DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Heart, Lung, and Blood Institute
Office of Acquisitions, DERA
Rockledge 2, Room 6016
6701 ROCKLEDGE DR MSC7902
BETHESDA MD 20892-7902

Phone: (301) 435-0340
Fax: (301) 480-3338

October 10, 2007

Reference: Request for Proposals No. NHLBI-HR-08-06
Subpopulations and Intermediate Outcome Measure in COPD Study SPIROMICS: Genomics and Informatics Center

Dear Ladies and Gentlemen:

You are invited to submit a proposal in accordance with the requirements of the above referenced Request for Proposal (RFP). This RFP is prepared in accordance with the Uniform Contract Format prescribed by the Federal Acquisition Regulation.

Your attention is directed to Section C which contains the Statement of Work and Reporting Requirements. Sections L and M, includes proposal preparation instructions and evaluation factors for award. Technical information specific to this solicitation is addressed in Section L, Technical Proposal Instructions. General Instruction, and Business Proposal Instructions are also found in Section L. The balance of solicitation contains provisions, clauses and special requirements which will be made a part of any resultant award and therefore should be reviewed by you as to the effects on performance capability and technical and cost considerations in the development of your proposal. The contract will be tailored to the final negotiations and modified, as necessary, for the costs and other elements as negotiated prior to award.

Please note the due date for proposals is December 15, 2007. The address for submission of proposals is contained in Section J, Attachment 1. Questions regarding this RFP should be directed to my attention.

Yours truly,

Pam McCord-Reynolds

Pam McCord-Reynolds
Contract Specialist
CVLD Contracts Branch

SPIROMICS—GIC
NHLBI-HR-08-06

Attachment 1
Additional Information Specific to this Solicitation

- Section C - Statement of Work/Reporting Requirements
  - C.1. Statement of Work
  - C.2. Reporting Requirements
- Section F - Deliveries or Performance
  - F.1. Deliveries
- Section L - Instructions to Offerors

Additional Technical Proposal Instructions

a. Background and Overview of Study
b. Phasing
c. Study Committees
d. Estimated Level of Effort
e. Page and Formatting Limitations
f. Technical Proposal Table of Contents
g. Travel
h. Constraints
i Offerors Must Address
j Phenotyping Example for Proposal Purposes

Additional Business Proposal Instructions

a. Business Proposal Table of Contents
b. Cost Proposal Worksheet (posted with RFP)
c. Packaging and Delivery of the Proposal
d. Propoal Intent Response Sheet

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. The contractor shall participate as the Genomics and Informatics Center in a cooperative effort with other Clinical Centers (CC), and Radiology Center (RC) investigators and representatives of the National Heart, Lung, and Blood Institute (NHLBI) to form a Steering Committee (SC) that serves as a governing body of SPIROMICS. Specifically the Contractor shall:

Throughout the contract period (7/01/2008 - 7/30/2015, 7 years)

1. Provide expertise in bioinformatics, in the design and conduct of clinical research studies, in pulmonary medicine, and in genetics, genomics, and proteomics. Provide support for protocol development, including study design, sample size calculations and simulations, and for the analysis of study data.

2. Provide administrative guidance, oversight, and support for SPIROMICS as a whole; promoting interactions among the SPIROMICS Centers and assuring coordination and uniformity of study activities at all sites.

3. Plan, make arrangements for, and support the meetings of the Steering Committee (SC) and its subcommittees, of the External Advisory Committee (EAC), and of the Observational and Safety Monitoring Board (OSMB). Prepare minutes of SC and External Advisory Committee meetings and distribute these to the members. Prepare draft minutes of the open sessions of all OSMB meetings and teleconferences.

4. Make payments for the SC chair.

5. Make payments for the honoraria and travel expenses of academic members of the EAC.

6. Make payments for the honoraria and travel expenses of OSMB members.

7. Develop and maintain a password-protected study web site for the distribution of study documents, forms, and information, including indicators of study progress and performance. Develop and maintain a public web site that provides information about SPIROMICS to prospective research subjects. This information shall include a summary of study aims, design, schedule, and eligibility criteria; a listing of the Clinical Centers (CCs) with contact information; and a link to the National Heart, Lung, and Blood Institute (NHLBI) public web site. Accepted industry tools and applications shall be used to develop the web sites. The sites must comply with all applicable Federal regulations, including Section 508 of the Rehabilitation Act of 1973 (29 USC 794d). See http://www.section508.gov and http://www.nih.gov/icd/od/ocpl/resources/wag/.

8. Establish and maintain a computer system and software needed for the storage and analysis of study data. It is anticipated that data will be collected from approximately 3,200 subjects and that it will include demographics, medical history, medications, results of clinical laboratory tests, outcomes, and responses to several questionnaires, as well as extensive genetic, genomic, and proteomic data. Security provisions shall be put in place to prevent the theft or unauthorized release of study data. A backup electronic copy of study data shall be maintained off-site.

9. Convey EAC recommendations to the SC and the NHLBI.

10. Report to the OSMB regarding SC recommendations, study performance and progress, subject enrollment, and adverse events.

During Phase I (7/31/2008 to 4/30/2009, 9 months)

11. Have primary responsibility for writing the SPIROMICS Protocol document.

12. Develop and curate a controlled vocabulary, with definitions and ontological relationships, for all key terms needed to define the SPIROMICS cohorts, phenotypes, and outcomes using best practices and existing non-proprietary sources as appropriate.

13. Write a model informed consent document and develop of checklist of key elements.

14. Write and maintain a Manual of Operations that details the methods, procedures, and operations of SPIROMICS.

15. Develop study forms for the collection of data at the CCs, subject education materials, and tools for advertising SPIROMICS that can be easily adapted for local use.

