A pilot randomized crossover trial of cleaning indoor air to reduce acute exacerbations of COPD (CARE) study

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1. Purpose of the Study:

Given the importance of indoor air pollution as a contributor to acute exacerbations of COPD (AECOPD), we will study the health impact of reducing indoor air pollution in patients with COPD using high-efficiency particulate air (HEPA) filtration units.

Specifically we will explore whether 2 months of home air cleaning with the HEPAirX® air filtration system in the living room and bedroom of each subject's home results in:

1. **Improved functional status measured by:**
    a. **St. George's Respiratory Questionnaire (SGRQ) and**
    b. **Daily step counts (measured by Fitbit® wearable sensor)**

2. **Reduced levels of systemic inflammation,**
    a. **Plasma C-reactive protein (CRP) levels as a biomarker**

3. **Reduced risk for AECOPD**
    a. **Using healthcare encounter data**

2. Background:

B.1. **COPD and Indoor air pollution:** Descriptions, sources, and health effects of indoor air pollution have been summarized previously.(Weschler 2011; Zhang and Smith 2003) PM_{10} (particles <10 μm), $PM_{2.5}$ (particles <2.5 μm), ultrafine particles (particles <0.1 μm; UFP) as well as gaseous pollutants including carbon monoxide (CO), volatile organic compounds (VOC), and ozone (O_3), among many other pollutants, are found indoors. All of these particulate and gaseous pollutants are either emitted from an indoor source (e.g. cooking, other open flames, or leaks in the home heating system), are secondary products of pollutants emitted indoors, or directly infiltrate from outside.(Li and Hopke 1991) While all these pollutants can contribute to AECOPD, the size of the particle pollutants (PM_{10}, $PM_{2.5}$ and UFP) determines how deep in the respiratory tract particles can penetrate, with PM_{10} depositing in the trachea causing, $PM_{2.5}$ reaching the alveoli and UFP entering the systemic circulation.(Pope and Dockery 2006)
Both filtration of particles (e.g. PM_{10}, $PM_{2.5}$, and UFP) and ventilation with outdoor air to reduce gaseous pollutant concentrations have been shown to improve human health and functional status.(Fisk and Brunner 2012; Fisk 2013; Seppanen and Fisk 2004) The HEPAirX filtration and ventilation device is a trademarked, patented (U.S. Patent # 7,802,443), U.S. FDA approved Class II medical re-circulating air cleaner, built by Air Innovations, Inc. (North Syracuse, NY). ***We have previously shown it to be proficient in reducing levels of several gaseous pollutants (via ventilation) and PM (via filtration);*** **(**see Preliminary evidence section for a full description of the HEPAirX).

B.2. **Indoor air pollution and inflammation:** Both local (pulmonary) and systemic inflammation play key roles in airways diseases such as COPD. We and others have extensively assessed airway inflammation during air pollution studies (Huang et al. 2012; AP Pietropaoli et al. 2004; Zuurbier et al. 2011) and in COPD patients specifically have shown airway inflammation following increases in air pollution concentration over the previous days.(Adamkiewicz et al. 2004; A Pietropaoli et al. 2004) Air pollution also appears to induce systemic

inflammation. (Brook et al. 2010; Croft et al. 2017) ***Plasma C-reactive protein (CRP) is a measure of systemic inflammation***, and is an acute phase protein known to increase in the hours and days following an inflammatory stimulus. Persistently increased CRP after an AECOPD has been previously associated with an increased risk for recurrent AECOPD (Perera et al. 2007) and increased mortality from COPD.(Leuzzi et al. 2017) While the clinical significance of reducing CRP levels in COPD patients following AECOPD is not established, decreased systemic inflammation related to decreased levels of indoor air pollution is expected to lower the risk for recurrent AECOPD.

