HEALTH EFFECTS INSTITUTE

Attachment 1

RESEARCH AND REVIEW PROCESSES

Revised: April 2016

1. INTRODUCTION

HEI is non-profit organization whose mission is to provide public and private decision makers with independent, impartial, timely, and high quality science on the health effects of emissions from motor vehicles, fuels, and other sources of environmental pollution. Producing scientific research results of the highest quality is central to maintaining HEI's credibility and all studies funded by HEI are expected to adhere to HEI's policies and procedures outlined in this document.

HEI receives its core funds from the U.S. Environmental Protection Agency and from the worldwide motor vehicle industry, and other private and public organization. HEI accomplishes its mission by seeking:

- To identify the areas of highest priority for health effects research on pollutants and issues of greatest concern.
- To fund and oversee the conduct of high quality research in the priority areas.
- To provide independent review of HEI-supported research and reanalysis that evaluates, summarizes, and enhances the understanding and credibility of the results.
- To communicate the results of HEI research and analyses to public and private decision makers and the scientific community in an understandable and timely manner.

HEI is governed by a Board of Directors whose members are leaders in science and policy and committed to the public-private partnership that is central to HEI, but are not affiliated with its sponsors. HEI activities are performed working two scientific committees and staff. The HEI Research and Review Committees select, oversee, and evaluate the scientific activities of the Institute. The committees are multidisciplinary in nature and are composed of distinguished scientists who are knowledgeable about scientific issues related to study of the health effects of air pollution. The Research Committee develops and oversees HEI's research program. The Review Committee, which has no role in selecting or overseeing the studies, evaluates and interprets each study. At each stage, Committee members who have a conflict of interest in reviewing either an application or a final report recuse themselves from all such deliberations according to well-established procedures. The Institute's small scientific staff is highly qualified and actively engaged in all scientific activities, and works closely with both the Committees.

2. FUNDING AND OVERSIGHT OF RESEARCH IN HIGH PRIORITY AREAS

A. Identification of Areas of the Highest Priority

On a periodic basis, HEI consults its sponsors about their recommendations for research priorities on the basis of their projections of research needs associated with regulatory activities, changes in the use of technologies and fuels, and new scientific information that raises concerns. In addition, HEI encourages scientists and others in government, industry, and environmental and health organizations to provide input about priorities for HEI research. HEI believes that the contributions of diverse sponsors and other stakeholders both in the US and internationally results in five-year *Strategic Plans* that are comprehensive and broadly relevant and that stands the best chance of accurately anticipating the emerging questions of science and regulation. The latest Strategic Plan for the years 2015 – 2020 was published in April 2015 (http://pubs.healtheffects.org/view.php?id=439).

B. Solicitation of Research Applications

The HEI Research Committee works with HEI staff to develop requests for applications (RFAs) on specific themes and issues identified in the Strategic Plan. As the first step in developing an RFA, HEI may organize a workshop or conduct a literature review so that it can learn about important research questions or techniques in a given area. Through each RFA solicitation, HEI's goal is to develop a coherent program of studies that together provide information on a high priority research topic. The RFA includes scientific and regulatory background on the topic, questions that need to be investigated, and possible approaches and study designs that HEI deems appropriate and any specific QA issues, if necessary. Additional materials included with the RFA provide details of the application procedure and selection, and research management processes, requirements for the use of human subjects and quality assurance. (See http://www.healtheffects.org/funding.htm for examples).

HEI publicizes the publication of RFAs by advertisements and announcements on professional society websites and list-serves, print sources including scientific journals, and HEI's extensive mailing list of scientists with an interest in air pollution health effects.

Any member of the scientific community is free to respond to an RFA. Investigators are selected for funding through an open and competitive process. All submitted applications are reviewed through a three-step process, summarized below. Thus, HEI selects investigators for funding through an open and competitive process which is open to all in the scientific community.