16. Develop a system, with realtime error checking, for the electronic transfer of study data from the CCs and RC to the GIC.

17. Develop procedures for both automated and manual audits of data quality, for data quality control, and for the correction of data entry errors.

18. Develop procedures for assuring CC compliance with the SPIROMICS Protocol and for informing the NHLBI when there are deviations from the Protocol.

19. Submit the Protocol and the model informed consent document for review to an OSMB 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 OSMB reviews.

20. Submit the NHLBI-approved SPIROMICS Protocol (or summary thereof) and model informed consent document for local Institutional Review Board (IRB) approval.

21. Provide a member to the SC. With the assistance and guidance of the SC:

    a. Develop a Protocol for SPIROMICS that includes a summary of the study; the background and significance; the study design and methods including eligibility requirements, phenotyping measures, outcome assessments, and statistical analyses; plans for training of staff; plans for recruitment and retention; plans for monitoring and reporting data quality and subject safety; 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; and limitations of the study. SPIROMICS shall be designed to 1) identify subpopulations of COPD subjects that are likely to be similar with respect to the molecular mechanism of disease and 2) identify and validate indices of disease severity and progression that are likely to be useful as intermediate outcome measures in clinical trials.

b. Develop a controlled vocabulary and definitions for key terms needed to describe SPIROMICS cohorts, phenotypes, and outcomes.

c. Develop a model informed consent document.

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

e. Write a Manual of Operations that details the methods, procedures, and operations of SPIROMICS.

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

During Phase II (5/1/2009 to 01/31/2015, 5 years 9 months)

23. Obtain and maintain IRB approval(s) for all participating sites.

24. Plan, coordinate and conduct the training and certification of CC staff in SPIROMICS procedures and data and specimen management.

25. Develop metadata definitions representing the SPIROMICS data set, annotate the data, and design data transfer protocols and standards. The metadata elements must be interoperable with an accepted information grid. Where appropriate, the contractor may utilize existing, non-proprietary informatics tools, resources, and standards.

26. Assure that the informed consent documents approved by the IRBs of the CCs contain all of the key elements of the SPIROMICS model informed consent document.

27. Assist the CCs with electronic submission of study data and the correction of entry errors. Communicate with the CCs as needed to obtain missing data.

28. Establish and maintain a repository of study biospecimens and assist the CCs with shipments of biological specimens. The repository shall employ facilities, such as an emergency generator, that will ensure the maintenance of biospecimens without degradation. Package and ship collections of samples to core laboratories that are designated to perform biomarker, genetic, genomic, and/or proteomic assays with SPIROMICS specimens. Manage the transfer of study data from core laboratories to the GIC, including the results of high throughput genetic and genomic analyses. Incorporate core laboratory data into the SPIROMICS dataset.

29. Organize and conduct telephone conference calls involving staff of the CCs (e.g., clinical coordinators) to assure uniformity of study performance, identify problems with study procedures and tools, and develop potential solutions to these problems.

30. Implement study procedures for data quality control and assurance and error correction. Refine and improve these procedures as needed to ensure the integrity of study data.

31. Implement procedures for assuring CC and RC compliance with the SPIROMICS Protocol. Refine and improve these procedures as needed. Monitor CC performance and conduct site visits of CCs as needed to investigate problems of performance or data quality.

32. Monitor study progress. Prepare statistical and graphical summaries of enrollment, characteristics of screened individuals determined to be ineligible, data completeness, data quality, and protocol compliance.

33. Prepare interim summaries of study activities and outcomes for review by the OSMB. Make presentations of study data to the OSMB.

34. Report adverse events and unanticipated problems in accordance with NHLBI/NIH policies.

35. Submit recommendations of the SC for modifications in protocol or model informed consent documents to the OSMB for review. The OSMB will advise the NHLBI regarding approval of changes in the Protocol. Revise the Manual of Operations as required by protocol revisions approved by the NHLBI on the basis of OSMB reviews.

36. Perform statistical analyses as required for publications describing SPIROMICS design and procedures and interim data. Participate with other SPIROMICS investigators in the preparation of presentations and manuscripts.

37. Provide member of the SC. This committee shall:

    a. Identify problems that might compromise the successful completion or scientific integrity 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.

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

38. The contractor shall not begin Phase III activities until the final study contact has been completed for all enrolled subjects.

During Phase III (2/1/2015 to 7/30/2015, 6 months)

39. Work with the CCs and RC to obtain missing data. Assess data quality, and work with the CCs, RC, and core laboratories to resolve issues related to the reliability of data.

40. Perform statistical analyses of study data. Participate with other SPIROMICS investigators in the preparation of presentations and manuscripts for the reporting of study results.

41. Prepare and provide to the NHLBI a limited access data set in accordance with the NHLBI Policy for Distribution of Data (available at: http://www.nhlbi.nih.gov/resources/deca/policy_new.htm). This data set shall include genetic, genomic, and proteomic data obtained by SPIROMICS.

42. Disseminate study results.

43. Ship unutilized biospecimens to a repository to be identified by the NHLBI, together with an electronic codebook that links specimens to individual data in the limited access data set.