B.3. **Impaired functional status:** ***Pulmonary and systemic inflammation contribute to the characteristic findings of AECOPD including increased respiratory symptoms of cough, sputum production, dyspnea and reduced functional status*** (defined as an inability to perform daily activities, fulfill usual roles, and maintain well-being).(Perera et al. 2007; Society 2013) The St. Georges Respiratory Questionnaire (SGRQ) is an established, clinically relevant measure of respiratory symptoms, activity level, and impacts on daily life, and is a measure of functional status regularly used and validated in COPD patient populations.(Jones et al. 1992) The questionnaire is a fixed format 50 item survey completed by the study subject asking questions in three parts: 1) levels of symptomatology including frequency (over the course of a week) of wheezing, cough, sputum production, and breathlessness, including the duration of episodes of wheeze and breathlessness, 2) physical activities (e.g. housework) that may be caused or are limited by breathlessness, and 3) impacts of these symptoms (e.g. employment, inhaler/medication needs, panic, disturbances of daily life, etc.). It is a self-assessment of respiratory symptoms and functional status, and provides a quantification of the impacts of airflow limitation on health and well-being. Previously, in a study of severe COPD patients, increased indoor residential $PM_{2.5}$ concentrations were associated with impaired functional status measured by the SGRQ.(Osman et al. 2007)
Consumer level wearable sensors are increasingly being used in clinical trials for mobility and functional status outcomes.(Izmailova et al. 2017) We will use a Fitbit® brand step counter as a secondary measure of functional status, due to its superior performance to other devices in an observational study examining patients' movement after AECOPD.(Prieto-Centurion et al. 2016)

C. Significance, Impact and Anticipated Outcomes

This pilot study is significant and likely to have a high impact on URMC and its clinical treatment of COPD patients for several reasons. First, if we show that indoor air cleaning improves functional status, reduces systemic inflammation as well as the number of AECOPD encounters, we will provide an easy to use, relatively inexpensive treatment option that URMC and other medical facilities can use to protect their COPD patients against air pollution mediated health effects and hospital re-admissions. Second, having fewer hospital re-admissions for these COPD patients would reduce the treatment expenses of medical facilities such as the URMC providing their clinical care. Given the need of the URMC and other medical facilities to reduce their risk-adjusted 30-day COPD hospital re-admission rate to <20% or else face financial penalties from the Center for Medicare and Medicaid Services (CMS), this study is particularly timely. Third, if we find that indoor air cleaning protects COPD patients from AECOPD and/or improves their functional status, then a larger NIH funded study to

confirm these findings, investigate pathophysiologic mechanisms, and examine whether specific components of pollutant mixtures are driving any health response(s) will be warranted.

However, if we find that air cleaning using the HEPAirX does not reduce AECOPD and/or improve functional status in these COPD patients, then other in-home strategies to reduce COPD patients' exposures to indoor air pollution may need to be investigated. For example, more comprehensive whole home filtration and air cleaning systems (which arguably would be much more expensive than the 2 air cleaners/home we will study here) could be installed in the homes of COPD patients to protect them from indoor air pollution exposure. Other options for these COPD patients upon initial hospital discharge may also need to be considered, including social work assistance to consider different residential locations in areas with lower levels of indoor and outdoor air pollutants and second hand smoke exposure.

Figure 1. HEPAirX integrated energy recovery ventilator and air cleaner

D. <u>HEPAirX Air Cleaning System.</u> The second generation HEPAirX integrated energy recovery ventilator and air cleaner (**Figure 1**) improves on older and other current devices through combined high-efficiency filtration (reduced particles) and ventilation (reduced gaseous pollutants). It is a trademarked, patented (U.S. Patent # 7,802,443), U.S. FDA approved Class II medical re-circulating air cleaner, built by Air Innovations, Inc. (North Syracuse, NY) to provide improved indoor air quality in the bedrooms of asthmatic children. The device is being used in the current study in the FDA-approved manner. Units to be used in the proposed study have a 99.97% efficient filter for particles 0.3 µm in size. The device provides a clean air delivery rate (CADR) of 9 per hour with 1.8 of them being outdoor air. Using ***the initial version of this system, mounted in bedroom windows, we reduced PM_{10}, CO, CO_2, and VOC concentrations in the bedrooms, decreased pulmonary inflammation, and improved pulmonary function in pediatric asthma patients***.(Xu et al. 2009) Using the second-generation units we again ***substantially improved air quality in bedrooms (CO: -55%, VOC: -59% and PM10: -54%) with the HEPAirX system in full operation (unit on) compared to the placebo mode (unit on, but no filtration or ventilation).*** In this study, a placebo mode was added to the HEPAirX to provide only recirculation (without filtration or ventilation using outdoor air) and temperature control of the room air. ***This same placebo mode of the second generation device, which allows a comparison of health effects associated with air filtration and ventilation and the expected pollutant reductions will be used in our proposed study.***

