DRIIVE (Data and Research on Interventions to Improve the V ehicular Environment)
MSKCC NON THERAPEUTIC PROTOCO .

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Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

Participating Institutions – If multicenter study coordinated by MSKCC:	**PI's Name**	**Site's Role**
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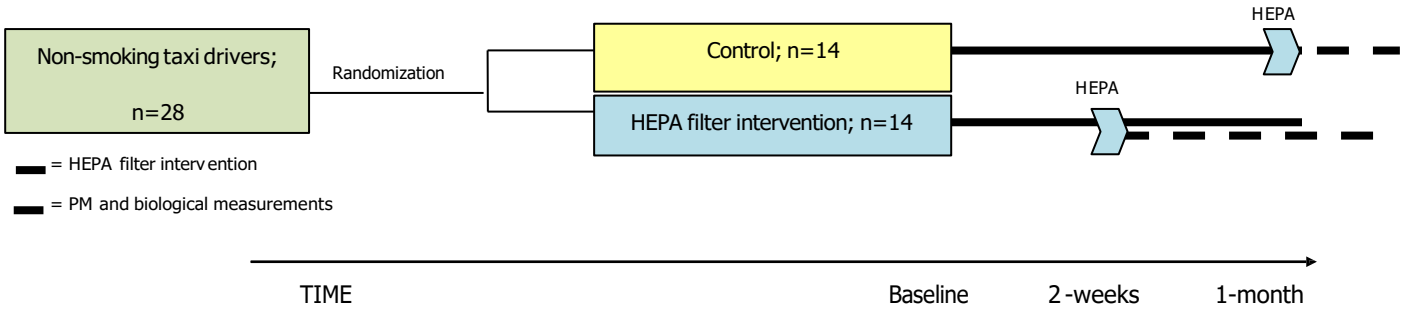
1.0 PROTOCOL SUMMARY AND/OR SCHEMA

New York City (NYC) is home to 100,000 taxi drivers, of whom 92% are immigrants. The overwhelming majority are men. This large, male taxi driver population faces poor health outcomes that can be mitigated through scalable, targeted interventions. NYC taxi drivers work long hours (10-12 h/d shifts, ~6d/wk), most often in heavy traffic. Exposure to high levels of particulate matter (PM) and air pollution are closely linked to lung cancer and cardiovascular disease (CVD).

DRIIVE (Data and Research on Interventions to Improve the Vehicular Environment) is a community-engaged translational pilot project that will utilize a two parallel arm design to obtain preliminary data on associations between Particulate Matter (PM)/air pollution and physiologic measurements and biomarkers in taxi drivers, and to determine the impact of a HEPA filter (to remove PM and volatile organic compounds) intervention on such physiologic measurements and biomarkers. DRIIVE is funded by the New York State Department of Health Empire Clinical Research Investigator Program (ECRIP), which trains physicians in clinical research in New York. Drivers will be randomized to one of two groups: Intervention or Wait-list Control. In total, two groups of 14 participants in each group will be recruited: 1) Wait List Control group, who will receive a HEPA filter at the end of the 1 month participation period and 2) Intervention group, who will receive a HEPA filter two weeks into their participation period. The project will be completed within a 2 year timeframe.



**The HEPA filter intervention depicted above by "• • •" will be introduced after 2 weeks in the Intervention group, and at the end of the study for the Wait-list control group. PM and biological measurements will be conducted throughout the study in all 2 groups and is depicted above by "▬▬"*

2.0 OBJECTIVES AND SCIENTIFIC AIMS

1a) To collect preliminary data on in-vehicle excess PM exposure, including size distribution, mass concentration, and chemical composition among taxi drivers (measured during work shifts and at home).

1b) To conduct a preliminary assessment of the correlation between PM exposure and physiologic and biochemical markers associated with increased risk of lung cancer and/or CVD. Physiologic and biochemical markers will include pro/anti-inflammatory cytokines, epigenetic changes (associated with cancer and/or inflammation), and high-sensitivity C-reactive protein, blood pressure, and reduced heart rate variability (associated with CVD).

2) To use a randomized wait-list controlled design to conduct a pilot study of whether a targeted intervention, installation of a portable car high-efficiency particulate air (HEPA) filter (to remove PM), results in a reduction of in-vehicle PM exposure and associated physiologic and biochemical markers among taxi drivers.

3) To collect data on the feasibility of conducting a larger RO-1 type (NIH granting mechanism) randomized wait-list controlled pilot study among New York City taxi drivers.

3.0 BACKGROUND AND RATIONALE

There are approximately 240,000 taxi/limousine drivers in the U.S. (1). By 2020, this number is expected to increase by 20% (1). New York City (NYC) is home to 100,000 taxi drivers, among whom 92% are immigrants (2, 155). Forty percent of those are South Asian (originating from India, Pakistan, Bangladesh, Nepal, and Sri Lanka) (2), followed by large numbers of drivers from the Dominican Republic, Mexico, former USSR, Haiti, Nigeria, Ethiopia, Columbia, Ecuador, and Jamaica (2). The overwhelming majority of taxi drivers are minority men. They are at great risk for increased cancer risk and poor cardiovascular health due to a number of occupation-related factors, including stress, diet, sedentary lifestyle, and poor health care access (18-21).

They work long hours (10-12 h/d shifts, ~6d/wk (2)), most often in heavy traffic, and are exposed to environmental contaminants. This exposure, including to ambient particulate matter (PM) (even low-level exposure to fine airborne PM [PM smaller than 2.5 micrometers ($PM_{2.5}$)]), increases health risk (13, 22, 23). Even short-term exposure (i.e., while driving) to peak particle concentrations appears to be linked with adverse health effects (24-27). A vehicle cabin is a relatively confined space where drivers are exposed to high concentrations of PM. In comparison to outdoor/indoor microenvironments, in-vehicle PM levels are often very high, originate from external sources, including road traffic (28), and can be 3-5 times that of outdoor PM values (29). In a study examining PM levels in private cars, values in moving vehicles exceeded those in parked cars by 9.2 times for PM_{10} (PM smaller than 10 micrometers) and 3.8 times for $PM_{2.5}$ (28). These conditions can potentially be improved at very low cost, with a HEPA filter, with a resultant diminution of lung cancer and cardiovascular disease (CVD) risk in this vulnerable group of minority men.

The association between mortality with $PM_{2.5}$, sulfate particles, and sulfur dioxide (SO_2) was illustrated in a study that demonstrated their role in increasing all-cause, cardiopulmonary, and lung cancer mortality (4, 49). Several additional studies have linked PM exposure to lung cancer (14, 15, 50). A 26-year prospective study found that each 10 $\mu g/m^3$ increase in $PM_{2.5}$ exposure concentration was associated with a 15-27% increase in lung cancer mortality among never-smokers (14). Another study found that each 10 $\mu g/m^3$ increase in $PM_{2.5}$ was associated with an adjusted increased risk of all-cause mortality of 14% (95% CI: 7, 22%), and with a 37% (95%CI: 7, 75%) increase in lung cancer mortality (15). Many studies (although none in the U.S. to date) have demonstrated a high prevalence of lung cancer among taxi drivers, suggesting a possible association with PM (16, 17). In a large population-based study of Danish male drivers, the odds ratio (OR) for lung cancer among taxi drivers was 1.6 (95% CI 1.2 – 2.2) after adjusting for socioeconomic status (16). As the duration of driver employment increased, the lung cancer risk also increased significantly: the highest risk was found among long term taxi drivers with 10 years of lag time between lung cancer diagnosis and first employment (OR 3.0; 95% CI 1.2 – 6.8) (16). A prospective study of drivers in Geneva found that professional drivers, including taxi drivers, had significant excess risk compared to the general population for all causes of death (standardized mortality ratio (SMR) 115, 90% CI 1.07-1.23) and for all cancers (SMR 125, 90% CI 1.12-1.40) (51). Cause-specific analysis showed significant excesses for lung cancer (SMR 150, 90% CI 1.23-1.81) (51). In DRIIVE, we will collect data on biomarkers associated with lung cancer, including cytokine levels, changes in white blood cell profiles, and changes in the epigenome to further elucidate the possible mechanisms underlying increased lung cancer risk (52-55).