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.

a. **Technical Reports**

1) Quarterly Technical Progress Reports: The GIC shall submit reports quarterly that document and summarize the results of the contract, including recommendations and conclusions based on experience and results achieved. A report is not required for the period when the Final Technical Report is due. The GIC shall submit the reports in a concise narrative form and include a table of contents, tabular material, and exhibits as needed. Extensive reference material is not desired, but such references needed to fully understand events may be included. The reports shall be written in sufficient detail to be used as a reference document. The reports shall include but not be limited to:

(a) A cover page containing the following information:

1) Contract number

2) Contractor's name and address

3) Principal investigator’s name

(b) Description of overall progress including:

1) List of current personnel.
2) Current problems which may impede progress along with proposed corrective actions.
3) Study progress and performance, including information about the inclusion of women and members of minority groups and their subpopulations for each study being performed under this contract (in accordance with the Inclusion Enrollment Report format included in Section J), follow up rates, forms completion, and data quality.
4) Progress made in scientific research, including a list of manuscripts published or accepted for publication related to the trial objectives.
5) Work to be performed during the next quarter.

2) Final Technical Report: This report is to include a summation of the work performed and results achieved for the entire contract period of performance. This report shall be in sufficient detail to describe comprehensively the results achieved. The report shall also include the final Inclusion Enrollment Report for clinical research populations (in accordance with the Inclusion Enrollment Report format included in Section J).

b. **Other Deliverables**

3) Adverse Events Reports: These reports shall be submitted in accordance with NHLBI policies found at: http://www.nhlbi.nih.gov/funding/ethics.htm

4) Study Documents: The GIC shall provide paper and electronic copies of the initially approved SPIROMICS Protocol, model informed consent document, Manual of Operations, patient education documents, advertising materials, and study forms. Electronic copies of these documents shall also be provided after each revision, if any.

5) Checklist and Informed Consent Documents: A completed checklist, verifying the inclusion of all key elements of the model informed consent document, for each informed consent document approved by a CC IRB. 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.

6) Study Web Site: A CD or DVD copy of all pages of the Study Website.

7) Public Web Site: A CD or DVD copy of all pages of the Public Website.

8) SC Meeting Minutes: Minutes of SC meetings and telephone conference calls.

9) EAC Meeting Minutes: Minutes of EAC meetings and telephone conference calls.

10) OSMB Meeting Minutes: Minutes of OSMB meetings and telephone conference calls.

11) Controlled Vocabulary/Ontology: This shall consist of a list of terms that are sufficient for precisely describing the SPIROMICS cohorts, subject phenotypes, and outcome measures, together with definitions of these terms and a description of the ontological relationships between terms in the context of pulmonary research.

12) Metadata Elements/Data Transfer Standards: These shall employ a uniform system of annotation and be appropriate for the sharing of SPIROMICS data in a standardized format. The metadata elements must be interoperable with an accepted information grid.

13) Published Abstracts and Manuscripts.

14) Dissemination Plan: The GIC shall prepare a dissemination plan to effectively communicate the study results to those who can use this knowledge to improve the efficiency of COPD research. It is anticipated that this plan will include dissemination via submission for publication in scientific literature and presentation at national meetings.

15) Biological Samples: Collection of biospecimens assembled for phenotypic analyses.

16) Biospecimen Collection: All unutilized biospecimens, together with an index of the codes used for labeling.

17) Limited Access Data Set: The GIC shall provide a final limited access data set for SPIROMICS with full documentation. The data set shall include all phenotypic and

outcome data for all subjects with reductions and redactions only as needed to ensure subject privacy. The data set and documentation shall be prepared in accordance with the NHLBI Limited Access Data Policy: http://www.nhlbi.nih.gov/resources/deca/policy_new.htm).

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	Quarterly Technical Progress Reports	Project Officer Contracting Officer	Thirty days after the end of the reporting period.
2	Final Technical Report	Project Officer Contracting Officer	On or before contract expiration date
3	Adverse Event Reports	Project Officer OSMB	In accordance with NIH and NHLBI policies
4	Study Documents	Project Officer Contracting Officer CCs and RC	Prior to initiation of Phase II activities
5	Checklist and Informed Consent Documents	Project Officer	Within 8 calendar days of receipt of IRB approval documents from the CC
6	Study Web Site	Project Officer	Prior to initiation of Phase II activities
7	Public Web Site	Project Officer	Prior to initiation of Phase II activities
8	SC Meeting Minutes	Project Officer	Within 15 calendar days after meeting
9	EAC Meeting Minutes	Project Officer	Within 15 calendar days after meeting
10	OSMB Meeting Minutes	Project Officer	Within 8 calendar days after meeting
11	Controlled Vocabulary/ Ontology	Project Officer	3 months after initiation of Phase II
12	Metadata Elements/Data Transfer Standards	Project Officer	18 months after initiation of Phase II

Item	**Description**	**Deliver to**	**Delivery Schedule**
13	Published Abstracts and Manuscripts	Project Officer Contracting Officer	Within 30 days after publication
14	Dissemination Plan	Project Officer Contracting Officer	Within 30 days after initiation of Phase III activities
15	Biological Samples	Core Laboratories to be identified	According to Protocol and Manual of Operations
16	Biospecimen Collection	Repository to be identified	On or before contract expiration date
17	Final Limited Access Data Set	Project Officer	90 days prior to contract expiration date

Copies of deliverables shall be sent to the following addresses:

Addressee	**Item**	**Quantity**
Project Officer for SPIROMICS National Heart, Lung and Blood Institute Division of Lung Diseases Rockledge Two Building, Room 10144 6701 ROCKLEDGE DR MSC 7952 BETHESDA MD 20892-7952	1-14 17	1 1
Contracting Officer for SPIROMICS National Heart, Lung and Blood Institute Office of Acquisitions, DERA Rockledge Two Building, Room 6016 6701 ROCKLEDGE DR MSC 7902 BETHESDA MD 20892-7902	1-2 4 13-14	1 1 1
OSMB Members (To be identified)	3	1
Clinical Centers and Radiology Center (To be identified)	4	1
Core Laboratories (To be identified)	15	In accordance with Protocol
Biospecimen Repository (To be identified)	16	1

SECTION L—INSTRUCTIONS TO OFFERORS

ADDITIONAL TECHNICAL PROPOSAL INSTRUCTIONS

a. **Background and Overview of Study**

COPD affects 12-24 million people in the U.S. and is a major cause of disability. Mortality due to COPD has risen sharply over the past several decades despite a major decline in smoking prevalence in the 1970's and 1980's. COPD is now the fourth leading cause of death among adults, with an annual mortality of approximately 125,000 persons. There is no cure, and treatments are only moderately effective at relieving symptoms. Novel approaches for prevention and treatment of COPD are urgently needed.

