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ADDITIONAL MATERIALS AVAILABLE ON THE HEI WEB SITE

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.

Correspondence may be addressed to Dr. Mark W. Frampton, Pulmonary & Critical Care, University of Rochester Medical Center, 601 Elmwood Ave., Box 692, Rochester, NY 14642-8692; e-mail: *mark_frampton@urmc.rochester.edu*.

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Multicenter Ozone Study in Elderly Subjects (MOSES)

Data Management Plan

Version 08JAN2014

Prepared by:
Patti L. Arsenault

Data Management Plan Signatures

Approved by:

Anne Stoddard

NERI Principal Investigator Name	**Signature**	**Date**

Patti L. Arsenault

NERI Project Manager Name	**Signature**	**Date**

Patti L. Arsenault

NERI Clinical Data Manager Name	**Signature**	**Date**

Maria Costantini

Client	**Signature**	**Date**

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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 <u>Data Management</u> 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

MOSES Data Flow

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Clinical Sites

Local Storage

- Enroll Subjects
- Collect and enter data
- Resolve data queries
- Ship specimens
- Upload flow data

Monitor patient accrual, data quality and timeliness using standard real-time reports available via the web.

NERI
Data Coordinating Center

UR Holter Core

RTI Core

SPUT Core

BAU Core

Receives BAU materials. Performs assessment and direct enters into EDC

Monitor accrual, data quality and timeliness. Monitor and query site data via the web. Monitor specimen shipments and results. Close and lock database. Conduct statistical analysis.

Internet

MERGE Healthcare

Blood Cores
MPTF
Assay Gate
Flow

FLOW Core

Labs produce results in excel and email to NERI

Downloads, processes and produces results

Firewall

Secure Web Servers

Oracle Database

Last update: 08JAN2013

Figure 2 – MOSES data storage diagram
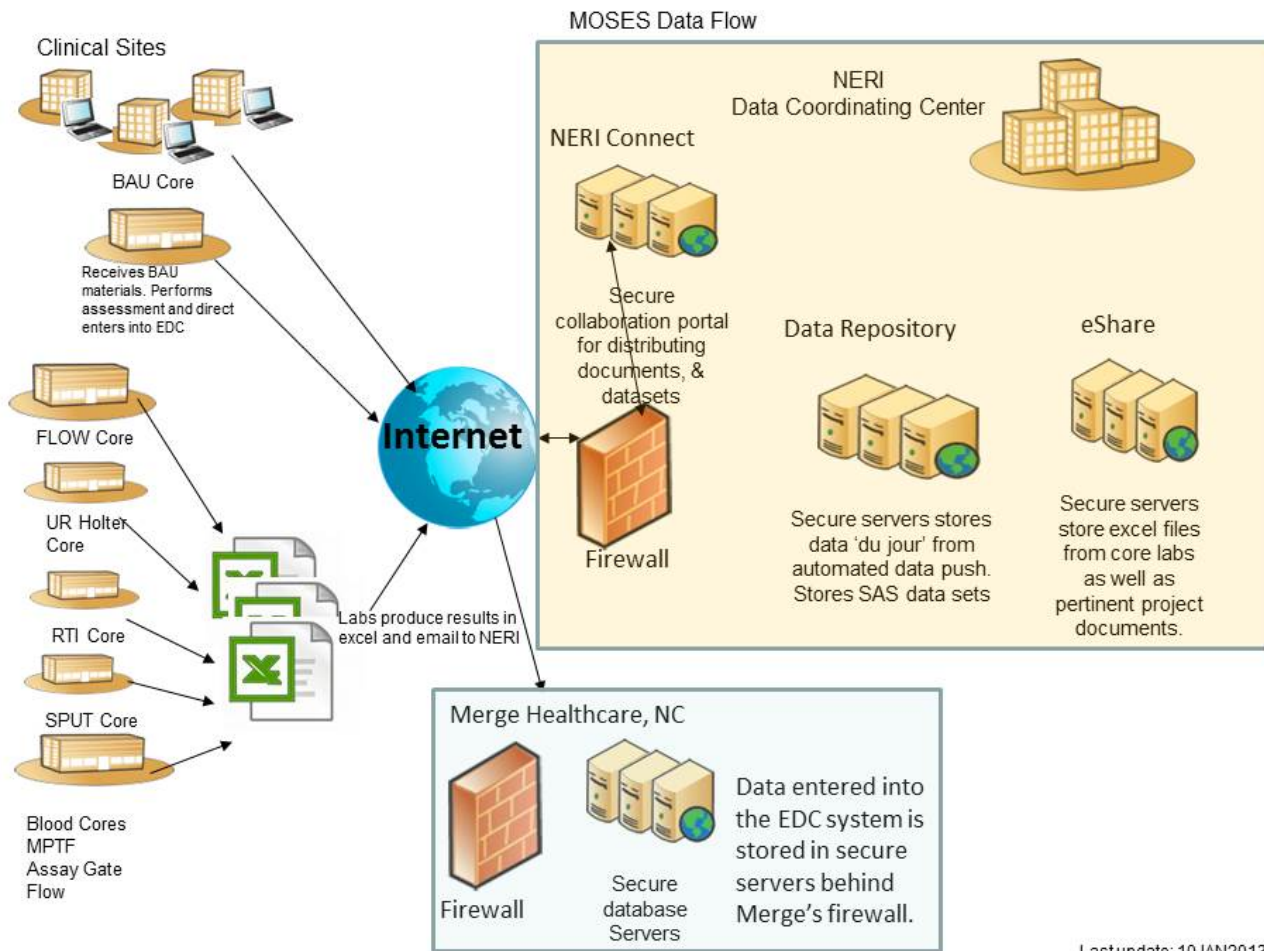
CRF Tracking