The health effects of PM are related to both particle size and chemical composition (56, 57). Fine particles, $PM_{2.5}$, produced mostly by vehicle emissions, can penetrate more deeply into the airways than PM_{10}. Lung airways and alveoli retain mostly $PM_{2.5}$ rather than PM_{10}; 96% of the effectively retained particles are $PM_{2.5}$, of which 5% are ultrafine particles (<0.1 μm) (58, 59). Fine and ultrafine particles are also more likely than coarse particles to induce inflammation and oxidative damage. Elemental and organic carbon together make up a significant fraction of ambient particles. In particular, elemental carbon, a pseudo-marker of traffic pollution such as that caused by diesel engines, has been found to be significantly correlated with cardiopulmonary morbidity and mortality, and thus important to assess (144, 145).

There are data showing that increased levels of inflammatory cytokines (e.g. TNF-α, interleukin-6, interleukin-8) and bronchoalveolar lavage fluid are correlated with lung cancer. The interleukin-1 family of cytokines, including IL1-beta, is a key pro-inflammatory cytokine which regulates the expression of several genes involved in the inflammatory process. There is ample evidence, moreover, that PM stimulates alveolar macrophages and human bronchial epithelial cells to release proinflammatory cytokines, including IL-6 and Il-1beta.

There is a growing understanding of the role of epigenetics in complex human diseases, especially respiratory diseases including lung cancer and asthma. Exposure to environmental carcinogens, including particulate air pollution, traffic particles, cigarette

smoke, and cadmium, has been reported to alter normal DNA methylation patterns. Importantly, Palmisano et al. found that alterations to *p16* and *MGMT* methylation can be identified in 100% of patients with squamous cell lung carcinoma up to 3 years before clinical diagnosis. Suitable biosamples for lung disease biomarker studies include DNA obtained from buccal cells, which will be used here.

The Harvard Six Cities Study was the first large, prospective cohort study that demonstrated that chronic exposure to air pollutants is independently related to cardiovascular mortality (3). It showed that elevations of $PM_{2.5}$ and sulfates demonstrated the strongest associations with CVD. Fine particulate air pollution is a risk factor for CVD via mechanisms that likely include altered cardiovascular autonomic function (associations have been seen between elevations in $PM_{2.5}$ and increases in systolic blood pressure (30) and reduced heart rate variability (31-38), inflammation, and accelerated atherosclerosis (5, 39-41). Short-term exposure to PM has been associated with elevated proinflammatory markers, including interleukin 1-beta (IL-1β), interleukin 6 (IL-6), tumor-necrosis-factor alpha (TNF-α), and high sensitivity C-reactive protein (hs-CRP), which may potentially mediate harmful subclinical cardiovascular effects (30, 42-45). There is epidemiologic evidence that CRP is a strong predictor of future CVD risk (46) and that elevated hs-CRP is highly associated with poor cardiovascular prognosis (47, 48). DRIIVE will contribute to the understanding of the associations between these mechanisms and increased CVD risk.

Products of diesel combustion, such as polycyclic aromatic hydrocarbons (PAHs), are also relevant to drivers (164, 165).Many individual PAHs are genotoxic carcinogens (165). One of the parent PAHs, pyrene, is metabolized to 1-hydroxypyrene and excreted in the urine, has been widely used as a biomarker for PAH exposure, and has been shown to be elevated in studies including taxi drivers (166-168). Increased incidences of cancer have been associated with occupational PAH exposure, including lung cancer (169). PAHs may also contribute to the atherosclerotic process and inflammation, increasing cardiovascular disease risk (170).

Various reviews have shown that 1 hydroxy pyrene (1-OHP) is a biomarker of exposure to poly-cyclic aromatic hydrocarbons from traffic related air pollution (161, 162). 1 hydroxy pyrene is a major metabolite of pyrene and it is used to estimate overall exposure to PAH. Work specifically on taxi drivers has shown that urinary 1 OHP levels were increased in drivers compared with non-occupationally exposed subjects. Elevated 1-OHP levels were also shown to be associated with elevated levels of pro-inflammatory cytokines and were negatively associated with levels of antioxidants in exposed taxi drivers. (163). In DRIIVE we look to show the impact of use of a HEPA filter on 1 OHP levels in drivers by sampling levels pre-and post implementation of filter.

PRELIMINARY STUDIES

Immigrant Health and Cancer Disparities Service (IHCD)

One of IHCD's long-standing community based participatory research programs (CBPR) is the South Asian Health Initiative (SAHI), founded in 2004. Dr. Gany has led SAHI in several projects on cardiovascular disease (CVD) and cancer risk reduction (104): South Asians Engaging in Hypertension Awareness and Treatment, an NIH-funded RCT of the impact of linguistically and culturally appropriate educational materials on hypertension (105); Smokeless Tobacco Oral Pathology Prevention and Awareness Network (STOP PAAN) (103); and the Health Camp Project (106). In Gany's —Drive By Readings‖ study, over 100 taxi drivers were followed through their tuberculosis screening and treatment, with the results impacting TB policy in NYC (107). Additional taxi driver initiatives include: STEP I (Supporting Taxi Drivers to Exercise through Pedometers), funded by the NYS Department of Health Empire Clinical Research Investigator Program (ECRIP), to investigate the health knowledge, attitudes, and beliefs of South Asian taxi drivers. Drivers described high work-related stress, health risk, and poor health care access (21). STEP II, also funded by ECRIP, was a randomized controlled trial to evaluate the efficacy of a culturally responsive pedometer/motivational interviewing exercise intervention among taxi drivers (108). 74 male South Asian taxi drivers participated. 15% of the drivers who completed the study improved ≥ 2000 steps from their baseline (108). Step On It! is a cancer and CVD risk reduction case management project for NYC taxi drivers at John F. Kennedy airport, and a parallel effort in San Francisco in partnership with the Palo Alto Medical Foundation Research Institute (109). Airport holding lots are places where the taxi driver community can congregate to eat, talk, play games, walk/exercise, and pray. We have been successful in engaging the taxi driver community at airport holding lots in our risk reduction interventions. 480 taxi driver participants at JFK were enrolled in Step On It!, 50% of the taxi drivers did not have a primary care provider and 51% did not have health insurance prior to the intervention. 51% more are now engaged in ongoing care. 33% of the drivers were subsequently diagnosed with diabetes or hypertension and prescribed medication (109). CICHD facilitated the formation of the Taxi CAB (Community Advisory/Action Board) in 2010 to help further develop, implement, provide feedback to and context for results, and disseminate the taxi driver research program. The CAB has identified exposure to air pollution, and its impact on health, as an important issue for drivers. In Gany protocol X12-025, a pilot survey study to assess NYC taxi drivers' knowledge, beliefs and awareness of health risks associated with air pollution, 100 NYC drivers, including both yellow taxi (N=77) and livery (N=23) cab drivers, were surveyed. Sixty-seven percent of respondents had worked as drivers for at least three years, with 17% having worked more than 15 years. Drivers were evenly dispersed in age, with 17% between 18 and 30 years old, 24% between 31 and 40 years old, 26% between 41 and 50 years old and 32% over 50. Eighty-eight percent of all drivers were foreign-born. Over half of all surveyed drivers (56%) believed that they are exposed to more air pollution than those who are not taxi drivers, while 25% did not believe as such, and 19% were unsure. Most drivers thought that air pollution in general causes health problems (81%), while 19% did not agree or were unsure. A belief that air pollution causes health problems was significantly associated ($p<0.05$) with drivers who had at least 10 years of taxi driving