The HEPAirX device fits into a standard double hung window (Figure 2) and provides the heating or cooling required to maintain a constant, comfortable room temperature. A built-in air-to-air heat exchanger captures the energy in the exhaust air to pre-condition the incoming outside air. Please see the letter from Michael Wetzel (CEO: Air Innovations; Manufacturer of HEPAirX) for his support of this study, and the provision of 20 HEPAirX air cleaning devices at no cost other than the HEPA filters used during the study.

3.1. Study Population. We will recruit a total of 20 adult (≥18 years of age) men and women with severe COPD (forced expiratory volume (FEV1) < 50%), who live in Monroe County (New York), have completed pulmonary rehabilitation for over 1 month, and have suffered from an AECOPD in the past year.

Number of Subjects:
We will enroll a total of 20 patients in our study who have completed pulmonary rehabilitation in Monroe County, New York.

Gender of Subjects: There are no restrictions on gender for this study with approximately 60% of subjects expected to be female.

Age of Subjects: All adults over the age of 18 will be included in the study with the average age of subjects enrolled expected to be around 65 years old.

Racial and ethnic origin: There are no restrictions on race/ethnicity for participation in the study. We anticipate enrollment demographics in the study will be similar to our clinic population, of which 85% of patients are white, 10% African American, and 5% from other groups.

Inclusion criteria: We will prospectively recruit a total of 20 adult (≥18 years of age) men and women with severe COPD (FEV1 < 50%), who live in Monroe County, have completed pulmonary rehabilitation (over 1 month since completion), and have suffered from an AECOPD in the past year. Subjects must have standard sized windows in their bedroom and living room amenable to installation of the HEPAirX® device. All subjects must also expect to sleep each night of the 4 months (2 months of Period 1, and 2 months of period 2) in either their bedroom or living room for at least 6 hours/night, and not use other air filtering devices during the study.