While airflow obstruction is the defining characteristic of COPD, there are many other manifestations of COPD, including cough, sputum production, emphysema, exercise impairment, decreased arterial oxygen content, dyspnea, weight loss, and exacerbations of symptoms. Individual patients often show some characteristics of the disease severely while being relatively normal with respect to others, and within the COPD population there is only poor correlation among the various indicators of disease severity. This heterogeneity suggests that a number of different pathogenetic processes may contribute variably to the development and progression of COPD. From a practical standpoint, heterogeneity imposes a major barrier to progress in clinical research. It requires the study of large numbers of subjects to sample the diverse population, and it weakens the value of any single clinical parameter as a measure of outcome. Despite the fact that recent progress in pathogenetic research has suggested rational pathways and targets for intervention, few clinical trials are being performed. This is largely due to the large sample sizes and long follow-up times that are required – even for seeking proof of concept for a putative therapy. Therapeutic trials in COPD would be greatly accelerated by: 1) a means of selecting pathogenetically homogeneous subpopulations, and 2) the identification of intermediate outcome measures that detect disease progression or treatment response within a time frame of one year or less.

SPIROMICS will support the prospective collection and analysis of phenotypic, biomarker, genetic, genomic, and clinical data from subjects with COPD for the purpose of identifying subpopulations and intermediate outcome measures. This observational study will likely obtain 1) baseline historical, clinical, biomarker, CT radiological, genomic, and genetic data; 2) repeat CT images, biomarkers, and gene expression profiles after a relatively short period (e.g., 9-12 months after enrollment); and 3) long-term follow-up by conventional measures of COPD progression (rate of decline in FEV_1, exacerbation frequency, decline in quality of life, and mortality) over three or more years. Putative subpopulations will be identified by cross-sectional analyses of the radiological, biomarker, genomic, and genetic data obtained at baseline. Follow-up clinical data will be used to identify and validate intermediate outcome measures, such as CT image, biomarker, and genomic measures whose spontaneous changes over a period of approximately one year correlate with long-term outcomes.

SPIROMICS contractors will design and conduct an observational study of subjects with COPD. Molecular fingerprinting and extensive subject phenotyping will be performed to identify disease subpopulations and to identify and validate surrogate markers of disease

severity which will be useful as intermediate outcome measures for future clinical trials. Secondary aims are to clarify the natural history of COPD, to develop bioinformatic resources that will enable the utilization and sharing of data in studies of COPD and related diseases, and to create a collection of clinical, biomarker, radiographic, and genetic data that can be used by external investigators for other studies of COPD.

The ultimate goal of the National Heart, Lung, and Blood Institute (NHLBI) is to enable clinical trials of potential therapies for COPD and speed the development of treatments that will improve the length and quality of life for patients with COPD.

Approximately 3200 research subjects will be enrolled, phenotyped, and followed at approximately six Clinical Centers (CCs). A Genomics and Informatics Center (GIC) will have primary responsibility for developing a scientific plan for achieving study aims; analyzing phenotypic and high-throughput molecular data; operating a repository of biospecimens; developing bioinformatic resources; data management; providing overall management and oversight of the study; and disseminating study results. The Radiology Center will have primary responsibility for standardizing imaging methods at the Clinical Centers; establishing a repository of CT image data; assessing and assuring quality of CT images; and analyzing CT images to obtain quantitative measures that may indicate the presence and/or severity of COPD or other lung diseases.

b. **Phasing** — SPIROMICS will be performed in three Phases over a seven year period:

Phase	Description of Primary Activity	Dates
I	Protocol development and forms design	07/31/2008 – 04/30/2009
II	Subject enrollment and phenotyping	05/01/2009 – 01/31/2015
III	Data analysis and dissemination of results	02/01/2015 – 07/30/2015

Phase I (Planning and Preparation; 9 months): During Phase I, SPIROMICS investigators will meet to develop the Protocol(s), model informed consent document(s), Manual of Operations, and study forms. The SC will develop procedures and tools for training of staff, data management, and quality assurance/quality control of study activities and data. The RC will have primary responsibility for standardizing imaging methods at the CC. The GIC will have primary responsibility for developing a scientific plan for achieving study aims.

Phase II (Subject Enrollment, Characterization, and Follow-up; 5 years 9 months): This phase will include training of staff, subject screening, recruitment, evaluation, and follow-up at the CCs. The RC will establish a repository of CT image data; assess and assure quality of CT images; and analyze CT images to obtain quantitative measures. The GIC will analyze phenotypic and high-throughput molecular data; operate a repository of biospecimens; develop bioinformatic resources; manage data; provide overall management and oversight of the study; and disseminate study results. Phase II will conclude when all subjects have been enrolled and their follow-up assessments completed.

