INtervention Study In overweiGHT patients with COPD (INSIGHT COPD)

Study Protocol

January 28, 2021

1.0. **SUMMARY OF EDITS:**

8/22/2016; v3.0,

- Section 3.0: Replaced Eric Gunnink, biostatistician, with Peter Rise, who starts August 2016
- Tables 6 and 8: Added as baseline and outcome data element in order to measure Framingham Risk Score
- Section 9.3.1 and 9.6.3. added clarifications and details about intervention format, structure, and content
- Tables 8 and 11: Eliminated spirometry from the 12-month follow-up visit to reduce unnecessary participant burden and reduces needed site resources
- Sections 9.3.2 and 9.7: Updated site payment and participant remuneration information based on finalized capitation allowance. Instead of paying control participant $50 as control equivalence, we will provide control participants with a Fitbit at their 18-month visit

10/25/2017; v3.01

- Section 3.0: Update Lifestyle Coach staff from UIC
- 9.2.4.3: Grammatical error corrected

03/29/2018; v3.10:

- Section 8.1.1. and 9.3: changed FEV1 % predicted from >40 to >30
- Section 9.4: changed mMRC eligibly criteria from a score of 2 to 1

07/18/2018; v4.00:

- Section 3.0: Removed staff to avoid frequent protocol modification; staff information readily available elsewhere
- Throughout: changed target number of participants from 1000 to 680; primary outcome to six-minute walk test distance only at 12 months, with weight moved to secondary
- Section 8.7.: removed payments to site section, updated recommended payment to patients given elimination of 18-month visit
- Section 11.0: added detail about retention efforts

09/04/2018; v4.10:

- Section 8.7: corrected a typo in the amount of recommended payment to participants
- Section 11.: Provided more detailed retention strategies and requiring at least one phone call four-to-eight months after randomization.

10/31/2018; v5.00:

- Section 8.1.1. and 9.3: changed the spirometry eligibility criteria from the ratio of Forced Expiratory Volume in one Second (FEV1) to Forced Vital Capacity (FVC) being less than the lower limit of normal (LLN) to FEV1/FVC being less than a fixed value of 0.70.

01/28/2021; v5.10:

- Throughout: corrected minor typos
- Throughout: corrected inconsistencies in listing secondary outcomes
- Throughout: Removed references to the Fitbit Zip because of model change
- Section 2.0: added abbreviations section
- Section 4.0 and 16.0: updated staff
- Section 10.2 and 10.5: clarified how we are determining diabetes and high blood pressure
- Section 10.2.4.3: corrected description of data entry process
- Section 10.3.1: updated intervention introduction procedures

- Section 10.5: added details on valid reasons for out-of-window visits
- Section 10.6.3: removed incorrect description about automated reminders
- Section 11: Table 10 updated with clarification about source of Other Measures; added details about some measurements; clarified procedures for measurements
- Section 14: updated *a priori* analysis plan
- Section 15: added that PLG will share de-identified data set with NHLBI's data repository

2.0. ABBREVIATIONS

6MWT: six-minute walk test
AE: adverse events
ATS: American Thoracic Society
BMI: body mass index
BP: blood pressure
CMS: Centers for Medicare and Medicaid Services
COIN: Center of Innovation
COPD: Chronic Obstructive Pulmonary Disease
CVD: cardiovascular disease
CVDR: cardiovascular disease risk
CVRFs: cardiovascular risk factors
DPP: Diabetes Prevention Program
DSMB: Data Safety and Monitoring Board
EHR: electronic health records
FEV1: forced expiratory volume in one second
FRS: Framingham Risk Score
FVC: forced vial capacity
GEE: Generalized Estimating Equations
GLB: Group Lifestyle Balance
GOLD: Global Initiative for Chronic Obstructive Lung Disease guidelines
HIT: health information technology
HRQoL: health-related quality-of-life
ICMJE: International Committee of Medical Journal Editors
ICS: inhaled corticosteroid
INSIGHT COPD: INtervention Study In overweiGHT patients with COPD
IRB: Institutional Review Board
LABA: long acting beta-agonists
LMM: linear mixed-effects model
MAR: missing at random
MI: multiple imputation
MICE: multivariate imputation by chained equations
MID: minimum important difference
ML: maximum likelihood
mMRC: modified Medical Research Council
MOP: Manual of Procedures
NEMO: Network Management Core
NHANES: National Health and Nutrition Examination Survey
NHLBI: National Heart, Lung, and Blood Institute
OC: operations committee
PCS: physical component scores
PCT: Pragmatic Clinical Trial
PLG: Protocol Leadership Group
PTC: Pulmonary Trials Cooperative
QoL: quality-of-life
RCT: randomized control trial
REDCap: Research Electronic Data Capture

REML: restricted maximum likelihood
SAE: serious adverse events
SD: standard deviation
SF-12v2: 12-Item Short Form
SGRQ: St. George's Respiratory Questionnaire
SGRQ-C: St. George's Respiratory Questionnaire for COPD Patients
SIBCR: Seattle Institute for Biomedical and Clinical Research
SpO2: blood oxygen saturation level
UC: usual care
UIC: University of Illinois Chicago

