HEI RESEARCH AND REVIEW PROCESSES

Revised January 2015

The mission of the Health Effects Institute (HEI) is to provide high quality, impartial scientific information to inform public and private decision makers about the health effects of pollutants emitted from motor vehicles and other sources in the environment. Producing scientific research results of the highest quality is central to maintaining HEI's credibility. To that end, all studies funded by HEI are expected to adhere to HEI's procedures for quality assurance and quality control.

HEI's scientific work is overseen by two expert multidisciplinary Committees that work with HEI's scientific staff. The HEI Research and Review Committees are composed of distinguished scientists who are knowledgeable about various aspects of study of air pollution and its health effects. HEI's Board of Directors reviews the credentials of prospective new members of the Research and Review Committees and approves their appointments. New members are appointed to four-year terms, which can be renewed once with approval of the Board. Periodically, HEI seeks nominations for members of its committees from the scientific community and its sponsors. Curriculum vitae and conflict of interest disclosure statements are kept on file at HEI for all Research and Review Committee members. All HEI Staff Scientists have doctoral degrees in disciplines relevant to HEI's research program.

The HEI Research Committee works with the scientific staff to develop and oversee HEI's research program, and the Review Committee, which has no role in selecting or overseeing the studies, works with scientific staff members to review and interpret each study. HEI's Committees and scientific staff have developed extensive quality assurance and quality control procedures to evaluate and ensure the quality of all studies at the time of their selection for funding, during the course of the research, and after they are completed. The application of these procedures is tailored to the importance and complexity of the studies; there is more extensive oversight and review of human studies and major animals studies designed to produce data of potential regulatory significance than of pilot studies or exploratory, mechanistic studies.

HEI's Board of Directors approves all studies before they are funded as well as Research Reports on completed studies before they are published. Specifically, the Board approves the process by which the applications for research are reviewed and selected by the Research Committee, and the process by which the Review Committee evaluates the Investigator's Report and develops its Commentary on the Report. Although the Research Committee usually recommends studies for funding, sometimes ad hoc expert oversight committees are appointed by the Board of Directors to oversee special projects; they may make recommendations to the Board about funding of studies.

SELECTION OF STUDIES FOR FUNDING

HEI investigators are selected through a competition open to the entire scientific community in response to Requests for Applications (RFAs) and other research solicitation mechanisms. Selecting well-designed studies with well-qualified investigators experienced in the methods to be used is a critical part of assuring the quality of a scientific study.

Application Requirements

The following information is required in applications for research submitted to HEI:

- Description of project plan, including specific objectives, significance, related previous studies, and experimental plan and methods;
- Detailed budget for the first 12-month period and estimated budget for the total project;
- Information on current and pending support for investigators proposed for the project, including the extent of overlap of the projects with the proposed work;
- Description of resources and environment;
- Biographical sketch for the Principal Investigator and other key professional personnel and consultants involved in the project; and,
- For human studies, the following information is also required as a part of the application, and approval of the protocol by the Institutional Review Board (IRB) at the investigator's institution is required:
    - Source of potential subjects, derived material, or data; description of the characteristics of the subject population, such as their anticipated number, age, gender, ethnic background, and state of health; and criteria for inclusion and exclusion;
    - Description of the recruitment and informed consent procedures to be followed and the information to be provided to prospective subjects;
    - Description of potential risks to the subjects–physical, psychological, social, legal, or other–and an assessment of their likelihood and seriousness;
    - Description of the procedures for protecting against or minimizing potential risks and of the procedures employed to safeguard confidentiality; and,
    - Discussion of the risks in relation to the anticipated benefits to the subject and to society.

Mechanisms of Solicitation of Research; Review and Selection Process for Each

HEI uses a variety of mechanisms for soliciting proposals for research. The nature of these and rationale for them are explained in this section along with the specifics of the process of review and selection for each.

RFAs for Research on Specific Topics

The topical RFAs are the main mechanism by which HEI funds research. RFAs are generally developed on high priority topics identified in an HEI Strategic Plan or as fields develop or as research needs are identified by HEI sponsors, Committees, Board, and by other members of the scientific community. For each RFA solicitation, HEI's goal is to put together a coherent program of studies that provides complementary information on a high priority research topic. Applications received in response to the RFAs are evaluated in a two-step process, which is described below.

External Review

Working with the Research Committee – which has experts in topics relevant to any particular RFA -- HEI staff organize an ad hoc review panel of experts in scientific areas spanning the variety of topics and methods relevant to the objectives of the RFA. As much as possible, HEI avoids using experts who have any conflicts of interest with applicants responding to the RFA. Each application is assigned to two or three members of this panel, according to their expertise and experience, who each provide a written critique. If necessary, additional reviews on specialized topics are sought from appropriate experts not on the panel. Reviewers are asked to address the:

- Relevance of the proposed research to objectives of the RFA;
- Scientific merit of the research design, approaches, methodology, analytic methods, and statistical procedures;
- Adequacy of personnel and facilities; and,
- Reasonableness of proposed costs.

Applications are reviewed at a meeting of the expert panel, which is chaired by one or two members of the Research Committee. The assigned reviewers present their critiques on each study, the panel discusses the strengths and weaknesses, and members of the review panel assign a numerical score to each proposal that reflects their assessment of its scientific merit. Reviewers leave the room during discussion of any applications for which they have a conflict of interest and do not score them; the absence of their score is accounted for in the final tally. HEI staff and Committee members participate in discussion of the applications but do not score them. The average score for each application provides a means of ranking the scientific quality of the applications.

Internal Review and Selection of Studies for Funding

After the panel meeting, a staff summary of the applications and panel discussion, the critiques, and scores are sent to the Research Committee, which discusses the applications at a regularly scheduled meeting. Committee members who have a direct interest in a proposal, or whose close colleagues are applicants, may not participate in the review of any such proposal. This is communicated from the first appointment letter to the Committee and rigorously enforced. In some instances, this can result in a member not being allowed to participate in the drafting of the RFA if the conflict is too close.

The Committee's review generally focuses on the applications ranked most highly by the review panel. The Committee further considers these applications with respect to how well they address HEI's objectives and how they contribute to a coherent program with minimal overlap as well as the quality of the science. In some cases, Research Committee may choose to also consider a proposal with a somewhat lower score; this is rare and generally occurs is in the interest of funding a well-rounded program. The Committee recommends studies to the Board of Directors for funding.

Other Types of Research Requests

<u>RFA for Walter A. Rosenblith New Investigator Award</u>

The Walter A. Rosenblith New Investigator Award was established in 1999 to provide support for outstanding investigators beginning their independent research careers with the goal of attracting talented scientists into air pollution research. The award provides support up to $150,000 in total costs per year for up to three years and is awarded annually to one or more applicants.

In contrast to the topical RFAs described above, the proposed research under the New Investigator Award can be on any topic relevant to priorities in HEI's Strategic Plan. In addition to a research proposal, the application requires the following material:

- A cover letter from the applicant describing the candidate's interest in the award and how this project fits with his or her career goals, including information about the applicant's long-term career plans and how the HEI award would contribute to these plans;
- Two letters of reference from well-established scientists familiar with the candidate's professional capabilities, but not directly involved in the proposed project, that address the candidate's scientific achievements and potential to pursue an independent research program, and how the HEI award could contribute to this potential;
- A letter from the department chair, dean, or other administrator at the candidate's present institution, indicating a tangible institutional commitment to the candidate and his or her research;
- A mentoring plan specifying one or more senior scientists who will be available for consultations during the project;
- Letters from the mentor(s) indicating their commitment and a plan for regular consultations with the applicants; and
- Copies of 3 recent publications and a list of all publications.