experience. Thirty-four percent of respondents stated they were —not worried‖ about being exposed to air pollution while driving, while another 40% said they were —a little or somewhat worried‖. Nineteen percent reported that they believed they had a health problem attributable to air pollution exposure. In Gany protocol X12-021, a pilot investigation of particulate matter concentrations in NYC taxi cabs, we measured levels of in-vehicle Particulate Matter (PM) concentration in a convenience sample of 7 NYC Taxi Cabs. In-vehicle PM levels were measured through *Personal DataRams*(pDR) and *Microaethalometers*, which were placed on the passenger seat or console area of the taxicab for the full 6-hour shift. Near-roadway outdoor air monitoring of PM and BC concentrations was also conducted using aerosol monitors. Compared with previously published results of personal exposure studies conducted in NYC (156, 157), taxicab PM and BC concentrations were elevated. Average concentrations of PM per 15-minute interval for all seven shifts indicated large intra- and inter-car variability. Per shift average PM concentrations ranged from 4 $\mu g/m^3$ to 49 $\mu g/m^3$ and 1-minute peak levels measured up to 452 $\mu g/m^3$. Black carbon levels were also elevated, and reached over 10 $\mu g/m^3$. Peak in-vehicle PM levels were short and sporadic, and may have been influenced by external events, such as passenger smoking, as recalled by drivers after their shift. Roadside air monitoring was conducted at three large taxi passenger pick-up stands in midtown Manhattan, all located at traffic hubs and mass transport terminals. Monitoring during morning and evening rush hours revealed ambient PM levels to be near or greater than the EPA 24 hour NAAQS of 35 $\mu g/m^3$ for $PM_{2.5}$. Average levels at each taxi stand were 44 $\mu g/m^3$ (SD ± 32), 58 $\mu g/m^3$ (SD ± 10), and 76 $\mu g/m^3$, (SD ± 43) and peak levels were as high as 434 $\mu g/m^3$, mirroring peak in-vehicle values. Levels of black carbon were also found to be high; peak levels at one taxi stand were as high as 12 $\mu g/m^3$. Average taxi stand BC and PM levels were significantly higher than levels recorded at the closest New York State Department of Environmental Conservation‘s air monitoring site (Division Street) (158). As a sedentary occupational group with a disproportionate prevalence of disease, taxi drivers are likely at greater risk from air pollutant exposure than those working away from roadways. Community-engaged interventions are needed to limit their exposure to high levels of PM and BC. The proposed DRIIVE project will move the preliminary data a step forward and the CAB will continue to play a central role in planning, implementation, and dissemination.

NYU Department of Environmental Medicine's NIEHS P30 Center of Excellence

The NYU/NIEHS Center develops programs around community environmental risks, with a focus on NYC taxi drivers. Dr. Gany is the MSKCC Co-PI with Dr. Zelikoff of the NIEHS Center Community Core. Community initiatives are developed through town hall meetings, workshops/educational forums, health fairs, and/or provider education developed with the community, and guided by community-based focus groups and interviews with community leaders and other stakeholders. Dr. Zelikoff is also an active toxicology researcher in reproductive- and immune-toxicology associated with inhaled environmental/occupational pollutants (110-124). She has worked with Dr. Gany on maternal exposure studies with gutka, a smokeless tobacco product (115, 125).

Drs. Gordon and Zelikoff have collaborated on a number of studies on the adverse effects

of inhaled particles. In the COARSE PM study, size-segregated ambient PM was collected during 2 seasons at several urban and rural sites in the NYC metropolitan area and in central California. The toxicity of extracted PM was tested both *in vitro* and *in vivo* and the findings were correlated with PM components. In general, coarse $PM_{10-2.5}$ and heavy metals produced the greatest toxicity. Importantly, PM composition was a more important indicator of toxicity than PM mass concentration alone, a finding with potentially significant regulatory policy impact in the U.S. (manuscript in preparation). In a collaborative study, by CIHCD and the NYU/NIEHS Center, of ambient PM, real time DataRam monitors found that at taxi stands PM levels were near or greater than the EPA 24 hour National Ambient Air Quality Standards (NAAQS) of 35 $\mu g/m^3$ for $PM_{2.5}$. Peak levels were as high as 140 $\mu g/m^3$ PM (133). Dr. Gordon is currently completing the GWB (George Washington Bridge) Study, which investigates the contribution of traffic-related air pollutants to CVD. Healthy volunteers walked for two hours along traffic at three NYC sites which differ significantly in traffic-related pollution. Ambient PM exposure assessment and several similar health endpoints (e.g., inflammatory cytokines in the blood, and ECG, heart rate, pulmonary function) were evaluated. Results showed significant changes in blood pressure, and serum interleukin (IL)-1 levels associated with exercise along the diesel-laden GWB traffic (manuscript in preparation). In the proposed application, we will use similar techniques to monitor adverse physiologic/biochemical changes in drivers while monitoring in-vehicle PM exposures.

4.1 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.2 Design

This study is proposed to be carried out across a two year period including an intervention period and dissemination of results to the Taxi Network community. Twenty eight non-smoking male NYC cab drivers will be recruited and randomized to one of two study arms, an Intervention Group (to receive the HEPA filter 2 weeks into their 4 week period of participation) and a Wait-list Control Group (to receive the HEPA filter at the end of their 4 weeks of participation). For the Intervention and Wait-list Control Group drivers, during the first 2 weeks, measurements (e.g. biological markers and air monitoring) will be taken under usual conditions. At the end of the initial two weeks, portable HEPA air purifiers (136) will be placed in the Intervention Group drivers‘ cars and the air monitoring and biological parameters will be repeated for another 2-week period, to determine changes in PM levels and physiological measurements as a result of this targeted intervention. The Wait-list Control Group drivers will not receive a HEPA air purifier at this time, but will also have the air monitoring and biological parameters repeated for another 2 weeks. At the end of the 1 month period of measurements for both groups of drivers, the Wait-list drivers will then receive a HEPA air purifier, so that they may also potentially benefit from the intervention being tested in this study, but no further measurements will be taken. Drivers will serve as their own controls before/after work and before and after the intervention.

Our taxi network CAB (Community Advisory/Action Board) will be engaged in the implementation and dissemination of the proposed study. This Taxi CAB represents the full range of the taxi driver experience, including varied shifts, income, education, age, ownership/lease arrangements, and countries of origin. The Taxi CAB will be instrumental in study recruitment and dissemination of results. The CAB will meet quarterly, with additional meetings as needed. This study is conducted in collaboration with Drs. Gordon and Zelikoff's research teams at New York University Department of Environmental Medicine, and Dr. Pengfei Zhang, working from the City College of New York (CCNY). Biological specimens collected will be immediately transported to MSK BAIC Core facilities for temporary storage and will be shipped later to either NYU or CCNY (outlined in the assessment and evaluation-section 7).

4.3 Intervention

Over the course of the study, we will monitor several biological and physiological markers associated with lung cancer and CVD risk, along with ongoing air monitoring of work-sites and residences of all study participants. HEPA filters were selected as the intervention because of their effectiveness in removing PM and volatile organic compounds (VOCs), ease of use, relatively low-cost, small size, light weight, and lack of interference with drivers' normal practices (136). In a previous study by Pui et al., placing the air recirculation mode on (and with a cabin air filter in place already installed by the car manufacturer, not all cars have cabin air filters), was successful at substantially removing ultrafine particles, although was still relatively inefficient (45.5% particle removal efficiency) compared to a HEPA filter (137).

The study will require 4 weeks of participation. Drivers will be recruited and randomized to either the control condition or the HEPA filter intervention condition. The in-vehicle (for all drivers PM exposure levels and physiologic and biochemical markers will be measured over the course of 1 month. For the first two weeks of the 1-month period, measurements will be taken under usual conditions (*without HEPA filters*) for all participants.