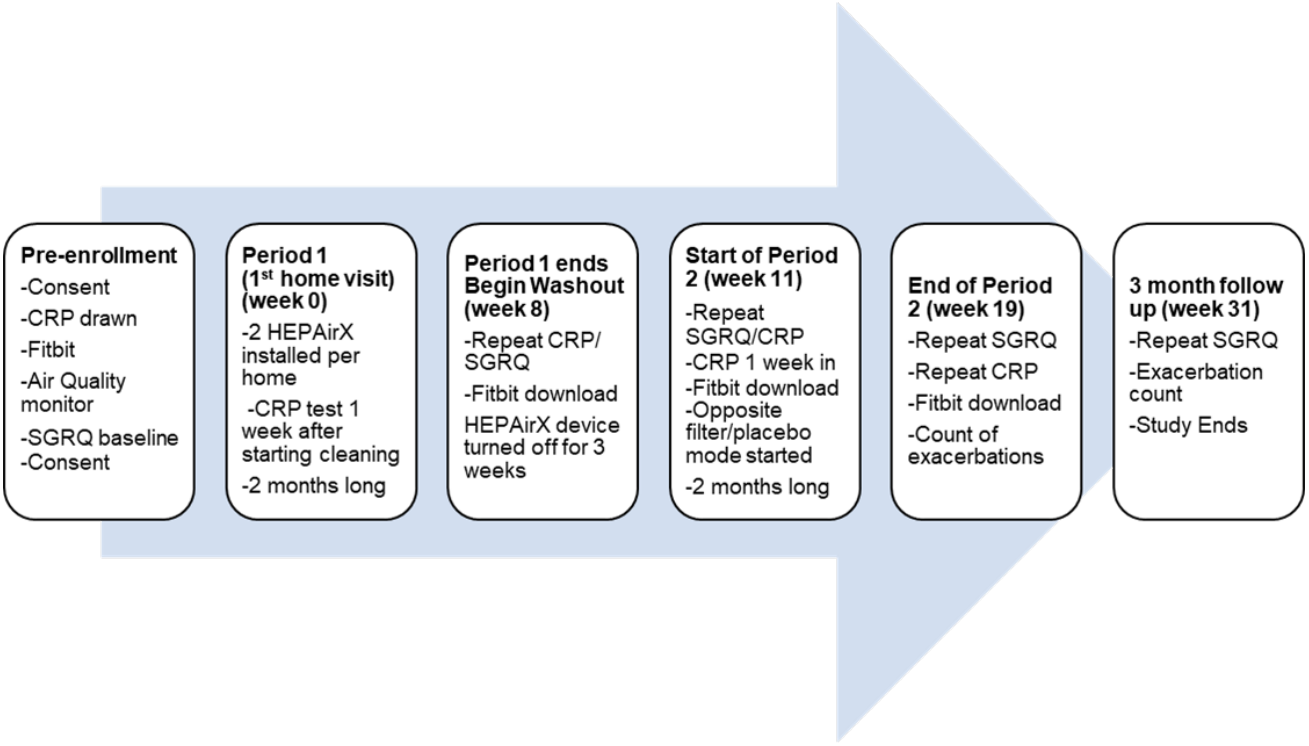
Exclusion criteria: Exclusion criteria include subjects who are under age 18 and do not meet the inclusion criteria as defined above. Exclusion criteria include subjects under age 18, those who were smoking at the time of their prior COPD exacerbation, current smokers, those who live with an active smoker, homes with wood burning appliances, patients on chronic systemic corticosteroids (>3 months continuous use in past 1 months), those who are planning to move in the next 12 months, those with an occupation that has a high pollutant exposure (e.g. professional drivers), those who already have a home air filtration device(other than basic furnace filter) and those who do not meet the inclusion criteria as defined above.

Vulnerable subjects: We do not plan to enroll vulnerable subjects.

Discussion of subject population: We plan to enroll patients who have disease severe enough that an intervention of indoor air quality may benefit their health in a perceivable (Aims 1-3) way. This population is also more mobile than a homebound population making it safer/less disruptive to travel for blood draws at the University.

4. Subject ID, Recruitment and Consent:

We will enroll eligible patients (severe COPD and exacerbation history) who have completed the University of Rochester Pulmonary Rehabilitation program over 1 month prior to enrollment into our study. Contact will be made by telephone to determine their level of interest by the PI or coordinator of the study (Croft or Johnston). For those expressing a desire to participate during that phone call, potential subjects will be scheduled to come in to review the study in more detail. Once the study has been reviewed with the subject in detail and all of their questions have been answered, written informed consent will be obtained by a study team member before the study procedures begin. All subjects will have capacity to consent for themselves. Subjects will be provided with a copy of the signed consent form for their records. Please see attached consent form for full details.



5. Study Activities

Summary of Project Methods and Study Procedures

We propose a double-blind, randomized crossover trial (both study participant and clinical staff are blinded to randomized group) to assess whether 2 months of bedroom and living room air cleaning, in the homes of COPD patients with AECOPD in the past year, improves functional status, lowers systemic inflammation, and decreases the risk for AECOPD when compared to a 2 month period using a 'sham filter' (i.e. placebo mode

described above). Descriptions of our study population, protocol and statistical analyses are provided below.

E.1. Study Population. We will recruit a total of 20 adult (≥18 years of age) men and women with severe COPD (FEV1 < 50%), who live in Rochester, NY, have completed pulmonary rehabilitation, and have suffered from an AECOPD in the past year. **E.2. Health Outcomes**. Our primary endpoints will be the symptom score from the St. George's Respiratory Questionnaire (SGRQ; marker of functional status) described above in Section B.3 and the average daily count of steps taken using a Fitbit® brand wearable sensor (Aim 1). Our secondary endpoints are Plasma CRP measurements (Aim 2) and healthcare contacts for AECOPD (Aim 3). The subjects will wear the Fitbit® watch around their wrist during waking hours, which will automatically collect the daily count of steps and report this electronically to the research team via a secure account (Described below). The subjects will travel to the URMC lab at the specified time (described below) to have their plasma CRP drawn.