Applications for the New Investigator Award are reviewed in a 2-step process, involving external and internal review. Since the topics of these applications are typically very diverse, HEI does not form evaluation panels but instead sends each application to two or three experts who evaluate the scientific merit of the proposal and how promising the applicant is. Subsequently, during its review, the Research Committee considers several factors including the applicant's potential for being a leader in the field; institutional support for the investigator; mentoring plan; and, quality of the research proposal, especially with regards to containing new ideas. The Committee also evaluates the scientific merit of the research design, approaches, methodology, analytic methods, and statistical procedures; adequacy of the personnel and facilities; and reasonableness of proposed costs. The Board of Directors formally approves funding recommendations. If there are a large number of applications (> 8 or so), a subcommittee of the Research Committee meets by conference call for an initial screening to separate the better applications from the lower quality ones so that the Committee can focus attention on the most promising applications at its meeting.

<u>Request for Preliminary Applications (RFPA) on the Health Effects of Air Pollution</u>

The preliminary application process is a mechanism for investigators to apply for funding on topics outside those defined by topical RFAs but within HEI's current research priorities

as described in a Strategic Plan. Though not meant to be a major funding pathway, it serves as a useful mechanism for bringing fresh ideas to HEI.

Investigators are asked to submit a short (5-page) preliminary application providing rationale for the work and the approach that would be taken. Two or three Research Committee members are assigned to review each application, which are subsequently discussed by the whole Committee at a regular meeting. If the Committee finds the proposal worth pursuing, the investigator is asked to submit a full application. The full application is reviewed by two or three outside experts, who evaluate the research design, approaches, methodology, analytic methods, and statistical procedures; the adequacy of the personnel and facilities; and the reasonableness of proposed costs. The Research Committee finally discusses the application at a subsequent meeting, taking into account the reviewers' comments, and decides whether to recommend it to the Board of Directors for funding.

Requests for Qualifications (RFQs)

This mechanism is used periodically for projects that involve narrowly defined topics such as re-analyzing a specific data set or implementing a particular protocol that has been developed by the Research Committee or for obtaining specific technical assistance. In 2008, HEI used an RFQ mechanism to find vendors to perform quality assurance-quality control audits and related functions. Decisions about contracting with appropriate QA-QC teams were made by staff that has previous experience in this area. If the objectives of the RFQ are more technical or scientifically more complex, outside experts and the Research Committee are also involved in issuing the RFQ and selecting the appropriate team.

Project Negotiation

Before making a final recommendation to the Board, the Research Committee may ask the Principal Investigator to address certain issues raised by reviewers about study design or methods; the Committee may also request modifications in the project plan of a study, such as deletion of parts of the proposed project that are less relevant to HEI's objectives or changes in the range of exposure concentrations of pollutants. Besides improving the plans for a particular study, these changes enable HEI to mold diverse investigator-designed studies into a coherent program in a specific research area. The Committee recommends a study for funding to the Board only after it is satisfied with the final work plan.

Board Approval

Irrespective of the solicitation mechanisms, all studies must be approved for funding by the HEI Board of Directors. The Research Committee recommends studies through the mechanisms discussed above to the HEI Board of Directors for approval for funding. The Board reviews and approves the studies with particular attention to the process by which applications were reviewed, how selections were made, how conflict of interest issues, if any, were managed and whether any lower-ranked proposals were recommended for funding.

Research Agreement

HEI's Research Agreement, which is negotiated and signed by the investigator's institution and HEI, normally covers a one-year period and is renewable upon satisfactory progress. The Research Agreement:

- States that all work performed by the investigator shall be in conformance with the Statement of Work for the study;
- States that key investigators may not be changed without written approval of HEI;
- Sets forth HEI's right to provide technical oversight;
- Sets forth conditions for the use and protection of human subjects and the care of laboratory animals;
- Sets forth requirements for periodic progress reports and the final report on the completed study;
- Sets forth HEI's rights to inspect the work of investigators to assess and assure the scientific quality;
- States HEI's rights to obtain a copy of all data recorded, generated, analyzed, and summarized in the course of the study and to further analyze, publish, deliver, or dispose of these data as it believes appropriate; and,
- Requires that all notes and records for the study be retained for a period of five years after submission of the final report and that HEI be notified prior to disposition of the material so that HEI can store the records if it considers that necessary.

Records of Decisions

Detailed minutes of the discussion and decisions at the Research Committee meeting are written, approved by the Committee, and kept on file. All reviews, summaries of discussions, and correspondence regarding each application are filed with the investigator's application at HEI. These become part of the permanent file of funded studies, as does the signed and fully executed agreement with the investigator's institution.

PROJECT MANAGEMENT AND STUDY OVERSIGHT

HEI has two main goals in funding research: building a coherent, high quality research program in selected areas and providing timely, relevant information to its sponsors. In order to accomplish these goals, HEI oversees investigators' research and monitors their progress through progress reports, workshops, and site visits. Usually two or three Research Committee members review progress reports or participate in site visits or workshops; however, if serious problems arise in studies, they are discussed at Research Committee meetings.

The level of oversight by the Research Committee and staff is tailored to the nature of each study. As stated above, project plans are developed for each study and incorporated into the Research Agreement. The scope of research conducted must be consistent with the project plan. If results suggest new directions for research, such changes must be approved by the Research Committee; if necessary, the contract is amended to allow modifications in the project plan.

All investigators are encouraged to adhere to quality assurance and quality control standards and guidelines applicable to their field of research and according to HEI guidelines. Studies that use human data are required obtain approval from their Institutional Review Board and submit a quality control/quality assurance plan to HEI; HEI in turn seeks approval from EPA before study is begun.

For studies that use human subjects, HEI requires that special quality assurance procedures be implemented that conform to HEI and federal policies. The investigators/institutions must comply with the latest regulations and guidelines issued by the US Department of Health and Human Services and the Environmental Protection Agency. The protocols and procedures to be used for the study must be approved by the Institutional Review Board and by the EPA human subjects office. Additionally, HEI may establish one or more committees to oversee different aspects of the study, including subject safety during subject testing. HEI may also establish an external data management and analysis center.

Although HEI's Research Agreement normally covers a one-year period, HEI intends to fund studies for the number of years initially planned, usually 2 or 3 years. Yearly renewal provides an opportunity for the Research Committee to evaluate progress and, as necessary, provide comments and recommendations to the investigator. Though the progress report is the main mechanism for overseeing studies, it is often supplemented by other steps such as site visits. In addition, all investigators present posters on their HEI-funded research at the HEI Annual Conference.

Progress Reports

All HEI investigators submit yearly (10-month) progress reports that are the basis for renewal of their studies for the following year. The Principal Investigator is also asked to submit a 5-month progress report for each study year that is used to check on general progress and provides an opportunity for feedback from the Research Committee. The 10-month progress report/renewal application provides information on the investigator's progress in meeting the goals for that year and the results obtained; it also presents a plan and detailed budget for the subsequent year. The progress report is reviewed by a Staff Scientist assigned to the study, who prepares a memo for the Research Committee that highlights any problems as well as interesting results. The memo and progress report are sent to all members of the Research Committee, but the 2, 3 or more members assigned to oversee the study are asked to review the report and recommend whether or not HEI should renew the contract for the following year.

