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Study Title: Motivational Interviewing and Air Cleaners for Smokers With COPD (MOVE COPD)

Principal Investigator: Dr. Nadia Hansel

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MOVE COPD Study Statistical Analysis Plan

Study Statistics

Primary outcome variable.

Outcome for Specific Aim #1 was assessed at the end of each monitoring period (except exacerbations and health care utilization outcomes, which was assessed by monthly telephone calls).

The primary outcome was health-related QOL determined using St. George's Respiratory Questionnaire (SGRQ).

Quality of Life: Health-related QOL was determined using the St. George's Respiratory Questionnaire (SGRQ). The SGRQ is a disease specific instrument that contains 50 items in three subscales (symptoms, activity, and impact). Each response has an empirically derived weight, and the total score is calculated from responses to all 50 items.

Secondary outcome variables.

Dyspnea was assessed using the University of California, San Diego Shortness of Breath Questionnaire (UCSD SOBQ, secondary primary outcome) and the Modified Medical Research Council Dyspnea Scale (mMRC), respiratory health status by COPD Assessment Test (CAT) and clinical COPD questionnaire (CCQ). Cough and sputum symptoms were measured by the Cough and Sputum Assessment Questionnaire (CASA-Q). Functional capacity was measured by 6-minute walk distance (6MWD). Information on exacerbations was collected by monthly telephone calls. Moderate exacerbations were defined as those requiring use of systemic steroids and/or antibiotics or urgent health care visit; and severe exacerbations were those requiring emergency department (ED) visit or hospitalization. Pulmonary function was measured as FEV1 and FEV1% predicted according to ATS guidelines.

Clinical and Exposure Assessments.

Demographics, smoking history, comorbidities, medication use, and body mass index (BMI) were assessed. Participants kept a daily Time Activity Diary (TAD) during each week of sampling to track time spent indoors and home smoking behaviors. Indoor air quality was monitored over a one-week period, at each monitoring period, in the room the participant reported spending the most awake time. Measurements included PM2.5 and particles with diameter less than 10 μm (PM10), nitrogen dioxide (NO2), and airborne nicotine. Residential addresses were geocoded to assess census tract poverty rate. Active smoking during study was determined by self-report number of cigarettes smoked per day and salivary cotinine. Smoking in the home was measured by air nicotine, daily report of anyone smoking in home, number of people smoking, and number of cigarettes smoked in home, averaged over the week.

Lung Function: Pulmonary function testing was assessed as FEV1 and FEV1% predicted, that is FEV1, adjusted for age, height, and sex. This was performed according to ATS guidelines using a KOKO® (Pulmonary Data Services, Inc., Louisville, CO) pneumotach connected to a laptop computer. Predicted values for FEV1 and FVC were calculated by formulae of Hankinson, et al. At each examination 3 sets of values will be obtained, and the highest set of FEV1 and FVC measurements were used in the analysis.

Outcomes for Specific Aim #2 (Markers of inflammation and oxidative stress).

Blood: Blood was collected, and several systemic markers of inflammation were selected based on their relevance to long-term outcomes in COPD and air pollution. For example, serum leukocytes, CRP, TNFα, IL-6 and IL-8 have been found to be elevated in subjects with COPD and CRP and TNFα have been associated with exacerbations and disease severity; CRP, IL-6 and IL-8 have been associated with annual decline in lung function in individuals with COPD; and fibrinogen has been linked with worse COPD severity and future mortality. In addition to their relevance to COPD, these systemic markers of inflammation have been selected because of their relevance to air pollution (this will include analysis of complete blood count-CBC). Specifically, PM and poor indoor air quality have been associated with increased pro-inflammatory cytokines TNFα , IL-6, IL-8, IFNγ and CRP. Serum was stored at -80°C.

Markers of oxidative stress: Have been associated with COPD and environmental exposures. 8-lsoprostane will be analyzed in serum, and urine using 8-isoprostane F2a Assay Kit.

Urine: Was collected for measurement of markers of inflammation, including 8-isoprostane, as this marker has been shown to be elevated during exacerbations of COPD and has been linked with environmental exposures, including SHS and PM.

Additional Participant Characterization.
A baseline survey was administered to document respiratory status and COPD severity, using survey tools described above. In addition, the baseline survey collected information on:
Demographics: Age, gender, race/ethnicity, socioeconomics stats (SES) including education, employment, marital status, household income, and type of health insurance; family history of lung disease, dietary patterns.
Comorbid illnesses associated with COPD or that can worsen was assessed by self-report in questionnaire, including gastroesophageal reflux, cardiovascular disease, osteoporosis, diabetes, depression/anxiety using the Hospital Anxiety and Depression Scale (HADS), and others.
Home and Other Environment Characteristics: Detailed questions about the current environment was collected with surveys developed from our previous studies. Questions determined exposure to SHS (number of cigarettes smokes in home, by whom), self-reported evidence of mold, evidence of moisture problems, exposure to pets, pests, and other key indoor environmental exposures.
Anthropometric Measurements including height, weight for calculation of body mass index (BMI).
Nicotine dependence measured using the Fagerstrom Test for Nicotine Dependence which is a standard instrument for assessing intensity of physical addiction to nicotine.
Smoking status and quantity. Salivary cotinine was measured to assess smoking status at each visit and to provide a quantitative assessment of exposure.