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 <u>copy</u> 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.

Build: Visit Schedule : Grid — Build : Visit Schedule : Order | Build : Visit Schedule : Rules

Revision: 7 -- MOSES Rev 1.7 — View — Schedule View Rules Permissions

Visit Schedule Grid: (* = Added By Rule Only)

	Screen-Train	Pre Exposure 1 *	Exposure 1 *	Post Exposure 1 *	Pre Exposure 2 *	Exposure 2 *	Post Exposure 2 *	Pre Exposure 3 *	Exposure 3 *	Post Exposure 3 *	Administrative Event	Withdrawal
General	X											
Home and Health	X											
Medications	X											
Vitals (Screening)	X											
Inclusion/Exclusion	X											
Spirometry	X		X			X			X			
CBC (NERI entered)	X											
Vitals (Training)	X *											
PES Assign	X *			X			X					
Vitals (Pre and Post)		X		X	X		X	X		X		
Randomization Packet		X										
PES Return and Process		X			X			X				
CBC		X	X	X	X	X	X	X	X	X		
Blood Tracking		X	X	X	X	X	X	X	X	X		
BAU Tape/CD		X	X		X	X		X	X			
BAU Results		X *	X *		X *	X *		X *	X *			
Flow Results		X *	X *	X *	X *	X *	X *	X *	X *	X *		
SM Results		X *	X *	X *	X *	X *	X *	X *	X *	X *		
MPTF Results		X *	X *	X *	X *	X *	X *	X *	X *	X *		
PES Lab Results		X *			X *			X *				
Vitals (Exposure)			X			X			X			
Symptom Pre Exposure			X			X			X			
Spirometry Pre Exposure			X			X			X			
Randomization Exposure Envelope			X			X			X			
Exercise			X			X			X			
Symptom In Chamber			X			X			X			
Symptom Post Exposure			X			X			X			
Spirometry Post Exposure			X			X			X			
Randomization Assignment - Exposure Level			X			X			X			
Holter Flash Card				X			X			X		
Holter Results				X *			X *			X *		
Symptom Questionnaire				X			X			X		
Sputum Tracking				X			X			X		
Sputum Results				X *			X *			X *		
Protocol Deviation											X	
Adverse Event Report Form											X	
Withdrawal												X

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 <u>automatic</u> 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 <u>manual</u> query is generated by the CDM or statistician for questionable text fields or potentially inconsistent data found while performing cross form checks which cannot logistically be performed during data entry. <u>Manual</u> 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

<u>Automatic</u> 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. <u>Manual</u> 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.

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

Flow Cytometry	Sent to NERI directly from Flow lab	Once per month	Excel spreadsheet
Sputum	Sent to NERI directly from Sputum lab	When available	Excel spreadsheet

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.