Phase III (Data Analysis and Dissemination; 6 months): The final phase will include data analysis, reporting, and sharing.

c. **Study Committees**

The SC will consist of a study Chairperson selected by the NHLBI; a representative from each of the six CCs, GIC, RC; and the NHLBI Project Officer. The Committee will work during Phase I to develop the SPIROMICS Protocol, MO, and study forms. During Phase I the SC will meet approximately monthly either in person or by telephone conference call.

The SC will monitor study progress during Phase II and make recommendations for changes in study procedures as appropriate. During Phase III the Committee or a delegated subcommittee will analyze the data and report the study findings. During Phases II and III the SC will meet twice a year and hold monthly telephone conference calls. Each CC, GIC, RC, study Chair, and NHLBI will have one vote on issues pertaining to SPIROMICS. Subcommittees of the SC will be established as needed for specific purposes (e.g., Executive and Publications Subcommittees).

An External Advisory Committee (EAC) will provide scientific advice to the SC and the NHLBI on issues of phenotyping, outcome measures, biospecimen processing and analysis, genetics, genomics, proteomics, data analysis, study feasibility, and the potential impact of SPIROMICS results on future clinical trials. EAC members will be appointed by the NHLBI. This Committee is expected to consist of approximately nine voting members, three members will be from academic institutions not affiliated with SPIROMICS and up to six members from pharmaceutical or biotechnology companies which have made substantial contributions or commitments to SPIROMICS (such as monetary contributions, subject data and specimens procured in separate studies that incorporate the SPIROMICS Protocol, or in kind contributions of high throughput specimen analyses). Additional scientific experts from these companies may attend meetings and participate in discussions of the EAC with the prior approval of the NHLBI. The EAC will meet three times during Phase I and annually during Phase II. EAC members may be acknowledged as a group in publications of the SPIROMICS group, but it is expected that the members of the Committee will not participate directly in data analysis or serve as authors on SPIROMICS papers.

A Observational and Safety Monitoring Board (OSMB) will be established to 1) evaluate the SPIROMICS Protocol and the model informed consent documents recommended by the SC and 2) monitor overall study progress and performance, data quality, and subject safety. The Board will periodically evaluate study procedures, review reports of adverse events, and perform interim assessments of study outcomes. This Committee is expected to consist of approximately six members. The Board will meet once during Phase I and once per year during Phases II and III. The OSMB will also conduct teleconferences as needed. The Board is advisory to the NHLBI.

d. **Estimated Level of Effort**

The Government considers the types of personnel and estimated levels of effort identified below to be required for completion of the GIC objectives. 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. In addition to personnel of the GIC, the contractor will be responsible for the travel and salary/honoraria costs of the Study

Chair, to be appointed by the NHLBI. Effort by the Study Chair is estimated to be 15% in all phases.

Labor Category	% Effort Phase I	% Effort Phase II	% Effort Phase III
Principal Investigator	30	30	30
Co-investigator - Pulmonary	30	10	20
Co-investigator - Genetics	20	10	20
Co-investigator - Genomics	20	10	20
Co-investigator - Proteomics	20	10	20
Statistician	50	20	100
Bioinformaticist	50	50	50
Semantic Specialist	100	17*	-
Project Manager/Coordinator	50	100	25
Repository Technician	25	67**	25
Programmer	100	35	100
Data Manager	50	100	100
Data Analyst	-	50	100
Secretary/Scheduler	50	50	50
Total	595	559	660

* Levels of effort estimates by year are outlined in the Excel workbook posted with the solicitation.

Offerors shall ensure that no personnel are 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.

e. **Page and Formatting Limitations**

The Technical Plan (objectives, approach, methods and procedures, schedule and phenotyping protocol) of the technical proposal shall not exceed 40 single-sided pages or 20 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. Appendices shall not exceed a total of 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. 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.

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.

f. **Technical Proposal Table of Contents**

1. Cover Page Page 1

   Cover page should include: RFP Title and Number, Name of Organization, Name of Principal Investigator, Address, and Telephone Number.

2. Table of Contents Page 2

3. Abstract/Project Objectives (NIH 1688) Page 3

4. Government Notice of Handling Proposals Page 4

5. Technical Plan Page 5—#

   The Technical Plan shall not exceed 40 single-sided pages or 20 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) Schedule Page #
   (5) Analysis Plan (including molecular phenotyping and data analysis) Page #
   (6) Subcontractors (if applicable) Page #

6. 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) Other Staff (Bioinformaticist, Coordinator) Page #

   [Note: Include a resume/CV/biosketch for PI and co-investigators in

   the Appendices]

7. Facilities, Equipment, and Other Resources Page #

   Describe all facilities, equipment and other resources available.

8. Summary of Related Activities Page #

9. Technical Proposal Cost Summary Page #

10. Human Subjects Page #

    See Instructions to Offerors, Technical Proposal Instructions.

11. IT System Security Plan Page #

12. Appendices Page #

Appendices shall be limited to 30 single-sided pages or 15 double-sided pages.

g. **Travel**

The GIC will be responsible for providing meeting rooms for all SC, EAC, and OSMB meetings. The GIC will also be responsible for paying the travel and honorarium costs of the Study Chair, OSMB members and the three academic members of the EAC. Offerors should propose costs for six members of the OSMB and three academic members of the EAC. Honorarium shall not exceed $200 per day for OSMB and EAC academic members. *[Note: OSMB and EAC member meeting expenses, e.g., coffee breaks, and honorarium, should be reflected in the cost proposal as Other Direct Costs. Travel related expenses, e.g., airfare, perdiem, and ground should be reflected as Travel Costs. No travel related expenses should be included for the six non-academic EAC members.]*

During Phase I, the PI and up to two co-investigators and up to two other staff will attend five meetings of the SC. These meetings will take place in Bethesda, MD, and will each last two days. The PI and SC Chair will attend three meetings of the EAC and one meeting of the OSMB. These meetings will take place in Bethesda, MD, and will each last one day.