E.3. **Study Protocol.** We will conduct a randomized, blinded, crossover trial, where each of the 20 total subjects will be randomly assigned to **Group A** (Period 1 = 8 weeks of filtration/ventilation mode, 3 week washout period, Period 2 = 8 weeks of placebo mode [device runs but no filtration/ventilation]) or **Group B** (Period 1 = 8 weeks of placebo mode, 3 week washout period, Period 2 = 8 weeks of filtration/ventilation mode). Subjects will be blinded to which group they are randomly assigned, and only staff installing and monitoring the HEPAirX device and air pollution monitoring equipment, and not staff collecting or analyzing health outcomes, will know the assigned group. In the placebo mode of operation, the HEPAirX unit operates in exactly the same way (i.e. will look and sound the same), but it does not filter air to remove particles or have outdoor air exchanges to reduce gaseous pollutants. With 20 HEPAirX machines available and 2 required per subject, the timing of enrollment will be split into 2 groups of 10 patients (Two 19 week periods).

After getting informed consent from each study participant, we will schedule the 1st home visit within 2 weeks. Once consent to participate in the study has been obtained, we will provide subjects with:

- Five simple indoor air quality monitors which the subject will plug into an electrical outlet and set on a tabletop in a low traffic area of their living room and bedroom.
- Subjects will also be given a Fitbit® activity tracker at this time, which will be worn on their wrist during waking hours.
- Subjects will also be given a smartphone to use for syncing the Fitbit watch (charged every 4 days as well).

Period 1: (First 8 week intervention: Either filtering/ventilation mode or sham mode): Subjects will visit the main URMC lab to have plasma CRP drawn (Blood Draw 1 of 4, perform a 6 minute walk test with their Fit Bit and wearable sensors. Study staff will then visit the subject's home, check on the indoor air quality pollution monitors, and install and turn the HEPAirX® devices "On" to start Period 1 (**Visit 1**). At this time (Visit 1) the subjects will complete the SGRQ (survey 1 of 5). **Washout Period:** After 8 weeks of either filtration or placebo operation, the subject will have another blood draw for CRP at our URMC lab (2 of 4), perform a 6 minute walk test with their Fit Bit and wearable sensors and study staff will return (**Visit 2)** to turn off the two devices for a 3 week **Washout** period. A SGRQ will also be administered at this time (Survey 2 of 5). This 3 week period was included to ensure that the Pre-filtering Period 2 health measurements are not impacted by the Period 1

filtration/ventilation. While previous studies suggest a 1 week washout is adequate for PM and other pollutant levels to return to baseline levels, we chose a 3 week washout period to ensure that the subjects' functional status will also return to baseline levels.

Period 2: (Second 8 week intervention): After the washout period, the subject will again have drawn at our URMC lab (Blood Draw 3 of 4), perform a 6 minute walk test with their Fit Bit and wearable sensors and they will complete another SGRQ (Survey 3 of 5). Study staff will then return to the subject's home (**Visit 3**) to change the HEPAirX® device to the appropriate setting depending on the subjects' Group (A or B).

After 8 weeks of operation, staff will return to the subject's home **(Visit 4)** to retrieve the HEPAirX® device, Fitbit® activity tracker, smartphone and air quality monitor. At this time, another SGRQ will be administered (Survey 4 of 5) and the subject will also submit their final blood sample for CRP (Blood Draw 4 of 4), perform a 6 minute walk test with their Fit Bit and wearable sensors. The subject will complete their final survey (Survey 5 of 5) three months after Visit 4 (week 31), concluding the study.

Each subject will receive a total of $620 in personal checks (over the course of the study) to offset electricity costs to run the HEPAirX® and costs for travel to URMC for blood draws. Checks will be given at each home visit for the portions of the study completed at that time point. Leftover blood from CRP analysis will be stored for the duration of the study and banked for future analysis, which will include the possibility for genetic analysis (See Blood collection section below for details). During the two eight week blocks, we will check in by phone 4 weeks into the study to make sure no problems have arisen and will be available to visit the home as needed during this period.

