OFFICE OF HUMAN RESEARCH ETHICS
Institutional Review Board

APPLICATION FOR IRB APPROVAL OF
HUMAN SUBJECTS RESEARCH
Version June 25, 2009

Part A.1. Contact Information, Agreements, and Signatures

Date: June 24, 2010
Title of Study: IRB#04-1677 (formerly GCRC #2067)

Physiological changes in adults with metabolic syndrome exposed to concentrated ultrafine Chapel Hill air particles

Name and degrees of Principal Investigator: Robert Devlin, PhD (PI, EPA), Candice Bailey, PhD (EPA), Martha Sue Carraway, MD (EPA)
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UNC-CH PID: EX. 6 Pager: N/A
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For trainee-led projects: __ undergraduate __ graduate __ postdoc __ resident __ other
Name of faculty advisor:
Department: Mailing address/CB #:
Phone #: Fax #: Email Address:
Center, institute, or department in which research is based if other than department(s) listed above:

Name of Project Manager or Study Coordinator (if any): Mike Schmitt, MSPH
Department: United States EPA Mailing address/CB #: CB#7315, 104 Mason Farm Road, Room 438, Chapel Hill, NC 27599
Phone #: 919-966-0647 Fax #: 919-966-6271 Email Address: schmitt.mike@epa.gov

List **all other project personnel** including co-investigators, and anyone else who has contact with subjects or identifiable data from subjects. **Include name, location (UNC or specific outside location), role and email address for each person who should receive electronic copies of IRB correspondence to PI.**
EPA investigators:

EX. 6

Name of funding source or sponsor (*please do not abbreviate*): United States Environmental Protection Agency
__ not funded _X_ Federal __ State __ industry __ foundation __ UNC-CH
__ other (specify):

For external funding, RAMSeS proposal number (from Office of Sponsored Research):

For industry sponsored research (if applicable):

Sponsor's master protocol version #: Version date:

Investigator Brochure version #: Version date:

Any other details you need documented on IRB approval:

Checklist of Items to Include with Your Submission

Include the following items with your submission, where applicable.

- Check the relevant items below and include one copy of all checked items 1-11 in the order listed.
- Also include two additional collated sets of copies (sorted in the order listed) for items 1-6.

Applications must "stand alone" and should provide all information requested, i.e., complete answers must be contained in the application. While you may reference other documents with supporting information, do not respond solely by stating "see attached."

Applications will be returned if these instructions are not followed.

Check	Item	Total No. of Copies
☐	1. This application. One copy must have original PI signatures.	3
☐	2. Consent and assent forms (include DHHS-approved sample, when one exists), fact or information sheets, phone and verbal consent scripts.	3
☐	3. HIPAA authorization addendum to consent form.	3
☐	4. All recruitment materials including final copies of printed advertisements, audio/video taped advertisements, scripts, flyers, letters, and emails.	3
☐	5. Questionnaires, focus group guides, scripts used to guide phone or in-person interviews, etc.	3
☐	6. Documentation of reviews from any other committees (e.g., Clinical and Translational Research Center (CTRC), Oncology Protocol Review Committee, or local review committees in Academic Affairs).	3
☐	7. Protocol, grant application or proposal supporting this submission, if any (e.g., extramural grant application to NIH or foundation, industry protocol, student proposal). This must be submitted if an external funding source or sponsor is checked on the previous page.	1
☐	8. Addendum for Multi-Site Studies where UNC-CH is the Lead Coordinating Center.	1
☐	9. Data use agreements (may be required for use of existing data from third parties).	1
☐	10. Only for those study personnel *not* in the online UNC-CH human research ethics training database (http://cfx3.research.unc.edu/training_comp/): Documentation of required training in human research ethics.	1
☐	11. For drug studies, Investigator Brochure if one exists. If none, include package insert for previously approved uses..	1

Principal Investigator: I will personally conduct or supervise this research study. I will ensure that this study is performed in compliance with all applicable laws, regulations and University policies regarding human subjects research. I will obtain IRB approval before making any changes or additions to the project. I will notify the IRB of any other changes in the information provided in this application. I will provide progress reports to the IRB at least annually, or as requested. I will report promptly to the IRB all unanticipated problems or serious adverse events involving risk to human subjects. I will follow the IRB approved consent process for all subjects. I will ensure that all collaborators, students and employees assisting in this research study are informed about these obligations. All information given in this form is accurate and complete.

_____ _____

Signature of Principal Investigator Date

Faculty Advisor if PI is a Student or Trainee Investigator: I accept ultimate responsibility for ensuring that this study complies with all the obligations listed above for the PI.

_____ _____

Signature of Faculty Advisor Date

Note: The following signature is not required for applications with a student PI.

Department or Division Chair, Center Director (or counterpart) of PI: (or Vice-Chair or Chair's designee if Chair is investigator or otherwise unable to review): I certify that this research is appropriate for this Principal Investigator, that the investigators are qualified to conduct the research, and that there are adequate resources (including financial, support and facilities) available. If my unit has a local review committee for pre-IRB review, this requirement has been satisfied. I support this application, and hereby submit it for further review.

_____ _____

Signature of Department Chair or designee Date

_____ _____

Print Name of Department Chair or designee Department

Part A.2. Summary Checklist *Are the following involved?*	Yes	No
A.2.1. Existing data, research records, patient records, and/or human biological specimens?	__	_X_
A.2.2. Surveys, questionnaires, interviews, or focus groups with subjects?	__	_X_
A.2.3. Videotaping, audiotaping, filming of subjects, or analysis of existing tapes?	__	_X_
A.2.4. Do you have specific plans to enroll subjects from these vulnerable or select populations: a. UNC-CH students or UNC-CH employees? b. Non-English-speaking? c. Decisionally impaired? d. Patients? e. Prisoners, others involuntarily detained or incarcerated, or parolees? f. Pregnant women? g. Minors (less than 18 years)? ***If yes***, give age range: to years	 __ __ __ _X_ __ __ __	 _X_ _X_ _X_ _X_ _X_ _X_ X__
A.2.5. a. Are sites outside UNC-CH engaged in the research? b. Is UNC-CH the sponsor or lead coordinating center for a multi-site study? ***If yes***, include the ***Addendum for Multi-site Studies***. ***If yes***, will any of these sites be outside the United States? ***If yes***, is there a local ethics review committee agency with jurisdiction? (provide contact information)	__ __ __ __	_X_ _X_ __ __
A.2.6. Will this study use a data and safety monitoring board or committee? ***If yes:*** UNC-CH NC TraCS DSMB? (must apply separately) Lineberger Cancer Center DSMC? Other? Specify:	__ __ __ __	_X_ __ __ __
A.2.7. a. Are you collecting sensitive information such as sexual behavior, HIV status, recreational drug use, illegal behaviors, child/physical abuse, immigration status, etc? b. Do you plan to obtain a federal Certificate of Confidentiality for this study? c. Is this research classified (e.g., requires security clearance)?	__ __ __	_X_ _X_ _X_
A.2.8. a. Investigational drugs? (provide **IND #**) b. Approved drugs for "non-FDA-approved" conditions? *All studies testing substances in humans must provide a letter of acknowledgement from the UNC Health Care Investigational Drug Service (IDS).*	__ __	_X_ _X_
A.2.9. Placebo(s)?	__	X__
A.2.10. Investigational devices, instruments, machines, software? (provide **IDE #**)	__	_X_
A.2.11. Fetal tissue?	__	_X_
A.2.12. Genetic studies on subjects' specimens?	_X_	__
A.2.13. Storage of subjects' specimens for future research? ***If yes***, *see instructions for* ***Consent for Stored Samples***.	_X_	__
A.2.14. Diagnostic or therapeutic ionizing radiation, or radioactive isotopes, which subjects would not receive otherwise? ***If yes***, *approval by the* ***UNC-CH Radiation Safety*** ***Committee*** *is required.*	__	X__
A.2.15. Recombinant DNA or gene transfer to human subjects? ***If yes***, *approval by the* ***UNC-CH Institutional Biosafety*** ***Committee*** *is required.*	__	_X_
A.2.16. Does this study involve UNC-CH cancer patients? ***If yes***, *submit this application directly to the* ***Oncology Protocol Review Committee***.	__	X_
A.2.17. Will subjects be studied in the Clinical and Translational Research Center (CTRC) or is the CTRC involved in any other way with this study? If yes, obtain the ***CTRC Addendum*** *and submit completed application (IRB application and Addendum) directly to the CTRC. The CTRC includes facilities located on the 3rd floor of the Main Hospital (formerly GCRC) and Ground floor Burnett-Womack (formerly CCCT).*	X__	__
A.2.18. Will gadolinium be administered as a contrast agent?	.._	.._X_
A.2.19. Will subjects' Social Security Number (SSN) be collected for: a. processing payments greater than $200 per year, to support IRS reporting (see also B.6)? b. processing payments of any amount through UNC-CH Accounts Payable? c. use as a unique identifier for study tracking purposes for national registry or database?	 __ __ __	 _X_ X X__