Social Cognitive measures: For each SCT construct, participants were asked to rate how much confidence, importance, and motivation they had to implement a home smoking ban or quit smoking on a 10-point scale, where 1 is "not at all sure, not at all important, don't want to do it at all", 10 is "completely sure, extremely important, really want to do it every day", and 5 is "somewhere in between". We administered our previously validated measure of SHS positive and negative expectancies and knowledge of SHSe harm, which has been shown to be associated with SHS air nicotine levels.

Analytical approach

We used descriptive statistics to characterize the patient sample, using proportions or means with standard deviations where appropriate. Descriptive statistics of central tendency and variability were generated. The distributions of each variable were assessed for normality, and appropriate transformations were made as necessary.
Primary analysis included an Intention-to-Treat analysis including all subjects randomized and having data at baseline and 6-month. The primary outcome measured included SGRQ score, and the secondary primary outcome, dyspnea, UCSD SOBQ. These outcomes were selected based on preliminary data showing an association with pollutant exposure and because they are measured with standardized instruments, which allowed for comparability across clinical trials. Furthermore, patient-reported outcomes provide insight into the practical effects of disease on everyday life and dyspnea is the primary reason for patients seeking medical care.
Secondary outcome measures included: CAT score, FEV1 and % change in FEV1 after albuterol. In addition, we evaluated respiratory exacerbations which were defined as a worsening of respiratory symptoms requiring antibiotics or oral corticosteroid use and acute health care utilization. The primary outcome for Specific Aim #2 is serum CRP concentrations, however several inflammatory and oxidative stress markers as outlined above will be measured.

In order to compare the change over time in our outcomes between treatment groups, analyses will consist of generalized linear mixed model (GLMM) to account for within-person correlations of the outcome. For the primary outcome measure we used a linear model:

$$E[Y_{ij}] = b0 + b1\ visit_j + b2\ treat_i + b3\ treat_i * visit_j + a'\ visit_j * z_i$$

where Y_{ij} is the total SGRQ score for the i^{th} individual on the visit j, $treat_i$ is the treatment group indicator, $visit_j$ is a numeric visit number, and z_i is a vector of potential baseline covariates. The parameter b3 is the parameter of interest as it quantifies the effect of treatment on reducing COPD symptoms over time. For the analyses of respiratory exacerbations, we used cross-sectional logistic regression of exacerbation event (yes/no) over the course of 6-month follow-up on treatment group, adjusted by the potential baseline covariates; the parameter of interest was the odds ratio of the treatment group, as it represents the effect of treatment on the likelihood of having COPD-related exacerbations.

Confounding: Models above were constructed with and without adjustment for baseline covariates not adequately balanced after randomization and potential prognostic factors. Some potential covariate candidates included age, gender, race, other air pollutants (e.g., ambient pollutant concentrations), climate factors (temperature, humidity), season of recruitment, social

factors (e.g., educational attainment, household income), disease severity, medication use including inhaled corticosteroid use (participants were encouraged to bring their medications to visits), smoking pack-years, presence of HCSB, smoking status and quantity of active cigarette smoking (measured by self-report and salivary cotinine), and baseline level of the outcome.

POWER:

Pre-specified power calculations.

The study was powered for a single outcome. Based on a prior study, pre-intervention and baseline data from the Randomized Clinical Trial of Air Cleaners to Improve Indoor Air Quality and Chronic Obstructive Pulmonary Disease Health: Results of the CLEAN AIR Study,[1] the trial was designed to have a sample size of 120 randomized participants (n=60 per arm), for 80% power to detect a group difference if 1.75 in change of SGRQ score, assuming a SD of 16.7 and residual SD of 6.3, based on within person correlation of 0.86 and an alpha of 0.05, (2-sided).

Table 1 summarizes the power of a two-sided test that the coefficient b3 in the model above is greater than zero at a significance level of 0.05. Power is calculated to detect shown differences in effect size for our main outcomes between groups for a sample size of 60 subjects per group. We used conservative estimates of means and standard deviations to account for uncertainty about actual observed effect sizes and variability and to minimize the chance of Type II error. We assumed a within subject correlations based on the previous study. We show adequate statistical power across a variety of assumptions. For example, we will have 90% power to detect a difference of 2.02 in total SGRQ score and a 1.49 difference in CAT score between groups. The minimal clinical important difference in SGRQ and CAT score is 4 and 2, respectively, therefore we have adequate power to detect a meaningful clinical impact. Furthermore, a similar improvement in SGRQ is seen with traditional COPD therapy, as mean between group difference in SGRQ was 2.7 favoring tiotropium, and 3.1 favoring salmeterol/fluticasone therapy compared to placebo in the UPLIFT[2] and TORCH[3] trials, respectively. These therapies are currently recommended as first line therapy for COPD based on GOLD Guidelines. For Specific Aim #2 we will test the difference between groups and systemic and pulmonary markers of inflammation. Similar to power analysis for Specific Aim #1, Table 1 shows we will have 80% power to detect a 1.15 ng/ml difference in serum CRP between groups. Thus, we demonstrate adequate power across several primary and secondary outcomes.

Table 1 power for sample size of 120 (60 per group)

	Within Corr.	Residual SD	Power = 0.8 Effect size	Power = 0.9 Effect size
Specific Aim #1				
SGRQ Total	0.86	6.3	1.75	2.02
CAT	0.77	3.7	1.30	1.49
FEV_1 (L)	0.94	0.13	0.024	0.027
Specific Aim #2				
Serum IL-8 (pg/ml)	0.55	1.47	0.72	0.83
Serum CRP (ng/ml)	0.32	1.92	1.15	1.33

References

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