In the first year of Phase II, GIC staff will conduct a meeting for training CC staff in study operations. For proposal purposes, offerors may assume that this meeting will take place at the GIC location, four staff from each CC, the PI from the RC, NHLBI Project Officer, and study Chair will attend this training. During Phase II, the PI, two co-investigators, and two other staff will attend semiannual meetings of the SC in Bethesda, MD, each lasting one day. The PI and one other staff member will attend annual meetings of the EAC and OSMB in Bethesda, MD, each lasting one day. The PI and two other staff members will also participate in site visits (no more than four total) to CCs as needed. For the purposes of estimating site visit costs, the offeror should assume that the GIC will visit sites in Los Angeles, Denver, Chicago, and Washington, DC, during year two.

During Phase III, the PI, two co-investigators, and two other staff members will attend two meetings of the SC in Bethesda, MD, each lasting one day. The PI and one other staff member will attend a final meeting of the EAC and OSMB in Bethesda, MD, during Phase III. To disseminate the results of the study, the PI and one co-investigator will also attend one national scientific meeting. For proposal purposes the offeror should assume that this meeting will be held in Chicago, IL ,and will last three days.

h**. Constraints**

Contributions by partner organizations such as pharmaceutical companies are being explored. These contributions may be in the form of funding for the study, performance of assays or data analysis, or contributions of subject data and specimens collected. It is anticipated that non-government contributions of funds, data, specimens, and assays will have a total value of approximately $12,000,000. The scope of the overall study, including the number of CCs, the number of subjects enrolled, and the extent of clinical and molecular phenotyping may depend on the contributions of partner organizations. The Government reserves the right to make no contract awards for SPIROMICS if the total funds available at the planned time of award (including contributions of both the

Government and partner organizations) are insufficient to support a study of sufficient size to achieve the stated objectives.

i. **Offerors Must Address**

The Technical Proposal must document the capabilities of the offeror and plans for carrying out all aspects of the Statement of Work. Specifically, the offeror's proposal shall:

1. Identify the names, degrees, training, qualifications, role in project, and effort for each staff member proposed.

   [Note: The personnel and levels of effort listed in Section L were formulated by NHLBI staff experienced in the conduct of multi-center research studies, utilizing recent experience. These estimates are for information only and are not to be considered restrictive for proposal purposes.]

2. Document the expertise and experience of the PI in the design, conduct, and administration of large, multi-center clinical research programs, including expertise in data management, quality control, and data analysis. The proposal shall document the expertise and experience of the PI or a co-investigator in clinical research related to COPD and, specifically, in clinical and laboratory phenotyping of subjects with COPD. The proposal shall document the expertise and experience of the PI, co-investigators, and other professional staff in each of the following areas as evidenced by training, external support, and publications: biostatistics, bioinformatics (including development and use of controlled vocabularies, ontologies, metadata elements, and data transfer protocols), genetics, genomics, and proteomics.

3. Document the experience of the Project Manager/Coordinator and other support staff in the coordination and administration of multi-center clinical research studies, including electronic data entry and transmission with error checking and correction, adverse event reporting, record keeping, and methods for maintaining the confidentiality of personal data.

4. Document the expertise and experience of staff in the transport, processing, labeling, and storage of biospecimens.

5. Describe in detail plans and a timetable for identification of terms necessary for precise description of SPIROMICS cohorts, phenotypic measures, and outcomes; for identification or development and for review by subject matter experts of definitions for these terms; and for the creation and curation of a controlled vocabulary and ontology appropriate for SPIROMICS data. Describe in detail plans and a timetable for the development, review, and curation of metadata elements describing the SPIROMICS data set, for expressing these metadata elements in a format that is interoperable with an existing information grid, and for standardized data transfer.

6. Describe in detail proposed plans for the molecular phenotyping of SPIROMICS subjects by high throughput analyses of blood, urine, and sputum specimens obtained from all subjects at baseline and a second time (9-12 months) after enrollment. Identify data to be obtained and how that data will be processed and analyzed.

7. Describe in detail proposed methods for identifying subpopulations of subjects with COPD by cross-sectional analysis of clinical, biomarker, molecular, and radiographic data obtained at baseline. The proposal should describe the statistical approach that will be employed, the specific data to be used in the analysis, the capabilities and limitations of the approach, and the estimated sample size required.

8. Describe in detail proposed methods for identifying and validating potential intermediate outcome measures by comparing changes in clinical, biomarker, molecular, and radiographic phenotypes of subjects over the first 9-12 months after enrollment to their long term (e.g., three year) outcomes, such as mortality and changes in FEV_1, quality of life, dyspnea score, oxygen saturation, and six minute walk test distance. The proposal should describe the statistical approach that will be employed, the specific data to be used in the analysis, the capabilities and limitations of the approach, and the estimated sample size required. If the proposed methodology involves analysis of separate groups of subjects for identification and validation of possible intermediate outcome measures, the proposal should describe how these groups will be specified and the numbers of subjects in each.

9. Describe the proposed organization, administration, and day-to-day operations of the GIC. Describe plans for management of the study, including the work of committees and boards.

10. Describe proposed plans for training and certifying CC staff in data and biospecimen acquisition and transmission.

11. Document the availability to this study of all facilities, computer hardware and software, other equipment, and personnel that are required for data management and analysis, including the electronic transmission, storage, and backup of study data. Identify where the computer systems will reside and who will have access. Describe procedures for ensuring the security of study data, including procedures for data backup and for preventing accidental or malicious loss, corruption, or unauthorized release of the data.

