Research Report 192

Multicenter Ozone Study in oldEr Subjects (MOSES):
Part 1. Effects of Exposure to Low Concentrations of Ozone on Respiratory and Cardiovascular Outcomes

Mark W. Frampton et al.

Additional Materials 4. Data Coordinating and Analysis Center Management Plan

These Additional Materials were not formatted or edited by HEI. These documents were part of the HEI MOSES Review Panel’s review process.

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Multicenter Ozone Study in Elderly Subjects (MOSES)

Data Management Plan

Version 08JAN2014

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Data Management Plan Signatures

Approved by:

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<tr>
<th>Name</th>
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<tr>
<td>Anne Stoddard</td>
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# Table of Contents

## Contents

- Overview ......................................................................................................................... 4
  - NERI’s Data Management Scope of Work ........................................................................ 4
  - NERI’s Data Management deliverables ........................................................................ 4
- Case Report Form Design ................................................................................................. 4
  - CRF development ............................................................................................................ 4
  - CRF approval ................................................................................................................... 4
  - CRF standard sections .................................................................................................... 4
  - Displaying coded variables ........................................................................................ 5
  - CRF Versioning .............................................................................................................. 5
- Trial Workflow .................................................................................................................. 5
  - Description of trial workflow ......................................................................................... 5
  - Process of what happens to data once collected ......................................................... 5
  - Process of what happens should a data point fail a validation .................................... 5
    - Figure 1 – Data Flow .................................................................................................. 6
    - Figure 2 – MOSES data storage diagram ................................................................. 7
- CRF Tracking .................................................................................................................... 8
  - Location of data entry .................................................................................................... 8
  - Location of hard copies .................................................................................................. 8
    - Figure 3: Database Design ......................................................................................... 9
- Data Entry and Verification ............................................................................................... 10
  - Manual review of data ................................................................................................ 10
  - Time allowed for entry ............................................................................................... 10
  - Data Validation ............................................................................................................ 10
    - Edit checks ............................................................................................................... 10
    - Edit check modifications ......................................................................................... 10
    - Communication of programming changes to sites ................................................. 11
- Discrepancy Management ............................................................................................... 11
  - Description of the query process ................................................................................. 11
  - Description of the query resolution process ............................................................... 11
- Safety and Data Monitoring ............................................................................................. 11
- Third Party Imaging and Measurements ......................................................................... 11
- Data Management Deliverables ...................................................................................... 12
  - Timeline and Delivery of Reports .............................................................................. 12
- Quality Control (QC) ...................................................................................................... 12
  - QC Measures to be followed ..................................................................................... 12
- Acceptable modifications ................................................................................................. 12
- Archival ............................................................................................................................. 12
  - Archiving process ....................................................................................................... 12
Overview

**NERI's Data Management Scope of Work**

The New England Research Institutes, Inc. (NERI), Watertown, MA will provide data management services including CRF development, database design and CRF programming, database security and maintenance of study data, site training in the electronic data capture (EDC) system, site support for the EDC system and monitoring of data collection and data cleaning with resolution of discrepancies through a query process.

**NERI's Data Management deliverables**

EDC System capable of managing data collected at 3 sites including:
- Case Report Forms
- Site Management tools
  - Forms and procedures to manage the Personal Exposure Sampler (PES) process
  - Procedures to manage specimens to be sent to central laboratories
- Integrated central laboratory results
- Training materials for the EDC
- Data Management Plan
- Query management
- Data cleaning
- Site assistance with EDC and query management
- Raw data set for NERI statisticians

**Case Report Form Design**

**CRF development**

CRFs are designed at the time that the protocol is being developed and/or amended. The NERI Principal Investigator (PI) and statistician provide input to the CRF content development process, ensuring that the data elements contained in the CRF meet the requirements for data collection to fulfill the stated objectives of the investigational plan. The NERI Clinical Data Manager (CDM) develops the CRFs. The CDM ensures that the CRF is optimal for both data collection and data entry as specified in the protocol.