Part A.3. Conflict of Interest Questions and Certification

The following questions apply to **all investigators and study staff** engaged in the design, conduct, or reporting results of this project **and/or their immediate family members.** For these purposes, "family" includes the individual's spouse and dependent children. "Spouse" includes a person with whom one lives together in the same residence and with whom one shares responsibility for each other's welfare and shares financial obligations.

A.3.1. Currently or during the term of this research study, does any member of the research team or his/her family member have or expect to have:		
(a) A personal financial interest in or personal financial relationship (including gifts of cash or in-kind) with the sponsor of this study?	__ yes	_X_ no
(b) A personal financial interest in or personal financial relationship (including gifts of cash or in-kind) with an entity that owns or has the right to commercialize a product, process or technology studied in this project?	__ yes	_X_ no
(c) A personal financial interest in or personal financial relationship (including gifts of cash or in-kind) with an entity engaged in the performance of this project as a subcontractor, sub-recipient or vendor?	__ yes	_X_ no
(d) A board membership of any kind or an executive position (paid or unpaid) with the sponsor of this study or with an entity that owns or has the right to commercialize a product, process or technology studied in this project?	__ yes	_X_ no
A.3.2. Has the University or has a University-related foundation received a cash or in-kind gift from the sponsor of this study for the use or benefit of any member of the research team?	__ yes	_X_ no
A.3.3. Has the University or has a University-related foundation received a cash or in-kind gift for the use or benefit of any member of the research team from an entity that owns or has the right to commercialize a product, process or technology studied in this project?	__ yes	X__ no

If the answer to ANY of the questions above is *yes*, the affected research team member(s) must complete and submit the form, which is accessible online at http://coi.unc.edu. List name(s) of all research team members for whom any answer to the questions above is *yes*:

_____

Certification by Principal Investigator: By submitting this IRB application, I (the PI) certify that the information provided above is true and accurate regarding my own circumstances, that I have inquired of every UNC-Chapel Hill employee or trainee who will be engaged in the design, conduct or reporting of results of this project as to the questions set out above, and that I have instructed any such person who has answered "yes" to any of these questions to complete and submit for approval a Conflict of Interest Evaluation Form. I understand that as Principal Investigator I am obligated to ensure that any potential conflicts of interest that exist in relation to my study are reported as required by University policy.

_____ _____

Signature of Principal Investigator Date

Faculty Advisor if PI is a Student or Trainee Investigator: I accept ultimate responsibility for ensuring that the PI complies with the University's conflict of interest policies and procedures.

_____ _____

Signature of Faculty Advisor Date

Part A.4. Questions Common to All Studies

For all questions, if the study involves only secondary data analysis, focus on your proposed design, methods and procedures, and not those of the original study that produced the data you plan to use.

Complete answers must be provided. While you may reference other documents with supporting information, do not respond solely by stating "see attached."

A.4.1. **Brief Summary**. Provide a *brief* non-technical description of the study, which will be used in IRB documentation as a description of the study. Typical summaries are 50-100 words. *Please reply to each item below, retaining the subheading labels already in place, so that reviewers can readily identify the content.*

Purpose: The purpose of this study is to examine the acute health effects of concentrated ambient ultrafine (UF) particulate matter (PM) exposure in patients with metabolic syndrome. Without lifestyle changes or medical intervention these patients are at considerable risk for developing diabetes and cardiovascular disease. Our hypothesis is that PM exposure in this population will result in changes in endothelial response as assessed by flow-mediated dilatation of the brachial artery and various heart rate variability and blood endpoints. This study and similar studies of susceptible populations are needed to provide the EPA with information regarding the health risks associated with ambient levels of UF PM.

Participants: Approximately 30 individuals with metabolic syndrome, aged between 25 and 70, will serve as participants.

Procedures (methods): Subjects will undergo two exposures: once to clean air (control) and once to an atmosphere containing ultrafine (UF) concentrated air particles (CAPs) coming from the surrounding, ambient Chapel Hill air drawn from above the roof of the Human Studies Facility on Mason Farm Road. Each exposure will be for 2 hours with at least 2 weeks of interval between exposures. The order of the air and UFP exposures will be randomized. For each exposure vital signs, clinical chemistry, vascular function, and cardiac function will be evaluated pre, immediately post and 24 hr post exposure.

A.4.2. **Purpose and Rationale**. Provide a summary of the background information, state the research question(s), and tell why the study is needed. If a complete rationale and literature review are in an accompanying grant application or other type of proposal, only provide a brief summary here. If there is no proposal, provide a more extensive rationale and literature review, including references.

The World Health Organization estimates that over 1 million deaths each year are attributable to acute exposures to airborne particular pollution (PM). Between 50,000 and 70,000 deaths in the U.S. are attributable to acute PM exposures. Chronic exposure to PM in the U.S. has been reported to result in shortening of life span by two years. Clearly, PM is a major public health problem. The EPA is required to set standards that adequately protect Americans from air pollutants, including PM. By law, these standards must be revisited every five years, taking into account the latest research findings, to ensure that the standard continues to be protective. In a 2007 report to Congress the OMB reported that of all Federal regulations that were in place between 1996-2006, benefits due to clean air standards set by the EPA accounted for nearly two thirds of the benefits that were achieved by all Federal regulations. OMB estimates that benefits derived from the Clean Air Act account for between 62 – 430 billion dollars each year.

Since, by law, the EPA is required to continually take the latest science into account when revisiting standards for PM, there is a continuing need for research to better define concentrations of PM that causes changes in humans, to identify which size fractions and components of PM are responsible for health effects, and to understand the mechanisms by which PM causes effects. In addition, the Clean Air Act mandates that the EPA set standards to protect susceptible populations, such as those with cardiopulmonary disease, the young, and the elderly. Therefore, there is a need for research to identify and characterize these populations. More than 150 epidemiology studies have shown associations between exposure to PM and increased mortality. These studies indicate that people with severe cardiovascular disease and severe lung disease (e.g. advanced COPD) are the primary targets of PM. However, studies conducted by researchers in Chapel Hill and elsewhere have shown that exposing healthy people or people with mild disease to air pollutants can provide important information in support of standard setting. For example, healthy individuals exposed to PM experience mild pulmonary inflammation, small changes in autonomic nervous system control of heart rate, and small changes in clotting/coagulation components in their blood. These small changes in healthy individuals have been shown to not be clinically relevant in this population, but can provide insights into how PM can cause adverse effects in people with severe cardiopulmonary disease. They also help determine which sizes of PM and which components cause the largest effects. Although many studies have been done in which animals have been exposed to PM, most of them have failed to provide information that has been as informative or useful to the EPA as epidemiology or controlled human exposure studies. The EPA bases air pollution standards almost exclusively on human studies, with animal studies playing a minor supporting role.