Particulate matter concentrations will be measured/monitored through *Personal DataRams* (pDR) (*personal*DataRam™ model *p*DR-1200). The DataRam measures particulate matter through optical impedance, and produces per-minute averages. Therefore, the time that the DataRam is ―on‖ will be directly reflected in the data that is produced. The pDR is 24 ounces, 6.3 inches in height, 8.1 inches in width, and 2.4 inches in depth, and is thus very portable. One pDR will be provided to each enrolled participant. All participants will monitor PM at their homes in the room in which they spend most of their off work hours; the DataRam will then be moved to the bedroom at night (or during sleeping hours). For drivers, the pDR will record PM levels throughout the work shift while the vehicle is in motion, momentarily stopped, or parked.
Black carbon exposures will be measured/monitored through BGI 400 Personal Sampler Pump. The BGI pump is a constant air flow sampler that has broad applications in industry hygiene and environmental testing. It is compact, 6.75 inches in height, 3.1 inches in width and 2.3 inches in depth, which is ideal for mobile projects. It is attached to an external

Nickel Metal Hydride battery, which is 5.75 inches in height, 3.60 inches in width and 1.10 inches in depth. BGI pump connects with a Tygon or ID tubing, ¼ inch in diameter, which is attached to a plastic cassette on the other end, where the pre baked quartz filter is placed. The BGI pump and filter will be placed in the vehicle of the participant at the beginning of their work shift and picked up at the end of their shift. All participants will monitor black carbon exposures at minimum for one work shifts on week 1 and week 4 of the study, or a maximum of three work shifts every week.

PAH exposure will be measured through portable passive Polyurethane Foam Filter (PUF) sampler sized 10 cm by 2.2 cm diameter (171). The PUF filter will be place in the vehicle of the drivers at the beginning of their work shift and picked up at the end of their shift. Drivers will monitor PAH through PUF sampler one day every week.

The intervention of HEPA air filters will be introduced after 2 weeks of participation in the Driver Intervention group (but not in those of the control drivers' cars. The HEPA air purifier is 7.5"x 8.5", 6 lb, and covers up to 150 sq feet. An accompanying auto adapter kit contains a cigarette lighter adapter, 7 foot cord, and a seatbelt clip to secure the filter (159). Air monitoring and measurements of PM exposure levels and physiologic and biochemical markers will be continued for another 2-week period to assess the extent of risk reduction achieved by this targeted intervention. Two weeks should be more than sufficient to measure risk reduction by the HEPA filter intervention, as the study by Pui et al. showed that with the air recirculation mode on and a cabin filter in place, in-cabin aerosol concentration was reduced to below typical office air concentrations in approximately 3 minutes (137). HEPA filters will be given to drivers in the Wait-list Control Group at the end of the 4 weeks of participation.

Physiologic and biochemical markers will be measured by trained study staff twice per week and twice per day on 1 work day and 1 non-working day per week, for a total of four measurements per week (see section 7 for details). Physiologic and biochemical markers to be measured include: high-sensitivity C-reactive protein, blood pressure, and reduced heart rate variability – data to be downloaded via a smart phone (associated with CVD), and pro/anti-inflammatory cytokines (i.e., interleukin (IL)-1b, -6, -8, -10, tumor necrosis factor (TNF)-α, and interferon (IFN)-γ), and epigenetic changes associated with cancer and/or inflammation (see Figure 1 below and section 7 for details).

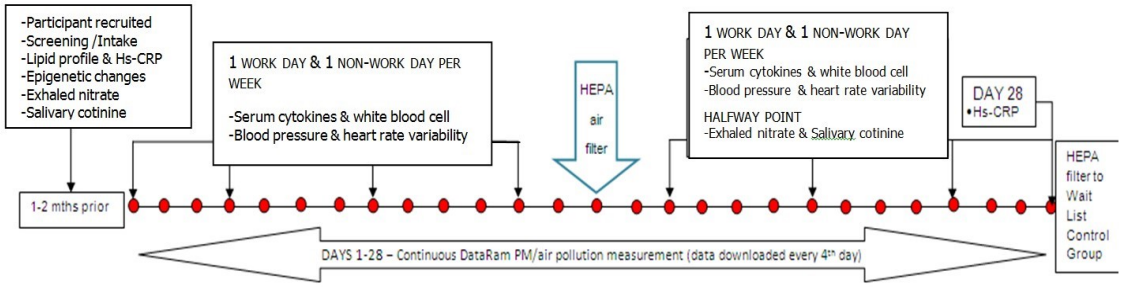


Figure 1: DRIIVE Phase 1 - participant recruitment, screening, testing, intervention timeline in years 1, 2, and 3.

Polycyclic aromatic hydrocarbon (PAH) exposures will also be assessed through measurements of the urinary metabolite 1 hydroxy pyrene. Drivers will be asked to give a urinary sample in the morning after several days of work. They will be provided with a 100 cc sterilized polypropylene container. (Urinalysis Cup Kit). This will be collected by the study team, protected from sunlight and transported to *BAIC* for storage in a -20 degree freezer. Samples will ultimately be analyzed using liquid chromatography-tandem mass spectrometry (LC-MS-MS) by collaborating facility City College of New York. PAH exposures will also be measured through PUF sampler sized 10 cm by 2.2 cm diameter (171). Drivers will monitor PAH through PUF sampler one work day every week. The PUF filter will be place in the vehicle of the drivers at the beginning of their work shift and picked up at the end of their shift. The study team will transport the sampler to the collaborating facility City College of New York for analysis.

The study team will be trained on screening and recruitment procedures, downloading DataRam results on PM measurements, on fingerstick blood, salivary, and buccal swab sampling procedures, and on storage/handling of samples (e.g. shipping dangerous goods training). Samples collected will be transported immediately by study staff to NYU for storage and analysis. If any critical abnormal/irregular health measurements are identified in the process of data collection, study staff will be trained to refer participant to low-cost health services.

Prior to study implementation, the study team will conduct a series of validation testing along with necessary calibration checks for all study equipment (including pDRs, air pumps and HEPA filters). Taxi Network CAB members will assist in trial runs to ensure all equipment and logistical concerns are optimized before equipment is provided to study participants.

5.0 CRITERIA FOR SUBJECT ELIGIBILITY

Describe the characteristics of the subject population.

5.1 Subject Inclusion Criteria

Drivers:

- Full-time New York City cab drivers;
- Non Smokers (assessed by modified BRFSS smoking question within screening tool)
- Male;
- Between the ages of 21 and 90;
- No immediate plans (within the next 3 months) to leave the City for vacation or for trips back to their home country,;
- Driver for at least 3 years;*
- Driving schedule does not include overnight shifts, nor does driver have an additional job overnight;
- Own a smart phone (in order to collect heart rate variability data)
- Should self-report —Very wellll or —Wellll level of English fluency (according to the standard US census question).
- Have working cigarette lighter receptacle/socket inside taxi cab

**The requirement to have worked at least 3 years in the U.S. should minimize any acute health effects/disease due to high levels of contaminants associated with country of origin.*

5.2 Subject Exclusion Criteria

Drivers:

- Smoker or uses smokeless tobacco products;
- Resides in a smoking household (where 1 or more household members smoke);
- Has a sleep disorder (including insomnia, delayed sleep phase syndrome (DSPS), narcolepsy, night terror, sleep apnea, sleep walking);
- Has a current or previous diagnosis of any type of cancer;
- Has a diagnosis of an inflammatory, autoimmune, or chronic infectious disease (including rheumatoid arthritis, lupus, chronic liver disease, multiple sclerosis, fibromyalgia, inflammatory bowel disease, psoriasis, HIV);
- Has a serious cardiopulmonary medical condition (including cardiovascular disease, congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), restrictive lung disease, interstitial lung disease, asthma, acute or chronic bronchitis, cystic fibrosis, pneumonia, tuberculosis, pneumoconiosis, pulmonary hypertension, pulmonary embolism, pleural effusion, pneumothorax, obesity hypoventilation syndrome, neuromuscular lung disease).
- Self reports —wellll level of English fluency and indicates a preference for an interpreter.

