Security Awareness Training

(ii) Access Control

-Network (ex: firewall)

-System (ex: network OS, tcp wrappers, SSH)

-Application (ex: S-LDAP, SSL)

-Remote Access (ex: VPN)

-Monitoring and support (ex: IDS, pager, NOC)

(iii) Protection against data loss

-OS security (ex: patch management, configuration)

-Application security (ex: patch management)

-Database security

-Back-up and recovery

-Fault tolerance, high availability

(iv) Malicious Code Protection (ex: Antivirus, filtering of e-mail attachments, etc)

(v) Physical Security

-Access control (ex: locks, guards)

-Power condioning and/or UPS

-Air conditioning

-Fire protection

(2) The offeror's SSP shall demonstrate that it complies with the Computer Security Act of 1987; Office of Management and Budget (OMB) Circular A-130, Appendix III, "Security of Federal Automated Information Systems;" and the DHHS Security Program Policy.

(3) Offerors shall include an acknowledgment of its understanding of the security requirements.

(4) Offerors shall provide similar information for any proposed subcontractor developing or accessing an AIS.

(c) **Required Training for IT Systems Security**

DHHS policy requires that contractors receive security training commensurate with their responsibilities for performing work under the terms and conditions of their contractual agreements.

The successful offeror will be responsible for assuring that each contractor employee has completed the following NIH Computer Security Awareness Training course prior to performing any contract work: http://irtsectraining.nih.gov/. The contractor will be required to maintain a listing of all individuals who have completed this training and submit this listing to the Government.

Additional security training requirements commensurate with the position may be required as defined in OMB Circular A-130 or NIST Special Publication 800-16, “Information Technology Security Training Requirements." These documents provide information about IT security training that may be useful to potential offerors.

(d) **References**

The following documents are electronically accessible:

(1) OMB Circular A-130, Appendix III:

http://www.whitehouse.gov/omb/circulars/a130/a130appendix_iii.html

(2) DHHS Personnel Security/Suitability Handbook:
http://www.hhs.gov/ohr/manual/pssh.pdf

(3) DHHS Information Security Program Policy:
http://www.hhs.gov/read/irmpolicy/FINALHHSInformationSecurityProgramP.doc

(4) NIH Applications/Systems Security Template:
http://irm.cit.nih.gov/security/secplantemp.doc

(5) NIH Security Plan Outline:
http://irm.cit.nih.gov/nihsecurity/Security_Plan_Outline.doc

(6) NIST Special Publication 800-16, “Information Technology Security Training Requirements:”

http://csrc.nist.gov/publications/nistpubs/800-16/800-16.pdf

Appendix A-D:
http://csrc.nist.gov/publications/nistpubs/800-16/AppendixA-D.pdf

(7) NIH CIT-Policies, Guidelines and Regulations:

Table 1 - Categories of Safeguarded Agency Information:

http://irm.cit.nih.gov/security/table1.htm

Table 2 - Security Level Designations for Agency Information:

http://irm.cit.nih.gov/security/table2.htm

Table 3 - Positions Sensitivity Designations for Individuals Accessing Agency Information:

http://irm.cit.nih.gov/security/table3.htm

(8) NCI Information Technology Security Policies, Forms and Procedures for Contracts:

http://ais.nci.nih.gov/