12. Document the availability to this study of all facilities, equipment, and personnel that are required for the receipt, processing, archiving, and storage of biological specimens as specified for collection in the Sample Protocol for Proposal Purposes. Identify where the specimens will reside, who will have access, and how the specimens will be secured from unauthorized individuals.

13. Describe proposed procedures for data entry at the CCs, transmission to the GIC, storage, and backup. The proposal should describe methods for ensuring the integrity and privacy of data transmission. Describe plans for the transfer, storage, and analysis of data sets that are obtained through high throughput analyses of biospecimens (e.g., genetic, genomic, and proteomic analyses).

14. Describe proposed methods for assessing and reporting the quality of data received from the CCs and core laboratories and for the correction of entry errors.

15. Describe plans for arranging and coordinating meetings of SPIROMICS committees and boards. The proposal should include discussion of plans for obtaining meeting

rooms and reimbursing appropriate individuals for travel, hotel, and per diem expenses.

16. Provide any other information needed to allow the reviewers and the Government to judge the capability of the offeror to accomplish the Statement of Work of the GIC.

j. **Phenotyping Example**

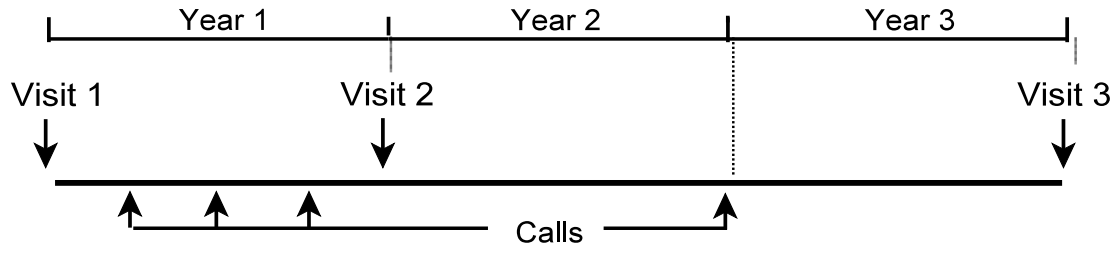
[NOTE: The following Phenotyping Example is provided for proposal purposes to establish a uniform basis for the cost proposal. It is included herein for information purposes only. The actual phenotyping protocol will be developed during Phase I by the contractors and may differ significantly from the example provided. This Phenotyping Example is not intended to limit or restrict what GIC offerors may propose in their plans for achieving the SPIROMICS objectives. Together with plans for how to identify subpopulations and identify and validate intermediate outcome measures, GIC proposals may include plans for study design (cohorts, inclusion/exclusion criteria, follow up schedule) and procedures for molecular phenotyping (genetic, genomic, and possibly proteomic) that differ substantially from those described in this example.]

SPIROMICS subjects are enrolled into five cohorts that allow comparisons between diseased and control (nonsmoking or smoking) subjects and to permit separate analyses of follow-up data in three cohorts of subjects with varying degrees of disease severity. Nonsmoker and smoker controls are age-matched to a random sample of the diseased subjects. The five cohorts of SPIROMICS subjects are as described below.

COHORT	Nonsmoker	Smoker	Mild COPD	Moderate COPD	Severe COPD
Pack-Years	0	>10	>10	>10	>10
FEV_1/FVC	≥ 70%	≥ 70%	< 70%	< 70%	< 70%
FEV_1 (% pred)	≥ 80%	≥ 80%	≥ 80%	≥ 50% and < 80%	< 50%
Number	200	200	1,600	800	400

Enrollments in each cohort are stratified by center. Subjects are excluded for age < 45 years, pulmonary hospitalization within the past 6 weeks, clinical diagnosis of asthma, or serious comorbid condition expected to result in death within 3 years.

The timeline for contacts with SPIROMICS subjects is shown in Figure 1.



Study procedures are as follows.

Visit 1:	Screening for eligibility
	Pre- and post-bronchodilator spirometry
	Consent
	Height and weight
	Medical history and physical
	Diffusing capacity
	Pulse oximetry
	St. George Respiratory Questionnaire
	Dyspnea questionnaire
	Berlin Sleep Apnea Questionnaire
	Blood draws (serum, plasma, DNA)
	Urine sample
	Sputum collection
	Six minute walk test
	High-resolution chest CT
Visit 2:	Pre- and post-bronchodilator spirometry
	Weight
	Interim medical history
	Pulse oximetry
	St. George Respiratory Questionnaire
	Dyspnea questionnaire
	Blood draws (serum, plasma)
	Urine sample
	Sputum collection
	Six minute walk test
	High-resolution chest CT
Visit 3:	Pre- and post-bronchodilator spirometry
	Weight
	Interim medical history
	Pulse oximetry
	St. George Respiratory Questionnaire
	Dyspnea questionnaire
	Six minute walk test

Biospecimen Procurement and Analyses

Biospecimens obtained at baseline (Visit 1) are as follows:

Blood	10 ml for leukocyte RNA (with globin depletion)
	10 ml for leukocyte RNA (with neutrophil depletion)
	10 ml for DNA
	10 ml for plasma (cell pellet preserved as back-up source of DNA)
	10 ml for serum for clinical chemistries

Urine	50 ml random sample
Sputum	Spontaneous or induced by inhalation of hypertonic saline aerosol

Biospecimens obtained at Visit 2 are as follows

Blood	10 ml for leukocyte RNA (with globin depletion)
	10 ml for leukocyte RNA (with neutrophil depletion)
	10 ml for plasma (cell pellet preserved as back-up source of DNA)
Urine	50 ml random sample
Sputum	Spontaneous or induced by inhalation of hypertonic saline aerosol

DNA obtained at Visit 1 is genotyped for 500,000 SNPs distributed across the genome, with analysis of copy number and loss of heterogeneity, and is tested for additional SNPs in the candidate genes for airway diseases listed below.

