U.S. ENVIRONMENTAL PROTECTION AGENCY

OFFICE OF INSPECTOR GENERAL

Science and Research

EPA Implemented Prior OIG Recommendations, but Additional Guidance Could Strengthen the Human Subjects Research Program

Report No. 17-P-0350 **August 1, 2017**

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Abbreviations

CFR	Code of Federal Regulations
DOE	U.S. Department of Energy
EPA	U.S. Environmental Protection Agency
HHS	U.S. Department of Health and Human Services
HSR	Human Subjects Research
HSRRO	Human Subjects Research Review Official
IRB	Institutional Review Board
NAAQS	National Ambient Air Quality Standards
NHEERL	National Health and Environmental Effects Research Laboratory
NIH	National Institutes of Health
OIG	Office of Inspector General
ORD	Office of Research and Development
PHREO	Program in Human Research Ethics and Oversight
$PM_{2.5}$	Particulate Matter
RECAP	Responses to Exposure to Low Levels of Concentrated Ambient Particles in Healthy Young Adults (study)
SOP	Standard Operating Procedure
SOZIAL	The Interaction of Social Factors With Air Pollution (study)
UNC	University of North Carolina
VHA	Veterans Health Administration (U.S. Department of Veterans Affairs)

Cover photo: Chamber used for controlled exposure ozone studies at the EPA's Human Studies Facility, which is located at the University of North Carolina at Chapel Hill. (EPA OIG photo)

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U.S. Environmental Protection Agency
Office of Inspector General

17-P-0350
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At a Glance

Why We Did This Review

In response to a congressional request, we determined whether the U.S. Environmental Protection Agency (EPA) implemented the recommendations in Office of Inspector General (OIG) Report No. 14-P-0154, *Improvements to EPA Policies and Guidance Could Enhance Protection of Human Study Subjects*, issued March 31, 2014. We also determined how the EPA recruits and compensates human study subjects and whether the EPA considered the practices and policies of other federal agencies that conduct human subjects research (HSR) studies.

The EPA's HSR studies are governed by 40 CFR Part 26, including Subpart A, which is known as the Common Rule. This regulation sets the standards for conducting research involving human subjects. The EPA conducts controlled exposure HSR studies to better understand the health effects of pollution on humans.

This report addresses the following EPA goal or cross-agency strategy:

- *Addressing climate change and improving air quality.*

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EPA Implemented Prior OIG Recommendations, but Additional Guidance Could Strengthen the Human Subjects Research Program

What We Found

The EPA can take additional measures to track its HSR guidance and provide greater public transparency of the agency's HSR studies.

The EPA implemented the recommendations from the OIG's 2014 report, including issuing and revising HSR guidance and improving management controls for the HSR study approval process. The EPA also used this guidance and these controls, as applicable, in two HSR studies conducted after we issued our 2014 report. During this current review, however, we found that the EPA did not track revisions to its intranet guidance. The EPA could reduce risk to the program by maintaining prior versions of its guidance. In addition, we found that public transparency could be improved. While the EPA posted information about its controlled exposure HSR studies on a National Institutes of Health website and on the public website of its contractor that recruits study subjects, the agency did not post basic information about these studies on its own public website.

We also found that the EPA's practices for recruiting and compensating human study subjects are similar to those of other federal agencies. For example, the EPA and other agencies that conduct HSR may use contractors to recruit study subjects, and an Institutional Review Board approves the compensation received by study subjects. In addition, we found that interagency collaboration informs the EPA's HSR program. For instance, the EPA consults with other agencies about record retention, grant reviews and informed consent.

We found areas where the EPA could improve its procedures. For example, during our review, the EPA discussed three procedures related to its HSR program: (1) subjects participating in multiple studies must undergo waiting periods between each study to ensure that biological changes return to a baseline level, (2) the number of bronchoscopies that can be performed on a study subject in 1 year are limited, and (3) nurses and physicians who conduct the initial health exams on study subjects evaluate whether participation is in a subject's best interest. However, the EPA did not have any guidance documenting these procedures. Based on our current findings, the EPA developed guidance regarding screening and tracking HSR participation.

Recommendations and Planned Agency Corrective Actions

We recommend that the EPA track and document revisions to HSR guidance and post basic information about the agency's open and closed HSR studies since 2016. The EPA concurred with all recommendations and provided planned corrective actions and completion dates that meet the intent of the recommendations. All recommendations are resolved.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

THE INSPECTOR GENERAL

August 1, 2017

MEMORANDUM

SUBJECT: EPA Implemented Prior OIG Recommendations, but Additional Guidance Could Strengthen the Human Subjects Research Program
Report No. 17-P-0350

FROM: Arthur A. Elkins Jr.

TO: Robert Kavlock, Acting Assistant Administrator and EPA Science Advisor
Office of Research and Development

This is our report on the subject review conducted by the Office of Inspector General (OIG) of the U.S. Environmental Protection Agency (EPA). The project number for this review was OPE-FY16-0030. This report contains findings that describe the problems the OIG has identified and corrective actions the OIG recommends. This report represents the opinion of the OIG and does not necessarily represent the final EPA position. Final determinations on matters in this report will be made by EPA managers in accordance with established audit resolution procedures.

The EPA offices having primary responsibility over the issues evaluated in this report are the Office of the Science Advisor and the National Health and Environmental Effects Research Laboratory, both within the Office of Research and Development.

Action Required

The agency agreed with all recommendations and provided planned corrective actions and completion dates that meet the intent of these recommendations. Therefore, the agency is not required to provide a written response to this final report. Please update the EPA's Management Audit Tracking System as you complete the planned corrective actions for the two recommendations. Please notify my staff if there is a significant change in the agreed-to corrective actions. Should you choose to provide a response to this final report, we will post your response on the OIG's public website, along with our memorandum commenting on your response. You should provide your response as an Adobe PDF file that complies with the accessibility requirements of Section 508 of the Rehabilitation Act of 1973, as amended.

We will post this report to our website at www.epa.gov/oig.

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Chapter 1
Introduction

Purpose

In response to a July 2016 congressional request, the Office of Inspector General (OIG) conducted a review to make the following determinations:

- Whether the U.S. Environmental Protection Agency (EPA) implemented the recommendations in OIG Report No. 14-P-0154, *Improvements to EPA Policies and Guidance Could Enhance Protection of Human Study Subjects*, issued March 31, 2014.
- How the EPA recruited and compensated human research study subjects.
- Whether the EPA considered the practices and policies of other federal agencies engaged in human subjects research (HSR) studies.