The EPA has been conducting controlled human exposure studies to air pollutants on the UNC campus for more than 30 years. During that time more than 6000 volunteers have been studied without a single serious adverse event being observed. These studies have consistently been cited by the EPA as "key" studies when it re-evaluates the science every five years. Indeed, the current ozone standard rests largely on studies done in Chapel Hill by EPA and UNC investigators. The current building that houses EPA and UNC environmental investigators on the UNC campus was built by UNC in recognition of the importance of this research effort to UNC and the State of North Carolina.

Epidemiologic studies report associations between ambient air pollution particulate matter (PM) and various indices of cardiopulmonary morbidity and mortality at particle concentrations below current EPA air quality standards. Ambient PM is a complex mixture that includes bioactive and toxic compounds of natural and anthropogenic origin, several of which have been theorized to be causative or contributory to the adverse effects of PM inhalation. Various physicochemical properties such as particle size and surface area are linked to the health effects of PM; however, the mechanisms underlying these health effects are not well understood. Furthermore, associations identified in epidemiologic studies are stronger for "fine" particles (less than 2.5 μm) than for "coarse" particles (between 2.5 and 10 μm) which has lead to a surge of in vivo and in vitro studies attempting to delineate the biological effects of particles of different size fractions. A leading hypothesis contends that smaller particles induce a greater physiologic response because they can be carried deep inside the lung during inspiration; therefore a clinical study which exposes subjects to the smallest particle fraction (so-called ultrafine particles) is an important undertaking. Ultrafine (UF) particles have been specifically associated with a worsening of pre-existing pulmonary diseases and have been shown to have higher inflammatory "potency" than larger particles. These particles are primarily derived from fossil fuel combustion by electric utilities, automobiles, and smelting processes. As nearly all Americans are exposed to particles from these sources, the EPA has put a high priority on clinical studies which test the effects of these particles on human health. Because of their very small size UF particles normally contribute relatively little to the total PM mass, but they have a

very large surface area, which could act as a carrier of noxious substances such as metals and organics. In addition, these particles are generated in such high numbers by internal combustion engines that UF particles greatly outnumber fine and coarse particles in ambient air. Measurements taken at roadsides in Minnesota indicate the presence of well over one million UF particles/cm^3 on heavily trafficked roads.

Research to date suggests that subsets of the population may be at a greater risk for developing PM-associated health problems than the general public. Those that appear to be at greatest risk include the elderly and those with pre-existing cardiopulmonary disease or diabetes. Studies conducted in our facility (IRB #95-EPA-310) have shown that healthy volunteers primarily exhibit mild pulmonary inflammation and systemic effects following exposure to concentrated air particles (CAPs). Elderly subjects exposed to similar CAPs levels have been shown to experience decreases in heart rate variability and greater changes in blood factors associated with blood coagulation (IRB #GCRC-1541). Those with pre-existing cardiopulmonary disease have been shown in epidemiologic studies to be at increased risk for ambient PM-associated myocardial infarction, cardiac arrhythmias, and changes in various blood endpoints suggesting inflammatory processes and damage to the vascular endothelium. Patients with existing cardiovascular disease and diabetes may be especially vulnerable to the effects of PM due to existing endothelial cell dysfunction, a hallmark of those diseases. It has been established that the vascular endothelium acts as a highly selective barrier and secretes vasoactive substances such as angiotensin, endothelin, prostacyclin, and nitric oxide which are responsible for regulating systemic vascular resistance and platelet adherence. In addition, a number of these same substances have important effects on vital organs such as the heart, lungs, and kidney. As the function of the endothelium becomes compromised, as in diabetes and other cardiovascular diseases, the endothelial barrier becomes more permeable and there is increased release of pro-coagulant factors (factor VII, thrombin, tissue factor), chemotactic factors (monocytes and smooth muscle cells), and vasoconstrictive substances (endothelin and prostanoids). Therefore, because of the substantial differences in underlying physiology between healthy and diseased individuals, it is important to study susceptible patient populations in order to identify individuals at greater health risk. Current studies of susceptible populations taking place in our group involve the exposure of asthmatics (IRB #99-EPA-80) and smokers (GCRC #1538) to "fine" CAPs.

Patients with metabolic syndrome are a growing subset of the world-wide population that has emerging risk factors for cardiovascular disease. The Adult Treatment Panel III in the third report of the National Cholesterol Education Program characterizes metabolic syndrome patients as those having three of the following: increased abdominal girth, elevated blood pressure, dyslipidemia, elevated fasting triglycerides, and elevated fasting blood glucose. The National Health and Nutrition Examination Survey III has suggested that 24% of the American adult population meet the definition of metabolic syndrome. Applied to the 2000 census, this suggests that approximately 47 million adult Americans are afflicted with the syndrome. Metabolic syndrome also carries with it a number of metabolic abnormalities which contribute to endothelial dysfunction manifesting in a pro-inflammatory and pro-thrombotic state due to the increased production of cytokines and C-reactive protein. Without lifestyle changes or medical intervention these patients are at considerable risk for developing diabetes and cardiovascular disease.

Human exposure studies are essential in order to determine the effects of a "real-world" UF PM exposure in a potentially susceptible population without overt disease. In vitro and in vivo instillation studies are limited by the uncertainty associated with extraction of particles from filters or other substrates as it is not clear if all components get extracted or if the extraction process alters the chemistry of the particles. Furthermore, particles tend to agglomerate during extraction and their altered size range results in potential deposition in the lung at sites different

from where "real-world" unextracted particles would deposit when inhaled. Thus it is important to use "real-world" particles whenever possible. A new generation instrument is now available that allows concentration of particles in the UF to "low-fine" range (0.03-0.25 μm). **The purpose of this study** is to examine the acute health effects of concentrated ambient UF PM exposure in patients with metabolic syndrome. Our **hypothesis** is that PM exposure in this population will result in changes in endothelial response as assessed by flow-mediated dilatation of the brachial artery and various heart rate variability and blood endpoints. This study and similar studies of susceptible populations are needed to provide the EPA with information regarding the health risks associated with ambient levels of UF PM.

A.4.3. **Subjects.** *You should describe the subject population even if your study does not involve direct interaction (e.g., existing records).* Specify number, gender, ethnicity, race, and age. Specify whether subjects are healthy volunteers or patients. If patients, specify any relevant disease or condition and indicate how potential subjects will be identified. Researchers are reminded that additional approvals may be needed from relevant "gatekeepers" to access subjects (e.g., school principals, facility directors, hospital or healthcare system administrators).

Approximately 30 individuals with metabolic syndrome, aged between 25 and 70, will serve as participants. There is no gender or racial restriction. Pregnant women or nursing mothers will be excluded from participation because of possible (unknown) effects on the fetus or young infant. All female participants of child-bearing potential will therefore be tested for pregnancy at the time of admission into the study and again immediately prior to exposure

A.4.4. **Inclusion/exclusion criteria.** List required characteristics of potential subjects, and those that preclude enrollment or involvement of subjects or their data. Justify exclusion of any group, especially by criteria based on gender, ethnicity, race, or age. If pregnant women are excluded, or if women who become pregnant are withdrawn, specific justification must be provided.