CAT = catalase
mEPHX1= Microsomal epoxy hydrolase 1
GSTP1 = glutathione S-transferase P1
GSTM1 = glutathione S-transferase M1
GSTT1 = glutathione S-transferase T1
HMOX1 = heme oxygenase 1
SOD1 = superoxide dismutase1
SOD2 = superoxide dismutase2
SOD3 = superoxide dismutase3
TGFb1 = Transforming Growth Factor 1
LTBP4 = Latent Transforming Growth Factor b Binding protein-4
MMP1 = Matrix Metalloprotease 1
MMP9 = Matrix Metalloprotease 9
MMP12 = Matrix Metalloprotease 12
MMP14 = Matrix Metalloprotease 14
SERPINE2 = Serine proteinase Inhibitor 2
ADAM33 = A Disintegrin and Metalloproteinase 33
Tissue Inhibitor of Metalloproteinase-2 = TIMP-2
Elastin
AAT = a1 antitripsyn
CYP2A6= Cytochrome P450 2A6
CYP1A1= Cytochrome P450 1A1
CYP1B1= Cytochrome P450 1B1
CYP2E1= Cytochrome P450 2E1
NRF2 = Nuclear factor-E2 p45-Related Factor 2
IL1b = Interleukin 1b
IL1RN = Interleukin 1 receptor antagonist
IL4RA = Interleukin 4 receptor A
IL13RA1 = Interleukin 13 receptor A1
TNFa = Tumor Necrosis Factor a
CXCR1 = Interleukin 8 receptor a
CXCR2 = Interleukin 8 receptor 2
VDBP = Vitamin D Binding protein /GC-Globulin
VEGF = Vascular Endothelial Growth Factor
b defensin-1
TLR1 = Toll-like receptor 1
TLR2 = Toll-like receptor 2
TLR3 = Toll-like receptor 3
TLR4 = Toll-like receptor 4
TLR6 = Toll-like receptor 6
SP-B = Surfactant Protein B
CLCA1 = Calcium Activated Chloride Channel 1
CFTR = Cystic Fibrosis Transmembrane Regulator

ADRB2 = B2 Adrenergic Receptor
SIRT1 = Sirtuin 1
SIRT2 = Sirtuin 2

Plasma, blood cells, urine, and sputum specimens from Visits 1 and 2 are analyzed as follows.

Plasma	Blood Leukocytes*	Urine	Sputum
Proteomic analysis TNF-a IL-1b, -4, -6, -8, -11, -13, -17 IL-1RN TGF-b LTBP4 MMP-1, -2, -8, -9, -12 TIMP-1, -2 VEGF MCP-1 CRP sE-selectin	RNA for 47,000 genomic transcripts	Proteomic analysis Elastin degradation peptides 8-isoprostane	CD8+ T cells TNF-a IL-1b, -4, -6, -8, -11, -13, -17; IL-1RN Defensins SP-B/-A TGF-b SERPINE2 GST isoenzymes CYP (1B1/1A1) Mucin 5 LTBP4 MMP-8, -9, -12 TIMP-1, -2 Leptin Elastin fragments GSSN/GSST

* Separate analyses performed for samples with and without depletion of neutrophils.

Bronchoscopy Substudy

Subsets of 60 subjects from each of the five cohorts (300 subjects total) are enrolled in a substudy to correlate biomarkers in exhaled breath condensate, bronchoalveolar lavage (BAL) fluid, and bronchial epithelial brushings with other study data at baseline. BAL cells and bronchial epithelial brushings are analyzed for gene expression using the same methodologies described above for blood cells. The BAL supernatants are analyzed by proteomic methods and for the same biomarkers described above for plasma. Exhaled breath condensate is analyzed for 8-isoprostane, H_2O_2, and malondialdehyde.

ADDITIONAL BUSINESS PROPOSAL INSTRUCTIONS

a. **Business Proposal Table of Contents**

b. **Cost Proposal Excel Workbook**

A detailed cost breakdown shall be submitted using the Excel Workbook posted with this RFP.

c. **Packaging and Delivery of Proposal**

DUE DATE: 4:00 p.m. local time on December 14, 2007

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-08-06, Subpopulations and Intermediate Outcome Measure in COPD Study SPIROMICS: Genomics and Informatics Center TO BE OPENED BY AUTHORIZED GOVERNMENT PERSONNEL ONLY"

NUMBER OF COPIES:

Technical Proposal: Original and Thirty (**30**) Copies

Business Proposal: Original and Five (**5**) Copies

IF HAND-DELIVERED:
Review Branch, Division of
Extramural Research 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 Research Activities
National Heart, Lung, and Blood Institute
Rockledge 2, Room 7091
6701 ROCKLEDGE DR MSC 7924
BETHESDA, MD 20892-7924

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

d. **PROPOSAL INTENT RESPONSE SHEET**

RFP No.: NHLBI-HR-08-06

TITLE OF RFP: Subpopulations and Intermediate Outcome Measure in COPD Study SPIROMICS: Genomics and Informatics Center

If you intend to submit a proposal, please furnish the information requested below and return this page by **November 15, 2007**. 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:

E-MAIL ADDRESS:

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