If there are serious issues regarding progress, methods, results, or analyses, or the investigators encounters unexpected hurdles, the study is discussed by the Research Committee. A site-visit may also be organized in such situations. These steps generally result in mid-term corrections in the direction of the study. Sometimes the PI is given a no-cost extension if they are behind in their work. Also, in additional work – not originally foreseen – is to be performed, a contract amendment may be needed.

In the final progress report during the last year of the study the investigator is asked to outline the timeline for completion of the data analysis and final report writing, as part of HEI's recent efforts to provide more timely, high quality results.

Site Visits

If more in-depth scrutiny of a research program is indicated, HEI conducts a site visit to the investigator's laboratory with the help of a few Research Committee members, HEI Staff and external expert consultants. Site visits may be conducted because of concern about

progress or problems in the study, but often the purpose is to have a detailed scientific review and discussion of progress, results, and the future course of work. The HEI staff prepares a report on the site visit – including the recommendations made by the site visit team. This report is reviewed by selected members of the Research Committee and sent to the investigator. The Staff Scientist discusses with the investigator how HEI's recommendations may be addressed.

For certain studies, especially those using human subjects, HEI generally also organizes QA/QC site visits, conducted by a third party, independent auditor.

Workshops

Periodically, HEI organizes workshops for investigators working on related research projects. Research Committee members and expert consultants also participate in these meetings, which afford an opportunity for investigators doing related research to understand each other's research better and to explore opportunities for coordination of studies and collaboration. Often representatives of HEI's sponsors are invited to these workshops—and sometimes investigators funded by other agencies, who are conducting similar types of studies, will be invited. Frequently, investigators decide to use similar exposure levels or to exchange samples in order to do additional analyses. Such modifications of studies increase the coherence of the research program, make possible direct comparisons among the studies, and improve the quality of information from the set of studies. These modifications are incorporated into the Research Agreement for a study by means of amendments of the project plan, budget, or study duration.

Special Quality Assurance Procedures

The procedures described above are used in oversight of all HEI studies to ensure that they are designed and conducted well and produce reliable, meaningful data. In addition, HEI selects studies with regulatory relevance to be subject to additional procedures that further assure that the data are acquired under well-defined conditions and are reliable and traceable.

Termination of Studies

When concerns about a study are raised in evaluating progress reports or from information provided at a site visit, HEI makes every effort to provide advice to the investigator that will help to correct problems and get the study back on track. Over the years, Research Committee members and consultants have provided assistance to investigators to address a variety of problems in studies. However, if the Research Committee decides that the study cannot be completed in a satisfactory manner and will not yield high-quality, meaningful results within a reasonable time frame and budget, then it terminates the study. This is done infrequently.

FINAL REPORT AND STUDY REVIEW

One of HEI's goals is to publish research reports of that are of value to sponsors, scientists, regulators, government officials, and the interested public. When a study is completed, the investigator is required to submit a comprehensive final report that describes the study and its findings. This includes both results in which effects were found ("positive results") and

results in which no effects of a pollutant were seen ("negative results") because, if studies are well-conducted, negative results are as important as positive results in understanding the health effects of pollutants. The HEI Review Committee, which has no role in the review of applications or in the oversight of studies, evaluates the Investigator's Report by an unusually rigorous process that goes well beyond that generally used by journals.

The objectives of the review process are:

- To ensure that the Investigator's Report is complete, accurate, and clear;
- To provide a rigorous review of the Investigator's Report in order to evaluate the strengths, weaknesses and significance of the research findings; and,
- To write a Commentary that puts the research results into a broader context of scientific knowledge and regulatory policy, points out their strengths and limitations, and discusses the interpretation, conclusions, and implications of the findings.

In addition, the Commentary, by providing a succinct summary of the study and its findings, has an important function in communicating the results to a broad audience that may not read the detailed report. The Review Committee's Commentary is published by HEI together with the Investigator's Report as a Research Report and made available to HEI's sponsors and the public; the Reports are also available from the HEI website.

The HEI review process involves external review by several scientists with appropriate technical expertise, followed by discussion and overall evaluation by the HEI Review Committee. Generally, three members of the Review Committee (including a statistician) serve as the primary reviewers of the report. A compilation of the comments of the external reviewers, together with a summary of the Review Committee's initial discussion (summarized as an Initial Review), is sent to the investigator, who has an opportunity to respond to these comments and revise the report. For particularly complex studies, the Committee may organize a small panel to the review the study. The revised Investigator's Report is discussed by the Review Committee at a subsequent meeting, where the Committee also decides on acceptability of the report. Once accepted, HEI staff – working with the primary reviewers – draft a Commentary on the study. The draft is sent to the entire committee as well as selected members of the Research Committee for comments, and finally to the investigator for his or her comments. HEI makes a strong effort to respond to, by revising the commentary, the comments and concerns of the investigator, unless there are genuine differences in views or interpretation of the study. The Investigator's Report is also edited by science editors in the HEI Publications Department. After these steps are completed, the Research Report is published.

The HEI review process probes each study and report in depth. As with the research management process, the review of reports is tailored to the nature of the study and its findings. The Review Committee may ask investigators to make significant changes in their reports, including alternative statistical analyses, or alternative interpretation of results. The Review Committee's Commentary on the evaluation of each study and the investigator's interpretation of the results are very important in assuring the quality of the information reported on the study and the interpretation of the study results. Additionally, the commentary puts the research in its scientific and, if appropriate, regulatory context.

To improve efficiency and to streamline our review and publication processes -- while maintaining the highest level of scientific quality -- HEI is now asking for more streamlined reports that provide the most important results and interpretation; details of methods, results and analyses are provided in web-only appendices. As in the past, HEI conducts full-scale peer review of all studies and asks investigators to make revisions. The HEI Review Committee then prepares a shorter, focused Critique, rather than a detailed commentary. In a small number of cases, i.e. important reports that are expected to be of interest in the regulatory context, HEI requests more extensive reports that will receive full editing and a full length Commentary.

Occasionally, when the Review Committee decides that the results of a study are not interpretable due to problems with methods or study design, the Committee decides not to publish the investigator's final report. The unpublished reports are listed on HEI's website and available upon request; a very short explanation for not publishing the report is written for them and appended to the report.

QA/QC Responsibility

Overall responsibility for quality assurance and quality control procedures for HEI studies rests with Dr. Rashid Shaikh, Director of Science and HEI QA/QC Officer. For individual studies, the Principal Investigator has the responsibility for development of procedures and methods to assure quality of the results. That work is overseen by Dr. Shaikh, HEI's scientific staff, and members of the Research Committee. Under HEI's special QA procedures, a qualified individual is selected by HEI to serve as QA Officer for individual studies to aid in HEI's assessment of quality assurance activities in a study. The QA Officer may conduct periodic audits to evaluate quality control procedures, ascertain compliance with the study protocol and SOPs, and examine records. He or she reports to HEI's Director of Science.