To keep the subject blinded with regard to mode of the HEPAirX® during Periods 1 and 2 (i.e. Filtration mode or Placebo mode), the device will be sealed to prevent the subject from opening it. Further, with or without the filter, there are no differences in temperature control, air flow (device still conducts 9 air changes per hour, recirculating indoor air without filtering or ventilating with outside air), or noise. Subjects will keep the device running constantly during both 8 week intervention periods, with temperature being the one variable the subject can control. We can determine its usage using an elapsed time meter on each unit. Subjects will keep a time-activity diary, particularly noting when cooking or cleaning occurs and when they are in the bedroom. This diary will also include instances of when patients feel symptoms of upper or lower respiratory infection (sinus congestion, runny nose, cough, increased sputum production)

PROTOCOL (METHODS AND PROCEDURES)

We will record patient information from the medical record into a secure database after the patient has given written informed consent.

1) **Blood Collection:** Blood will be collected from a peripheral vein at the URMC lab (10mL total) using their standard technique to assess (1) plasma for CRP measurements (5ml) at the aforementioned intervals and 2) separate tube (5ml) of blood will be drawn for storage and may be used for genetic analysis. This blood will be stored (banked) for future analysis under a separate RSRB protocol (#00004357).

2) **Home Activity Monitoring:** We will ask participants to wear a wristband step counter (FitBit®; Wavelet health, Mountain View, Ca) while at home which will measure continuous activity in the form of steps. It will also collect data on heart

rate which will also be a proxy for activity. Participants will be dispensed a wristband (and charger) to wear at home for the entire study period. This Fitbit® will be synced to our secure tablet computer at the home visit intervals and we will access the data on the secure web-based portal. We will manage the accounts for each Fitbit®, but the subjects will have temporary access to the accounts. Subjects will be provided with a smartphone which will have only Wi-Fi capabilities and the Fitbit app installed. Subjects will sync their Fitbit with this device on a weekly basis. In this case, the wristband uploads the data to the app through blue tooth technology and ultimately onto a secure HIPAA compliant cloud. Subjects will be given the charging cord and instructed to charge the Fitbit® device every 7 days. When the study is complete, the FitBit® and smartphone will be collected at the final home visit. If the patient is not able to coordinate this data collection, we will help them sync their watch during home visits and will be available to help as needed through the study.

3) Home air quality monitoring

The simple corded air quality monitors (for particles and CO_2, provided once consent has been obtained, will be placed in the subjects' home and will take continuous measurements over the course of the study. This will be checked at the midpoint of the study and collected at the conclusion of the study. The monitors, will be sent to AirViz so they can extract the anonymized raw data from the air quality monitors and review the information captured to ensure data quality. Once QA review is complete, the data will be forwarded to us for our research analysis at the end of the study. AirViz Inc. will not receive any information that identifies the subjects, nor will they take part in analyzing or interpreting the results of the air quality data. Furthermore, after removal from subject homes, the filters from the HEPAirX® devices will be retained (not discarded) and will be used in a future analysis with links retained to subject ID and current study outcomes.

4) **Clinical Data Collection.** The patients will receive standard of care diagnostic testing and treatment throughout the period of the study. We will collect relevant data to the evaluation and ongoing management of COPD into a secure, web-based data portal. We will maintain identifying information so that we could later add to the database as new diagnostic testing or new insights relevant to old diagnostic testing become available.

5) **Subject Withdrawals**: This is described to the participant in the consent form. Subjects can withdraw at any point in the trial. If the subject withdraws prior to the installation of the air quality monitor, they will be replaced by another participant.

6) Additional community resources: If agreeable, patients will be able to consent to having their name released to our partners in Community Health who will contact them to consider whether they are eligible to participate in the Rochester Healthy Homes Partnership,

6. Risks and Benefits:

Risks: This study is minimal risk, as we are simply implementing an intervention that will clean the indoor air of our subjects. The blood draws will impose a small amount of physical pain to the subject. The activity monitor is a noninvasive device worn around the wrist. The SGRQ should have minimal risk for psychological stress. For the outcome of measuring exacerbations, we will be using already existing information on these patients located in the medical record. There is a small risk of loss of confidentiality and a small risk of loss of privacy due to our accessing of your identifiable information including lab work and our entry into your home for installation of the indoor air cleaners. Please see our data storage and confidentiality plan for our methods to protect against these potential losses of confidentiality and privacy. Having an indoor air cleaner may expose the subjects to the stress of thinking of the dangers of indoor air quality

Benefits: There will be at most a transient benefit to the individual subjects.