Background

The OIG previously reviewed the EPA's implementation of its HSR program in response to a 2012 congressional request. The objective of that review was to determine whether the EPA followed applicable laws, regulations, policies, procedures and guidance when it exposed human subjects to diesel exhaust emissions or concentrated airborne particles. We found that the EPA followed applicable regulations when conducting HSR. However, we also identified improvements that the EPA could make to its policies and guidance to enhance the protection of study subjects. Issued on March 31, 2014, our final report included eight recommendations, which are broadly summarized below:

- Strengthen HSR study approval procedures.
- Ensure the adequate documentation of annual ethics training for research investigators.
- Strengthen language in guidance and participant consent forms related to health risks.
- Improve guidance related to adverse event reporting and clinical follow-up responsibilities.

In an April 24, 2015, memorandum, the agency certified that it had completed the corrective actions in response to the report's recommendations.

EPA's Controlled Exposure HSR Program

In the EPA's controlled exposure HSR studies, human subjects are intentionally exposed to pollutants under controlled conditions to determine a causal relationship between pollutant exposure and health effects. The EPA's Office of Research and Development (ORD) prepares multiyear strategic research action plans in conjunction with the Office of Air and Radiation to help determine research priorities. The National Health and Environmental Effects Research Laboratory (NHEERL) within ORD conducts the EPA's controlled exposure HSR at the agency's Human Studies Facility located at the University of North Carolina (UNC) at Chapel Hill, North Carolina.

The ORD researchers conducting controlled exposure HSR are organizationally separate from the Office of Air and Radiation personnel who use the research results to inform policymaking. According to EPA staff, this separation is important to maintain the independence of the scientific research. From fiscal year 2014 through fiscal year 2016, the agency spent about $12.4 million to support controlled exposure HSR.

Controlled Exposure HSR Helps EPA Measure Effects of Air Pollutants on Human Health

The Clean Air Act requires the EPA Administrator to establish a national research and development program for the prevention and control of air pollution. According to the Clean Air Act, the Administrator shall conduct a research program on the short- and long-term effects of air pollutants on human health. The Clean Air Act also states that the Administrator shall conduct the necessary studies—including epidemiological, clinical, laboratory and field studies—to identify and evaluate the exposure to and effects of air pollutants on human health. This research helps the EPA set National Ambient Air Quality Standards (NAAQS) for pollutants considered harmful to public health. The Clean Air Act also requires the EPA to periodically review and revise the NAAQS, as appropriate.

> In reaching a decision on the latest ozone NAAQS, the EPA Administrator placed "the most weight on information from controlled human exposure studies … [noting] that controlled human exposure studies provide the most certain evidence indicating the occurrence of health effects in humans following specific O_3 [ozone] exposures."
>
> *NAAQS for Ozone, 80 Federal Register 65291, 65362-3 (October 26, 2015)*

According to the EPA's 2009 Integrated Science Assessment for Particulate Matter,[1] the "most direct evidence of a causal relationship between pollutant exposures and human health effects comes from controlled human exposure studies."[2] These studies involve exposing individuals to various air pollutants in a controlled laboratory setting to evaluate the mechanisms by which a pollutant may affect an individual's health.

[1] Integrated science assessments provide comprehensive reviews of the policy-relevant scientific literature published since the last NAAQS review and are a critical part of the scientific basis for establishing the NAAQS.
[2] EPA, *Integrated Science Assessment (ISA) for Particulate Matter*, December 2009.

Large chamber used for controlled exposure studies. (EPA OIG photo)

Ethical considerations regarding HSR generally limit the effects that can be evaluated to those that are transient, reversible and of limited short-term consequence.

An example of an EPA HSR study related to NAAQS is the *Responses to Exposure to Low Levels of Concentrated Ambient Particles in Healthy Young Adults* study (also referred to as RECAP). The EPA also conducts controlled exposure HSR that is not directly related to the NAAQS. For example, one recently completed study, *The Interaction of Social Factors With Air Pollution* (also referred to as SOZIAL), was designed to help understand how social factors such as psychological stress may modify how people respond to air pollution. Table 1 provides an overview of the SOZIAL and RECAP studies.

Table 1: Information about the SOZIAL and RECAP studies

Study name	Pollutant and concentration exposure	Study purpose	Participants	Status *(as of June 2017)*
SOZIAL	Ozone (300 parts per billion)	To understand how social factors, such as stress, impact how people respond to air pollution	40 healthy adults, 18–33 years old with differing perceptions of stress	Study completed, now in data analysis
RECAP	Particulate matter ($PM_{2.5}$) (35–50 µg/m^3) [a]	To determine whether exposure to $PM_{2.5}$ in doses close to the EPA's current air standard will cause cardiovascular changes in healthy adults	Up to 20 healthy adults, 18–35 years old	Study in progress

Source: EPA NHEERL (modified by OIG).

[a] The concentration is in micrograms per cubic meter (µg/m^3).

Health Effects Associated With Exposure to Ozone and $PM_{2.5}$

The EPA has determined that a number of health effects are associated with exposure to ozone and $PM_{2.5}$. These determinations, which are described in the

EPA's integrated science assessments, are based on a review of all relevant controlled human exposure, epidemiological and toxicological studies. Table 2 summarizes the health effects that the EPA has associated with exposure to ozone and $PM_{2.5}$.

Table 2: Health effects associated with exposure to ozone and $PM_{2.5}$ [a]

Pollutants	Short-term exposure health effects (hours to days)	Long-term exposure health effects (months to years)
Ozone	• Shortness of breath. • Coughing. • Inflamed airways. • Increased frequency of asthma attacks and increased susceptibility to lung infection.	• Aggravation of asthma. • Likely to be a contributor to asthma development. • May increase mortality risk from respiratory causes.
$PM_{2.5}$	• Respiratory effects. • Cardiovascular effects. • Mortality.	• Respiratory effects. • Cardiovascular effects. • Mortality. • Reproductive and developmental effects. • Cancer.

Source: OIG analysis of the EPA's integrated science assessments for ozone and $PM_{2.5}$ and of an EPA website describing the health effects of ozone and $PM_{2.5}$.

[a] The EPA's integrated science assessment applies a weight-of-evidence approach to determining the causal relationship, or association, between pollutant exposures and health effects. The weight of evidence for the causal relationship between exposure and the health effects listed in this table varies. For example, the weight of evidence supporting a causal relationship between ozone exposure and cardiovascular effects is more limited than the weight of evidence supporting a causal relationship between ozone exposure and respiratory effects.