3.0. FUNDING SOURCE

National Heart Lung Blood Institute: 1U01HL128868

4.0. RESEARCH CONSORTIUM / STAFF

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5.0. **ABSTRACT**

Approximately 70% of patients with Chronic Obstructive Pulmonary Disease (COPD) are obese or overweight. Tobacco smoking that causes COPD also is associated with other poor health habits that can lead to obesity and cardiovascular disease. Symptoms of COPD are often non-specific and include dyspnea and exercise intolerance. COPD treatment guidelines recommend stepped escalation of inhaled medications to improve these symptoms, but make little mention of the effect of co-existing obesity or weight loss interventions because of insufficient evidence. Cardiovascular disease is a leading cause of mortality among patients with COPD, and obesity is associated with important risk factors for cardiovascular disease including dyslipidemia, hypertension, and diabetes. Comprehensive lifestyle interventions that include calorie-controlled healthy eating, increased physical activity, and behavioral self-management strategies consistently result in modest, clinically significant weight loss and associated reductions in cardiovascular risk factors. That overweight and obese patients with COPD would reap similar clinical benefits from modest weight loss is an intuitive - but untested - concept. Therefore, we are conducting a multicenter, patient-level randomized, pragmatic clinical trial to produce first-ever data on the effectiveness of an evidence-based self-directed lifestyle intervention for 12 months targeting modest weight loss and increased physical activity among overweight and obese patients with COPD. We are serving as a Protocol Leadership Group (PLG) for the National Heart, Lung, and Blood Institute's (NHLBI) "Multi-Site Clinical Trials for the Pulmonary Trials Cooperative (PTC)" in order to test if intervention participants have better outcomes through 12 months of follow-up compared to usual care control patients in terms of exercise tolerance using the *6-Minute Walk Test*. Secondary outcomes include weight loss, dyspnea using the modified Borg scale, generic and symptom-specific quality of life using the *12-Item Short Form* (*SF-12v2)* and *St George's Respiratory Questionnaire for COPD Patients (SGRQ-C),* and major cardiovascular risk factors using Framingham risk score, central obesity by waist circumference, blood pressure and BMI. We will oversee enrollment of approximately 680 patients at multiple clinical sites, chosen and contracted by the PTC's Network Management Core (NEMO). As the PLG for the INSIGHT COPD trial, we will cooperate with NEMO and will provide trial oversight, and data management and reporting.

6.0. BACKGROUND

Obesity is common and may lead to ineffective or even harmful care among patients with COPD. COPD is defined by airflow limitation that is not fully reversible, affects approximately 12 million Americans, and is the 3rd leading cause of death in the U.S.[1,2] Unlike all other major causes of morbidity in the U.S., COPD is the only major condition that has not had significant improvement in mortality in the past 30 years.[3] The leading cause of COPD is cigarette smoking, which is often accompanied by other unhealthy lifestyle habits that lead to physical limitation and weight gain. Being overweight or obese is a leading, if not the leading, COPD comorbidity, affecting up to 70% of patients with COPD. Among obese patients, attribution of dyspnea and other symptoms to COPD is common despite evidence that obese patients with COPD have less severe airflow limitation[4,5] and are less responsive to guideline recommended escalation in inhaled therapies than their non-obese counterparts.[4] Despite the known increase in the work of breathing directly attributable to obesity,[6-11] recently revised (2014) Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines[12] do not address the problem of obesity, except by stating that "it is not advisable to aim for a BMI of less than 21 kg/m^2." The lack of guidance highlights the gap that can lead to the inappropriate use of inhaled medications to treat symptoms of airflow limitation that is potentially attributable to obesity. Obesity directly affects both the physiologic measure of airflow limitation by forced volume of expired gas in 1 second percent (FEV1%) predicted and the report of dyspnea severity, leading to an overestimation of COPD patients' disease severity and potential overtreatment. Obese patients that receive drug treatments for their presumed COPD severity may be subjected to known potential harms such as pneumonia related to unnecessary inhaled corticosteroid (ICS) use[13,14] or potential cardiovascular risk associated with short- and long-acting inhaled bronchodilators.[15-19] Exposing patients to medications that are not effective can only increase the risk, even if the overall risk is small.

Treatment of obesity may modify other comorbid cardiovascular risk factors (CVRFs) in patients with COPD. COPD is an inflammatory disorder that is closely linked to cardiovascular risk;[20,21] in fact, cardiovascular mortality is more common than COPD-specific mortality, highlighting the significance of modifying CVRFs, among patients with COPD.[22] Inhaled bronchodilators and ICS reduce systemic markers of inflammation, but do not improve cardiovascular risk or mortality, among patients with COPD.[23] Smoking cessation is the only treatment known to reduce mortality and improve lung function decline in COPD patients without severe resting hypoxemia,[11] and it reduces cardiovascular risk, but it can also lead to significant weight gain.[22,24,25] The weight gain linked with smoking cessation: (1) is often a concern of patients who are contemplating smoking cessation;[24,26-29] (2) reduces the benefits of smoking cessation on lung function by 38% in men and 17% in women;[30] and (3) lowers protection of cardiovascular risk by worsening of lipid profiles, risk of type 2 diabetes and hypertension.[31,32] In contrast, modest weight loss (3-5% of starting weight) through calorie-controlled healthy eating alone or in combination with exercise effectively lowers major CVRFs, e.g., hypertension, dyslipidemia, diabetes, and inflammatory biomarkers including C-reactive protein.[33-39] That obese patients with COPD would reap similar cardiovascular benefits from modest weight loss is an intuitive - but untested - concept.