Compensation

Payment to Subjects

Each subject will receive a total of $580 in the form of a check to offset electricity costs to run the HEPAirX and travel for blood draws.

1. Compensation for driving to the lab (using a compensation of $0.565 per mile with a uniform estimate of 30 miles travel for each of 4 CRP): $80 per study subject
2. Compensation for scheduled home visits: $25 per visit = $100 per study subject
3. Compensation for energy costs: $400 for study = $400 per study subject

Total compensation per subject = **$580**

Costs to Subjects

There is a possible risk that the energy costs from the use of HEPAirX device will exceed the energy cost estimated by our technical team. To help protect subjects from this additional cost, we will have subjects submit their prior month's utility bill to help with estimation. We will be able to provide reasonable additional compensation to the subjects.

7. Data Storage and Confidentiality:

Any confidential and private data will be protected and stored in a separate dataset at the University of Rochester in specified and protected locations (protected institutional SMDNAS drive of Dr. Daniel Croft), distinct from the main analysis dataset. The data from the air quality monitoring device within the home will only be collected at the end of each of the two periods (whether filter or placebo). At the end of the study, these air quality data will be aggregated and sent to the analyst Kelly Thevenet-Morrison study in a blinded fashion. Similarly the Fitbit monitoring data will be downloaded from the devices at least at the end of each period (though patients will be syncing data throughout the study every 4 days). The Fitbit username and password will be managed by the investigators (Daniel Croft, Carl Johnston and Sanjna Prasad). For blinding purposes, the identifying information

indicating the order of intervention will be located in a separate password protected file and will be managed by Kelly Thevenet-Morrison. Other than files with personal health information which will be password protected on the secure SMDNAS drive of the Principal Investigator Dr. Daniel Croft with access granted to, Dr. David Rich, Mrs. Kelly Thevenet-Morrison (analyst/programmer), Dr. Carl Johnston, Sanjna Prasad, Amy Rovitelli and Dr. Philip Hopke only. Also, we will utilize the date/time of any possible hospital admission and/or date/time of emergency department evaluation for COPD exacerbations to use in matching specific date/times of air pollution measurements. Identifying information will be retained for future analyses.

8. Data Analysis:

E.4. **Statistical Analysis.** We will generate descriptive statistics for each subject, indoor air pollutant concentrations during each filtering/placebo mode session, and our main outcomes in Aim 1-Aim 3 (Aim 1: SGRQ symptom score and average daily step count; Aim 2: plasma level of CRP; Aim 3: number of healthcare encounters for AECOPD), comparing the change in each between the filtration and placebo groups. Given the crossover design, each subject will serve as their own control. Our statistical analyses are described below.

We will fit a random effects ANOVA model regressing the 8-week (Post-filtering SGRQ score (Aim 1) against the Pre-filtering SGRQ score, period ('Period 1' versus 'Period 2'), and filtering mode ('filter/ventilation mode' versus 'placebo mode'). If necessary, we will transform both post-filtering and pre-filtering SGRQ score to better satisfy model assumptions. Subjects will contribute two observations to the analysis and subjects will be included as random effects, recognizing correlations due to repeated measures on the same subject. Filtering mode will test whether the 'filtration/ventilation mode' produced a significant effect on subsequent SGRQ score than the 'placebo mode'. Next, the final survey 3 months after the 19 week intervention period concludes will be compared to survey 4 to explore the duration of observed changes. We expect that in view of the "washout period" between Period 1 and Period 2, there will be no carry-over of the effect of the intervention in Period 1 on the results for Period 2. Including period in the model allows us to assess the plausibility of this assumption. This same analysis used for Aim 1 will also be used for Aim 2, plasma CRP.