EPA's HSR Regulation, Policy and Guidance

The two major criteria governing HSR at the EPA are 40 CFR Part 26, *Protection of Human Subjects*, and EPA Order 1000.17A, *Policy and Procedures on Protection of Human Subjects in EPA Conducted or Supported Research*.

40 CFR Part 26

The EPA is one of 15 federal departments and agencies, including the U.S. Department of Health and Human Services (HHS), that adopted rules governing the protection of human subjects participating in HSR. The federal regulation at 40 CFR Part 26—including Subpart A, which is known as the Common Rule—sets forth the regulatory framework under which the EPA conducts research involving human subjects. A revised Common Rule was issued in January 2017.

The Common Rule mandates that an Institutional Review Board (IRB) review HSR proposals. The regulation specifies IRB membership, functions and

operations, and research approval criteria. A UNC at Chapel Hill Biomedical IRB reviews the EPA's controlled exposure studies.

Furthermore, the Common Rule requires agencies to develop procedures to ensure that unanticipated problems involving risks to subjects are reported to the IRB and other agency officials. The Common Rule also sets requirements for informed consent. According to the regulation, investigators must give prospective study subjects sufficient opportunity to consider whether to participate.

EPA Order 1000.17A

Updated in June 2016, EPA Order 1000.17A establishes the agency's procedures and responsibilities for implementing the requirements set forth in 40 CFR Part 26. The order applies to all research involving human subjects that the EPA conducts or supports, as well as to the determination of exempted research. Also included in EPA Order 1000.17A is the following key policy:

> All human subjects research conducted or supported by EPA must either be approved or be acknowledged as exempt research by the EPA Human Subjects Research Review Official (HSRRO) before any work involving human subjects research can begin.

The order describes the responsibilities of the Principal Investigator, HSRRO, Human Subjects Officer, Project Officer, program office and regional office. These stakeholders all have a role in ensuring compliance with the order.

Other Guidance Documents

In response to the OIG's 2014 report, the EPA developed guidance and posted it on ORD's intranet to provide a single location where investigators and staff can obtain the latest HSR information. The HSR intranet pages contain information and resources on how to determine whether an activity constitutes HSR, criteria for study approval, standard consent form language, and adverse event reporting. ORD's Program in Human Research Ethics and Oversight, which is located within the Office of the Science Advisor, also developed standard operating procedures (SOPs).

Responsible Offices

The EPA's Office of the Science Advisor and NHEERL, which are both within ORD, have primary responsibility for the subjects covered in this review.

Scope and Methodology

We performed our review from September 2016 through May 2017. We conducted this performance audit in accordance with generally accepted

government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusions based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objectives.

To determine whether the EPA implemented the OIG's March 2014 report recommendations for the agency's HSR program, we reviewed 40 CFR Part 26, *Protection of Human Subjects*; EPA Order 1000.17A, *Policy and Procedures on Protection of Human Subjects in EPA Conducted or Supported Research*, approved June 15, 2016; EPA guidance; and the EPA's HSR study documents. We also interviewed ORD managers, and we determined whether the EPA implemented the OIG's recommendations in the following two studies conducted after we issued our March 2014 report:

- *SOZIAL*. The EPA's HSRRO approved the SOZIAL study in June 2014.
- *RECAP*. The EPA's HSRRO approved the RECAP study in November 2016. When we began our review, RECAP was the only study to be approved after the EPA completed the corrective actions to address our prior review's recommendations in April 2015.

We reviewed SOZIAL's and RECAP's protocols, external reviews, consent forms, IRB approval documentation and other documents. We met with the EPA Principal Investigators involved with these studies, NHEERL managers, and Office of the Science Advisor staff.

We also met with scientists from ORD's National Center for Environmental Assessment and with staff from the Office of Air and Radiation's Office of Air Quality Planning and Standards who use the results of the EPA's controlled exposure HSR.

To determine how the EPA recruits and compensates human research study subjects, we reviewed the EPA's recruitment and compensation procedures, including recruitment scripts and flyers, as well as the EPA recruitment contractor's statement of work. We also reviewed numerous other documents related to the EPA's HSR, including the following materials:

- Documents used for the recruitment of human subjects.
- Study cards documenting the collection of demographic information from human subjects.
- HSR ethics training log.
- Study approval flowchart.

In addition, we interviewed staff from the UNC at Chapel Hill Biomedical IRB to discuss the policies they use to review HSR, as well as the EPA's HSR policies and procedures.

To determine whether the EPA considered the practices and policies of other federal agencies engaged in human subject studies, we first interviewed an EPA manager to identify which agencies the EPA consults with regarding HSR practices. Based on that interview, we met with HSR management and staff from the U.S. Department of Energy (DOE); the U.S. Department of Veterans Affairs (the Veterans Health Administration [VHA]); and HHS, including the Office for Human Research Protections and the National Institutes of Health (NIH). We confirmed that the EPA had consulted with these agencies about HSR issues, and we reviewed relevant HSR procedures from these agencies to determine whether they and the EPA engage in similar HSR practices.

To obtain other perspectives, we interviewed an author who has written about HSR to discuss concerns regarding the EPA's HSR program. We also spoke with the EPA's former HSRRO to discuss improvements made to the EPA's HSR program operations and with a University of Michigan professor who conducted HSR funded by EPA grants.

Chapter 2
EPA Implemented Prior OIG Recommendations

The EPA implemented the eight recommendations from the March 2014 OIG report regarding the agency's HSR program, including revising or issuing guidance and further strengthening management controls for the HSR approval process. The EPA also used this guidance and these controls, as applicable, in two studies conducted since we published that prior report. While performing this current review, however, we noted that the EPA maintained only the most current version of its HSR guidance. The EPA could reduce program risk by maintaining prior versions of its guidance. For example, if questions were raised after a study concluded, such records would be needed to determine whether the EPA followed the guidance in effect at the time the study was conducted.

EPA Implemented Prior OIG Recommendations to Improve Its HSR Program

The following table summarizes our prior report's recommendations, the corrective actions the EPA took to improve its HSR program, and whether these actions were implemented in the SOZIAL or RECAP study.