6.0 RECRUITMENT PLAN

Study staff will work in collaboration with the previously established IHCD Taxi Network Community Advisory Board and community partners such as South Asian Council for Social Services (SACSS) to recruit participants for this study. SACSS is our subcontracted community partner in the IHCD Taxi Network initiative and the Co-Director or the IHCD South Asian Health Initiative. Under the direction of Ms. Sudha Acharya, SACSS provides various community services including health care access counseling and insurance enrollment. Members of SACCS were previously on-boarded as MSKCC non-employee affiliates and will be a part of the study team to assist with identifying potential study candidates through their previous relationships with the taxi driver community. Study staff will enroll a convenience sample of drivers by approaching potential participants at driver-frequented sites across NYC- including taxi garages, taxi bases, parking stands, taxi relief and shift change stands, gas stations, restaurants, and religious and community organizations. Study staff will approach drivers who are present at these locations including drivers who are waiting in their parked and stationary vehicles. Staff will also utilize partnerships with CBOs and local and ethnic newspapers, radio stations and media outlets such as the Union Fouta and Murid Islamic Community of America radio station and newspaper to accrue study participants. Flyers (Appendices F) for Drivers will be distributed in the community setting for recruitment as well. The flyers will be posted in various community locations drivers frequent including garages, taxi bases, parking stands, gas stations, restaurants, religious and community organizations to garner interest in the study. A screening tool (see Appendix A) will be used to identify eligible participants (drivers). All those who meet inclusion/exclusion criteria will be informed of the risks and benefits of study participation and, if willing to participate, asked to read and sign a written informed consent document. Consenting professionals will use general teach-back method in which we will ask drivers if they understand what participation entails to ensure they are informed of the study procedures.

Following informed consent, participants will be assigned a participant number and administered the Intake Assessment (Appendix B). Participant drivers will also be randomized to either the Intervention or Wait-list Control Groups, as described above. A convenient time and place will then be arranged to complete the informed consent and Intake. Driver pairs will participate in the study in approximately the same time frame to avoid seasonal differences in PM levels.

During consent procedures, participants will be informed that they will receive a $200 incentive over the course of the study for their participation to account for the time commitment required of participants. This will be distributed as 4 weekly incentives totaling $50.00 each, which can be viewed as compensating study participants $7 each day for carrying around monitors throughout their daily lives and allowing us to conduct biologic assessments 2 days a week. All participants will also be informed that they will receive a HEPA air purifier. Given the intensity of the proposed study measurements and the

associated time required of participants, for which drivers could result in lost earnings, the $200 incentive is commensurate with the degree of commitment demanded.

Consenting professionals will emphasize the need to meet with participants 2 days a week to conduct study testing, and will discuss and compile a list of 2-3 future meeting locations for data collection. Convenient locations may include enclosed taxi garages, taxi relief stands, semi-private spaces within public venues, MSKCC offices or our community partner locations. Staff will not conduct any assessments at a participant's home.

During the initial conversation between the investigator/research staff and the potential study participant, the potential participant may be asked to provide certain health information that is necessary to the recruitment and enrollment process. They will use the information provided by to confirm that the potential participant is eligible and to contact the participant regarding study enrollment. If the person turns out to be ineligible for the research study, the research staff will destroy all information collected on the patient during the initial conversation, except for any information that must be maintained for screening log purposes.

In most cases, the initial contact with the prospective subject will be conducted either by the investigator or the research staff. The recruitment process outlined presents no more than minimal risk to the privacy of the patients who are screened and minimal PHI will be maintained as part of a screening log. For these reasons, we seek a (partial) limited waiver of authorization for the purposes of (1) reviewing medical records to identify potential research subjects and obtain information relevant to the enrollment process; (2) conversing with patients regarding possible enrollment; (3) handling of PHI contained within those records and provided by the potential subjects; and (4) maintaining information in a screening log of patients approached (if applicable).

7.1 ASSESSMENT/EVALUATION PLAN

All potentially eligible participants will be required to complete a study screening tool to confirm eligibility. Participants that undergo informed consent procedures will be required to complete an intake assessment to gather details on personal demographics and health information that may relate to study outcomes. Enrolled drivers will be provided a log to compile a detail account of vehicle air-flow conditions while driving during study participation.

Screening tool (Appendix A), a brief questionnaire administered to potential to assess if study eligibility requirements are met. Includes questions on age, residence, country of origin, previous travel and travel intentions, modified BRFSS tobacco use classification questions (160); English proficiency, smoking status, cab driving experience, current occupation(s), and status of pre-existing conditions relevant to study (e.g. sleep disorders, autoimmune conditions). (5 min to complete)

Intake assessment (Appendix B) administered to all study participants includes 3 sections of questions: (1) demographic and health access information, (2) medical history and (3) physical activity and nutrition. (10-15 min to complete)

Log-book (Appendix C), given to drivers to record environmental manipulations within the area they are driving or their vehicle. This includes air exchange levels within the cab (documenting whether the DataRam is used, HEPA filter and air conditioning is on, vents and windows are open, the vehicle make or model of taxi cab or the neighborhoods driven in during shift). This also includes documenting neighborhoods travelled thru, whether they were in high traffic jams, or travelled thru tunnels. In our preliminary work (X12-021), we have succeeded in encouraging drivers to complete a similar log-book. When we meet with drivers to conduct biological measurements, or contact them for any other reason, we will remind them to complete their log-books using the text reminder system described below.

During biological assessments (2 days per week), the make and model of the vehicle used by driver participants will be logged by study staff to account for variances within the current air filtration systems of the cab, because taxi drivers may rent different vehicles each day.

Environmental Measurements, Physiologic and biochemical markers
For all participants, measurements for environmental, physiologic and biochemical markers will taken twice a week, and twice per day for a total of four data collection time points per week. This will include one work day per week (on the last work day of their work week) and on 1 day per week off from work. On work days measurements will be taken both immediately before (to establish pre-work biological parameters) and immediately after their work shift, and on non-work days measurement will be taken at approximately the same times during their day(s) off. In addition, blood pressure will be measured, data on heart rate variability will be downloaded, and a blood sample will be taken from each participant via finger stick to provide for measures of inflammatory markers and changes in white blood cell profiles. Salivary cotinine levels will also be measured twice (once at Intake and at the halfway point) for all participants to assess any exposure to smoking or smokeless tobacco products. High sensitivity C-reactive protein will be measured once during Intake and again at end of the 1 month period of participation. Buccal swabs will also be taken once during Intake for all participants, to measure epigenetic changes associated with inflammation, cancer and heart disease. Measurements will take place at locations most convenient for participants. Locations may include enclosed taxi garages, taxi relief stands, semi-private spaces within public venues, MSKCC offices or our community partner locations. Staff will not conduct any assessments at a participant‘s home. All measurements will be collected by trained study staff including both IHCD research and outreach personnel. Samples will be collected and transported immediately to MSKCC Core facilities, located on the 4th floor of the Breast and Imaging Center for storage. Samples will be shipped to NYU facilities for processing by Dr(s) Gordon and Zelikoff (see Lab Manual for shipping details). Trained study research and outreach personnel will be handling the specimens.
*Please see Appendix 4 RSA guide/lab manual for full details on all procedures.

1. **PM values** (measured daily):
   In-vehicle and residence PM will be measured using calibrated, personal DataRam monitors (Thermo Scientific) that measure real-time PM levels (measured range = 1 µg to 400 µg/m^3). For drivers, the DataRam will be placed inside the cab on the island between driver and front passenger seat during workshifts. All participants will monitor PM at their homes in the room in which they spend most of their off work hours; the DataRam will then be moved to the bedroom at night (all participants will receive daily text messages as reminders to do this). The DataRam will be zeroed prior to use and all data internally logged and displayed on an LCD monitor. DataRam PM measurement files (hourly averages) will be downloaded every week at the same time as blood/ salivary samples are taken. To maximize efficiency in the field, gravimetric calibration will be performed by comparison with a filter sampler and programming of a calibration constant. Teflon and quartz filters will be used to capture PM (a time-averaged sample) for subsequent gravimetric and trace element analyses, including sulfur and organic and elemental carbon analyses (micro-balance/XRF instrumentation available at NYU's NIEHS Center of Excellence Facility Core). A portion of the glass-fiber filter will be cut for organic analysis. This portion of the filter will be extracted via pressurized liquid extraction (ASE 100 system, Dionex) with hexane: dichloromethane (1:1, v/v) at 90°C and 1500 psi (140). The extracts will be concentrated using a Turbovap and cleaned before analysis. BFRs polybrominated diphenyl ethers (PBDEs) will be analyzed via gas chromatography-mass spectrometry with negative chemical ionization (GC-NCI-MS) (141). Parent PAHs will be analyzed with GC-MS in electron impact ion (EI) mode and selected ion monitoring (SIM), whereas nitro-PAHs and oxy-PAHs (quinones) will be analyzed via GC-NCI-MS and SIM (142). Another portion of the glass-fiber filter will be cut for metal analysis. This portion of the filter will be extracted via microwave digestion and trace metals will be analyzed via inductively coupled plasma-mass spectrometry (ICP-MS) according to the method of Kulkarni et al.(143).
   DataRam data downloads will be sent to study collaborators Drs. Gordon and Zelikoff at NYU for analysis.