Obese patients are more likely to be misdiagnosed with COPD and receive inappropriate medications. In our recently published manuscript,[40] we identified 5,493 patients who underwent pulmonary function testing and carried a clinical diagnosis of COPD. Of these patients, 75% were overweight or obese. We found that after excluding patients for other pulmonary conditions (e.g., asthma), overweight and obese patients were less likely to have spirometric confirmation of COPD (**Table 1)**.

Table 1. Overweight and obesity associated with lower probability of having COPD on spirometry

BMI category	Proportion* with COPD (95%CI)
18.5-<25	0.64 (0.61-0.66)
25-<30	0.53 (0.50-0.55)
30-<35	0.43 (0.40-0.45)
35-<40	0.37 (0.33-0.41)
>40	0.30 (0.25-0.35)
*Adjusted for age, smoking status, race, comorbidity	

We also found that obese patients without COPD were not only less likely to have current inhaled medications appropriately stopped (adjusted absolute proportion 9%, p<=0.01), but were also more likely to have new inhaled medications started (adjusted absolute proportion 5%, p=0.02). Although some of these patient may have had airflow obstruction masked through obesity, these results support the rationale that obese patients are likely being inappropriately diagnosed and treated for COPD, potentially missing the opportunity to appropriately reduce symptom burden and improve CVRFs through a lifestyle intervention.

Body mass index (BMI) explains dyspnea symptoms more than severity of airflow limitation. We sought to assess factors associated with the explained variability in moderate to severe dyspnea, based on modified Medical Research Council (mMRC) dyspnea scores, among 376 patients with COPD. We included sociodemographics, health behaviors, comorbid illnesses, and measures of severity of COPD (medications, FEV1 % predicted). In fully adjusted models, the total amount of explained variance was modest (10.5% total); however, 37.8% of the explained variance in dyspnea was attributable to BMI, comparable to the amount of the explained variance attributable to FEV_1 (35.8%). This finding has important implications because dyspnea symptoms are among the most prominent of COPD, and BMI accounts for a significant amount of the explained variance.

Obese patients have less severe disease, more symptoms, worse health-related quality-of-life (HRQoL), and receive more treatment. We examined the association of obesity and effects on symptoms, HRQoL measures, and medication use in patients with COPD.[4] Patients were predominantly either overweight (n=115, 32%) or obese (n=138, 38%). Obese and overweight subjects had better lung function (obese: mean FEV1 55.4% ±19.9% predicted; overweight: mean FEV1 50.0% ±20.4% predicted) than normal weight subjects (mean FEV1 44.2% ±19.4% predicted; p<0.05 both comparisons), but obese patients reported worse dyspnea (adjusted OR of MRC score ≥2= 4.91; 95% CI, 1.80 to 13.39), poorer HRQoL as measured with St. George's Respiratory Questionnaire (SGRQ) [Minimum Important Difference (MID) for SGRQ total and domains = 4 points; total score: adjusted score 5.93 (95% CI 0.97, 10.88), impact: adjusted score 5.37 (95% CI 0.11, 10.63), and activity: adjusted score 8.16 (95% CI 1.93, 14.40)], and were more likely to be prescribed medications to control COPD symptoms [Long acting beta-agonists (LABA): OR 2.21 (95% CI 1.14, 4.31); ICS: OR 2.34 (95% CI 1.25, 4.40)] than normal weight subjects. We also recently analyzed data from the Burden of COPD study that was performed in the Pacific Northwest. As part of that study, we assessed the effect of obesity on SF-12 adjusting for FEV1% predicted. Consistent with our other preliminary data, patients who were obese had worse HRQoL on physical component scores (Obese PCS score (95% CI): -3.1 (-1.5 to -4.6)) and similar mental health component scores.

Obese patient with COPD have worse six-minute walk test (6MWT) distance and reported dyspnea despite having better lung function. Over a 6-month period, our multicenter CONCERT team recruited over 1,200 patients, of whom 54% had spirometrically confirmed COPD. We found that 73% of the COPD cohort was overweight (35%) or obese (38%). Consistent with our other preliminary data, and when compared to normal weight individuals, we found that obese patients had less severe COPD (FEV1 % predicted 56.7 vs. 44.3 for normal weight; p<0.05) and similar 6MWT distance. Adjusting for the severity of airflow limitation, obese patients had shorter 6MWT distances and worse end-exercise Borg dyspnea scores (**Table 2**).