Table 3: Implementation of the 2014 OIG recommendations

Summary of 2014 OIG recommendations	EPA's corrective actions	Action implemented in SOZIAL or RECAP?
1. Revise human research guidance to include an internal review and approval process for significant study modifications.	• Defined "significant modifications." • Revised guidance to require significant study modifications to go through the same approval process as the initial study approval. • Revised flowchart of the protocol review and approval process.	Not applicable. The SOZIAL and RECAP studies did not have any significant modifications.
2. Implement a procedure for documenting HSR study investigators' continuing annual ethics education.	Developed an ethics training log to document the completion of continuing annual ethics training for its HSR investigators.	Yes.
3. Revise the human research policy to eliminate the Division Human Research Officer position.	Eliminated the Division Human Research Officer position and removed references to it in policy and guidance.	Not applicable.
4. Develop management controls to ensure management reviews and approvals are properly documented and follow guidance.	• Developed an electronic approval system to ensure the proper documentation of management reviews and approvals. • Developed a repository for documents needed for review during the HSR review process.	Yes.

Summary of 2014 OIG recommendations	EPA's corrective actions	Action implemented in SOZIAL or RECAP?
5. Revise HSR guidance to include a definition for "reasonably foreseeable risks."	• Commissioned a National Academy of Sciences, Engineering, and Medicine task force to define "reasonably foreseeable risk." • Developed an interim definition of "reasonably foreseeable risks," pending completion of the task force, and provided examples of risk information that should be included in consent forms. • The National Academy of Sciences, Engineering, and Medicine issued a report in 2017 titled *Controlled Human Inhalation-Exposure Studies*, which concurred with the EPA's interim definition that "a risk is reasonably foreseeable if we have some credible evidence to expect that [a potential harm] may occur." The EPA has posted this definition of "reasonably foreseeable risks" on its intranet site.	Yes.
6. Revise HSR guidance to include procedures for ensuring that consent forms consistently present the risks of pollutants.	Developed standard risk language for consent forms that includes carcinogenic effects of pollutants, where applicable.	Yes.
7. Include in the HSR consent forms any known or likely carcinogenic effects of pollutants.	Developed standard language concerning carcinogenic risk from $PM_{2.5}$ and diesel exhaust.	Yes.
8. Revise HSR guidance to adopt UNC at Chapel Hill's IRB SOP definitions and reporting timeframes for adverse events and unanticipated problems. Establish the EPA's clinical follow-up responsibilities after adverse and serious adverse events. Include a summary of the agency's clinical follow-up responsibilities in study protocols and consent forms.	• Defined "adverse events" and "unanticipated problem(s)" involving risks to subjects or others. • Revised guidance to state that investigators are expected to follow IRB definitions and reporting timeframes for adverse events and unanticipated problems for their projects. • Developed standardized language for clinical follow-up responsibilities, and directed investigators to include standard language in consent forms.	Yes.

Source: OIG Report No. 14-P-0154, *Improvements to EPA Policies and Guidance Could Enhance Protection of Human Study Subjects*, March 31, 2014.

The 2016 congressional request listed specific questions concerning the EPA's implementation of the OIG's 2014 recommendations. The OIG's responses to these questions are included in Appendix A.

EPA Needs to Track and Document Revisions to Intranet Guidance

In response to several OIG recommendations issued in the 2014 report, the EPA developed an intranet site for the Program in Human Research Ethics and Oversight (PHREO), which supports the ethical conduct and regulatory compliance of the EPA's HSR. This intranet site is accessible agencywide and contains the policy and guidance documents related to HSR. The site defines HSR and provides guidance to help EPA employees determine whether their research activities should be considered HSR. However, during this current review, we found that the EPA was not maintaining prior versions of its guidance or otherwise tracking and documenting revisions to its guidance on the intranet site.

The EPA could reduce risk to the program by maintaining prior versions of its guidance. We believe such records may be needed to determine whether the EPA followed the guidance in effect at the time a study took place—for example, to respond to questions after the conclusion of the study. The agency said it plans to incorporate the HSR guidance available on its PHREO intranet site into its SOPs and will update the SOPs whenever the HSR guidance changes. Because the EPA retains prior versions of its SOPs, this practice will also ensure that prior versions of HSR guidance remain accessible.

Conclusions

The EPA implemented the recommendations in the OIG's 2014 report on the agency's HSR program. These actions should improve the implementation of the EPA's HSR program. However, we found that the EPA does not currently track and document revisions to its intranet guidance; these actions are needed to ensure changes are archived for future oversight activity.

Recommendation

We recommend that the Assistant Administrator for Research and Development:

1. Track, document and post revisions to the EPA's human subjects research guidance on the Program in Human Research Ethics and Oversight intranet site.

Agency Comments and OIG Evaluation

The agency concurred with the recommendation and provided acceptable planned correction actions and a completion date. Recommendation 1 is resolved. Appendix B contains the agency's response to our draft report.

Chapter 3
EPA HSR Practices Generally Align With Other Federal Agencies, but EPA Could Improve Transparency on Its Website

The EPA's practices for conducting HSR generally aligned with the practices of DOE, VHA and HHS, including the use of contractors for the recruitment of human subjects, the collection of demographic data from participants, and the compensation of participants. However, the EPA could be more transparent by posting HSR study information on its public agency website.

An EPA manager informed us that the agency consults with DOE, VHA, NIH and other federal agencies regarding HSR practices. We therefore interviewed HSR staff from DOE, VHA and NIH; reviewed their HSR policies and procedures; and compared their HSR practices to the EPA's HSR practices.

EPA Contractor Recruits Human Subjects

The EPA uses a contractor, which at the time of our review was FEFA LLC, to recruit human subjects for its controlled exposure HSR. An EPA Contracting Officer's Representative provides oversight of the FEFA contract. The EPA research staff and the contractors meet to discuss the basic recruitment needs for the study. In consultation with the EPA research staff and the EPA-created study protocol and consent forms, the contractor develops draft recruitment materials, such as website announcements, newspaper and internet ads, and a script and questionnaire to use when speaking with potential human subjects. A nongovernmental website is used for recruiting because the contractor does not have access or authority to use an "epa.gov" web domain. The development of the recruitment website is included in the statement of work in the EPA's contract with FEFA.

The IRB and HSRRO review the developed recruitment materials as part of the approval process. Once the IRB and the HSRRO approve the study, the contractor begins the recruiting process. The contractor collects basic information about the potential study subjects and schedules appointments for them to participate in additional screenings and tests at the EPA's Human Studies Facility.

EPA managers said their HSR studies neither target nor exclude any particular demographic or socioeconomic group during the recruitment process. These EPA managers also stated that their studies are open to anyone who wants to participate and meets the study criteria. We found that EPA-developed study protocols provided to the recruitment contractor contained inclusion and

exclusion criteria to guide the selection of study subjects based on the requirements of the study. In addition, the SOZIAL study protocol included these inclusionary instructions:

> Every effort will be made to include women and minorities in this research. Advertising will be placed in a variety of locations to allow widespread access to recruitment information.