Inclusion criteria:

- Metabolic syndrome as defined by the participant having at least **three** of the following criteria:
  - Abdominal obesity: Men waist circumference >102 cm (>40 in)
    Women waist circumference >88 cm (>35 in)
  - Triglycerides: ≥150 mg/dL
  - HDL cholesterol: Men <40 mg/dL
    Women <50 mg/dL
  - Blood pressure: ≥130/≥85 mmHg
    OR
    have a history of high blood pressure requiring medication
  - Fasting glucose: ≥100 mg/dL and ≤126 mg/dL
- Normal resting electrocardiograph (ECG).
- Participants must be fluent in English, as the EPA HSF does not employ language translators necessary to ensure participant safety for those who do not fully comprehend English.

Exclusion criteria:

- Current smoker or smoking history within 3 months of study (defined as more than one pack of cigarettes in the past 3 months).
- Oxygen saturation below 95% at the time of physical exam.
- Blood pressure ≥160/≥100 mmHg

- Fasting blood glucose >126 mg/dl
- Hypersensitivity to nitroglycerin or other nitrates
- Any chronic medical condition including active pulmonary disease, cardiovascular disease (coronary artery disease, heart failure, rhythm disturbances, etc.), neurological disease, liver disease, kidney disease, muscular disease, diabetes, other endocrine disease, hematologic/lymphatic disease, immune deficiency or autoimmune disease.
- **Medications specifically prohibited** include nitrates or other vasodilators (exception here includes erectile dysfunction medications if the participant agrees to refrain for 96 hours prior to study), anti-arrhythmics, physician prescribed anti-inflammatory agents, physician prescribed antioxidants, insulin and other medications for the treatment of diabetes. Participants must refrain from all over-the-counter anti-inflammatory agents, including aspirin, ibuprofen, and naproxen, and anti-oxidants for a period of one week prior to exposure. Low dose aspirin and statin regimens are acceptable. **Medications not specifically mentioned here may be reviewed by the investigators prior to a participant's inclusion in the study.** Additionally, medication regimens must remain constant during the study.
- Hepatitis B carriers
- Skin diseases or sensitivity precluding the use of ECG electrodes
- Active cancer, history of cancer within the last 5 years, untreated cancer. Potential participants may have a history of mild, treated skin cancer provided the condition does not interfere with ECG electrode placement.
- No exposure will be conducted within 4 weeks of a respiratory tract infection.
- History of serve migraines
- Pregnant women or nursing mothers

Participants with a history of seasonal allergies (hay fever, dust allergies, rhinitis) may be included in the study provided the participant has no respiratory symptoms within 4 weeks of a scheduled exposure; participants will not be studied during active allergy season. Participants with a history of childhood asthma may also be included if the participant has had no symptoms within 6 years or has a documented negative methacholine challenge. Additionally, females will be required to complete a menstrual history form.

A.4.5. **Full description of the study design, methods and procedures.** Describe the research study. Discuss the study design; study procedures; sequential description of what subjects will be asked to do; assignment of subjects to various arms of the study if applicable; doses; frequency and route of administration of medication and other medical treatment if applicable; how data are to be collected (questionnaire, interview, focus group or specific procedure such as physical examination, venipuncture, etc.). Include information on who will collect data, who will conduct procedures or measurements. Indicate the number and duration of contacts with each subject; outcome measurements; and follow-up procedures. If the study involves medical treatment, distinguish standard care procedures from those that are research. If the study is a clinical trial involving patients as subjects and use of placebo control is involved, provide justification for the use of placebo controls.

This will be a single-blinded study in which each participant will be exposed to filtered air and air containing concentrated UF particles. The study will follow a repeated measures design with participants serving as their own control. Exposures will be randomized with a minimum of 2 weeks between an individual participant's exposures.

Participant Qualification

Participants will be recruited by the Westat Corporation as described in (IRB Protocol# 95-EPA-66). Subjects will respond to advertisements posted in local newspapers or other periodicals, local radio spots, on the EPA website, and in flyers placed in local medicine and endocrine clinics. In addition, potential study subjects identified through the UNC Family Practice clinic will be mailed an invitation to participate and the use of a purchased mass mailing list could be used as a means of contacting potential participants. Upon contact the screening procedure will proceed as follows:

Initial telephone interview (Westat Corp): Participants will receive information regarding the study and their eligibility status will be assessed. The general script to be used by Westat for the description of this study is provided in this package. .

Metabolic syndrome criteria screening: Volunteers whose responses during the initial telephone interview indicate that they are likely to meet the study criteria will be scheduled for an appointment in the Westat recruitment office in the USEPA Human Studies Facility (HSF). Consent will be obtained using a separate screening form (Screening for metabolic syndrome criteria). We will draw a fasting blood sample (Chem-20, a complete blood count with differential, hepatitis B screen) and check their blood pressure to ensure the participants meet the metabolic syndrome criteria as mentioned above.

General medical history (Westat Corp.): After completing the screening blood draw, participants will receive a separate medical history consent form and a general medical history form from Westat Corp. Upon notification of qualifying for the study from our medical staff, each participant will be asked to sign the consent form and fill out the general information on personal and family medical history (IRB study #95EPA66). The participants will be asked to return these forms to the US EPA Human Studies Facility (HSF) (Mailing Address: US EPA, Attn: Medical Station, CB-7315, 104 Mason Farm Road, Chapel Hill, NC, 27599-7315

Physical exam: Participants not excluded during the initial screening procedures will be scheduled for a physical examination in the HSF to be performed by a licensed physician, nurse practitioner, or physician's assistant (IRB study #95EPA66). During this visit participants will sign an informed consent for a physical and the general medical history form completed previously by Westat Corp. will be discussed. Participants will then undergo an abbreviated physical exam and a 12-lead ECG to screen for baseline cardiac arrhythmias and ST segment and T-wave abnormalities.

Subject Information: Participants passing the previous screening procedures will provide informed consent to participate in the study. Following the exposure chamber and facemask measurements, the participant will be given a brief study walk-through to familiarize them with the exposure chamber and procedures. Once all qualification criteria have been met, the participant will be scheduled for the exposure. Prior to the scheduled exposure, each participant will be contacted and reminded to refrain from taking anti-inflammatory medications and antioxidants. Additionally, the participants will be provided with low-fat diet recommendations which each will follow on the exposure days and the day following the exposure.

Study Procedures: Day 1

Pre-exposure: On the day of the study, the participant will report to the medical station in the HSF at which time the general health of the participant will be evaluated and the appropriate pre-exposure measurements (HRV, blood sampling, urine pregnancy test for females) will be completed. Electrodes for telemetry and HRV measurement will be placed. The skin in the areas of electrode placement will be cleaned and shaved (if necessary) to ensure that the electrodes will remain securely attached. The leads connected to the ambulatory ECG monitor will remain in place overnight while the telemetry leads will be removed when the participant leaves for the day. The participant will be allowed to relax for 20 minutes in a reclined position after which a 10-minute resting HRV measurement will be obtained and blood samples will be taken. The participant will then be escorted to the NCMH CTRC for brachial artery ultrasound.

Brachial artery ultrasound: Brachial artery ultrasound to evaluate flow-mediated dilatation will be performed in the North Carolina Memorial Hospital (NCMH) Clinical and Translational Research Center (CTRC) using a 12.5 MHz imaging probe interfaced with an ATL HDI 5000 ultrasound machine. The diameter of the brachial artery will be measured at baseline, during reactive hyperemia and after administration of sublingual nitroglycerin. The subject will lie supine, and a pneumatic tourniquet will be placed around the right upper arm proximal to the target artery. Gated baseline images of the brachial artery will be acquired after 15 minutes of supine rest. The pneumatic cuff will then be inflated to a pressure of 200 mm Hg for 5 minutes, and increased flow will be induced by sudden cuff deflation. A second scan will be performed following deflation. The subject will rest another 10 minutes and a third ultrasound scan will be performed. Translingual nitroglycerin (~0.4 mg) will be administered, followed in three to four minutes by the final ultrasound study. Subjects will then rest quietly for 5 minutes. Images of the brachial artery will be acquired and stored on a personal computer, and subsequently analyzed using a semi-automated offline quantification system. Following the brachial artery ultrasound, the participant will receive a bag-lunch from the CTRC and then return to the EPA HSF and enter the exposure chamber for filtered air or particle exposure.