QUALITY ASSURANCE/QUALITY CONTROL PROCEDURES

FOR HEI FUNDED STUDIES

Revised November 2015

PART 1. GENERAL QUALITY ASSURANCE / QUALITY CONTROL PROCEDURES

1.1. Policy Statement

The mission of the Health Effects Institute (HEI) is to provide high-quality, credible, impartial, relevant scientific information on the health effects of pollutants from motor vehicles and other sources in the environment. All funded HEI studies are expected to have adequate QA/QC procedures in place to ensure that the data are collected according to a written protocol and Standard Operating Procedures (SOPs) and are traceable. The QA/QC guidelines provided in this document apply to all HEI-funded studies. For studies that involve human subjects and some animal studies of regulatory significance, HEI implements Special Quality Assurance Procedures (described in Part II) that include an external audit by an HEI selected audit team. HEI will inform the investigator after approval of the study whether the Special QA procedures will apply to his/her study.

1.2. Quality Assurance/Quality Control Components

QA procedures begin with the planning phase of the raw data collection and follow the subsequent transformations of the data. Generally, HEI requires that the investigators:

- Use a written protocol
- Use written standard operating procedures
- Involve qualified personnel
- Maintain written records
- Use appropriate data processing techniques
- Use quality control procedures for all data collected

A. ***A written research protocol*** defines the experimental objectives, research strategy and methodologies to be used. The protocol will be sufficiently complete and detailed as to ensure that the data collected are of known and documented quality. It will include, as applicable:

1. Name of Principal Investigator and any co-investigators
2. Study objectives
3. Scientific background and rationale
4. Anticipated significance of study results
5. Description of all experiments to be conducted with reference to a particular standard operating procedure when appropriate (see *Section B*)
6. Methods of data processing (see *Section E*)
7. Internal quality control procedures to be used (see *Section F*)

8. Safety precautions to be adopted
9. Plans for archiving the completed project, including the anticipated address and physical location for storage of all raw data, records, electronic media, reports, SOPs, and any specimens that are expected to be retained

For studies involving human subjects, the protocol should also contain:

10. Subject selection procedures to be used, including inclusion and exclusion criteria (when applicable)
12. Procedures used to maintain subject confidentiality
13. Copy of the blank form used to obtain Informed Consent from subjects
14. IRB approval

The protocol may be amended as necessary to accommodate changes to the experimental design. Any changes to the original protocol comprising items 1 through 14 shall be made in writing by preparing an amendment to the protocol that is signed and dated by the Principal Investigator. See also *Section III, Roles of Institutions and Individuals in Achieving Quality Assurance*, below. All amendments must be approved by HEI.

B. *Written standard operating procedures* will be used to document all routine, critical experimental procedures and measurement techniques for which variability must be minimized. Critical experimental procedures are those procedures that result in the acquisition of experimental samples or data used to draw scientific conclusions. Generally, SOPs cover procedures that are done routinely over time by the same person or by different individuals to minimize procedural variation.

Standard operating procedures will be developed by individuals knowledgeable of and experienced in the specific procedures. They will describe, in a stepwise manner, what, when, where, how, and why. The SOPs will be sufficiently complete and detailed to ensure that the data collected are of known and documented quality and integrity and are generated to meet measurement objectives such that there is a minimum loss of data due to out-of-control conditions. Routine quality control procedures should be covered by an SOP. Other items covered by an SOP might include: use and calibration of laboratory instruments, chemical sampling and analyses, preventive maintenance, data handling, maintenance and storage, etc.

Standard operating procedures will be uniquely identified and dated, and updated as needed. Copies of all current SOPs should be readily available for reference by the study team or by a third party designated by HEI, as needed. All SOPs that have been superseded will be maintained in a historical file. Deviations from SOPs should be documented.

C. *Qualified personnel* will conduct the proposed research. The qualifications of all participating individuals, and any training they receive for the conduct of the study, along with prior experience, should be documented in resumes that will be maintained as a part of the permanent record of the project.

D. *Recordkeeping procedures.* Written records will be maintained to document all aspects of the research effort. This shall include the use of bound notebooks, standard forms, and computer input and output. All written entries shall be made in indelible ink. The entries should be dated

and signed or initialed by the individual making the entry. Notebook entries shall be made in chronological order. If a blank space is left between entries, it shall be crossed-hatched to render it unusable. Entries shall not be erased or otherwise obscured. If any entry is to be changed because it is in error or for any other reason, a single line will be drawn through the entry and a correction made in the margin. The altered entry shall carry an explanation of the reason for the change, the date of the change, and the initials or the signature of the individual making the change. Similar procedures shall be adopted for electronic records.

The Principal Investigator for the project shall periodically review the records to verify their completeness and accuracy. This review shall be documented by the Principal Investigator signing and dating the reviewed record.

E. ***Data processing procedures*** should be documented in a Data Management Plan. Data processing includes all manipulations performed on raw (i.e. "as collected") information, verification or validation, storage, transfer, reduction, and statistical analysis.

Data analysis frequently includes computation of summary statistics and their standard errors, confidence intervals, tests of hypotheses relative to the parameters, and model validation (goodness-of-fit tests). Specific statistical procedures, programs, and code to be used should be documented either in the protocol or in a separate document. HEI staff may require submissions of these procedures during the course of the study or the review of the final reports.

F. ***Quality control procedures*** should be documented for all data collected, i.e. procedures the investigator will use for ensuring the quality of the data during the data collection, sample analyses, and data processing.

1.3. Roles of Institutions and Individuals in Achieving Quality Assurance

The Principal Investigator and his/her institution have the primary responsibility for the preparation of the protocol and all standard operating procedures and shall review and approve them by signing them. In addition, the Principal Investigator has the responsibility to prepare a Quality Assurance Plan, and submit it to HEI within the first months of the study (but no later than at the time of submission of the Year 1, 5-month progress report). HEI will work with the investigators to ensure that the QA plan is adequate and consistent with the agreed upon Statement of Work.

The QA plan shall include:

- The protocol, including the data analysis methods that will be used (see below)
- A list of SOPs
- A list of qualified personnel
- Record keeping procedures (how data will be collected, backed-up, collated, transferred, and stored)
- Documented data processing techniques
- Quality control procedures for all data collected

The protocol will be reviewed and approved by HEI. In many cases, the original Project Plan submitted with the HEI application can serve as the protocol, with added information as recommended by the HEI staff or the Research Committee. In some cases HEI may ask a group

of investigators to work together to harmonize their study design and methods and develop a common or comparable protocol. Subsequent modifications to the protocol shall be submitted to HEI in the form of written amendments. All amendments are subject to HEI approval before they can be implemented.

The Principal Investigator has the responsibility for the actual conduct of the research, adhering to the protocol and SOPs. He or she has the primary responsibility of managing all aspects of data collection, validation, storage, transfer, reduction, and analysis. The Principal Investigator also has the responsibility for assuring that the research is conducted by qualified personnel and in accordance with this quality assurance plan. Technical and supporting personnel should have a detailed knowledge of the SOPs used in the conduct of their research activities.

HEI reserves the right to conduct a QA audit of an HEI-funded study, whether or not there are reasons to suspect that adequate procedures are not in place. HEI may also conduct an audit of the final report submitted by the investigator after it has been accepted by the Review Committee.

PART 2. SPECIAL QA/QC PROCEDURES

HEI uses third-party quality assurance (QA) procedures for most research projects involving human subjects and other projects with a high potential for use in regulatory decisions. The special procedures augment the QA/QC procedures applied to all HEI studies (described above in Part 1) and assure that data are collected under defined conditions and are reliable and traceable. Accurate scientific conclusions are dependent on the validity of the underlying data and the precision with which they are reported. If there is a QA program in place at the institute at which the research is being conducted, then HEI will assess its adequacy and modify its QA procedures as necessary.