C. 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 detailed experimental plan and methods so that the technical quality of the proposed research may be evaluated;
- Biographical sketch for the Principal Investigator and other key professional personnel and consultants involved in the project so that the quality and experience of the team can be judged;
- Proposed budget;
- Information on current and pending support, and description of resources and environment available; and,
- For studies involving human subjects, a signed copy of the Protection of Human Subjects, Assurance Identification/IRB Certification/Declaration of Exemption Form (OMB No. 0990-0263. For other details of the HEI Human Subject Policy, see Appendix C).
- Response to any specific quality assurance requirements outlined in the RFA.

D. Selection of applications for funding

i. Step 1: External Review Panel

Research Committee members with expertise in the RFA topic work with HEI staff to identify and organize an external panel of experts spanning the areas relevant to the RFA. The Panel generally meets for a face-to-face meeting and reviews all the applications. Each member of the Panel is assigned a small number of applications and provides written comments on them; members are also expected to be familiar with other applications. Written reviews from additional experts may also be obtained, if necessary. The reviewrs are asked to address:

- Relevance of the proposed research to objectives of the RFA;
- Scientific merit of the research design, approaches, methodology, analytic methods, statistical procedures, and quality assurance or human subject issues (if relevant);
- Qualifications and experience of personnel;
- Adequacy of facilities; and,
- Reasonableness of proposed time commitment and budget.

The meeting of the ad hoc panel is chaired by one or two members of the Research Committee who have appropriate expertise. After discussion of all the proposals, members of the panel assign a numerical score to each proposal. Any member of the panel with a conflict on a specific proposal is recused from discussions and scoring of that proposal.

ii. Step 2: Research Committee Review

After the External Review Panel review, a staff summary of the applications and Panel discussion, the reviews, and scores are sent to the Research Committee, which discusses the applications at a regularly scheduled meeting. The Committee's review generally focuses on the applications ranked most highly by the review panel. In addition to the comments by members of the panel, the Committee considers the applications with respect to how well they address HEI's objectives and contribute to a coherent program with minimal overlap. In some cases, the Research Committee may also consider a proposal with a somewhat lower score so as to fund a well-rounded program. The Committee may also recommend modifications to the submitted proposal, for example, deletion of a part of a project that is less relevant to HEI's objectives, addition of personnel with requisite experience, or addition of analyses to improve comparability of different studies funded under the same RFA. Any member of the Research Committee who has a conflict of interest with any of the proposals is recused from discussion of that proposal and also from overall discussions and decisions by the Committee. The final outcome of Research Committee discussions is a recommendation of specific studies for funding which is sent to the HEI Board.

iii. Step 3: HEI Board of Directors' Approval

All studies to be funded by HEI must be first approved by the Board of Directors. HEI Director of Science prepares a summary of outcome of review of applications and the Research Committee's recommendations. During its discussion for approval, the Board reviews the information provided and the committee's recommendations, and also pays particular attention to the processes by which the RFA was developed, the applications were reviewed, selections were made, conflict of interest issues -- if any -- were managed, and whether any lower-ranked proposals were recommended for funding.

E. Research Agreement

After approval of a study by HEI's Board, the Institute develops a research contract (Research Agreement), which describes the obligations of the investigator, his/her institution and HEI, and which is negotiated and signed by the investigator's institution and HEI. HEI's Research Agreements are on a cost-reimbursement basis and are signed for one-year (with the option for renewal). The research agreement:

- States that all work shall be performed in conformance with the Statement of Work (developed based on the final approved proposal);
- States that key investigators may not be changed without HEI's approval;
- Sets forth HEI's right to provide oversight, including conducting site-visits;
- Sets forth the obligations to meet federal and EPA's regulations for the use and protection of human subjects and the care of laboratory animals;
- Sets forth the obligation to adhere to HEI's quality assurance and quality control policies;

- Sets forth requirements for periodic progress reports and the final report on the completed study;
- Sets forth HEI's rights to inspect the work to assess and assure the scientific quality, including quality assurance audits;
- States HEI's rights to obtain a copy of all data pertaining to the study and to further analyze, publish, deliver, or dispose of these data as it believes appropriate;
- 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; and,
- Requires that any publication, or abstract, or presentation resulting from the research acknowledge EPA funding using specific language and that a copy of any such publication be provided to HEI.