Exposure: In the chamber, the participant will sit for 2 hours at rest. Ultrafine particles (UF) will be concentrated from ambient Chapel Hill air drawn from above the roof of the Human Studies Facility on Mason Farm Road. Therefore, the particle concentration in the chamber will be dependent on the particle concentration in ambient air on the day of the study and will vary from day to day. UF particles will be measured in real time during each exposure. Particle number will be measured instead of particle mass because UF have very little mass. Typical UF concentrations in Chapel Hill air usually range from 4,000 – 12,000 particles/cc, with occasional high end concentrations as high as 35,000 particles/cc. The instrument used in this study will concentrate UF between 20-35 fold, depending on outside temperature, humidity and other barometric factors. Therefore we anticipate that **on average** most participants will be exposed to 110,00 -330,000 UFP/cc during their two hour session, assuming a concentration factor of 27.5 However, it is recognized that some days outside particle concentrations will be higher than these averages. If outdoor particle concentrations were 35,000 UFP/cc and the concentration factor were 35, subjects could be exposed to 1,225,000 UFP/cc. However, we will establish 600,000 particles/cc as a maximum, which is less than or equivalent to what people would inhale while driving along a heavily travelled highways in a city such as Los Angeles. This is being done, not because of safety concerns (we describe below studies in which volunteers have been exposed to particle concentrations much higher than this without experiencing discomfort or clinically relevant responses), but rather to ensure that we are not at the upper limit of environmentally relevant concentrations.

Therefore, personnel responsible for operating the chamber will monitor levels of UF in the chamber prior to a subject entering, and if the levels exceed 600,000 particles/cc clean air

will be used to dilute the particle stream to achieve a concentration of less than 600,000 particles/cc, measured over a 10 minute period. If particle concentrations begin to rise above that concentration during any 10 minute period while the subject is being exposed, additional clean air will be added as appropriate. In an ongoing study using the modified particle concentrator (IRB#07-0190) participants have been exposed to an **average** of 270,000 particles/cc. However, on some days the participants have been exposed to particle concentrations of 460,000; 1,181,000; 692,000; 404,000; 655,000; and 550,000 and experienced no symptoms of discomfort or clinically relevant responses. Additionally, participants in our facility have been exposed to diesel exhaust particle concentrations between 1 – 3 million and have experienced no symptoms of discomfort or clinically relevant responses (IRB# 99-EPA-283). Human exposure studies done elsewhere (Frampton et al., Environ. Health Perspec; 2008; 116:375-380) have exposed volunteers for several years to ultrafine carbon particle concentrations of 10 million particles/cc and have not reported any clinically relevant changes.

Telemetry and blood oxygen saturation will be monitored continuously throughout the exposure and blood pressure will be measured intermittently. Participants will also be monitored continuously by trained personnel for signs of respiratory distress, chest pain, significant cardiac arrhythmias, ataxia, or other signs of distress. The participants will be aware that they may terminate their exposure at any point should they deem necessary.

Post-exposure: Immediately following the exposure, the participant will be allowed to rest for 20 minutes and then HRV measurements and blood samples will be taken. The participant will then be escorted to the NCMH CTRC for the brachial artery ultrasound.

Prior to discharge the participants will be given instructions regarding the ambulatory ECG monitor and the time they are to return to the HSF the next day.

Study Procedures: Day 2

The study participants will return to the HSF at the appointed time the following day. The participant will be allowed to relax for 20 minutes in a reclined position after which a 10-minute resting HRV measurement will be obtained and a blood sample will be taken. Data card and batteries for the ambulatory ECG monitor will be changed, if necessary. The participant will be escorted to the NCMH CTRC for the brachial artery ultrasound. The participant will return to the HSF and discharge will follow. This regimen will then be repeated no less than 2 weeks later, at which time the participant will be exposed to either clean air or UF CAPs, depending on the exposure received during the first visit.

OUTCOMES:

Flow-mediated dilatation (brachial artery ultrasound). Changes in diameter caused by reactive hyperemia (endothelium-dependent vasodilatation) and administration of sublingual nitroglycerin (endothelium-independent vasodilatation) will be expressed as a percent change in diameter relative to resting values.

Heart rate variability (HRV) (holter monitor). Data will be gathered for approximately 24 hours and both time and frequency domain variables will be analyzed, as will abnormal responses (e.g. PACs, PVCs, bradycardia, tachycardia). Specific epochs that will be analyzed for changes in the frequency domain variables include times immediately prior to exposure, immediately following exposure, and approximately 24 hours after exposure (i.e. during the 10 minutes immediately following the 20 minute "resting" periods mentioned above).

Peripheral venous blood samples. The medical staff will draw approximately 80 mls of blood from each volunteer before exposure, immediately after exposure, and approximately 18 hours after exposure, for a total volume of about 240 mls over a 24-hour period. **Endpoint measurements will include *but may not be limited to* the following**: markers for specific and non-specific immune responses (cytokines, C-reactive protein), coagulation factors (von Willibrand Factor, factor IX, fibrinogen and its degradation products, thrombin), vasoactive factors (endothelin, catecholamines), and soluble components of PM (e.g. transition metals). As noted in the study consent form, the research participant can consent to participate in the research study with or without genotyping. If they consent to genotyping, some of their blood will be used for genotyping for specific genes related to adverse health effects associated with air pollution exposure.

As noted in the specimen storage with identifiers consent form, some of this blood will be stored for as-yet-undesignated research purposes.

A.4.6. **Benefits to subjects and/or society.** Describe any potential for direct benefit to individual subjects, as well as the benefit to society based on scientific knowledge to be gained; these should be clearly distinguished. Consider the nature, magnitude, and likelihood of any direct benefit to subjects. If there is no direct benefit to the individual subject, say so here and in the consent form (if there is a consent form). Do not list monetary payment or other compensation as a benefit.

Participants will receive no direct benefit from participating in this study other than receiving a medical examination and information obtained from laboratory results and procedures. Participants will have full access to their records and a discussion of the results of all tests will be provided at the participant's request. For society, this study will provide valuable new information on the effects of PM exposure on the cardiovascular system and inflammation in a growing subset of the population. The results from this human study will provide important data that assist the EPA in determining whether or not to retain the current standard on PM.

A.4.7. **Full description of risks and measures to minimize risks.** Include risk of psychosocial harm (e.g., emotional distress, embarrassment, breach of confidentiality), economic harm (e.g., loss of employment or insurability, loss of professional standing or reputation, loss of standing within the community) and legal jeopardy (e.g., disclosure of illegal activity or negligence), as well as known side effects of study medication, if applicable, and risk of pain and physical injury. Describe what will be done to minimize these risks. Describe procedures for follow-up, when necessary, such as when subjects are found to be in need of medical or psychological referral. If there is no direct interaction with subjects, and risk is limited to breach of confidentiality (e.g., for existing data), state this.