Table 2. Obesity associated with worse 6MWT distance and dyspnea at end exercise.

BMI Category	Distance walked (ft)	Borg dyspnea
18.5-<25	Referent	Referent
25-<30	-40.9 (25.1, -107.0)	0.02 (-0.39, 0.43)
30+	**-211.4 (-142.3,-280.5)**	**0.66 (0.23, 1.07)**

Obesity paradox among patients with COPD. Obesity has been associated with higher all-cause mortality in the general population.[41] However, the obesity paradox of COPD reviewed in a recent meta-analysis suggests that overweight or obese patients with COPD have better survival than those patients who are at or under normal weight.[42] A number of potential explanations have been proposed for this finding. First, the majority of the studies included in the meta-analysis measured weight cross-sectionally and did not incorporate changes in weight over time. Second, none of the included studies examined purposeful, modest weight loss. Together, these two issues raise the concern that people of lower weight were a mixture of individuals that had purposeful and unintended weight loss. Among patients with severe and very severe COPD, unintended weight loss as well as the inability to gain weight is a poor prognostic factor[43], because the resultant low weight is associated with increased loss of skeletal muscle mass, diaphragmatic weakness, and worse severity of airflow limitation.[44,45] Furthermore, in one study of patients with COPD who were followed longitudinally, an increase in BMI was associated with a non-statistical increase in mortality (BMI category gain: 3+: RR 1.3 (0.9-1.7)).[46] Among obese patients with COPD, high quality clinical trials that encourage modest weight loss through proven comprehensive lifestyle interventions focused on healthy eating, increased physical activity, and behavioral self-management are needed to better guide treatment decisions.

This Pragmatic Clinical Trial (PCT) has high scientific, clinical, and public health significance. Scientifically, the INtervention Study In overweiGHT patients with COPD (INSIGHT COPD) trial offers a new frontier in the COPD and obesity literature by investigating the effectiveness of the E-LITE self-directed lifestyle intervention among overweight and obese patients with spirometry-confirmed COPD. E-LITE has proven effective at producing clinically significant weight loss while improving fasting glucose and lipid control.[47,48] While achieving cost efficiency through simple and pragmatic intervention delivery, we will protect internal validity through patient-level randomization and external validity through broad entry criteria to the population whom it is to be applied and important patient-centered outcomes over a 12-month follow-up period. Clinically, COPD patients with comorbid obesity are a high priority population for behavioral weight loss treatment given the gaps in treatment guidelines and clinical practice, and the potential harm to patients, as discussed above. From a public health and policy perspective, both obesity and COPD are leading causes of morbidity and mortality in the U.S., and their coexistence is prevalent. The proposed adoption of our previously proven lifestyle intervention for weight loss in primary care—one that highlighted in the 2014 USPSTF behavioral counseling recommendations for cardiovascular risk prevention—to treat obesity in COPD aligns with the Institute of Healthcare Improvement Triple Aim: population health management, patient-centered outcomes, and per capita cost efficiency. This study was designed to have high significance scientifically, to clinical practice and the public.

7.0. INNOVATION

The INSIGHT COPD trial is the first experimental study of behavioral weight loss treatment for overweight and obese patients with COPD. On a population basis, the high prevalence of overweight and obesity in adults with COPD suggests an important opportunity to improve the lives of many such individuals. While the clinical treatment of COPD should continue to emphasize implementation of proven pharmacological and non-pharmaceutically based strategies,[12] the available evidence, as cited above, is sufficient to warrant the investigation of including evidence-based behavioral weight loss strategies as an adjunct therapy for COPD patients who are also overweight or obese. In the INSIGHT COPD trial, the primary objective is to investigate whether a highly efficient, self-directed lifestyle intervention focused on calorie-controlled healthy eating, increased physical activity, and behavioral self-management has clinical benefits for reducing weight and improving COPD and comorbid disease outcomes. As noted above, to date, the only studies that have examined obesity or weight loss in COPD have been observational or small studies of patients undergoing bariatric surgery. None of the studies have focused on using a lifestyle intervention that is guideline concordant and, equally importantly, can be applied to a large number of patients in an economical, pragmatic fashion.

The proposed intervention is the only direct adaptation of the landmark Diabetes Prevention Program (DPP) lifestyle intervention using a self-directed delivery approach in primary care. We have modeled the INSIGHT COPD intervention after the successful E-LITE self-directed intervention,[47-49] which uses a curriculum recognized by the National DPP program.[50] The E-LITE adaptions of the DPP intervention were patient-centered, low cost, and pragmatic. Delivery of healthcare requires the implementation of health plans developed in clinical settings (e.g., clinics) in the personal environments (e.g., homes, work places, and social settings). The E-LITE self-directed intervention is portable and designed to be implemented within patients' non-medical environment—enabling them to make healthy choices where they work, live, and play with ongoing support through *existing* health information technology (HIT), and if desired, support from trained lifestyle coaches. Although the intervention is designed to promote a sustained change toward healthier weight and lifestyle that have been shown to reduce the burden of diabetes and CVRFs, our preliminary results (below) and those of others[51-56] suggest that weight loss will lead to improvement in HRQoL (particularly physical health) and physical functioning, outcomes of much importance in COPD. Within the paradigm of outcome-driven clinical decision making, reimbursement, and quality assessment, demonstrated evidence of improvements in clinically relevant, patient-centered, universal health outcomes among patients with COPD and accompanying multimorbidity will have relevance to the wide practice and policy community.