2. **Black carbon exposure** (measured at minimum after 1 work shifts during week 1 and week 4, at maximum will be measured after 3 work shifts every week)
   In-vehicular black carbon concentrations will be measured using calibrated BGI Personal Sample Pumps (BGI Inc.) (provided by NYU) and pre baked quartz filters . Using the constant air flow, the quartz filter is able to trap black carbon levels in real time. For drivers, research staff will meet them at the beginning of their work shift with the BGI pump fully charged and the flow rate pre-set to 4L/min. The filter, sealed in aluminum foil, will be unwrapped immediately before the sampling, placed in the plastic cassette using a tweezer or forceps that is attached to the BGI pump via Tygon tubing. Staff will turn on the BGI pump and steadily place at the floor of the vehicle away from foot traffic with the Tygon tubing coming up to the island in between the driver and the passenger seat, where the cassette with the filter would rest in a secured position. Staff will record the start flow rate, start sampling time, and environmental condition in a log book.
   At the end of the shift, the staff will meet the driver to collect both USP and the filter. Staff will also record the end flow rate, end sampling time and changes in environmental conditions. The filter will be removed from the plastic cassette using a tweezer or forceps and immediately wrapped in aluminum foil and placed in ice packs within a cooler. Sampled filters will be transported in coolers with ice packs to BAIC

Core Lab Facility for storage in -80F freezers. This process will be repeated each time black carbon exposure is sampled during this study.

Following sampling, using standard flow rates (typically 2-4 liters per minute) and measurement time base (10 to 300 seconds), the filter will be removed from the sampling frame, wrapped in aluminum foil, and transported to the NYU NIEHS laboratory for analysis by NYU study collaborators Drs. Gordon and Zelikoff. There, a standard punch of the filter will be used for sample analysis. The filter sample is inserted into the analyzer, with a replicate sample as needed for quality control. EC and OC mass will be determined via calculation using the analyzer results and the sample portion (typically 1.5cm^2), i.e. the area of the standard punch. The entire NIOSH Method 5040, including how to make accommodations for changes in sample punch size and other quality control procedures, will be followed (http://www.cdc.gov/niosh/docs/2003-154/pdfs/5040.pdf).

3. **Blood pressure** (measured before and after work shift 1 work-day per week and at approximately same times on 1 non-work day per week): Blood pressure will be measured using a 9002 E-Sphyg 2 Digital LCD Desk Unit Sphygmomanometer (American Diagnostic Corporation; Hauppauge, NY). This will be performed by study staff. In the event that study staff are unable to coordinate a date and time to meet participants for BP measures, study participants will have the option to self monitor blood pressure using a portable MDS3001PLUS blood pressure unit (Medline, Mundelein, Illinois), which is given to the participant to keep at their home during the study. A log will be provided (see Lab Manual) and study staff will contact participants to obtain the BP recording after the scheduled BP collection time point.

4. **Heart Rate Variability** (measurements to be downloaded once a week)**:** Heart rate variability (HRV) describes the time intervals between heartbeats that vary as an individual breathes in and out (inhalation and exhalation), during a rest state. The heart speeds up when you inhale and slows down when you exhale. Reduced heart rate variability has been reported in several cardiological and non-cardiological diseases. Participants will be required on every day of study participation, to wear Ithlete strap when they wake up and before going to bed and sync the chest strap monitor to their smart phone. Participants will then follow breathing instructions provided by the smart phone app to measure HRV. The ithelete will download small changes in the heartbeat and the variance will be analyzed. HRV will be measured over time via an Ithlete ECG receiver, a small piece of hardware that picks up the signal from a heart rate monitor chest strap. The chest strap, ECG receiver, and Ithlete app will be supplied to each taxi driver being tested. Data are downloaded via a smart phone. (See HRV test procedure in appendix 4 for further details)

5. **Serum cytokines and white blood cell profiles** (measured before and after work shift 1 work-day per week on week 1 and week 4)**:** Serum cytokines (i.e., interleukin (IL)-1β, -6, -8, -10, tumor necrosis factor (TNF)-α, and interferon (IFN)-γ) will be measured using dried blood spot sampling and MesoScale Discovery (MSD) immunoassay system (www.mesoscale.com). As done previously in collaboration with the EPA, a drop of blood will be spotted onto a commercial sampling paper and allowed to dry. The sampling paper will be labeled with study ID, date, and the initials of the person conducting the collection. The paper, along with other study samples, will be transported immediately to the BAIC Core facilities, 4th floor storage at -80 Freezer, until shipped on ice to our EPA collaborator, , for analyses. Blood samples for testing

will be obtained by punching a disc from the center of the spot, followed by a simple liquid extraction of the sample. MSD assays employ a sandwich immunoassay format whereby captured antibodies are coated in a single spot on the wells of a MULTI-SPOT plate. Multiplex assays can measure 1-10 cytokines in a 96-well MULTI SPOT plate; each sample will be analyzed in duplicate. A second blood drop from the finger stick will be placed onto a glass slide, air-dried, stored in a locked box for later H&E staining and used for differential counts of white blood cell profiles as a systemic marker of inflammation. Slides will be shipped to Dr. Zelikoff at NYU for analysis. (See blood prick test procedures in appendix 4 for details).

6. **High sensitivity C-reactive protein *hs-CRP:*** Similar to the processes described above, the blood sample for hs-CRP analysis will be a drop of blood spotted onto a commercial sampling paper and allowed to dry. The sampling paper will be labeled with study ID, date, and the initials of the person conducting the collection. The paper, along with other study samples, will be transported immediately to the BAIC Core facilities, 4th floor storage at -80 Freezer, for analyses. (See blood prick test procedures in appendix 4 for details).

7. **Salivary cotinine** (measured at Intake and at the half-way point): Participants will be directed to use a saliva collection aid with a cryovial for collection of 1ml saliva sample. Saliva sample can only be collected at least one half hour after eating or drinking. Saliva samples will be frozen at -20°C. Cotinine will be measured with an EIA (Enzyme-immunoassay) (148). (See salivary cotinine test procedures in appendix 4 for details). Saliva samples will be transported to MSK BAIC Core facilities for temporary storage, until shipped to Drs. Zelikoff and Gordon at NYU for analysis.

8. **Epigenetic changes** (at Intake): We will use the minimally invasive buccal cell approach to identify traffic pollution-related epigenetic biomarkers in taxi drivers, because gene expression changes induced by inhaled pollutants in human subjects in buccal and/or nasal cells reflect those in bronchial epithelium (76, 149, 150). Buccal cells will be collected from study participants by gently scraping both left and right inner cheeks using special collection brushes (Gentra Puregene Buccal Cell Kit, Qiagen, Valencia CA). Methylation-specific PCR (MSP) (151) will be performed as routinely (134), using HotStar Taq DNA Polymerase kit (Qiagen), using MSP primers identified from the literature. Methylated (M) or unmethylated (U) status will be denoted per gene per participant. Buccal samples will be transported to MSK BAIC Core facilities for temporary storage and later shipped to collaborators at NYU for analysis. (See buccal swab test procedures in appendix 4 for details)

PAH (Polycyclic Aromatic Hydrocarbon) will be assessed via urine sample collection of Urinary 1 hydroxy pyrene and particulate matter collected via Polyurethane Foam Filter (PUF) sampler:

9. **PAH via Urinary 1 hydroxy pyrene:** Drivers will be asked to give a urinary sample twice during the study. The first urine sample will be collected on the morning at the end of the first or second work week of study. The second sample will be collected from drivers on the morning of the end of the fourth week of study participation. Drivers will be provided with a 100 cc sterilized

polypropylene container (Urinalysis Cup Kit). This will be collected by the study team, protected from sunlight and transported directly to *BAIC* for storage in a -20 degree freezer. Samples will ultimately be analyzed using liquid chromatography-tandem mass spectrometry (LC-MS-MS). This analysis will be carried out at the collaborating facility City College of New York.