2.1 Third-Party QA Oversight

HEI will generally engage one or more qualified individuals to serve as Quality Assurance consultants for the project. This individual will report to HEI's Director of Science and be responsible for overseeing the implementation of this Quality Assurance plan. The QA consultant will review the (draft) protocol for adherence to the QA requirements and notify HEI staff if modifications are necessary. The QA consultant shall maintain signed copies of the protocol and all SOPs.

The QA consultant may conduct periodic audits of the research while in progress and when it is completed to ascertain compliance with the HEI's special QA procedures. These audits shall include such matters as review of research procedures, notebooks, data forms, and data management activities. The audit shall be performed using the audit framework presented in the US Environmental Protection Agency's Guidance on Technical Audits and Related Assessment for Environmental Data Operations (EPA QA/G-7 2000, available at *www.epa.gov/quality/qs-docs/g7-final.pdf*).

2.2. Elements of a QA Audit

The key elements of a QA audit include:

1. Opening Meeting with the audit team, the Principal Investigator, and key project personnel.
2. Observation of the project activities being performed by the personnel who regularly perform such activities.
3. Review of written documents, such as QA Plans, calibration readouts, process data readouts, sample logs, custody papers, instrument logs, printouts from data spreadsheets, and maintenance notebooks (such records may be in electronic form).
4. Interviews with the project personnel to verify the results of observation and to clarify issues noted during observation or document review.
5. Objective Evidence Compilation, such as copies of notebook pages, logs, instrument and model outputs, and QC charts.
6. Closing Meeting, during which the QA consultant provides a verbal summary to the Principal Investigator of significant findings that need to be addressed.
7. QA Audit Report. The QA consultant prepares a "Business Confidential" report of the audit. The report shall detail the nature of the audit, significant findings, and any requirements for corrective action(s). The audit report shall be provided to the HEI Director of Science, who will then transmit it to the HEI project manager for transmission to and discussion with the Principal Investigator. If corrective action is required, the Principal Investigator will ensure that such action is taken and return the summary to the HEI project manager with a copy to the QA consultant noting the action(s) taken. All copies of the audit report are to be marked as "Business Confidential" and are to be destroyed after use or maintained in a file separate from other records of the project. These audit reports are only to be released to people directly involved in management of the projects. To give these reports to people who are not directly involved violates the confidential nature of the audits and potentially reduce the degree of candor required in communications within the project on matters requiring corrective action. The QA consultant shall maintain a log of all audits indicating for each audit: the date conducted, participating personnel, and the nature of the audit.

2.3. TIMING OF QA AUDIT

While the exact timing of the audits varies across studies, the followed guidelines should be followed when defining the general plan and scope of the QA oversight for a study:

A. Audits during the course of the research period

1. Clinical studies

One QA audit should be conducted at the beginning of Year 1 to ensure that all SOPs are in place, the protocol is followed, and a data management plan is in place. This audit should occur fairly early in the study so that problems, if found, can be remedied before too many subjects have been studied.

One QA audit during Year 2 to audit a subset of the data collected to verify that the data management procedures are adequately implemented and the data collected are traceable, the informed consents are signed, and the protocol is followed consistently. This audit is optional and would depend on the outcome of the initial audit or nature or duration of the study.

2. Epidemiologic, statistical, and other studies

   One audit at the end of Year 1 or during Year 2 to ensure that data collection is done according to the protocol, the data collected are traceable, and a data management plan is in place. If problems are encountered and not addressed adequately, a follow-up visit may be needed.

B. Audit of the final report

Unless there are specific reasons to expedite the review of a final report, the timing of the final report QA audit will be decided during the first discussion of the draft final report by the Review Committee. The following guidelines will be followed:

1. If the Review Committee thinks that the draft final report does not require additional analyses, then a QA audit of the draft report should be scheduled immediately so the investigators can address all issues raised by the auditors in the revised report.
2. If the Review Committee thinks that the draft final report requires substantive changes and/or (partial) reanalysis of the data, the QA audit should be conducted on the revised final report, as soon as it is received.
3. Regardless of the timing of the final report audit, the auditors should always be provided with the final "accepted" version of the report and asked to review it before issuing the final QA Statement, which will be printed in the final, published HEI Research Report.

REQUEST FOR APPLICATIONS 14-3

RFA 14-3: ASSESSING ADVERSE HEALTH EFFECTS OF LONG-TERM EXPOSURE TO LOW LEVELS OF AMBIENT AIR POLLUTION

INTRODUCTION

The Health Effects Institute (HEI) is seeking to fund studies to assess health effects of long-term exposure to low levels of ambient air pollution, including studies to evaluate all-cause and cause-specific mortality and morbidity endpoints. Request for Applications (RFA) 14-3 solicits studies to analyze and evaluate exposure-response function(s) for $PM_{2.5}$ and other pollutants at levels currently prevalent in North America, Western Europe, and other high-income regions, and related questions about health effects associated with long-term exposure to low levels of ambient air pollution. In addition, RFA 14-3 solicits studies to develop methods required for, and specifically suited to, conducting such research.

Before funding full studies, HEI seeks to determine whether potential studies are feasible and likely to meet the stated objectives. Therefore, HEI requires that all respondents to this RFA first submit a preliminary application, so that the HEI Research Committee and outside consultants may evaluate their feasibility. Subsequently, applicants will be informed whether or not to submit a full application. Details can be found in the section *Application Process, Deadlines, and Evaluation*.

BACKGROUND AND RATIONALE

Levels of ambient air pollution have generally declined over several decades in North America, Western Europe, and other high-income regions, due in large part to air quality regulation and subsequent improvements in vehicular technology and industry, although at the same time, some population groups in high-income countries are still exposed to higher levels of air pollution, for example, as a consequence of living close to major roads and other major sources. Current $PM_{2.5}$ annual average air quality standards are 12 and 25 $\mu g/m^3$ in the US and Europe, respectively. The WHO's worldwide current annual average $PM_{2.5}$ air quality guideline is 10 $\mu g/m^3$.

Epidemiologic studies have reported associations of air pollution with health effects in the general population even at levels below current air quality standards. Recent cohort studies that have provided $PM_{2.5}$-related mortality estimates are listed in Table 1. $PM_{2.5}$ exposure estimates in most studies were between 6 and 30 $\mu g/m^3$. They generally observe increased risk of all-natural and cause-specific mortality from chronic disease, although the estimates vary in size, especially with regard to cause-specific mortality, for reasons that are largely unexplained. Using the estimates from these studies in risk assessments of mortality and loss of healthy years of life attributable to air pollution leads to large estimates of attributable burden. The recent Global Burden of Disease (GBD) 2010 project estimated that 3.2 million premature deaths in 2010 worldwide were attributable to PM outdoor air pollution, with 103,027 and 165,598 premature deaths in the US and Western Europe, respectively (Lim et al. 2012). Estimates vary depending on the shape of the exposure-response function used, and particularly on assumptions made as to its form at both low and high concentrations of air pollution. For example, GBD 2010 assumed no $PM_{2.5}$-related effects below ~5 $\mu g/m^3$, because the cohort studies underlying these estimates did not provide reliable information below that level (Lim et al. 2012; Burnett et al. 2014).