8.0. RATIONALE OF E-LITE AS THE BASIS OF THE INSIGHT COPD INTERVENTION

The overall approach is based on *proven self-directed lifestyle interventions for weight loss in primary care.* The landmark DPP trial established the gold standard in diabetes prevention by demonstrating that an intensive lifestyle intervention targeting modest weight loss and increased physical activity markedly lowered type 2 diabetes incidence (by a mean of 58% net of control) among high risk adults across all age, sex, and race/ethnicity subgroups,[57] the benefit persisted for at least 10 years.[58] Weight loss was the dominant predictor of reduced diabetes risk where every kilogram of weight loss resulted in a 16% reduction in risk.[59]

Table 3. E-LITE intervention key components

	Self-Directed Intervention
1. DPP-GLB 12-weekly sessions*	Take-home DVD (cost: $7 a set)
2. Self-monitoring of progress toward weight & physical activity goals†	Daily monitoring recommended; Coach did *not* routinely review records (cost: free Heart360 and $65/patient for a pedometer and weight scale)
3. Personalized lifestyle coaching‡	As needed, patient-initiated (cost: minimal coach time—2 messages/month/patient)

*The DPP-based Group Lifestyle Balance (GLB) DVD has the 12 core curriculum sessions.[60] Dr. Ma's team includes a DPSC-certified GLB master trainer and several trained coaches.
†Via the American Heart Association free, secure web portal (www.heart360.org).
‡Via secure messaging. Coaches could view Heart360 patient self-monitoring records, which they used to tailor their progress feedback to participants via secure messaging.

Despite the enormous benefit of DPP on diabetes risk, the trial was highly intensive and did not readily lend itself into implementation in clinical practice.

Dr. Jun Ma and team have, through a series of primary-care–based trials, adapted the DPP from the individual and group based program to one where a highly efficient self-directed DVD-based version plus remote monitoring and coaching is comparable in terms of weight loss to more intensive coach-directed versions (see below). A pilot study by the DPP researchers who developed the DVD showed an intervention combining the Group lifestyle Balance (GLB)-DVD and telephonic lifestyle coaching was effective in a primary care practice.[60] As the first randomized control trial (RCT) that has successfully translated the DPP lifestyle intervention into primary care in the U.S.

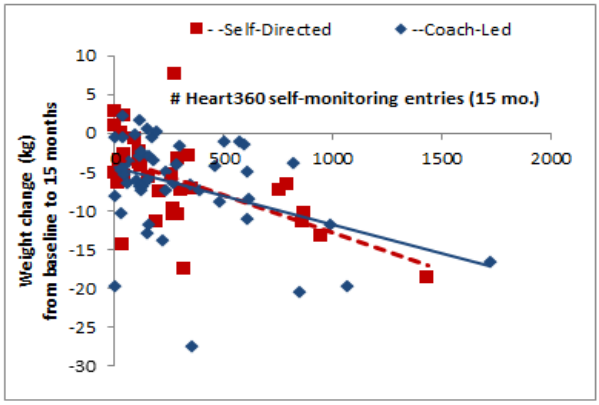


Figure 1. Correlation between weight change and Heart360 usage over 15 months of intervention.

The E-LITE study protocol[49] and primary[48] and additional publications[47,61-64] detail the design, methods, and outcomes. Briefly it was a 15-month pragmatic RCT (n=241) which, for the first time, demonstrated the effectiveness of a **highly portable and inexpensive** self-directed lifestyle intervention (**Table 3**) in a primary care setting that integrated the DPP-based 12-session GLB core curriculum[60,65,66] with technology-mediated lifestyle coaching and self-monitoring among overweight or obese adults with prediabetes and/or metabolic syndrome. Compared with usual care (UC), both E-LITE interventions led to significantly greater weight loss through 15 months, and lower levels of waist circumference, fasting plasma glucose, and total cholesterol,[48] with good reach and adoption.[61] Self-monitoring is the cornerstone of success in behavioral weight-loss interventions.[67] E-LITE results showed a positive relationship between Heart360 self-monitoring frequency and weight loss over 15 months (**Figure 1**).[62] With supplementary funding, results from an extended follow-up through 24 months showed sustained reductions in body weight, particularly in the self-directed intervention group (**Figure 2**).[47]

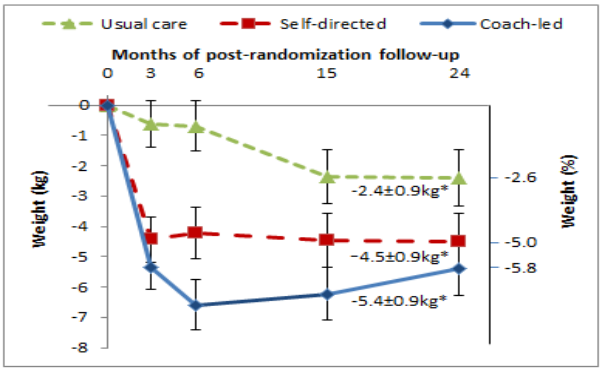


Figure 2. Estimated mean ± SE weight change over a 24-month period, in kilograms (left y-axis) and as percentages (right y-axis), in the intention-to-treat population.