F. Use of Human Subjects

For any research involving human subjects, HEI signs the Research Agreement only after written approval from EPA to proceed with that research has been obtained. HEI asks the investigator to submit documents to demonstrate that the institution will adhere to all applicable federal and EPA regulations, which are specified in the Research Agreement (see HEI's policy for the use of human subjects; Appendix C).

G. Quality Assurance–Quality Control Program

As detailed in Appendix B, 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), are traceable and meet data quality objectives. For studies that involve human subjects and some animal studies of regulatory significance, the HEI has additional requirements (see Appendix C). HEI conducts QA/QC audits, using third party, experienced auditors during the course of the study and during review of the final report.

H. Study Oversight and Project Management

HEI has a robust system for study oversight to ensure that the work funded conforms to HEI's expectations, meets scientific milestones, adheres to the highest standards of scientific quality and meets or exceeds requirements for QA/QC. To this end, each study is assigned to one or two staff members, who serve as project managers and oversee and coordinate all aspects of the work. They work closely with one or more members of the Research Committee who have expertise in the research topic. The staff oversee investigator's research and monitor its progress through a combination of progress reports, annual conferences, webinars and site visits. The level of oversight by the Research Committee and staff is tailored to the nature of each study. Any changes from the approved research plan or significant changes in the investigator's team is discussed by the Research Committee and specifically approved.

i. Progress Reports

All HEI investigators submit two progress reports each year: a 5-month and a 10-month progress report. The 5-month progress report is useful to ensure general progress and provides an opportunity for feedback from the Research Committee. The 10-month progress report, which also serves as a 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 and serves as a renewal application. Both reports are reviewed by Research Committee members with oversight responsibilities and approved for subsequent funding, provided there are no concerns. If any significant issues are identified, the report is discussed with the whole Research Committee and other oversight steps may be taken. 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 timely, high quality results. HEI staff scientist assigned to the study are responsible to ensuring that these reporting requirements are met and that the project meets its milestones.

ii. Annual Conference:

Each spring, HEI organizes a scientific conference where all HEI funded investigators are required to present posters. In addition to discussion during the poster sessions, the meeting also provides ample opportunities for the investigators to speak and seek advice from Research Committee members and with other scientists attending the meeting as well as interact with HEI staff scientist. The Research Committee also uses the poster sessions to learn about the progress that is being made and to discuss any problems that may arise during the course of research.

iii. Webinars

When the Committee or staff find that there is a need for a detailed discussion of the results and future plans for a study, HEI organizes a webinar with the investigative team during one of the regularly scheduled meetings of the Research Committee. The investigators are asked to present a summary of the results, any difficulties encountered and their plans for completion of the project. The investigator's presentation is followed by detailed discussion with the Committee which often results in specific recommendations from the Committee to the investigator. The staff scientist communicates the Committee recommendations to the investigator and ensures that they are followed.

iv. Site Visits:

If a more in-depth scrutiny of a study is indicated, the staff scientist organizes a site visit to the investigator's laboratory with the help of a few Research Committee member(s), HEI Staff and external expert consultant(s). Site visits may be conducted because lack of progress or other problems with the study, but often the purpose is to have an in-depth scientific review and discussion of progress, results, and the future

course of work, and inspect the facilities available to the research team. A detailed report from the site-visit team, with specific recommendations for follow-up and corrective actions – if necessary – is sent to the investigators and he/she is asked to provide a written response.

3. INDEPENDENT REVIEW OF COMPLETED HEI STUDIES

One of the unique aspects of HEI's work is the detailed review of all studies upon their completion and publication of a commentary from the HEI Review Committee.

A. The HEI Review Process

At the end of the research phase, each investigator is required under the terms of the Research Agreement to submit a comprehensive final report; this report is more comprehensive than a typical journal article and presents the background, methods, all results (positive and negative) and the investigator's interpretations and conclusions. As stated in the Introduction, the Review Committee – comprised of experts in various areas of environmental health – does not have any role to play during writing of the RFA or selection and conduct of studies; its role is to provide an independent review of the study upon completion and prepare a commentary to be published with the final report.