DOE, VHA and NIH can also use contractors to recruit human subjects. For example, a DOE manager said that contractors are generally used to recruit human subjects.

Selected Demographic and Other Information Collected From Study Subjects

When recruiting subjects to participate in controlled exposure HSR, the EPA contractor collects demographic information from each potential subject, including name, address, phone number, email, height, weight, race, gender, age and date of birth. The contractor also asks a few basic questions about the potential subject's medical history. The contractor does not collect information about economic status.

According to the EPA, the NHEERL nurses and physicians who screen the potential study participants further assess whether each individual meets the study eligibility criteria. The NHEERL nurses and physicians also look for signs that participation may not be in an individual's best interest. However, during our review, we found that the EPA did not have any guidance on the procedures NHEERL staff should use to evaluate study participants and make this determination. As a result of our finding, the EPA developed guidance for the screening and tracking of subjects who participate in EPA controlled exposure studies.

Similar to the EPA, the DOE and NIH gather demographic information about study participants.

EPA Documents Participation but Lacked Documented Guidance for Tracking Participation

The EPA uses study subject record cards to document each subject's participation in the agency's controlled exposure studies. For example, the subject record cards for the SOZIAL study show that five out of 40 study subjects previously participated in an EPA controlled exposure study, with the time between studies ranging from 34 to 2,351 days. However, the agency did not have guidance documenting how it should track and monitor study participation, such as the waiting period between studies and the number of medical procedures per year.

As a result of our finding, the EPA developed guidance for the screening and tracking of subjects who participate in EPA controlled exposure studies.

Other agencies track subject participation in HSR. The NIH intramural research program is able to track subject participation because the subjects are typically patients with medical record numbers. VHA tracks its HSR studies at the local VA facility level.

Study Participation Not Limited, but Waiting Periods Apply

The EPA does not limit the number of studies for which human subjects may participate, as long as the subjects are eligible for the studies. Each study has exclusion criteria included in the protocol and consent form. If a study subject meets one of the exclusion criteria, the subject would be excluded from the study. Each study has different exclusion criteria.

Examples of exclusion criteria in the SOZIAL study consent form

- Individuals with a history of acute or chronic cardiovascular disease, chronic respiratory disease, diabetes, or rheumatologic diseases.
- Individuals with asthma or a history of asthma.
- Individuals who are allergic to chemical vapors or gas.
- Females who are pregnant, attempting to become pregnant, or breastfeeding.
- Individuals who have smoked tobacco during the last 5 years, or individuals living with a smoker who smokes inside the house.
- Individuals with a body mass index greater than 35 or less than 18.

According to NHEERL managers, the EPA generally requires subjects to wait a minimum of 4 weeks before being allowed to start a new controlled exposure study, which allows biological effects in the subjects to return to a baseline level. An NHEERL manager also stated that there is a limit on the number of certain medical procedures allowed in a calendar year. For example, a study subject cannot undergo more than six bronchoscopies[3] in a calendar year. In addition, an NHEERL manager said that the NHEERL nurses and physicians who conduct the initial health exams on study subjects monitor the timeframes between studies and procedures and identify when participation in a study would not be in a subject's best interest.

While an NHEERL manager stated that participation restrictions were in place, we found that these restrictions were not documented in guidance. Guidance is necessary to ensure that NHEERL staff monitor subjects who want to participate in multiple studies. For example, one of the SOZIAL study subjects had participated in six studies since 2011, five of which were controlled exposure studies; this same subject also had four bronchoscopies in 1 calendar year.

[3] Bronchoscopy is a procedure that looks inside the lung airways. It involves inserting a tube with a light and small camera through the nose or mouth; down the throat into the trachea, which is commonly called the windpipe; and to the bronchi and bronchioles of the lungs.

As a result of our finding, the EPA developed guidance for the screening and tracking of subjects who participate in EPA controlled exposure studies. The guidance states the time restrictions between controlled exposure studies and between bronchoscopies. It also states the restrictions on the number of bronchoscopies a subject can have in a year.

EPA Compensates Participants in Controlled Exposure Studies

The EPA compensates study subjects who participate in its controlled exposure HSR studies. The EPA does not limit the number of studies for which a study subject can be compensated. The study's Principal Investigator initially proposes the level of compensation based on two key factors: time and inconvenience. Time is calculated based on the hours of participation a study requires. Inconvenience is calculated based on multiple elements, such as the type of procedures the study involves (e.g., heart monitoring and bronchoscopy) and/or the effort required or stress induced by study activities.

SOZIAL study compensation

Training Day	$25
Exposure Series #l	
Day 1	$450
Day 2	$250
Exposure Series #2	
Day 1	$450
Day 2	$250
Completion Bonus	$75
Total Study Compensation	**$1,500**

For example, assuming all other factors are equal, a study that requires a bronchoscopy would provide greater compensation than one that only requires heart monitoring, given the inconvenience and time associated with a bronchoscopy. A subject who begins but does not complete the study for any reason would still receive compensation for participation up to that point.

RECAP study compensation

Training Day	$25
Exposure Series #l	
Day 1	$500
Day 2	$250
Exposure Series #2	
Day 1	$500
Day 2	$250
Completion Bonus	$75
Total Study Compensation	**$1,600**

The compensation structure undergoes review during the approval process. The UNC at Chapel Hill Biomedical IRB reviews the EPA's compensation structure for each study and evaluates it in the context of previously reviewed HSR studies. According to the EPA's acting HSRRO, the HSRRO also reviews the compensation structure.

According to the RECAP and SOZIAL research protocols, the approximate total compensation for participation in RECAP was $1,600 and in SOZIAL was $1,500. Both studies compensate the study participant for an initial training day and for each exposure day. Each study offered a bonus after the study subject had completed all of the exposure sessions.

ORD management clarified the objective of compensating HSR participants:

> The goal of paying subjects for participating in research is to fairly compensate volunteers for their time and effort, but not at a level that would entice people to enroll in a study against their better judgement.

The federal agencies we interviewed also can compensate human subjects for participating in HSR. A VHA manager stated that human subjects are compensated for some studies but not others depending upon various factors, such as the type of study and whether the study has funds available to pay for subject participation. According to an NIH manager, NIH generally offers compensation for HSR participation to healthy volunteers or persons with diseases or disorders who participate in research that offers them little or no prospect of direct benefit. Managers from DOE, VHA and NIH stated that their agencies' IRB of record reviews the compensation structure of their studies.