A post-hoc analysis of E-LITE data found that mean standard deviation (SD) changes in the SF-12 physical component scores were 1.6 (4.7) in the self-directed intervention (p = .01), 0.7 (8.5) in the coach-led intervention (p = 0.51), and -0.4 (6.5) in the UC control group (p = 0.66). Increasing physical component scores were significantly correlated with weight loss in both interventions (**Figure 3**). The difference in physical component score change between the self-directed intervention and UC (p = .06; difference, 2.0; 95% CI, -0.1 to 4.0) was 4% of baseline (baseline M [SD], 50.5 [7.5]); 3% was the minimally important difference used in the DPP.[52] The SF-12 mental health scores changed slightly in both E-LITE intervention groups and did not differ significantly from usual care. These findings are consistent with the DPP and other behavioral weight-loss intervention studies.[51-54]

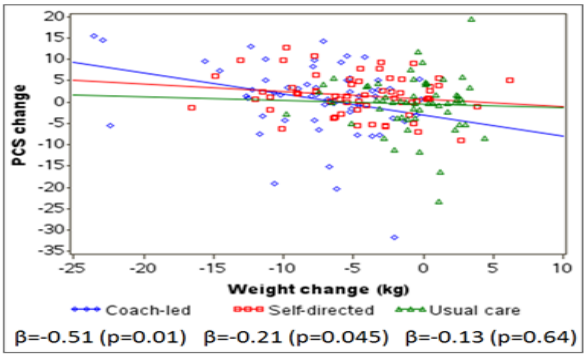


Figure 3. Correlation between changes in weight and SF-12 physical composite score (PCS) from baseline to 15 months.

An integral component to the E-LITE intervention was encouragement of graduated moderate physical activity. As noted above, E-LITE significantly improved SF-12 physical component scores when compared to UC control group. The major drivers of the SF-12 physical component scale scores are questions about the ability to perform physical activities. Although psychometrically valid, the magnitude of increases in SF-12 do not have inherent meaning to patients. From a patient-centered perspective, a common complaint among patients with COPD is the inability to walk significant distances and preliminary evidence suggests that the E-LITE intervention may improve exercise tolerance. The six-minute walk test distance is among the most commonly measured assessments of exercise tolerance. The measure is valid, reliable and responsive with a well-defined demonstrated minimally clinically important difference[68-72]. The measure has been used in multiple clinical trials of COPD and can be used to objectively measure dyspnea at end of test[73,74].

9.0. AIMS

The overall goal of our Protocol Leadership Group (PLG) is to produce first-ever evidence on the effectiveness of a proven pragmatic lifestyle intervention targeted at modest, clinically meaningful weight loss and increased physical activity in overweight or obese patients with spirometry-confirmed COPD. In the 12-month simple, pragmatic clinical trial (PCT), we efficiently focus on the intervention effects primarily on exercise tolerance; and secondarily on weight loss, dyspnea, generic and symptom-specific quality of life (QoL), and cardiovascular risk factors (CVRFs).

We will implement the E-LITE self-directed lifestyle intervention in a multicenter, patient-level randomized PCT of approximately 680 overweight and obese patients with COPD. Our specific aims are to test whether, compared with usual care (UC) controls, intervention participants have better outcomes through 12 months of follow-up, including:

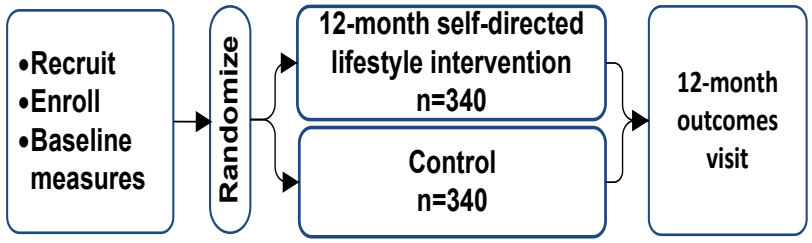
1. **Primary measures**: Exercise tolerance measured with the 6-Minute Walk Test (6MWT) distance at 12 months (primary endpoint).

2. **Secondary measures**: Greater weight loss, less dyspnea measured with the modified Borg scale, improvements in generic HRQoL by the SF-12v2, COPD symptom QoL by the SGRQ-C, and major CVRFs (central obesity by waist circumference, Framingham Risk Score, blood pressure, and BMI).