At this point, HEI also assigns another staff scientist to the report, who had not been involved in the research phase, to ensure no biases are introduced during the review process. During this process, the review scientist works with the Review Committee, the investigator, and HEI editorial staff.

During its review, the Committee generally seeks reviews from three or four outside scientists with in-depth expertise in the topic of the report. The Committee also includes biostatisticians so that the statistical methods and data analyses can be carefully scrutinized. The reviewers and the Committee pay particular attention to objectives of the research, appropriateness of the methods and analytical approaches, quality assurance or animal use/human subject issues, interpretation of the results, support for conclusions and description of caveats and limitations of the results, as well as additional analyses and revisions that may be needed. The investigator is given an opportunity to respond to the Committee's comments and revised the report before publication. HEI also edits the reports for clarity and completion. In some cases, the Review Committee may require submissions of some or all raw data and codes and analytical tables during review of the final report; a provision in the HEI Research Agreement gives HEI the right to do so.

B. Quality Assurance of Final Reports:

HEI takes a great care to ensure that the data published in HEI's research reports are error-free. Prior to publication, all HEI reports undergo a detailed editorial process; HEI editors pay close attention to internal consistency among reported data, summary tables and appendices, thus detecting and removing such errors. Second, final reports

of HEI studies (with the exception of most in vitro, atmospheric chemistry or modeling studies) are also subjected to audit by an external, third-party auditor (see Appendix B for details). Thus, both the external audit and internal editorial processes ensure that the data published by HEI are as accurate and error-free as possible.

C. Review Committee's Commentary

At the end of the review process, the Review Committee prepares a commentary on the report, with the goal to place the research into a broader context of scientific and regulatory questions, point out the strengths and limitations of the study, and discuss the conclusions, interpretations, and implications of the findings. The investigators report, which includes a detailed presentation of *all* results, and the Committee's commentary are published by HEI under the same cover as HEI Research Reports.

Over the years, HEI's sponsors have found HEI's review process and commentary to be a highly valuable final check to the quality of research and its findings, as well as its overall value to answering scientific and regulatory questions. Given the comprehensive nature of HEI reports, many in the sponsor and scientific communities rely heavily on HEI's carefully prepared and balanced commentaries to learn about the research and its findings. Additionally, the HEI review process is much more rigorous and detailed than review processes used by scientific journals, and it assures that the study is thoroughly scrutinized before its publication.

Very occasionally, if the results of a study are not interpretable, or if there are serious concerns about the methods used or the data collected – including quality assurance issues – the Review Committee decides to not publish the report. In such cases, HEI files the final report with a very short critique of the study, explaining the reasons for non-publication. This report is available from HEI upon request.

4. Communication of Results and Outreach

In preparing its commentaries, the Review Committee makes every effort to make the language accessible to non-specialist readers from the scientific, regulatory and other communities. Additionally, the committee prepares a "Statement" that succinctly summarizes the research, its background, findings, conclusions and the Review Committee's comments. To make the reports even more readily accessible, HEI prepares a four- or five-point summary of the research and commentary, under the title "What This Research Adds" and includes it as a part of the statement.

Final reports and the accompanying commentaries are widely disseminated through HEI's Website (www.healtheffects.org), printed reports, newsletters and other publications, annual conferences, and – where appropriate – by presentations to legislative bodies, public agencies and scientific organizations. For important reports, HEI also briefs its sponsors just before the report is released. HEI research reports are listed by bibliographic services such as the National Library of Medicine's Medline/PubMed database; thus, any report can be found through appropriate search engines and cited.

HEALTH EFFECTS INSTITUTE

Attachment 2

QUALITY ASSURANCE POLICIES AND PROCEDURES

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Given HEI's goals to provide high-quality and credible scientific information on health effects of air pollution, HEI requires that all studies that it funds have appropriate Quality Assurance/Quality Control (QA/QC) procedures in place; good QA/QC procedures ensure that data are collected under defined conditions as specified in a written protocol and Standard Operating Procedures (SOPs), are reliable and traceable, and the analyses are appropriate and reproducible. HEI's general guidelines for QA/QC are summarized below in part 1 of Appendix B. For studies involving human subjects and some animal studies of regulatory significance, HEI has additional requirements which are described in part 2. HEI's Quality Assurance Policies and Procedures are included in all RFAs published by HEI and are provided to all funded investigators. Additional details about acceptable quality management are available at https://www.epa.gov/quality.