10. **PAH via PUF sampler** (measured at one work day each week): Drivers' PAH exposure will be measured through portable passive PUF sampler sized 10 cm by 2.2 cm diameter (171). Drivers will monitor PAH through PUF sampler one day every week. The PUF filter will be place in the vehicle of the drivers at the beginning of their work shift and picked up at the end of their shift. Sampler will be tranported to collaborating facility City College of New York for extraction and analysis. The PUF filter will be extracted using dichloromethane according to the method of Jaward et al. (172). The extracts will be concentrated using a Turbovap and cleaned before analysis. Parent PAHs will be analyzed with GC-MS in electron impact ion (EI) mode and selected ion monitoring (SIM), and nitro-PAHs and oxy-PAHs (quinones) will be analyzed via GC-NCI-MS and SIM (173).

Genes in the epigenetics reference panel for this study include ten (10) genes that have been informative as epigenetic biomarkers in air pollution or lung cancer studies (69). These are: ***p16***- tumor suppressor, cell cycle regulator; ***hMLH1***- mismatch DNA repair gene; ***E-cadherin***- cell-cell adhesion molecule associated with epithelial to mesenchymal transition; ***RARβ2***- binds retinoic acid, regulates cell growth/differentiation genes; ***DAPK***-serine/threonine kinase involved in gamma-interferon induced apoptosis; ***RASSF1A***-interacts with DNA repair protein XPA, inhibits cell cycle arrest; ***RUNX3***, regulator of alveolar differentiation, frequently hypermethylated in lung adenocarcinomas; and ***FHIT***, the most common gene inactivated in lung cancer besides p53. We also include a few inflammatory response genes: ***IL-4***, whose promoter methylation decreased in mice exposed to diesel exhaust (DEP) and fungus (152) and ***IFNg***, interferon gene whose methylation increased in DEP/fungus exposed mice.

Pyrosequencing to detect global genome methylation levels (approximated by LINE-1 repeat methylation) will be performed per Colella (153) using a PSQ96MA System (Biotage/Qiagen). Recent studies show decreased LINE-1 methylation following exposure to traffic particulates, $PM_{2.5}$ and carbon black (71). Because pyrosequencing quantifies percent methylation of individual CpG sites, we can also use it for quantitative analysis of percent methylation of genes in the reference panel above, to supplement the qualitative M/U calls made by MSP. While the gene choices in a candidate gene approach are vast, support for the particular genes chosen here is evident in a recent study of non-small cell lung cancer in Asians (China) showing good correlation for *RASSF1A, RARB, hMLH1, p16, RUNX3 and DAPK* with lung cancer (154).
Due to the nature of the study, staff will handle and transport biological specimens that are categorized as potential toxic and infectious substances (dangerous goods-class 6, category b) To ensure good clinical practice procedures are followed, before study activation, all staff will complete the Dangerous Goods Shipping training and complete any additional MSKCC courses on handling biologic materials. Additional biospecimen collection training procedures will be provided by New York University.

A reminder system will be set up to increase study adherence. To remind participants to carry dataRAMs to work we will have daily text messages sent to mobile phones. We will provide participants with a friendly door knob sign to take home and place on bedroom doors as an additional reminder to carry their portable dataRAM monitors to bed and as a visual cue to remind them to make sure to take it with them when they leave for work.

Feasibility Data

Feasibility data will be collected to inform the conduct of a large scale randomized controlled trial assessing the impact of the HEPA filter intervention on reducing PM exposure and associated physiologic and biochemical markers. We will document the number of individuals approached for participation, the number refusing and reasons for refusal. We will document the time spent and the number of attempts to contact participants by phone and to meet in person. We will document adherence with study protocol, i.e. taking the dataRAMS to and from home and work, completing the multiple biological measurements. We will document the time spent conducting the study measurements. We will document dropout rates and reasons for drop out.

PARAMETERS-TIME POINTS*	At Intake	At Half-Way Point	1 Work Day per Week	1 Non-Work Day per week	1 work day (wk 1 & wk 4)	Every Day
Epigenetic Changes	X					
Hs-CRP	X					
Salivary Cotinine	X	X				
Serum Cytokines					X	
White blood cell profile					X	
Blood Pressure			X	X		
Heart rate variability						X
PM/Air Pollution						X
1-hydroxypyrene					X	
Black carbon			X			
PUF sample			X			

* Study Period = 28 Days

8.0 TOXICITIES/SIDE EFFECTS

There are minimal risks associated with participation in this study. Participants may experience pain undergoing fingerstick blood draw (e.g. soreness at puncture site) and

may experience dizziness or light-headedness. Staff will be trained to conduct fingerstick procedures and trained to identify participant's signs of distress during and after procedures. Participants may on occasion recognize problems or identify unmet clinical needs as a result of participating in a study such as this. If patients do report concerns of study burden, distress or mention specific medical concerns he will be informed to report this concerns to research staff who will be trained to alert study investigators who will make referrals to low cost community health services as appropriate.

9.1 PRIMARY OUTCOMES

The primary outcomes are:

- To collect preliminary data on in-vehicle excess PM exposure the personal DataRam will monitor/report the PM levels as time-averaged sample (hourly averages) that will be monitored at work site and at homes across all groups

- To conduct a preliminary assessment of the correlation between PM exposure and physiologic and biochemical markers associated with increased risk of lung cancer and CVD the personal DataRam will monitor/report PM levels (hourly averages) that will be analyzed in comparison to increased systolic blood pressure, reduced heart rate variability, and presence of biological markers related to lung cancer and CVD risk.

10.0 CRITERIA FOR REMOVAL FROM STUDY

Participants may be removed from the study protocol based on the following circumstances: 1) if they choose to voluntarily withdraw; 2) they are determined to be ineligible for the study; 3) they express significant distress related to completion of the study (the study staff will refer the participant to counseling and support services if needed); or 4) if the PI believes it is in the participant's best interest to do so.

11.0 BIOSTATISTICS

Overview. This pilot study follows a two parallel arm design. Drivers will be randomized to one of two groups, an Intervention Group (an in-vehicle HEPA filter will be provided) and a Wait-list Control Group (HEPA filter will be provided at the end of wait-list period). We plan to recruit a sample of n=14 participants in each group (n=11 per arm with analyzable (non-missing) data, assuming a 25% drop-out rate as described below).

General analytic strategies. The general data analytic paradigm for this pilot study will be descriptive statistics only. The aim is to collect pilot data to help guide a future randomized intervention study. Descriptive statistics and assessments of correlations will be sought to address the aims (see below). The sample size of 14 per condition was primarily determined by resources limitations. A sample of 14 per condition was deemed possible within the funding resources of no more than 2 years.

Analytic plans for the Specific Aims.

Aim 1a: The primary aim will be to collect preliminary data on in-vehicle excess PM exposure.

Descriptive statistics (means and standard deviations) will be sought on: 1) PM size distribution 2) mass concentration, and 3) chemical composition for all three groups. These observations will be used to evaluate to what extent the two groups were exposed to these environmental hazards. For each study participant, an area-under-the-curve (AUC) summary will be sought for each of the three PM measurements over appropriate time periods. Generally, a daily average will be calculated from the hourly PM assessments. Then the AUC of the 28 daily averages will be calculated per person to represent the summary of PM exposures during study participation.

Aim 1b: To conduct a preliminary assessment of the correlation between PM exposure and physiologic and biochemical markers associated with increased risk of lung cancer and/or CVD.