EPA Consults With Other Federal Agencies to Inform Its HSR Program

The EPA contacts other federal agencies as questions regarding its HSR program arise or as HSR policies are considered. One EPA manager described consulting with the DOE, VHA and NIH as well as other federal agencies on various HSR matters, including the retention of records, the review of grants prior to funding, and Common Rule issues such as informed consent. We interviewed staff from DOE, VHA and NIH and confirmed that EPA managers had consulted with them on HSR issues. Some of these agencies also recognized the EPA's active participation in a workgroup that facilitated recent revisions to the Common Rule.

The revised Common Rule states that there are multiple efforts underway to address variation in HSR guidance across federal agencies, but no regulatory requirement exists to consult with other departments and agencies before issuing a policy.[4]

EPA Can Further Improve Oversight and Transparency

In January 2017, the Common Rule was revised. Almost all of the revisions will go into effect in January 2018.[5] The revisions will impact informed consent for human subjects and bio specimens from human subjects, establish new categories of exempt research, and affect the oversight needed for research that receives expedited reviews or that has completed study interventions. According to an ORD manager, the EPA may revise certain aspects of its HSR program as a result of the revised Common Rule.

[4] Federal Policy for the Protection of Human Subjects, 82 Federal Register 7149, 7159 (January 19, 2017).
[5] One revision will not go into effect until 2020.

A DOE manager told us that, to improve transparency, DOE publishes basic information about its HSR studies on a publicly available website. The manager stated that additional public data fields associated with each of the agency's HSR studies were added following an extensive inquiry sent in 2010 to all federal agencies by the Presidential Commission for the Study of Bioethical Issues. This inquiry resulted in a 2011 Presidential Commission for the Study of Bioethics report titled *Moral Science: Protecting Participants in Human Subjects Research*, which recommended that, at a minimum, the following elements be made public about each federally funded HSR study: the title, investigator, funding and location.

The EPA voluntarily posts information about its controlled exposure HSR studies on clinicaltrials.gov, which is a site operated by NIH, and on the public website of its contractor who recruits study subjects. However, the EPA does not post information about its studies on the agency's public website.

Conclusions

The EPA's HSR practices regarding the recruitment and compensation of study participants and the collection of demographic information generally align with those of other agencies. In addition, the EPA, like NIH and VHA, tracks participation in HSR studies.

We also found that, although the EPA voluntarily posts information about its HSR on clinicaltrials.gov, the agency does not post basic information about HSR studies on its public website. The EPA can strengthen its HSR program operations and improve the transparency and public knowledge of its program by posting basic study information on the agency's public website.

Recommendation

We recommend that the Assistant Administrator for Research and Development:

2. Post basic information about open and closed EPA controlled exposure human research studies conducted since 2016 to the agency's public website, such as the title of the study, the number of participants, the pollutant the study subjects are exposed to, and a general description of the study.

Agency Comments and OIG Evaluation

The agency concurred with the recommendation and provided acceptable planned corrective actions and a completion date for the recommendation. Recommendation 2 is resolved. Appendix B contains the agency's response to our draft report.

Status of Recommendations and Potential Monetary Benefits

RECOMMENDATIONS						
Rec. No.	**Page No.**	**Subject**	**Status[1]**	**Action Official**	**Planned Completion Date**	**Potential Monetary Benefits (in $000s)**
1	10	Track, document and post revisions to the EPA's human subjects research guidance on the Program in Human Research Ethics and Oversight intranet site.	R	Assistant Administrator for Research and Development	12/31/17	
2	16	Post basic information about open and closed EPA controlled exposure human research studies conducted since 2016 to the agency's public website, such as the title of the study, the number of participants, the pollutant the study subjects are exposed to, and a general description of the study.	R	Assistant Administrator for Research and Development	12/31/17	

[1] C = Corrective action completed.
R = Recommendation resolved with corrective action pending.
U = Recommendation unresolved with resolution efforts in progress.

Responses to the 2016 Congressional Request Questions

1. **Are OIG's recommendations being utilized in the SOZIAL study?**

   See Chapter 2, Table 3, pages 8–9.

   The EPA HSRRO approved the SOZIAL study in June 2014. The EPA did not implement the corrective actions to address the 2014 OIG report recommendations until April 2015. As a result, the SOZIAL study did not fully implement Recommendations 6 and 8 of the 2014 OIG report. For more information, see Questions 3 and 5 below.

2. **Have OIG's 2014 recommendations been fully implemented and adhered to? If not, why not? Given the current state of federal law, regulations, policies, procedures, and/or guidance from EPA, please assess the impact of the recommendations from the 2014 Report.**

   See Chapter 2, Table 3, pages 8–9 and Chapter 2, "Conclusions" section, page 10.

   In response to several OIG recommendations, the EPA developed an intranet site for PHREO that is accessible agencywide and contains all policy and guidance documents related to HSR. The intranet site also includes a definition of HSR and a list of questions to help EPA staff determine whether their activities qualify as HSR. The EPA also developed the Human Subjects Research Application Portal, an electronic application meant to ensure that HSR studies (including research protocols and supporting documents) go through the proper approval process. These actions should improve the implementation of the HSR program.

3. **What is the current approval process/flow chart for human subject testing study approval? Was the proper approval process followed for the SOZIAL Study?**

   See Chapter 2, Table 3, 2014 OIG Recommendation 4, page 8.

