Quality Assurance Policies and Procedures

Introduction

Given HEI-Energy's goals to provide high-quality and credible scientific information on health effects of air pollution, HEI-Energy 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-Energy's general guidelines for QA/QC are summarized below in Part 1. For studies involving human subjects and some animal studies of regulatory significance, HEI-Energy has additional requirements which are described in Part 2. HEI-Energy's Quality Assurance Policies and Procedures are included in all solicitations published by HEI-Energy 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 their 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-Energy soon after start of 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-Energy's QA manager 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 PI has the responsibility for the actual conduct of the research, adhering to the protocol and SOPs, for his/her own group, and for 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 PI 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 research activities.

B. Role of HEI-Energy

i. Research Committee Approvals

The study protocol and QA plan are reviewed and approved by the HEI Energy Research Program Research Committee. Any subsequent modifications to the protocol are submitted to HEI-Energy in the form of written amendments. All protocols and amendments are subject to Research Committee approval before they may be implemented. In some cases, HEI-Energy 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-Energy and the investigator's institution stipulates that HEI-Energy reserves the right to conduct (and often does conduct) one or more QA audits of HEI-Energy-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-Energy 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-Energy or the investigator. HEI-Energy obtains their services through an open, competitive request-for-qualifications process. The auditor reports directly to HEI-Energy's Director of Science. HEI-Energy 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-Energy staff ensure that the auditor's recommendations are applied 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-Energy 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

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 PI 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
6. Methods of data processing
7. Internal quality control procedures to be used
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

Written SOPs 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.
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.

SOPs will be uniquely identified, 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-Energy, as needed. All SOPs that have been superseded will be maintained in a historical file. Deviations from SOPs should be documented.

iii. Qualified personnel

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.

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

v. Data processing procedures

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.

vi. Quality control procedures

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-Energy 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-Energy 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-Energy's policies for the use of human subjects, HEI-Energy obtains specific approval for the use of human subjects from the EPA before any such studies are started. In addition to requiring investigators to adhere to the general procedures outlined above under Part 1 for all studies, HEI-Energy imposes requirements for such studies (detailed below).

A. Written research protocol

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

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

B. Third-Party QA Oversight

As an important component of the procedures for human subject studies, HEI-Energy assigns the services of a third-party, independent, qualified and experienced professional QA/QC auditor to the study. HEI-Energy'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, in which the QA auditor prepares a "Business Confidential" report of the audit. The report details the nature of the audit, any significant findings and requirements for corrective action(s). The audit report is provided directly to the HEI-Energy Director of Science who, after review, forwards it to the HEI-Energy staff scientist who is managing the project for transmission to and discussion with the PI. If corrective action is required, HEI-Energy asks the PI to take appropriate action and document them in writing to HEI-Energy. HEI-Energy 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-Energy 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 a 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 is conducted 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-Energy 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-Energy, 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-Energy Research Agreement gives HEI-Energy the right to do so.