**CRF approval**

The NERI Clinical Data Manager will review and approve the CRF for programmability. The NERI PI and statistician will provide input to the sponsor where applicable.

**CRF standard sections**

Section A contains identifying information, generally subject ID number, visit and date of visit. Each subsequent section contains a logically grouped set of questions.
Displaying coded variables

Text responses are displayed on the eCRF. Each text response is associated with a code. For example, standard codes for Yes/No questions are Yes=1/No=0. The numeric code is the value stored in the database. Text and Coded responses are displayed together in the Help text for each field.

CRF Versioning

Any changes made to the initial approved page is handled by issuing a mid-study update (MSU). In an MSU, a modified CRF is given a new name. For MOSES, the name will include a _n where n= the MSU number.

Trial Workflow

Description of trial workflow

CRF information is entered at the study sites by study coordinators. Information entered into the data entry system will be identified by subject ID number; names will not be linked with subject data in the database. Clinical sites are responsible for maintaining records, in locked files, linking the subject name with the ID assigned for the study. Sites will have access to their own data and be able to view this data remotely, over the Internet.

Each site will also be shipped specimen labels with the appropriate subject ID. Shipping instructions for Soluble Marker, Sputum, PES filters, MP-TF can be found in Appendix F.

Figure 1 shows the flow of data to and from the sites, labs and data and statistical center. Figure 2 shows the data where it resides once collected.

Process of what happens to data once collected

The Study Coordinator obtains the pertinent information and completes the eCRFs in the EDC system. Source documents are to be maintained at site.

Process of what happens should a data point fail a validation

Should a data point fail a validation, the coordinator will receive an on-screen cue that a validation has failed. The coordinator will then open this message (a query) message with information about the data failure. This query will alert the user to choices that are allowed with this particular data item. The coordinator will either answer the query, validating that the data input is indeed correct, or enter the correct data. All queries that were open at some point are reviewed and closed by the DCC.
Figure 1 – Data Flow
Figure 2 – MOSES data storage diagram
CRF Tracking

Location of data entry
Most of the MOSES data are entered directly by the site into the electronic data capture system. Some MOSES data will be entered by NERI and other data will be uploaded via electronic means.

Location of hard copies
Most hard copy data including medical records, worksheets and paper copies of CRFs are stored at the clinical sites. The exception to this is the randomization (blinded) form. This is mailed in a sealed envelope to NERI. Should, for any reason, a hard copy of data, other than the randomization information, be sent to NERI, it will be returned to the clinical site.
Figure 3: Database Design
Figure 3 shows the database design from subject screening through completion as it is programmed.
Data Entry and Verification

**Manual review of data**
The CDM communicates with the site by email or by the automated query tool regarding any issues discovered after data entry. Sites are requested to update the data or provide an explanation within 7 days (or sooner in cases where data is being cleaned for reporting purposes). The Data Cleaning Plan can be found in Appendix C.

**Time allowed for entry**
Data entered close to the time of collection has a greater chance of being cleaner and having issues resolved. To this end, MOSES has established a 7 days to clean data rule. Sites are asked to enter visit CRFs on the same day as the visit takes place. When unable to accomplish data entry on the same day, sites are instructed to enter visit CRFs as soon as possible, and within 7 days of the visit. The 7 days to clean data rule includes resolving system generated edits.

Sites are instructed to enter adverse event information within 5 days of learning of the event. Serious Adverse Event (SAE) data should always be entered / reported within 24 hours of learning of the event.

Two CRFs are enabled for subject entry - the Home and Health Questionnaire and the Symptom Questionnaire. Whenever possible, sites should have the subject fill out these questionnaires at a computer. The data are directly stored into the database.

**Data Validation**

**Edit checks**
Validation ranges, series, or description of data to be entered into the EDC system are specified by the CDM, and approved by the PI, PD, and/or statistician prior to moving to production. These first line validations occur on-line, at the point of data entry for every field. A complete list of edit checks is included in Appendix A.

Edit checks post data entry include review of text fields and checks across forms which logistically cannot be performed at the time of data entry. These checks are specified by the CDM, and reviewed by the PD. The list of post data entry edit checks is included in Appendix B.