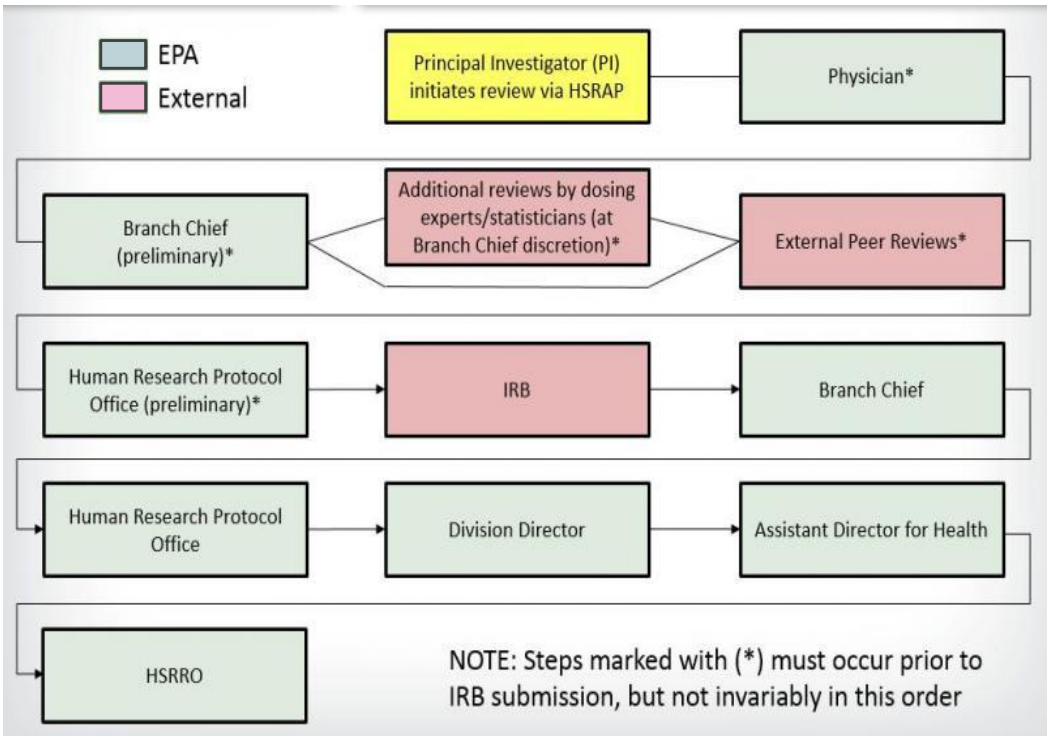
   The SOZIAL study approvals occurred before the 2014 OIG report recommendations were implemented. We found that the Branch Chief's preliminary review was not documented, but all other reviews were documented and completed in sequence.

   RECAP was the first study approved using the Human Subjects Research Application Portal. The proper reviews took place, but the preliminary Human Research Protocol Office Director review occurred after the IRB approval. This order of approval was inconsistent with NHEERL's study approval flowchart, which indicated that the Human Research Protocol Office review should take place before the IRB approval. The Director stated that he likely

had already approved the study but had not signed off on the protocol in the Human Subjects Research Application Portal until after the protocol was sent to the IRB. NHEERL managers stated that the reviews completed prior to the IRB review can be completed in any order. The RECAP study followed the order in the NHEERL study approval chart for the reviews completed after the IRB review.

As a result of our current review, the EPA revised its HSR approval flowchart to demonstrate the flexibility in the review process for reviews completed prior to IRB approval, as shown in Figure 1.

Figure 1: HSR review process for NHEERL



Source: EPA NHEERL.

We also compared the EPA's approval process to NIH's approval process for an NIH study titled *Cytochrome P450 Epoxygenase Pathway Regulation of Macrophage Function*. The EPA's approval process is similar to NIH's approval process. Both processes have multiple layers of review, including reviews by an IRB and agency management.

4. Has EPA considered protocols and procedures from other agencies that conduct human subject testing to inform and/or improve the conduct of EPA studies? If so, what protocols and procedures have been considered?

See Chapter 3, "EPA Consults With Other Federal Agencies to Inform Its HSR Program" section, page 15.

Other sections in Chapter 3 also discuss that the EPA's HSR practices regarding the recruitment and compensation of study participants and the collection of demographic information generally align with those of DOE, HHS and VHA. In addition, the EPA, NIH and VHA track participation in HSR studies.

5. **Given a relationship between Ozone and PM2.5, what is EPA OIG's assessment of the current informed consent language regarding particulate matter, specifically Ozone / PM2.5? Does the current language accurately reflect the potential long-term health hazards posed by short-term exposure to Ozone / PM2.5 common with many EPA tests on human subjects? If not, how might the language be adjusted to ensure human subjects are provided the most accurate accounting of the risks before providing informed consent?**

See Chapter 2, Table 3, 2014 OIG Recommendation 6, page 9.

The EPA OIG's initial assessment was that the agency's intranet guidance adequately defined short-term health effects for investigators to include in study consent forms. However, we found that the intranet guidance did not define any long-term health effects, except for nitrogen dioxide. After meeting with ORD managers, the EPA added long-term health effects language for ozone, PM and diesel exhaust in its guidance, as well as a statement that the agency is not aware of any permanent or long-term effects from short-term exposures to the pollutants in HSR studies. We subsequently concluded that the short-term and long-term health effects for ozone, PM and diesel exhaust are sufficiently reflected in EPA's intranet guidance.

Per Recommendation 6 of the OIG's 2014 report, the EPA revised its guidance to include short-term effects for pollutants. However, nitrogen dioxide was the only air pollutant for which the EPA provided standard language on long-term health effects. Further, EPA guidance did not direct investigators to include the upper pollutant concentration levels in consent forms. An NHEERL manager stated the belief that the agency had addressed Recommendation 6 (regarding short-term and long-term effects) by including the following statement in its guidance, which would be used in new consent forms:

> Breathing air pollution particles in this study might cause coughing, wheezing, shortness of breath, irritation of the eyes, ears, nose, throat or lungs, heartbeat changes, or increase your chance of catching a cold. These effects typically last no more than a few hours, but could last longer if you are especially sensitive. The maximum amount of air pollution particles to which you would be exposed in this study is about the same as spending a few days in a city with poor air quality like Los Angeles or New York City. A lifetime of exposure to air pollution is known to increase your risk of developing lung cancer. However, the two hours of exposure to air pollution particles [or "diesel exhaust particles" or "wood smoke emissions"] in this study is unlikely to increase your risk in any meaningful way, just as smoking a single cigarette would carry much less risk than a lifetime of smoking.

EPA managers and other scientists told us that there are no known long-term health effects that would result from such short-term exposures to the pollutants used in NHEERL's controlled human exposure studies. EPA staff also stated that the risk levels often publicized on the EPA's website regarding $PM_{2.5}$ and ozone reflect risks at the population level rather than the risks to one individual participating in a controlled exposure study.

Furthermore, according to an EPA manager, exposure conditions in the HSR studies differ from the exposure conditions experienced in the real world. For instance, the EPA takes various precautions—including the screening of potential subjects, the consent process, and the monitoring of subjects during the study—to help ensure subject safety. Study consent forms include a section describing the health characteristics of individuals who should not participate in the study.

The SOZIAL study consent form does not contain the standard health effects language for ozone that is on the PHREO intranet site because that study was approved before the EPA implemented its corrective actions to address the OIG's 2014 recommendations. However, the SOZIAL consent form does include language regarding short-term health effects that is similar to the language found on the intranet site, as well as language regarding long-term health effects about susceptible populations exposed to ozone. The SOZIAL consent form also includes the target pollutant concentration for the study.[6]

At the time of this current review, the RECAP study was the only HSR study that was approved after the EPA implemented its corrective actions in response to the 2014 OIG report. The RECAP consent form contained almost all of the standard $PM_{2.5}$ health effects language found on the PHREO intranet site, including the language concerning carcinogenic risk. The consent form also described the long-term health effects for susceptible populations, including respiratory and cardiovascular disease and possible death. The RECAP consent form contained the upper pollutant concentration to which study subjects would be exposed.