We will repeat the random effects ANOVA model, regressing the 8 week in Fitbit® measured average daily step count (Aim 1) (Post-filtering average daily step count) against the Pre-filtering average daily step count, period and filtering mode. Specifically the intervals selected for this analysis will be the week prior to Phase 1 compared to the final week of Phase 1 and the final week of the washout period compared with the final week of Phase 2. Indoor PM2.5 concentration will be analyzed similarly with the ANOVA model and will also use these same time intervals. We will repeat the random effects ANOVA model for average resting heart rate at the same time intervals.

For Aim 3, the number of healthcare encounters for AECOPD, we will fit a Poisson regression of the number of COPD exacerbations in 8 weeks as a function of filtering mode (Filtering versus Placebo) and period. Should there be very few healthcare encounters, instead we will use a logistic regression to model whether there were any healthcare encounters. This model will allow us to evaluate the impact of filtering model on healthcare

encounters, while adjusting for period (e.g. Group A (Filtration followed by Placebo) or Group B (Placebo followed by Filtration) to determine if the order of intervention affected the outcome). Next we will compare healthcare encounters for AECOPD at the 3 month follow up period with Phase 2 outcomes in a similar way. Since this is a pilot study, power calculations are not provided, and effect estimates from the regression analyses described above will be used as preliminary data in an application for a larger, adequately powered R01 funded study.

Post hoc analyses:

1. Autonomic function: In addition to average resting heart rate, we will determine if the data are robust enough to calculate heart rate variability.
2. Genetic response: As mentioned, the stored blood may be used in a future analysis on the genetic response to air pollution related to respiratory outcomes
3. Particle Chemistry: The particles on the filters will be analyzed in the future for composition and potentially even included in cell exposure studies to determine the mechanistic impact of the pollutants.

SAFETY AND REPORTABLE EVENTS

Adverse Event Definition

An adverse event is any symptom, sign, illness, or experience, which develops or worsens during the course of the study, whether or not the event is considered related to study drug.

Serious Adverse Event

A serious adverse event is defined as any adverse medical experience that results in any of the following outcomes:

- death;
- is life-threatening;
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect; or
- requires medical or surgical intervention to prevent permanent impairment or damage.

Recording Adverse Events

At each subject visit the site study staff will assess adverse events by recording all voluntary complaints of the subject and by assessment of clinical and laboratory features. At each study visit, the subject should be questioned directly regarding the occurrence of any adverse experience since his/her last visit.

While the subject is enrolled in the study, all adverse events, whether observed by the Investigator, elicited from or volunteered by the subject, should be documented. Each adverse event will include a brief description of the experience, the date of onset, the date of resolution, the duration and type of experience, the severity, and the relationship to any of the study procedures or devices, contributing factors, and any action taken with respect to the study procedures.

Responsibilities for Reporting Serious Adverse Events

The Investigator will record all serious adverse experiences that occur during the study period in the appropriate source documents and/or AE log as applicable from the time of signing consent to final study visit. The Investigator will also comply with regulations and RSRB policy regarding the reporting of adverse events.

9. References:

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Appendix: Data collection form

Study Number
Sex
Age
Race
Ethnicity
Home Address
Comorbidities (OSA, sinus, DM, CHF, COPD, CRF)
Smoking
Vaccines
FEV1 Forced expiratory volume
FVC Forced vital capacity
FEV1/FVC ratio
DLCO (diffusion capacity)
TLC (total lung capacity)
Inhalers
Inhaled steroid use
Systemic steroid use
Chronic Azithromycin Use

Number of hospitalizations in past year
Home O2 use (in Liters)
CPAP/BiPAP use at night
Statin use
Symptoms (i.e. Cough, shortness of breath)

SGRQ baseline
SGRQ Period 1 end
SGRQ Period 2 start
SGRQ Period 2 end
SGRQ 3 months from the end of period 2

CRP at baseline
CRP Period 1 Week 1
CRP Period 1 end
CRP Period 2 start
CRP Period 2 week
CRP Period 2 end

Exacerbation count end of period 2
Time to exacerbation
Exacerbation count at 3 months from period 2