The United States Environmental Protection Agency (US EPA) has used a variety of approaches for the estimation of risks at low levels of ambient air pollution in the National Ambient Air Quality Standard reviews, regulatory impact analyses, and burden assessments, reflecting shifting views within the scientific community regarding the shape of the concentration-response relationship and appropriate methods to reflect differences in the degree of confidence in risk estimates at low concentrations. The current approach used by the US EPA, consistent with the most recent versions of the Integrated Science Assessments for $PM_{2.5}$ and ozone, is to estimate risks for the full range of ambient concentrations experienced by populations, with no assumed threshold or lower bound. These estimates are accompanied by a discussion of the uncertainties associated with risk estimates at lower concentrations where the density of air quality data is lower. (US EPA 2009; US EPA 2010; US EPA 2013).

The scientific evidence for effects at levels below current air quality standards, the large estimates of the air pollution-attributable burden of disease, as well as the interest in reducing greenhouse gases, suggest that more stringent air quality standards and guidelines may be considered in the future. For these reasons, there is a need for additional investigation to improve our understanding of exposure-response function(s) for mortality and morbidity at low levels of $PM_{2.5}$, ozone, and other ambient air pollutants. Such studies would inform risk assessors and policy makers regarding exposure-response functions at levels of ambient air pollution currently prevalent in North America, Western Europe and other high-income regions.

OVERALL OBJECTIVES OF RFA 14-3

1. Fund studies to assess health effects of long-term exposure to low levels of ambient air pollution, including all-cause and cause-specific mortality and morbidity endpoints. Studies should analyze and evaluate exposure-response function(s) for $PM_{2.5}$ and other pollutants at levels currently prevalent in North America, Western Europe, and other high-income regions and may also address related questions about health effects at low levels of ambient air pollution.

2. Develop statistical and other methodology required for, and specifically suited to, conducting such research including, but not limited to, evaluation and correction of exposure measurement error.

SPECIFIC OBJECTIVES OF RFA 14-3

1. Compare and contrast alternative models and their uncertainty, e.g., threshold/non-threshold, linear/non-linear, and parametric/non-parametric, to characterize the exposure-response function(s) at low levels of ambient air pollution.
2. Explore possible variability in effect estimates at low levels among populations, and identify possible contributing factors. Such factors may include age, socio-economic position, health status, and access to medical care, as well as differences in air pollution sources and time-activity patterns.
3. Develop and evaluate exposure assessment methods suitable to estimate exposure to low levels of air pollution at various spatial and temporal scales in large study populations, including populations who reside in areas not covered by routine ground-level monitoring.
4. Develop, evaluate, and apply statistical methods to quantify and correct for exposure measurement error in risk estimates and in characterization of exposure-response relationships.
5. Develop and validate approaches to assess the impacts of co-occurring pollutants on health effect associations at low ambient concentrations.
6. Develop and validate indirect approaches to correct risk estimates for the effects of important potential confounding variables, such as smoking, in the absence of such data at the individual level.
7. Improve techniques for record linkage and methods for disclosure protection for optimal use of large administrative databases in air pollution and health research.

HEI encourages applicants to address more than one specific objective, if feasible, within the budget constraints.

CRITICAL STUDY DESIGN CONSIDERATIONS

To inform the development of RFA 14-3, the HEI Research Committee held a workshop in June 2014 with selected participants from the research and regulatory communities and the private sector. A number of considerations pertinent to study design issues discussed during the workshop are summarized below. The ability to address and integrate these considerations will be central to the funding decision.

Study populations. Large studies — as large as, or larger than, existing studies — will be needed to address the overall objectives with regard to the amount of exposed person-time at low levels of $PM_{2.5}$ and other pollutants. This could be accomplished via consortia combining existing studies, or by using data from very large populations obtained from, for example, administrative databases, such as census data or health insurance programs. A recent example of a study combining existing cohorts is the European Study of Cohorts for Air Pollution Effects (ESCAPE) study in which common exposure metrics — derived from a detailed measurement campaign, and land use regression modeling — were applied to diverse general population cohorts; subsequently the cohort-specific results were combined via meta-analytic techniques and corrected

for important (individual) level confounders such as smoking (see, for example, Beelen et al. 2013, Table 1). Alternatively, the data from multiple cohorts could be combined in one pooled analysis. A few examples exist of very large cohort studies using administrative databases (see e.g., Crouse et al. 2012, Zeger et al. 2008, Table 1). Crouse et al. (2012) assembled a 2.5 million-person cohort with relatively low exposure levels using Canadian Census data. The two design options are not mutually exclusive, and there may be alternative design options to address the overall objectives.

Both design options have their strengths and limitations. Strengths of cohort studies are that they typically collect detailed information on important potential confounders at the individual level; strengths of studies using administrative databases are that they can cover very large and 'representative' populations. Limitations of cohort studies may include that detailed information is only available at baseline, and that study populations may not be representative of general populations or specific sub-populations thereof. Drawbacks of using administrative databases include that relatively little information may be available on important potential confounders at the individual level, and record linkage may be challenging. Applicants designing studies should discuss the specific limitations of their study design and develop approaches to address them. Given the increasing demands on the broader scientific and policy communities to make datasets publically available — while maintaining confidentiality — studies that would improve techniques for record linkage and methods for disclosure protection would be of value.

In addition, smaller-scale studies that develop methods will be considered responsive, provided that the applicants make a strong case that such methods are applicable to study designs pertinent to RFA 14-3.

Geographic location. Studies in North America, Western Europe, and other high-income regions characterized by relatively low ambient air pollution levels would be considered responsive. Studies in other regions of the world will be considered, provided that the study includes sufficient exposed person-time at or near levels currently prevalent in high-income regions.

Exposure assessment. Studies should develop and evaluate methods to estimate exposure of large populations at relevant spatial and temporal scales in geographic areas characterized by relatively low ambient concentrations. In most cohort studies to date, exposure estimates have been based on residential proximity to routine ground-level air pollution monitors. The existing monitoring networks — even those in North America and Western Europe — have limited spatial coverage with typically few stations in suburban and rural locations. As a consequence, most cohorts to date focused on urban populations. In addition, most existing monitoring networks have insufficient density to capture small-scale (within-city) variation of air pollution, which can be quite substantial for certain pollutants (e.g., Cyrys et al. 2012; Eeftens et al. 2012).

Recent developments in satellite-based remote sensing, and other exposure methods and models (e.g., land use regression models and 'hybrid' models combining satellite data and land use regression models), and improvements in the quality and coverage of ground-level measurements have shown potential to provide air pollution estimates that cover large areas in a country, whole countries, or even multiple countries, with a sufficiently high degree of spatial resolution. These improvements allow exposure to potentially be estimated for large populations, including populations exposed to low levels of air pollution (e.g., Beckerman et al. 2013; Beelen et al. 2009; Hart et al. 2009; Novotny et al. 2011). Applicants will need to validate air pollution exposure estimates, in particular for the lower levels of exposure and when new methods and models are applied. Applicants should consider the design of the exposure assessment, and its requisite level of complexity, with regard to its ultimate effect on the accuracy and precision of the health effect estimates (Szpiro et al. 2011; 2013).

All studies should estimate exposure to $PM_{2.5}$ and preferably also include other criteria pollutants, such as NO_2, O_3, or other pollutants of interest (such as $PM_{2.5}$ components), especially when exposure will be assessed at different spatial scales including a within-city component. Applicants should, to the maximum extent possible, consider multi-pollutant modeling approaches to estimate effects of pollutants that are often highly correlated (see for a review, for example, Johns et al. 2012).