10.0. STUDY DESIGN

INSIGHT COPD is a simple, two-arm PCT in which approximately 680 overweight and obese COPD patients, aged 40 years and older, will be randomized to UC or UC plus the self-directed lifestyle intervention for 12 months. Follow-up assessment will occur at 12 months (Figure 4). We hypothesize that intervention participants will have better exercise tolerance at 12 months.

Figure 4. Overview of trial design



10.1. **Eligibility Criteria**

Eligible patients are age 40 years or older, overweight or obese, have COPD, and have symptoms of dyspnea. Inclusion criteria are broad to protect feasibility and generalizability. Exclusion criteria are aimed at ensuring each participant's safety and maximizing internal validity including minimizing error associated with the primary outcome, and preventing possible missing data. Specific criteria are:

10.1.1. ***Inclusion***

- 40 years or older at time of eligibility screening;
- Body mass index 25.0-44.9 kg/m^2;
- Smoked at least 10 pack-years of cigarettes;
- Modified Medical Research Council dyspnea score of 1 or higher, i.e., "I get short of breath when hurrying on the level …";
- COPD, defined as an FEV1/FVC less than 0.70 and FEV1% predicted greater than 30;
- Access to DVD player or internet in order to view the 12 GLB sessions;
- Consent to the study protocol/procedures including:
    - time and data collection requirements of the study;
    - randomization to one of the two intervention arms;
    - adherence to the recommendations of the study intervention as assigned;
    - authorizing extraction of relevant information from their medical records.

10.1.2. ***Exclusion***

- Inability to speak, read, or understand English;
- Active weight loss interventions including:
    - use of prescription weight-loss medications in the past 3 months,
    - current participation in group or individual weight loss programs provided by trained personnel (attending peer support groups or following a self-help weight management book, "boot camp," or diet is not an exclusion),
    - had bariatric surgery or plans to undergo bariatric surgery during the study period;
- Expected weight loss because of alternate explanations, such as from illness;
- Unable to ambulate to weight scale for weight measurement;
- Safety and/or adherence concerns due to severe physical or mental health issues or life expectancy <18 months;
- Pregnant, lactating, or planning to become pregnant during the study period;
- Participation in other intervention studies.

10.2. **Recruitment, screening, and baseline assessment**

NEMO-contracted clinical sites will enroll approximately 680 overweight and obese patients with spirometry-confirmed COPD. Clinical sites will have coordinators identified and trained to perform the protocol. Specific procedures are described in the Manual of Operations.

Patients may be identified in usual approaches including clinic, other patient or provider referrals as in other clinical trials. Given the volume and timeline for the recruitment processes, clinical sites may benefit from using an existing electronic health records (EHR) or clinical/COPD registry.

10.2.1. ***EHR/COPD registry-based pre-screen***

Using a Waiver of HIPAA Authorization, the screening process for each cohort begins with identification of individuals who meet the following inclusion criteria using relevant data in the patients' EHR or via a COPD registry as available by the site. Other criteria may be applied according to available resources:

- Age 40 years or older;
- BMI 25.0-44.9 kg/m^2 during the past 6 months;
- Diagnosis of COPD.

10.2.2. ***Initial invitation***

Sites send patients identified via the EHR or COPD registry an invitation to participate via EHR-integrated secure messaging (if user), email (if available and allowed by the Institutional Review Board [IRB]), or mail. A letter and/or Information Statement, depending on site IRB requirements, will describe the research activity and instruct patients how to self-screen online, request additional information, or decline further participation by returning an opt out postcard. The invitation also explains that clinical center staff will contact them on behalf of the study to assess interest if they do not respond within 2 weeks.

10.2.3. ***Initial online, telephone, and/or clinic recruitment***

Using a *Waiver of Documentation of Informed Consent, or Waiver of Consent* (depending on site IRB requirements), patients identified by any of the above methods, and who desire to be screened may complete a Research Electronic Data Capture (REDCap) on-line self-screen and/or telephone screen with a site coordinator. Those patients who choose to complete the on-line screen will answer brief questions regarding major exclusions (Table 4). If their answers indicate potential eligibility, or if no response has been received after two weeks of sending the invitation, sites contact the potential participant for a more detailed telephone screen. An "Eligibility Pre-review" can be conducted by the sites before contacting the participant (to screen for basic eligibility criteria (if site IRB approved). The telephone screen includes eligibility criteria listed in Table 4. The telephone screening questions may also be asked in-person if recruiting at a pulmonary clinic. If the potential participant is eligible based on their answers to the screening questions, the site coordinator asks spirometry safety questions prior to scheduling an in-person eligibility screen and baseline visit. The safety questions confirm that the participant has no temporary conditions that would preclude the subject from doing spirometry. In the event that the participant has a condition that would preclude testing in the short term, staff should arrange to call the participant back at a later date to complete another telephone screen and schedule the visit then.