General measures to minimize the risks: Medical screening of the potential participants is designed to exclude those that may be at risk from the study procedures. A physician is present in the HSF whenever a participant is undergoing any procedure at the facility. The physician will terminate the procedure at any time if he feels that it would be injurious to the participant's well-being to continue. Three nurses staff a fully stocked medical station and the NCMH is a short distance from the HSF. On subsequent days after exposure, participants will be urged to contact the medical station or the on-call physician should they experience any symptoms such as persistent cough, chest pain, dyspnea, or wheezing. Risks associated with specific study procedures are as follows:

- **Brachial Artery Ultrasound:** There are no known risks associated with imaging of the brachial artery. However, intermittent brief occlusion of blood flow to the forearm may cause mild discomfort and temporary sensations such as tingling and numbness until the blood pressure cuff is released. Approximately 0.5 % of participants develop painless petechiae in the arm

which is examined and these resolve within a few days. Sublingual nitroglycerin is a potent vasodilator, and may be associated with headache, flushing, and transient hypotension. These results are short-lived because the peak plasma concentration occurs within 4 minutes of administration and the plasma half-life is approximately 5 minutes. To minimize the risk of hypotension, the subject will remain lying down for 10 minutes after receiving nitroglycerin. In addition, individuals who may be at risk of excessive blood pressure lowering (i.e. individuals who have baseline systolic blood pressure < 90 mm Hg, or who have obstruction of the left ventricular outflow tract due to aortic stenosis or a dynamic outflow gradient) will be excluded. Allergic reactions to nitroglycerin have been reported, but are rare.

- **ECG, heart rate variability (holter monitor)** are non-invasive techniques commonly used for heart rate and rhythm analysis and entail little or no risk to the participant. There is the possibility that preparation of the skin for electrode placement and removal may cause hyperpigmentation, skin irritation, itching, or soreness in some participants.
- **Blood sampling** risks, including pain and hematoma formation, are considered mild and minimal. A licensed nurse will take blood samples.
- **Particle exposure** is not expected to produce any permanent adverse health effects at the concentrations being used in this study. Heart rate, electrocardiogram, and pulse oximetry will be monitored continuously. Participants will also be monitored for significant respiratory distress or dyspnea, chest pain, significant cardiac arrhythmias, pallor, and ataxia. Participants will be aware that they can terminate their exposure for any reason and still receive compensation for the entire exposure session. The investigator or duty physician will end the exposure if the participant is found to be suffering from any adverse effect which could be attributed to the exposure. More details can be found in the enclosed addendum.

A.4.8. **Data monitoring and analysis.** Tell how the qualitative and/or quantitative data will be analyzed. Explain how the sample size is sufficient to achieve the study aims. This might include a formal power calculation or explanation of why a small sample is sufficient (e.g., qualitative research, pilot studies). Describe the provisions for monitoring the data to ensure the safety of participants. These plans could range from the investigator monitoring subject data for any safety concerns to a sponsor-based DSMB, depending on the study.

Statistical analysis: Detailed description of analysis can be found in Appendix B. The research aim of this study is to provide the EPA with a means to evaluate some of the biological effects of ultra-fine air pollution particles. The study will follow a randomized, repeated measures design with each subject being exposed to clean air and concentrated particles on two separate occasions. The primary outcome will compare the mean pre-exposure flow-mediated dilation to the mean flow-mediated dilation 30 minutes and 24 hours following exposure. A second analysis will compare the mean pre-exposure heart rate variability measures to the mean measures taken 30 minutes and 24 hours following exposure. Both of these analyses will utilize an F-test to control for type I error, with flow-mediate dilation and heart rate variability as separate dependent variables and exposure and time from exposure as independent variables (for each). The blood endpoints and holter monitor analysis will be tested as exploratory hypotheses. Blood endpoints will compare the mean 30-minute and 24-hour post-exposure measurements to the mean pre-exposure measurements. There is no plan to control for type I error in analyzing these exploratory hypotheses. Previous reports suggest that these data will be normally distributed therefore the appropriate parametric tests (repeated measures ANOVA, paired t-tests) will be applied. A p value of 0.05 or less will be considered significant.

We anticipate that the proposed sample size will provide adequate (80%) power for detecting an absolute difference of 3% in flow-mediated dilation assuming a standard deviation of 4%. An N of 16 was derived using a β of 0.2 (power = 80%) and an α of 0.05. As this population may have a greater variance associated with the measurement, we have conservatively increased the N to 30. By increasing the N to 30 we calculate that our power will remain at 80% if the actual SD reaches 5.6%.

A.4.9. **Will you collect or receive any of the following identifiers?** Does not apply to consent forms.

__ No __ Yes *If yes, check all that apply*:

a. _X_ Names
b. _X_ Telephone numbers
c. _X_ Any elements of dates (other than year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death. For ages over 89: all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 and older
d. _X_Any geographic subdivisions smaller than a State, including street address, city, county, precinct, zip code and their equivalent geocodes, except for the initial three digits of a zip code
e. __ Fax numbers
f. _X_Electronic mail addresses
g. __ Social security numbers
h. _X_Medical record numbers
i. __ Health plan beneficiary numbers
j. __ Account numbers
k. __ Certificate/license numbers
l. __ Vehicle identifiers and serial numbers (VIN), including license plate numbers
m. __ Device identifiers and serial numbers (e.g., implanted medical device)
n. __ Web universal resource locators (URLs)
o. __ Internet protocol (IP) address numbers
p. __ Biometric identifiers, including finger and voice prints
q. __ Full face photographic images and any comparable images
r. __ Any other unique identifying number, code, or characteristic, other than dummy identifiers that are not derived from actual identifiers and for which the re-identification key is maintained by the health care provider and not disclosed to the researcher

A.4.10. **Identifiers in research data**. Are the identifiers in A.4.9 above linked or maintained with the research data?

__ yes _X_ no

A.4.11. **Confidentiality of the data**. Describe procedures for maintaining confidentiality of the data you will collect or will receive. Describe how you will protect the data from access by those not authorized. How will data be transmitted among research personnel? Where relevant, discuss the potential for deductive disclosure (i.e., directly identifying subjects from a combination of indirect IDs).

Risk of breach of confidentiality is minimal. All subjects will be assigned a study number which will be used for data recording – not the subject's name. The study number is all that will be entered into computer databases. All paper files that may contain the subject's name or screening number are securely locked in the EPA building that has limited access 24 hours/day. Any abnormal medical findings (CBC, ECG, brachial artery ultrasound image) will be discussed with the volunteer and the volunteer will be counseled to seek treatment from his/her personal physician if indicated. Samples will be stored at the U.S. EPA HSF. A numeric coding system will be used to ensure that subjects cannot be directly identified from the samples alone.

A.4.12. **Data sharing.** With whom will *identifiable* (contains any of the 18 identifiers listed in question A.4.9 above) data be shared outside the immediate research team? For each, explain confidentiality measures. Include data use agreements, if any.

_X_ No one
__ Coordinating Center:
__ Statisticians:
__ Consultants:
__ Other researchers:
__ Registries:
__ Sponsors:
__ External labs for additional testing:
__ Journals:
__ Publicly available dataset:
__ Other:

A.4.13. **Data security for storage and transmission**. Please check all that apply.

For electronic data stored on a desk top computer:
_X_ Secure network _X_ Password access __ Data encryption__ Password protected file(s)
__ Other comparable safeguard (describe):

For portable computing devices/external storage devices (e.g. laptop computer, PDA, CDs, memory sticks):
__ Power-on password __ Automatic log-off __ Data encryption __ Password protected file(s)
__ Other comparable safeguard (describe):

For hardcopy data (including human biological specimens, CDs, tapes, etc.):
__ Data de-identified by research team (stripped of the 18 identifiers listed in question A.4.9 above)
_ _ Locked suite or office _X_ Locked cabinet
__ Data coded by research team with a master list secured and kept separately
__ Other (describe):

A.4.14. **Post-study disposition of identifiable data or human biological materials**. Describe your plans for disposition of data or human biological specimens that are identifiable in any way (directly or via indirect codes) once the study has ended. Describe your plan to destroy identifiers, if you will do so.