PART 1. GENERAL QA/QC GUIDELINES AND PROCEDURES

A. Roles of Principal Investigators and Institutions

The Principal Investigator (PI) and his/her institution have the primary responsibility for the preparation of the protocol and all SOPs and shall review and approve them by signing them. In addition, the PI has the responsibility to prepare a Quality Assurance Plan, and submit it to HEI soon after starting the study, but no later than at the time of submission of the Year 1, 5-month progress report; in certain cases, the original Project Plan submitted with the grant application can serve as the protocol, with added information as recommended by the Research Committee or staff. HEI works with the investigators to ensure that the QA plan is adequate and consistent with the agreed upon Statement of Work. Contents of the QA plan are described below in this document. More detailed guidance can be found at EPA website, for example, see http://www.epa.gov/quality and http://cfpub.epa.gov/ncer_abstracts/index.cfm/fuseaction/display.files/fileID/7597

The Principal Investigator has the responsibility for the actual conduct of the research, adhering to the protocol and SOPs and his/her own group and those of any collaborators or sub-contractors. 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.

B. Role of HEI

i. Research Committee Approvals:
The study protocol is reviewed and approved by the HEI Research Committee. Any subsequent modifications to the protocol are submitted to HEI in the form of written amendments. All protocols and amendments are subject to HEI Research Committee approval before they may be implemented. 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.

ii. QA/QC Audits:
The Research Agreement between HEI and the investigator's institution stipulates that HEI reserves the right to conduct (and often does conduct) one or more QA audits of HEI-funded studies, whether or not there are reasons to suspect that adequate procedures are not in place or not being adhered to. The broad goals of such audits are to evaluate status of the work, ensure that adequate protocol and appropriate SOPs have been developed and being adhered to, observe laboratory procedures and experimental set up, and evaluate procedures for data collection and retention. It is the HEI practice to audit all studies using human subjects; decisions to audit other studies are made by the Research Committee and staff on a case-by-case basis, taking a number of factors into consideration.

The QA audits are conducted by third-party, experienced, professional auditors who are not affiliated with HEI or the investigator; HEI obtains their services through an open, competitive request-for-qualifications process. The auditor reports directly to HEI's Director of Science. HEI science staff/project manager generally accompanies the auditor during such visits. The audit is performed using the audit framework presented in the US EPA's Guidance on Technical Audits and Related Assessments for Environmental Data Operations (EPA QA/G-7, available at https://www.epa.gov/sites/production/files/2015-07/documents/g7-final.pdf). After the visit, the auditor prepares a report (see below for details) detailing the audit's findings and necessary corrections; HEI staff ensure that the auditor's recommendations are put into effect by the investigator.

C. Quality Assurance/Quality Control Plans and Procedures

QA procedures begin with the planning phase of the raw data collection and follow all the subsequent transformations of the data. HEI requires that the investigators: use a written protocol; use written standard operating procedures; involve qualified personnel in conduct of all phases of the study; maintain written records; use appropriate data processing techniques; and, use quality control procedures for all data collected.

i. ***A written research protocol*** defines the study's hypothesis and objectives and the 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 hypothesis and objectives
3. Scientific background and rationale
4. Anticipated significance of 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

ii. ***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 with similar training, to minimize procedural variation.

iii. SOPs will be developed by individuals knowledgeable of and experienced in the specific procedures. They will describe, in a stepwise manner, the what, when, where, how, and why of the procedure. 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.

iv. 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.

v. ***Qualified personnel*** who 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.

vi. ***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.

vii. 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.

viii. ***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.

ix. 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.

x. ***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.