As a result of this current review, the EPA has posted on its intranet site a summary of long-term health effects to be included in consent forms as appropriate for ozone, PM, nitrogen dioxide and diesel exhaust exposure. The summary also includes a place to specify the expected range of pollutant exposure for each study. In addition, the EPA added a statement in its guidance that the agency is not aware of any permanent or long-term effects from short-term study exposures.

Long-term health effects language for ozone, PM, nitrogen dioxide and diesel exhaust

Air pollution in the outside environment is associated with adverse health outcomes, which is why we are doing this study. In susceptible populations like older adults (greater than 65 years of age) or people with cardiac disease, asthma or diabetes, air pollution is associated with increased death rates and increased risk of respiratory and cardiovascular disease. However, this risk in healthy young adults is rare.

Source: EPA NHEERL guidance (posted on the EPA intranet).

[6] The SOZIAL study exposed human subjects to ozone. The concentration of ozone can be more easily controlled than $PM_{2.5}$. The study provided a target concentration that study subjects would be exposed to, which could be considered the upper pollutant concentration.

6. **How has EPA recruited subjects for their studies? What is the demographic, socio-economic, and frequency of these study participants?**

    - For recruitment efforts, see Chapter 3, "EPA Contractor Recruits Human Subjects" section, pages 11–12.
    - For demographic and socioeconomic information, see Chapter 3, "Selected Demographic and Other Information Collected From Study Subjects" section, page 12.
    - For frequency, see Chapter 3, "EPA Documents Participation but Lacked Documented Guidance for Tracking Participation" section, page 12.

7. **Is there a limitation on the number of studies human subjects may volunteer for?**

    See Chapter 3, "Study Participation Not Limited, but Waiting Periods Apply" subsection, page 13.

8. **Is there a limitation on the number of studies human subjects may be compensated for?**

    See Chapter 3, "EPA Compensates Participants in Controlled Exposure Studies" section, page 14.

9. **How often are human subjects compensated for participating in testing and how is the compensation structure determined?**

    See Chapter 3, "EPA Compensates Participants in Controlled Exposure Studies" section, pages 14–15.

10. **What are the determining factors for a study using uncompensated versus compensated human subjects?**

    See Chapter 3, "EPA Compensates Participants in Controlled Exposure Studies" section, pages 14–15.

11. **Why is the EPA utilizing EPAstudies.org, a non-government website, to conduct recruiting for tests involving human subjects?**

    See Chapter 3, "EPA Contractor Recruits Human Subjects" section, pages 11–12.

12. How should Congress effectively conduct oversight of testing involving the use of human subjects?

We plan to brief congressional staff about the responses we received from the EPA and other federal agencies regarding how Congress can more effectively conduct oversight of human subject testing. We also plan to brief congressional staff on our EPA findings and recommendations and how they might be applied across the government.

Congress could use the recent revisions of the Common Rule as a guide for future HSR oversight, which could include requiring the relevant federal agencies to report how they have incorporated the revised Common Rule into their HSR programs.

Agency Comments on Draft Report

June 13, 2017

MEMORANDUM

SUBJECT: Response to Office of Inspector General (OIG) Draft Report No. OPE-FY16-0030 "EPA Implemented Prior OIG Recommendations, but Additional Guidance Could Strengthen the Human Subjects Research Program" dated May 16, 2017

FROM: Robert Kavlock
Acting Assistant Administrator

TO: Carolyn Copper
Assistant Inspector General
Office of Program Evaluation

The EPA's Office of Research and Development (ORD) welcomes the opportunity to review and comment on the OIG's draft report titled *"EPA Implemented Prior OIG Recommendations, but Additional Guidance Could Strengthen the Human Subjects Research Program"* (Project No. OPE-FY16-0030) (Draft Report). We appreciate the OIG's confirmation that ORD scientists, administrators and leaders have worked diligently to implement the recommendations from the OIG's 2014 report. In turn, we believe OIG staff have been diligent in working to understand the goals and operational nuances of our human subjects research (HSR) program, and that their observations are largely accurate and balanced. Accordingly, we do not take issue with the overall content of the Draft Report, and our comments and suggestions below are intended to promote accuracy and clarity in the final product.

Immediately below are the ORD's responses to the OIG's specific recommendations. In the attachment, we provide additional detailed comments, including specific language suggestions with respect to statements in the Draft Report.

Recommendation 1: "Track and document revisions to the EPA's human subjects research guidance."

Response 1: The ORD agrees with this recommendation. As the OIG has described, the EPA's guidance on HSR topics was consolidated and standardized in response to the OIG's 2014 report, moving decentralized guidance to an intranet site. A byproduct of posting guidance documents online (in HTML format), where they can be both updated and accessed more readily, is the relative difficulty of tracking, dating and archiving revisions over time. As ORD described in our response to the OIG's preliminary Discussion Document, our plan going ahead is to use the recently-posted Standard Operating Procedures (SOP) Manual as the permanent home for guidance. The PDF format of the SOP Manual will lend itself to version tracking and archiving,

while still being accessible online. The ORD Office of Science Advisor (OSA) will review web-based guidance on the intranet to ensure that any sections that warrant tracking are incorporated in the SOP document.

Planned Completion Date: December 31, 2017

Recommendation 2: "Post basic information about open and closed EPA controlled exposure human research studies conducted since 2016 to the agency's public website, such as the title of the study, the number of participants, the pollutant the study subjects are exposed to, and a general description of the study."

Response 2: The ORD agrees with this recommendation. ORD currently provides this type of information on two websites, clinicaltrials.gov and epastudies.com. As described by OIG in the Draft Report, this latter website was created at ORD's request and its content is provided and controlled by EPA scientists. Accordingly, the Agency does post information about its studies on a public website controlled by EPA. In addition, ORD will post basic study information on epa.gov. As a result, the information will be available to the public from three websites.

Planned Completion Date: December 31, 2017

If you have any questions regarding this response, please contact Daniel Nelson, Director, Human Research Protocol Office, National Health and Environmental Effects Research Laboratory (NHEERL) at nelson.daniel@epa.gov.
Attachment
cc: Thomas Sinks
Daniel Nelson
Wayne Cascio
David Diaz-Sanchez
Robert Devlin
William Benson
Ronald Hines
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Appendix C

Distribution

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