Samples will be stored in a repository where only project members of the study will have access to the samples. Subjects at any time may request that their samples no longer be stored in the repository. Any analysis in progress at the time of the request or already performed prior to the request being received by the researcher will continue to be used as part of the research study. Once the researcher is notified, the subject's specimens will be destroyed. Consent will be obtained using the Storage of Biological Specimens with Identifying Information form.

Part A.5. The Consent Process and Consent Documentation (including Waivers)

The standard consent process is for all subjects to sign a document containing all the elements of informed consent, as specified in the federal regulations. Some or all of the elements of consent, including signatures, may be altered or waived under certain circumstances.

- If you will obtain consent in any manner, complete **section A.5.1**.
- If you are obtaining consent, but requesting a waiver of the requirement for a signed consent document, complete **section A.5.2**.
- If you are requesting a waiver of any or all of the elements of consent, complete **section A.5.3**.
- If you need to access Protected Health Information (PHI) to identify potential subjects who will then be contacted, you will need a *limited waiver of HIPAA authorization*. This is addressed in section B.2.

You may need to complete more than one section. For example, if you are conducting a phone survey with verbal consent, complete sections A.5.1, A.5.2, and possibly A.5.3.

A.5.1. **Describe the process of obtaining informed consent from subjects.**
Describe who will be obtaining consent (or permission) and from whom. Include discussion, as relevant, any waiting period between the initial consent discussion and obtaining consent, and steps that will be taken to minimize coercion or undue influence. If children will be enrolled as subjects, describe the provisions for obtaining parental permission and assent of the child. If decisionally impaired adults are to be enrolled, describe the provision for obtaining surrogate consent from a legally authorized representative (LAR). If non-English speaking people will be enrolled, explain how consent in the native language will be obtained. Address both written translation of the consent and the availability of oral interpretation. It is expected that the information in the consent document(s) will be communicated to participants or their LAR. *After you have completed this part A.5.1, if you are not requesting a waiver of any type, you are done with Part A.5.; proceed to Part B.*

Before being selected as participants, all volunteers will be required to read and sign a form asserting that they have read and understood the following: 1) participation is strictly voluntary, 2) the purpose of the study, 3) the nature and extent of participation, 4) the participant's rights to withdraw at any time, 5) the right of the participant to privacy, 6) the risks associated with participation, 7) the method and schedule of compensation, and 8) the limits of the University and investigator's liability.

One of the investigators will describe the study and answer any questions that each participant might have regarding his/her participation, the safety of the procedures, issues related to payment, etc. The investigator will then review the contents of the consent form before he/she and the participant sign it. Participants will have the opportunity to ask questions at any time during the study by contacting one of the investigators and/or the medical staff. Participants will be asked to sign a written informed consent form after all of their questions and concerns have been addressed. One signed copy of the written informed consent will be given to the participant while the investigators will retain the original.

A.5.2. **Justification for a waiver of *written* (i.e., signed) consent**. *The default is for subjects to sign a written document that contains all the elements of informed consent.* Under limited circumstances, the requirement for a signed consent form may be waived by the IRB if either of the following is true. *Choose only one:*

a. The only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality (e.g., study topic is sensitive so that public knowledge of participation could be damaging). *Participants should be asked whether they want documentation linking them with the research and the participants' wishes will govern whether they sign the form.* Note: This justification cannot be used in FDA-regulated research. __ yes __ no __ yes __ no
Explain.

b. The research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context (e.g., phone survey).
Explain.

If you checked "yes" to either (and you are not requesting a waiver in section A.5.3) consent must be obtained orally, by delivering a fact sheet, through an online consent form, or be incorporated into the survey itself. Include a copy of the consent script, fact sheet, online consent form, or incorporated document.

→ If you have justified a waiver of written (signed) consent (A.5.2), you should complete A.5.3 *only* if your consent process will not include all the other elements of consent.

A.5.3. **Justification for a full or partial waiver of consent.** *The default is for subjects to give informed consent.* A waiver might be requested for research involving only existing data or human biological specimens (see also Part C). More rarely, it might be requested when the research design requires withholding some study details at the outset (e.g., behavioral research involving deception). In limited circumstances, parental permission may be waived. This section should also be completed for a waiver of HIPAA authorization if research involves Protected Health Information (PHI) subject to HIPAA regulation, such as patient records.

__ Requesting **waiver of some elements** (specify; see SOP 28 on the IRB web site):
__ Requesting **waiver of consent entirely**
If you check either of the boxes above, answer items a-f.. To justify a full waiver of the requirement for informed consent, you must be able to answer "yes" (or "not applicable" for question c) to items a-f. **Insert brief explanations that support your answers.**

a. Will the research involve no greater than minimal risk to subjects or to their privacy? __ yes __ no
Explain.

b. Is it true that the waiver will *not* adversely affect the rights and welfare of subjects? *(Consider the right of privacy and possible risk of breach of confidentiality in light of the information you wish to gather.)* __ yes __ no
Explain.

c. When applicable to your study, do you have plans to provide subjects with pertinent information after their participation is over? *(e.g., Will you provide details withheld during consent, or tell subjects if you found information with direct clinical relevance? This may be an uncommon scenario.)* __ yes __ not applicable
Explain.

d. Would the research be impracticable without the waiver? *(If you checked "yes," explain how the requirement to obtain consent would make the research impracticable, e.g., are most of the subjects lost to follow-up or deceased?).* __ yes __ no
Explain.

e. Is the risk to privacy reasonable in relation to benefits to be gained or the importance of the knowledge to be gained? __ yes __ no
Explain.

If you are accessing patient records for this research, you must also be able to answer "yes" to item f to justify a waiver of HIPAA authorization from the subjects.

f. Would the research be impracticable if you could not record (or use) Protected Health Information (PHI)? *(If you checked "yes," explain how* not *recording or using PHI would make the research impracticable).* __ yes __ no
Explain.

Part B. Questions for Studies that Involve Direct Interaction with Human Subjects

→ ***If this does not apply to your study, do not submit this section.***

B.1. **Methods of recruiting.** Describe how and where subjects will be identified and recruited. Indicate who will do the recruiting, and tell how subjects will be contacted. Describe efforts to ensure equal access to participation among women and minorities. Describe how you will protect the privacy of potential subjects during recruitment. *For prospective subjects whose status (e.g., as patient or client), condition, or contact information is not publicly available (e.g., from a phone book or public web site), the initial contact should be made with legitimate knowledge of the subjects' circumstances. Ideally, the individual with such knowledge should seek prospective subjects' permission to release names to the PI for recruitment. Alternatively, the knowledgeable individual could provide information about the study, including contact information for the investigator, so that interested prospective subjects can contact the investigator.* Provide the IRB with a copy of any document or script that will be used to obtain the patients' permission for release of names or to introduce the study. Check with the IRB for further guidance.

Participants will be recruited for this study by the Westat Corporation, which has recruited participants for studies at the HSF since 1998. The manner in which this will be done is similar to that of past EPA studies and specific recruitment procedures are described in the participant recruitment protocol on file with the UNC Committee for the Protection of the Rights of Human Subjects (IRB #95-EPA-66). We have included copies of the advertisements, telephone interview scripts, and radio advertisement spots, which may be used by Westat for this particular study. The population targeted will be patients with metabolic syndrome in Chapel Hill, Raleigh, Durham, and surrounding areas that may be reached through the radio spots. In addition, a mass mailing list could be purchased when such a list can be identified. The targeted advertisement would be prepared and mailed, using staggered mailings to accommodate study staff availability. The respondents will be screened by phone and the recruitment protocol (IRB#95-EPA-66) followed. *Every effort will be made to recruit women and members of racial minority groups into this study.*

Some participants may be clinical patients of the study investigators or their colleagues and will also be referred to Westat Corporation for recruitment. In addition, a limited waiver of consent and HIPAA authorization for identification and possible recruitment of patients from the UNC Family Practice clinic is being requested. The description of study recruitment of Family Practice patients will occur as follows:

1. A study investigator from the Family Practice clinic staff will query the Family Practice patient database with specific inclusion/exclusion search criteria.
2. From this query, the Family Practice study investigator will construct a list of potential study subjects that appear to meet the study inclusion/exclusion criteria. **Only the name of the potential subject and the name of the contact physician will be recorded; no health information including medications, existing disease states, or other study qualifying information will be recorded or saved.** Only the Family Practice study investigators will have access to this list of potential subjects.
3. The potential subject's primary physician will be contacted to obtain permission to contact the subject.
4. The potential subjects will be mailed the approved letter of invitation to participate and a brief patient information sheet.