PART 2. QA/QC REQUIREMENTS FOR STUDIES USING HUMAN SUBJECTS

HEI frequently sponsors studies that use human subjects; such studies include epidemiological studies, exposure monitoring or exposure assessment studies, and some direct exposure (chamber or panel) studies. In view of the importance and special considerations associated with studies involving human subjects, and in order to meet the regulatory requirements specified both by the US Department of Health and Human Services and the EPA, HEI takes great care to ensure that such studies are conducted to meet the highest QA/QC and other applicable standards, while

safeguarding the health and well-being of the human subjects. As required under the terms of its grant from the EPA and as outlined in HEI's policies for the use of human subjects (Appendix C), HEI obtains specific approval for the use of human subjects from the EPA before any such studies are started. Also, HEI imposes additional requirements for such studies (detailed below), in addition to requiring investigators to adhere to the general procedures outlined above under Part 1 for all studies.

A. Written research protocol:

Along with the elements of a research protocol outlined above under Part A, HEI requires that the written protocol for studies using human subjects include the following:

10. Subject selection procedures for the study, including the inclusion and exclusion criteria;
11. Procedures used to maintain subject confidentiality;
12. Copy of the blank form used to obtain Informed Consent from subjects; and,
13. Current IRB approval.

B. Third-Party QA Oversight

As an important component of the procedures for human subject studies, HEI assigns the services of a third-party, independent, qualified and experienced professional QA/QC auditor to the study. HEI's QA audits for studies not using human subjects is decided on a case-by-case basis, as discussed above; however, *all* human subject studies are subject to detailed QA oversight, including QA audits.

C. Elements of a QA Audit

The key elements of a QA audit include:

1. Observation of the project activities being performed by the personnel who regularly perform such activities.
2. 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).
3. Interviews with the project personnel to verify the results of observation and to clarify issues noted during observation or document review.
4. Objective Evidence Compilation, such as review of notebook pages, logs, instrument and model outputs, and QC charts.
5. QA Audit Report and Follow-up. The QA auditor prepares a "Business Confidential" report of the audit. The report details nature of the audit, any significant findings and requirements for corrective action(s). The audit report is provided directly to the HEI Director of Science who, after review, forwards it to the HEI staff scientist who is managing the project for transmission to and discussion with the PI. If corrective action is required, HEI asks the PI to take appropriate action and document them in writing to HEI. HEI in turn sends the PI's response to the QA auditor for review. This

process may be repeated until the issues noted during the audit are satisfactorily resolved. HEI treats all QA reports "Business Confidential" and does not release them to anyone who is not directly involved in oversight of the study.

D. TIMING OF QA AUDIT

While the exact timing of the audits varies across studies, the followed general guidelines are as follows:

i. Audits during the course of the research period

a. Clinical studies

-- One QA audit is conducted at the beginning of the study to ensure that the protocol and all SOPs and a data management plan are in place, and the staff are familiar with these and are following them. This audit occurs early in the study so that problems, if found, can be remedied before too many subjects have been studied.

-- One QA audit around the mid-point of the study to audit, in addition to the elements listed above, a subset of the data collected to verify that the data management procedures are adequately implemented and followed, collected data are traceable, informed consents are obtained, and the protocol is followed consistently.

-- Additional audits may also be conducted with the goal of extending the second audit to later stages of the study or to the completed study and final data set.

-- Audit of the final report may be done remotely or on-site.

b. Epidemiologic 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, that the data management procedures are implemented and followed, and collected data are traceable.

-- If problems are encountered or not addressed adequately, a follow-up visit may be organized.

-- Audit of the final report may be done remotely or on-site.

ii. Audit of the final report

HEI subjects the final report from studies using human subjects to an audit, using the services of a third-party, external auditor experienced in quality assurance issues (generally the same expert who performs earlier audits on the same study). By visiting the laboratory or by connecting with it remotely, he/she audits raw data, analytical methods, and accuracy of reported data. The auditor also checks the final report for internal consistency. Going through HEI, the auditor's report is sent to the investigator for requisite action. Once all the issues identified during the audit are resolved, the auditor issues a report which is included in the published report.

In some cases, the Review Committee may require submissions of some or all raw data and codes and analytical tables during review of the final report; a provision in the HEI Research Agreement gives HEI the right to do so.