For each group, a correlation matrix will be constructed between the three components of the AUC outcomes described in Aim 1a and a set of physiologic and biochemical markers. Generally, Pearsons‘ correlation coefficients will be sought. If preliminary analyses found the variables to be skewed, then Spearman‘s rank correlation coefficients will be calculated instead. The purpose of these correlation coefficients are to examine the associations between the environmental exposure to air pollutants and physiologic and biochemical markers. Point-biserial correlation coefficients will be sought between the continuous AUC summaries of PM data and other binary variables of interest (e.g., methylation). These correlation coefficients can be sorted in descending order to help identify the top candidates of physiologic and biochemical markers that are most likely to be associated with PM exposure. Care will be taken to match the variables by time, using the time stamps from the PM measurements and the date of biomarker serum collection. For example, the AUC of PM in the first week will be associated with serum cytokines measured during the first week. This work will have to be done in a post-hoc manner, after we have all data sources. Then we will evaluate the best strategies to link them together by time. It helps to have automatic time stamps by the PM measurement devices, which is likely to minimize coding errors and missing data.

Aim 2: To use a randomized wait-list controlled design to conduct a pilot study of whether a targeted intervention, installation of a portable car high-efficiency particulate air (HEPA) filter (to remove PM), results in a reduction of in-vehicle PM exposure and associated physiologic and biochemical markers among taxi drivers..

We will calculate the difference in the three PM components and in physiologic/biochemical markers between the HEPA intervention condition and the Wait-List Control condition to obtain the pilot data needed for a future, larger study with the potential to provide remediation to potential harmful exposures to air pollution among NYC taxi drivers.

Aim 3: To collect feasibility data on conducting the proposed randomized wait-list controlled pilot study among New York City taxi drivers.

We will perform descriptive statistics to describe the feasibility data collected in this study (number of participants approached, number refused, number dropping out, time and effort required to conduct the study, adherence with the study protocol including carrying dataRAMS to and from home and work and completion of the multiple biological measurements, etc.). These data will inform a future, large-scale randomized controlled study.

12.1 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

12.2 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.

The individual signing the Eligibility Checklist is confirming whether or not the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

12.3 Randomization

Drivers will be randomized to one of the two arms: 1) Driver Wait list control arm or 2) Driver Intervention. After eligibility is confirmed and after consent is obtained, participants will be registered, and then randomized using the MSKCC Clinical Research Database (CRDB) or by calling the MSKCC Clinical Research Administration at 646-735-8000 between the hours of 8:30 am and 5:30 pm, Monday - Friday.

13.1 DATA MANAGEMENT ISSUES

The PI and research staff will be responsible for project compliance, data collection, data reporting, regulatory monitoring, problem resolution and prioritization and coordinating the activities of the protocol study team. An RSA will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordination of the activities of the protocol study team.
The data collected for this study will be entered into UNITY Web database, the Department of Psychiatry and Behavioral Sciences secure web-based database application, to be accessed by study staff. The hard copies of the study materials will be

kept in a locked, secured location and will only be accessible to study staff. Participants will be assigned unique identification numbers upon study entry which will be used to identify all the data. Questionnaire may be completed directly online by study staff using tablets, otherwise they will be entered into UNITY Web by research staff on site from hard copy surveys. All hard copy questionnaire data completed by participants will be identified only with a study code number. All data to be analyzed for reporting purposes will continue to be stripped of any identifying information. A list, matching participants' name and case numbers will also be kept in a secure area at MSKCC. All questionnaire data completed by participants will be identified only with a study code number.

The data collected for this study will be managed through UNITY Web Database, questionnaire and screening data will be entered into the research study web based database UNITY maintained by MSKCC. UNITY Web is a secure web based research database application that was developed and being maintained by the MSKCC Department of Psychiatry and Behavioral Sciences. The primary goal of UNITY Web is to streamline research data collection via the Internet and the ease of survey creation.

Data collection in UNITY Web can be accomplished directly over the Internet without establishing a VPN connection. Eliminating the VPN connection requirement can be crucial when conducting multi-site research studies with Institutions outside of MSKCC locations. UNITY Web was developed using the latest Microsoft .Net Framework with C# and JQuery. The application is being hosted by Microsoft IIS and the backend database is on Microsoft SQL Server. A number of various encryption methods were used from the user interface to the servers and as well as the communications between servers. All encryption methods used have either met or exceeded the requirements described in the standard HIPAA web application security guideline.

13.2 Quality Assurance

Registration reports will be generated regularly to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing and inconsistent data. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action. Random-sample data quality and protocol compliance audits will be conducted by the study team.

13.3 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled —Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials‖ which can be found at:

http://cancertrials.nci.nih.gov/researchers/dsm/index.html.

The DSM Plans at MSKCC were established and are monitored by Clinical Research Administration. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at

https://one.mskcc.org/sites/pub/clinresearch/Documents/MSKCC%20Data%20and%20Safety%20Monitoring%20Plans.pdf There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

13.4 Regulatory Documentation

Participating sites that are consulting and/or conducting specimen or data analysis should submit this protocol to their IRB according to local guidelines. Copies of any site IRB correspondence should be forwarded to MSK.

14.1 PROTECTION OF HUMAN SUBJECTS

Participants will be informed that participation is voluntary and that they have the right to withdraw at any time and/or leave any question blank if they do not feel comfortable answering. Confidentiality of each subject's self-report information and each patient's medical information will be protected with the utmost care. Each study subject will be given a unique numeric identifier upon study entry. Data sheets collected from each subject will be identified solely by a code number. A list matching subject names and code numbers will be maintained separately and kept in a secure area. This will preserve the anonymity of participants. All data will be used only for research purposes. IRB and HIPAA regulations concerning confidentiality will be strictly enforced. Hardcopies of the original questionnaires will be stored in locked file cabinets. Through the use of password security measures, restrictions will be applied to each user commensurate with their needs to access the data. Confidential information will not be routinely available to all members of the research team but rather on a —need to knowll basis. All study personnel will be instructed in the ethics of electronic data access, as well as receive training in both HIPAA issues and human subjects training. Similarly, all biological samples will be labeled only

with the unique subject number. Study staff will be trained on procedures for data collection and handling/storage of all biological samples and will follow standard procedures to minimize pain and bleeding. Staff will observe and record any signs of distress during fingerstick procedures. In the event that any abnormal or irregular health measures are identified, staff will be trained to alert study investigators and research manager, participant will be referred to low cost community health services. During weekly assessments, staff will be trained to check in with participants to identify if study participation has impacted their working environment (unintended consequences, such as passengers and others asking them about equipment despite its small size). In the event that a concern is reported staff will inform participants of their right to withdraw from the study and the study team will work them to mitigate problems.

14.2 Privacy

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

14.3 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

As this is a minimal risk study, we will only report SAEs (including deaths) that are believed to be at least possibly related to the protocol intervention.

SAE reporting is required as soon as the participant signs consent. SAE reporting is required for 30-days after the participant's last investigational treatment or intervention. Any events that occur after the 30-day period and that are at least possibly related to protocol treatment must be reported.

If an SAE requires submission to the IRB office per IRB SOP RR-408 _Reporting of Serious Adverse Events', the SAE report must be sent to the IRB within 5 calendar days of the event. The IRB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office as follows:

For IND/IDE trials: Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to saemskind@mskcc.org.

For all other trials: Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to sae@mskcc.org.

The report should contain the following information:

Fields populated from CRDB:

- Subject's initials
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following
    - A explanation of how the AE was handled
    - A description of the subject's condition
    - Indication if the subject remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

The PI's signature and the date it was signed are required on the completed report.

For IND/IDE protocols:
The CRDB SAE report should be completed as per above instructions. If appropriate, the report will be forwarded to the FDA by the SAE staff through the IND Office.

14.2.1

N/A

15.1 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

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17.0 APPENDICES

Appendix A. Screening Tool
Appendix B. Intake
Appendix C. Driver Log Book
Appendix D. RSA guide/Lab Manual
Appendix E. Data Collection log
Appendix F. Driver Recruitment Flyer