Applicants should make explicit, and justify, their choice of induction time(s) between exposure and health effects. Studies with the potential of characterizing exposure at different time scales to identify induction times would be of value.

Applicants proposing a study design that combines existing studies will need a common methodology to characterize exposure. Comparison between results from air pollution cohort studies to date is often hampered because the studies differ in the spatial scale of the exposure assignment.

Exposure measurement error — a potential source of bias in all epidemiologic studies (e.g., Sheppard et al. 2012) — is a particular challenge when assessing health effects of long-term exposure to low levels of ambient air pollution where effect sizes are expected to be relatively small. Therefore, studies should quantify exposure measurement error, and, if possible, adjust for it. Estimating exposure using nearest monitor to the residence typically results in underestimation of exposure, and models predicting outdoor concentrations at the residence better reflect personal exposure to ambient concentrations (e.g. Kioumourtzoglou et al. 2014). Moreover, residential mobility can affect long-term exposure of study subjects; ignoring residential mobility could potentially introduce substantial exposure measurement error (e.g., Hystad et al. 2012). Finally, the variability of individual time activity patterns, and longer term changes in those patterns, may further contribute to error. Proposed studies should take into account these potential sources of error in the exposure assessment, if possible, for all potential effects, and especially for effects with long induction times such as lung cancer.

Health outcomes. Health effects of interest are all-cause and cause-specific mortality and morbidity endpoints. Inclusion of additional health endpoints, such as adverse pregnancy outcomes, lung function, and well-established clinical markers of disease will be considered responsive.

If a proposal combines existing studies, a common methodology for effect assessment will be necessary. A common strategy for classifying and grouping adverse outcomes will be needed as well.

Control for important potential confounders. Studies need to control air pollution risk estimates for major potential confounders (e.g., smoking, socio-economic status) either by restriction or by direct or indirect adjustment approaches.

Studies using administrative databases typically include individual level information on age, sex, and race, but may not include important individual-level information on lifestyle risk factors, such as smoking habits, diet, alcohol consumption, or socio-economic status. If such a study is proposed, indirect approaches need to be developed and validated to correct risk estimates for important potential confounding variables, in the absence of such data at the individual level (Rothman et al. 2008). Indirect approaches have been used to correct for those factors in the analyses using, for example, standardized mortality ratios for COPD (e.g., Zeger et al. 2008), or using pre-existing comorbidities of COPD, diabetes, and hypertensive heart disease (e.g., Cesaroni et al. 2013). Using those alternative approaches requires careful consideration because comorbidities might act as intermediate variables. In addition, other approaches — typically used to control for confounders at a more aggregated (neighborhood) level — exist to control for various important confounders.

Precision and statistical power. Studies should be designed to maximize the number of people exposed at the low end of the exposure range, while also including sufficient people in the 'middle' or 'higher' end of the exposure range in geographic areas characterized by relatively low ambient concentrations. As a general guideline, current $PM_{2.5}$ annual average air quality standards from the US and Europe can be considered as the maximum value of what can be considered 'low' levels.

Applicants should assess and discuss the expected precision and statistical power of their estimates with regard to 1) whether risks at low levels can be detected and at what concentrations and 2) whether different models to characterize the exposure-response function(s) at low levels can be reliably distinguished. Assumptions needed for such calculations should be guided by previous relevant literature. Calculations should include some discussion of the influence of exposure measurement error.

METHODS DEVELOPMENT

RFA 14-3 also solicits proposals to develop methods required for, and specifically suited to, conducting research to assess adverse health effects of long-term exposure to low levels of ambient air pollution, either as part of a full study or as a stand-alone study. Examples of currently needed methods development and refinement include:

- Methods to quantify and correct for exposure measurement error in risk estimates.
- Multi-pollutant modeling approaches to estimate effects of pollutants that are often highly correlated.
- Opportunities to develop and validate alternative causal modeling approaches for application in such studies.

- Exposure assessment methods suitable to estimate exposure to low levels of air pollution in large study populations, including populations in areas not covered by routine ground-level monitoring. This may include comparing the performance of exposure assessment methods that differ in the spatial scale of the exposure assignment (e.g., city, zip code, or address), and characterizing exposure at different time scales to identify induction time(s).

This may also include validating exposure based on complex exposure models and remote sensing measurements.

- Methods for indirect approaches to correct risk estimates for the effects of important potential confounding variables, such as smoking.
- Techniques for record linkage and methods for disclosure protection for optimal use of large administrative databases in air pollution and health research. When using large administrative databases, such as the US Census, maintaining confidentiality will be especially important.

FUNDING AVAILABLE

Overall, a total of $5 to $6 million will be available under RFA 14-3. At the outset, HEI expects to fund a small number of large studies for up to 4 years. HEI also expects to fund some smaller-scale methods development studies.

POLICY ON DATA ACCESS

Providing access to data is an important element in ensuring scientific credibility, and is particularly valuable when studies are of regulatory interest. HEI has developed a policy to provide access to data for studies that it has funded in a manner that facilitates the review and validation of the work. The policy also protects the confidentiality of any subjects who may have participated in the study and respects the intellectual interests of the investigators who conducted the study. A copy of the *HEI Policy on the Provision of Access to Data Underlying HEI-Funded Studies* can be found in Appendix D (pages 53-54).

Applicants selected to submit full applications will be expected to include a plan for data sharing and accessibility at the end of the study. Where data are provided by a third party, a process for other investigators to obtain and work with the data should be outlined.

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Table 1 Recent Cohort studies of $PM_{2.5}$ and mortality

Cohort	**Country**	**Study population**	**Study size (number of total deaths)**	**Follow up years**	**Mean $PM_{2.5}$in µg/m³ (minimum-maximum)**	**Spatial scale***	**Reference**
Cohort studies							
Agricultural Health Study Cohort (AHS)	US	Farmers, spouses, and commercial pesticide applicators in Iowa and North Carolina	83,378 (5,931)	1993-2009	10 (SD=2)	Address (satellite, 10 km grid)	Weichtenthal et al. 2014
American Cancer Society (ACS)	US	Adults from 51 cities	499,968 (NA)	1982-2000	14.0 (6-22)	City	Krewski et al. 2009
Adventist Study of Health and Smog (AHSMOG)	US	Californian seventh-day Adventists	3,239 (250 for CVD)	1977-1998	29 (SD=10)	Address (interpolation)	Chen et al. 2005
California teachers	US	Female teachers in California	101,784 (4,147)	1997-2005	16 (3-28)	Address (interpolation)	Lipsett et al. 2011
Dutch Study on Diet and cancer (NLCS-AIR)	Netherlands	Elderly subjects	120,852 (17,286)	1987-1996	28 (23-37)	Address (LUR)	Beelen et al. 2008
Harvard Six city	US	Adults in 6 cities	8,096 (4,495)	1974-2009	16 (11-24)	City	Lepeule et al. 2012
Health Professionals	US	Highly educated men in Midwestern and northeastern states	17,545 (2,813)	1989-2003	18 (SD=3)	Address (LUR)	Puett et al. 2011
Japanese Cohort	Japan	Adults from 6 areas	63,520 (6,687)	1985-1995	17-42 (average of different cities) (SD=NA)	City	Katanoda et al. 2011
National English Cohort	UK	Primary care adult patients	835,607 (83,103)	2003-2007	13 (9-20) (2002 only)	Zip code (dispersion, 1 km grid)	Carey et al. 2013
Nurses Health	US	Women from northeastern metropolitan areas	66,250 (3,785)	1992-2002	14 (6-28)	Address (LUR)	Puett et al. 2009
US truckers	US	Men in trucking Industry	53,814 (4,806)	1985-2000	14 (SD=4)	Address	Hart et al. 2011
Veteran's study	US	Male veterans	23,872 (7,386)	1997-2001	14.3 (SD=3)	County	Lipfert et al. 2006
Women's Health Initiative (WHI)	US	Postmenopausal women from 36 metropolitan areas	65,893 (1,816 for CVD)	1994-1998	13.5 (3-28)	Zip code	Miller et al. 2007