**Edit check modifications**
Any change to validations in production are specified by the CDM, and reviewed and approved by the PI, PD, and statistician. Any change is thoroughly tested in the development environment before moving to the production environment. When a change is to be made, a decision on rerunning all existing forms will be made and if warranted, executed.
Communication of programming changes to sites
When a new version of a CRF is released for Production, the Sponsor notifies the sites about changes and updates and the form version is made available on the Project Administrative WebSite (FILESHARE). Sites are notified about minor programming changes on an “as needed” basis.

Discrepancy Management

Description of the query process
An automatic query is generated in the EDC system for validation failure at the point of data entry, and consists of a description of what the issue is and possible solutions. A manual query is generated by the CDM or statistician for questionable text fields or potentially inconsistent data found while performing cross form form checks which cannot logistically be performed during data entry. Manual queries are tracked in a query tool, and consist of a request for the site to explain and or update data in the EDC system.

Description of the query resolution process
Automatic queries are resolved when the data is updated in the EDC system and the field passes the validation or the site indicates that the data is correct as is and an override is provided. Manual queries are considered resolved either when the data in the EDC system has been updated so that the discrepancy no longer occurs, or when the Query tool indicates that the data is confirmed by the sites as correct and acceptable.

Safety and Data Monitoring
The CDM works with the statistical team to support every effort with data cleaning and reporting. An agreed upon structure for reporting to the Data and Safety Monitoring Board will be put into place.

Third Party Imaging and Measurements
Third party data are expected from the following labs using the following methods. Core lab details, addresses and contacts are maintained in the Manual of Operations. This table will be completed once details are worked out with each lab.

<table>
<thead>
<tr>
<th>Data Source</th>
<th>Route to NERI</th>
<th>Frequency</th>
<th>Format</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holter</td>
<td>Sent to NERI directly from Holter lab</td>
<td>Quarterly</td>
<td>Excel spreadsheet</td>
</tr>
<tr>
<td>Blood (screening)</td>
<td>Data are downloaded by NERI RA on a weekly basis. Data are entered and double entered.</td>
<td>Every week</td>
<td>Download at NERI and entered directly.</td>
</tr>
<tr>
<td>BAU</td>
<td>Direct data entry into EDC system.</td>
<td>When available</td>
<td>NA</td>
</tr>
<tr>
<td>PES</td>
<td>Sent to NERI directly from PES lab</td>
<td>When available</td>
<td>Excel spreadsheet</td>
</tr>
<tr>
<td>Micro Particle Tissue Factor</td>
<td>Sent to NERI directly from MPTF lab</td>
<td>When available</td>
<td>Excel spreadsheet</td>
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Data Management Deliverables

**Timeline and Delivery of Reports**

A variety of reports are available in the EDC system. Some reports are created at regular intervals.

Appendix G contains samples of as well as the distribution plan for these reports.

**Quality Control (QC)**

**QC Measures to be followed**

As this protocol is utilizing an EDC system, double data entry is not feasible on site entered data. The following QC measures are noted:

- During data entry, validations will occur on all fields.
- All data entry and modifications are recorded into the study’s audit log.
- The CDM will perform review of open text fields, overrides and field and form comments. If any field reviewed is unclear or questionable, a query will be issued.
- Site personnel are given a training packet and asked to data enter it. Access to the production site is not granted until this training exercise has been completed in development. Details about training procedures can be found in Appendix E – eCOS Help Manual.

**Acceptable modifications**

Whenever possible, any data change in the EDC system is to be made by clinical site study coordinators. In the event that NERI will modify form data, the site and / or the central lab will be notified of the modification and reason. Every change made in the EDC system is audited in the study’s database and identified by user performing the change and a date time stamp. Self evident corrections made to the data base are identified in Appendix D.

**Archival**

**Archiving process**

Archiving of study documents and datasets will occur within 60 days of study closure. Clinical data from the EDC system and supporting tables (as SAS datasets) as well as Codebooks/CRF Attribute Reports will be provided to the Sponsor.