5. Upon mailing of the invitation letters, the list of potential subjects will be shredded and properly disposed of.

Participants will be asked to call the recruitment office. During the telephone interview, the volunteers will receive information regarding the study and their eligibility status will be assessed. Participants whose responses indicate that they are likely to meet the criteria will be scheduled for an appointment in the Westat recruitment office in the Human Studies Facility.

B.2. **Protected Health Information (PHI).** If you need to access Protected Health Information (PHI) to identify potential subjects who will then be contacted, you will need a *limited waiver of HIPAA authorization*. If this applies to your study, please provide the following information and complete Section C.

a. Under this limited waiver, you are allowed to access and use only the minimum amount of PHI necessary to review eligibility criteria and contact potential subjects. What information are you planning to collect for this purpose?

b. How will confidentiality/privacy be protected prior to ascertaining desire to participate?

c. When and how will you destroy the contact information if an individual declines participation?

B.3. **Duration of entire study and duration of an individual subject's participation, including follow-up evaluation if applicable.** Include the number of required contacts and approximate duration of each contact.

It is anticipated that the duration of this study will be approximately two years. Participant recruitment and screening is expected to be continuous throughout the study until the intended number of participants is reached. Scheduling constraints imposed by concurrent studies in the Human Studies Division are expected to limit the rate at which participants can be exposed to 1-2 per week. An individual participant's exposures will be separated by at least 2 weeks. Required visits (generally, 7 visits with a total time commitment of approximately 26 hours) by participants and an estimated duration of each visit are as follows:

1. General medical history, fasting blood glucose and blood pressure screening — 1 hour
2. Physical exam — 1 hour
3. Train/information — 2 hours

Exposure 1

4. Day 1 — 8 hours
5. Day 2 — 3 hours

Exposure 2

6. Day 1 — 8 hours
7. Day 2 — 3 hours

B.4. **Where will the subjects be studied?** Describe locations where subjects will be studied, both on and off the UNC-CH campus.

All aspects of the study except the brachial artery ultrasound will be carried out at the EPA Human Studies Facility on the UNC at Chapel Hill campus. Brachial artery ultrasound will be performed in the Clinical and Translational Research Center (CTRC) located at NCMH in Chapel Hill.

B.5. **Privacy.** Describe procedures that will ensure privacy of the subjects in this study. Examples include the setting for interviews, phone conversations, or physical examinations; communication methods or mailed materials (e.g., mailings should not indicate disease status or focus of study on the envelope).

All interviews, phone conversations, and physical examinations will be conducted in private rooms in the U.S. EPA Human Studies Facility. This facility is guarded and only individuals working in the building have access beyond the guard's desk without an escort. Additionally, subjects will need to initial the consent form indicating whether or not they would be willing to participate in the study with another volunteer present.

B.6. **Inducements for participation.** Describe all inducements to participate, monetary or non-monetary. If monetary, specify the amount and schedule for payments and if/how this will be prorated if the subject withdraws (or is withdrawn) from the study prior to completing it. For compensation in foreign currency, provide a US$ equivalent. Provide evidence that the amount is not coercive (e.g., describe purchasing power for foreign countries). Be aware that payment over a certain amount may require the collection of the subjects' Social Security Numbers. If a subject is paid more than $200.00 per year, collection of subjects' Social Security Number is required (University policy—see SSN Guidance) using the Social Security Number collection consent addendum found under forms on the IRB website (look for Study Subject Reimbursement Form).

Participants will receive monetary compensation for their time ($12/hour) and participation in the study. A participant who is unable to complete the study for voluntary reasons will receive full compensation for his/her participation to the point of their withdrawal from the study. If a participant arrives for a scheduled exposure session and is subsequently canceled by the investigator, the participant will be awarded full compensation for that exposure session as if they had completed both Day 1 and Day 2. If a participant develops an illness or injury which would exclude them from participation in the study, they will be paid for that portion of the study which has been completed. Payment will be made after each segment of the study, unless the participant specifies otherwise.

The following table details the expected compensation for completion of the entire study:

Pre-study Qualifications	
Recruitment Screening and blood sample	$40
Physical Exam	$15
Additional /information (2hours)	$24
Exposure Sessions	
Air- day 1 (8 hours)	$96
Air- day 2 (3 hours)	$36
Particles- day 1 (8 hours)	$96
Particles- day 2 (3 hours)	$36

Blood sampling (6 @ $25 each)	$150
24-hour ambulatory ECG (2 @ $100 each)	$200
Brachial artery ultrasound (6 @ $50 each)	$300
Bonus for completion of the study	$100
Approximate Total Compensation	$1093

In addition, participants traveling from outside of Chapel Hill will be compensated for travel, and parking costs will be covered for all participants choosing to drive to the HSF. It is anticipated that using radio spots may increase our recruitment outside a reasonable commuting area. In the event a participant travels from outside our commuting area, the participant will be compensated for hotel accommodations and meals. Because the exposures are dependent on the outdoor concentrations of particles, there may be some days in which there are too few particles outdoors for an exposure (e.g. if it is raining). If this happens on a day a participant is scheduled to be exposed to particles, the participant will be rescheduled, and will receive payment of $132 for the time the participant would have spent at the HSF during the two-day study period.

B.7. **Costs to be borne by subjects.** Include child care, travel, parking, clinic fees, diagnostic and laboratory studies, drugs, devices, all professional fees, etc. If there are no costs to subjects other than their time to participate, indicate this.

All procedures and costs directly related to participation in this study will be free of charge to the participants.

Part C. Questions for Studies using Existing Data, Records or Human Biological Specimens

→ ***This section applies even if records are only used to identify potential subjects.***

→ ***If your study does not use existing data, records or specimens for any purpose, do not submit this section.***

C.1. What records, data or human biological specimens will you be using? *(check all that apply)*:

__ Data already collected for another research study
If applicant was involved in the original collection, please explain role:

__ Data already collected for administrative purposes (e.g., Medicare data, hospital discharge data)
__ Medical records (custodian may also require form, e.g., HD-974 if UNC-Health Care System)
__ Electronic information from clinical database (custodian may also require form)
__ Patient specimens (tissues, blood, serum, surgical discards, etc.)
__ Other (specify):

C.2. For each of the boxes checked in 1, how were the original data, records, or human biological specimens collected? Describe the process of data collection including consent, if applicable.

C.3. For each of the boxes checked in 1, where do these data, records or human biological specimens currently reside?

C.4. For each of the boxes checked in 1, do you have permission from the custodians of the data, records or human biological specimens (e.g., pathology dept, tissue bank, original researcher)? Include data use agreements, if required by the custodian of data that are not publicly available.

C.5. If the research involves human biological specimens, has the purpose for which they were collected been met before removal of any excess? For example, has the pathologist in charge or the clinical laboratory director certified that the original clinical purpose has been satisfied? Explain if necessary.

__ yes __ no __ not applicable (explain)

C.6. Do *all* of these data, records or specimens exist at the time of this application? If not, explain how prospective data collection will occur.

__ yes __ no If no, explain