Table 1 continued

Cohort	Country	Study population	Study size (number of total deaths)	Follow up	Mean $PM_{2.5}$ in µg/m3 (min-max)	Spatial scale*	Reference
Very large cohort studies, or combining existing cohorts							
Canadian national cohort	Canada	Nonimmigrant adults	2.1 million (200,000)	1991-2001	9 (2-19)	Enumeration area (satellite, 10 km grid)	Crouse et al. 2012
European Study of Cohorts for Air Pollution Effects (ESCAPE)	22 European cohorts (in 13 countries)	General population samples	367,251 (29,076)	1985-2007	7-31 (average of SDPP cohort in Sweden, and the SIDRIA cohort, Italy) (SD: 1.3-1.7)	Address (LUR)	Beelen et al. 2013
Medicare cohort	US	Elderly (>=65 years old) Medicare recipients	13.2 million (4.88 million)	2000-2005	13 (SD=4)	Zip code (within 6 miles of a monitor)	Zeger et al. 2008
New Zealand Census Study	New Zealand	Urban areas	1.06 million (17,937)	1996-1999	8 (0.1-19)**	Census tract area (dispersion)	Hales et al. 2012
Rome cohort	Italy	Adults in Rome	1.3 million (144,441)	2001-2010	23 (7-32)	Address (dispersion, 1 km grid)	Cesaroni et al. 2013

Abbreviations: CVD = cardiovascular disease; LUR = land use regression model; NA=not available; PM= particulate matter; SD= standard deviation; UK = United Kingdom; US = United States; *Spatial scale of exposure assignment; ** PM_{10}

RFA 14-3: APPLICATION PROCESS, DEADLINES, AND EVALUATION

The submission and review of applications for RFA 14-3 will entail a two-stage process: a preliminary application followed by a full application (upon request only). Full applications without pre-submission of a preliminary application will **not** be considered.

PRELIMINARY APPLICATION

Before funding full studies, HEI seeks to determine whether potential studies are feasible and likely to meet the stated objectives. Therefore, HEI requires that all respondents to this RFA first submit a preliminary application. In addition to a description of design features (e.g., study population, locations, exposure assessment approach, number of events, person-time exposed [if available]), applicants should provide a preliminary assessment of expected precision and power to support the proposed study. In addition, a brief description of the scientific rationale, study aims, statistical analyses, and anticipated results should be included.

Applicants proposing a study to develop methods should also submit a preliminary application and make the case that those methods are applicable to study designs pertinent to RFA 14-3.

Preliminary applications should include an estimated total budget and study duration. In addition, brief curricula vitae (CVs; maximum 2 pages per person) of the principal investigator and co-investigators should be provided.

Applicants should use the Preliminary Application Form, which can be downloaded from *www.healtheffects.org/funding.htm*. The preliminary application must be no more than seven pages in length (using 11-point font size and 1-inch margins; excluding references and CVs).

Deadline for Preliminary Applications

Preliminary applications should be submitted by e-mail in PDF format to *funding@healtheffects.org* no later than **FEBRUARY 16, 2015,** with a copy to Ms. Sarah Benckart (*sbenckart@healtheffects.org*). HEI will acknowledge receipt of the application.

Preliminary Application Evaluation Process

Preliminary applications will be reviewed by the Research Committee and outside consultants. They will decide whether 1) full applications are warranted, 2) other population(s) and/or researcher(s) needs to be added to the proposal and 3) whether the different preliminary applications received would best be combined under a common protocol for characterizing exposure and health analyses. Applicants will be informed whether or not to submit a full application within 4 weeks after the submission date.

For questions contact: Dr. Aaron Cohen (*acohen@healtheffects.org*, +1-617-488-2325) or Dr. Hanna Boogaard (*jboogaard@healtheffects.org*, +1-617-488-2306).

FULL APPLICATION

Invited full applications should provide in-depth information on aspects presented in the preliminary application: the study aims, design, rationale, methods, and statistical analyses. If data from other studies are going to be used, information on the type of data available (including the period, location, and frequency of when the measurements were taken) and quality assurance should be included. Applicants should also discuss whether they will need to obtain IRB approval. A letter from the investigator who owns the data should be submitted, stating his or her willingness to share the data with the applicant and with HEI, if requested (see Appendix D: *HEI Policy on the Provision of Access to Data Underlying HEI-funded Studies* on pages 53-54). In addition, the full application should include a plan for data sharing and accessibility at the end of the study.

Investigators invited to submit a full application should use forms F-1 to F-12 (see list on page 37) and consult the *Instructions for Completing the Application* found on pages 31-36. Application forms can be downloaded from *www.healtheffects.org/funding.htm*. Please note that the required font size is **11 point with 1-inch margins**.

Deadline for Full Applications

Full applications should be submitted to *funding@healtheffects.org* no later than **JULY 13, 2015**. The application should be in PDF format with a maximum file size of 20 MB.

After submission, please notify Ms. Sarah Benckart (*sbenckart@healtheffects.org* or +1-617-488-2345) of your submission; do not attach the PDF documents to this email. HEI will acknowledge receipt of the application.

Full Application Evaluation Process

Full applications will be evaluated in a two-stage process: an external review followed by an internal review.

EXTERNAL REVIEW

Applications undergo a competitive evaluation of their scientific merit by an ad hoc panel of scientists selected for their expertise in relevant areas. Applications may also be sent to external scientists for additional evaluation. The panel will evaluate applications according to the following criteria:

- Relevance of the proposed research to the objectives of the RFA.
- Scientific merit of the hypothesis to be tested, the study design, exposures and outcomes to be evaluated, accessibility to existing databases of ambient air, meteorological monitoring, registries, health care utilization or other resources as appropriate, proposed methods of data collection, validation, and analysis, including adjustment for potential confounding factors, such as smoking, and development of innovative analytic methods of data analysis.
- Personnel and facilities, including:
    - Experience and competence of principal investigator, scientific staff, and collaborating investigators,
    - Extent of collaboration among investigators in pertinent fields who will contribute to the conduct of the study,
    - Adequacy of effort on the project by scientific and technical staff,
    - Adequacy and validity of existing data and data to be collected,
    - Adequacy of facilities.
- Reasonableness of the proposed cost.

The applications ranked highly by the review panel may be additionally reviewed by a statistician regarding the experimental design and analytical methods.

INTERNAL REVIEW

The internal review is conducted by the HEI Research Committee and generally focuses on the applications ranked highly by the external review panel. The review is intended to ensure that studies funded constitute a coherent program addressing the objectives of the Institute. The Research Committee makes recommendations regarding funding of studies to the Institute's Board of Directors, which makes the final decision.