Sites may send a paper copy of the baseline questionnaires (SF-12v2 and SGRQ-C) to the potential participant for completion prior to the person's visit. Questionnaires will only be collected after the Informed Consent Form is signed. Table 4 summarizes the screening assessment questions and measures:

Table 4: On-line, telephone and/or in-person screen

Assessment/activity	Measure
Send invitation	• Refusals via postcard
On-line self-screening	Self-report: • Age • Sex • Pregnancy/lactation for those indicating "female" • Self-report height and weight for BMI calculation • Smoking history (yes/no) • Dyspnea (yes/no)

Telephone/In-person screen: eligibility criteria	Self-report: • Age • Sex • Pregnancy/lactation for those indicating "female" • Self-report height and weight for BMI calculation [Note: The above completed by phone only if not already done by patient online self-screen] • Smoking pack years • mMRC dyspnea scale score • Weight loss programs/surgery • Participation in other intervention studies • Expected weight loss for other reasons, e.g., illness • Willing/able to complete surveys in English • Willing to participate with intervention protocols • Able to ambulate for weight measurement • Able to return for 12-month follow-up • Access to DVD/internet for GLB sessions
Telephone/In-person screen: spirometry safety check [Complete if patient screened eligible]	• Temporary spirometry contraindications o Heart attack or unstable angina in last 30 days o Detached retina or eye surgery within past 30 days o Breathing problems gotten worse in the last week o New prescription for antibiotics or oral steroids for acute exacerbation) o Other

10.2.4. ***In-person visit: screen and baseline visit***

All study visits will take place at clinical sites, and require a well-illuminated, quiet, setting that protects patient privacy. In addition, a NEMO certified 6MWT course should be available in the immediate vicinity.

10.2.4.1. Informed Consent:

The visit begins with a site coordinator obtaining the participant's written informed consent. The coordinator reviews with the participant the Informed Consent Form, detailing the responsibility of the participant to INSIGHT COPD, the responsibility of the investigators and staff to the participant, and participant's personal risks and benefits, the concept of random assignment and what each treatment group involves, and stresses the importance of follow-up assessment even if he/she is not adhering to the assigned treatment. This process meets the ethical obligations to maximize participants' understanding of information required for an informed decision regarding participation in the INSIGHT COPD trial, and improves retention by developing rapport between the participant and research staff. Each stage in the screening and enrollment process includes a clearly written description of information relevant to that stage and ample opportunities to answer participants' questions. Even when printed information is provided, research staff must verify that the participant understands what he/she has read and heard.

To maximize retention and assure that participants fully understand the demands and nature of the study before they enroll, recruitment staff will carefully review study requirements with the participants, explain the concept of random assignment and what each treatment involves.

10.2.4.2. HIPAA Waiver:

Participants sign a HIPAA authorization in order that sites may review the medical record for eligibility confirmation, to supplement outcome measures as appropriate, and to share the research data with the PLG and NEMO.

10.2.4.3. Demographics and confirmation of eligibility:

After the participant has signed the Informed Consent Form, a site coordinator assesses the measures summarized in Table 5 in order to assess the participant's eligibility. For items already answered via the on-line survey or telephone/in-person screen, answers will be verified to confirm accuracy. Those who are not eligible will be so informed and free to leave.

The table below is a summary of activities included in the consent and eligibility confirmation process. All data will be either directly entered into the INSIGHT COPD REDCap database, or recorded on a paper form for later entry into REDCap. For self-report surveys, the following options are available depending on participant preference and site infrastructure:

- Completion prior to visit: sites may mail surveys to participants for completion at home and will be brought to the study visit. The coordinator will collect the completed surveys *only after* Informed Consent is signed and if the participant is found to be eligible to participate. The coordinator will review the responses for completeness and ask for clarification as necessary. Surveys responses will be entered into REDCap after the visit.
- Completion at the visit: If not completed prior to the visit, participants are strongly encouraged to complete the surveys on paper at the study visit with data entry by the coordinator after the visit. Alternatively, the coordinator may ask participants the questions and enter answers directly into REDCap.

Table 5: Consent, demographics, and eligibility confirmation

Assessment/activity	Measure
Informed consent and HIPAA authorization	Date of signature acquired (Informed Consent and HIPAA)
Demographics	Self-report: • Date of birth • Sex • Race • Ethnicity • Marital status • Educational • Employment status • Healthcare and prescription coverage
Self-report eligibility criteria (supplement/confirm telephone responses)	Self-report: • Date of birth • Pregnancy/lactation for those indicating "female" • Smoking pack years • mMRC dyspnea scale score • Weight loss programs/surgery • Participation in other intervention studies • Expected weight loss for other reasons, e.g., illness • Willing/able to complete surveys in English • Willing to participate with intervention protocols • Able to ambulate for weight measurement • Able to return for 12-month follow-up • Access to DVD/internet for GLB sessions
Height	Measure height
Weight	Measure weight
BMI	Calculated from height and weight
Spirometry	Measure pre and post bronchodilator: • FEV1/FVC • FEV1

	• FVC

10.2.4.4. Additional baseline measures:

For those who are determined to be eligible to participate, the coordinator assesses the measures summarized in Table 6.

Table 6: Additional baseline measures

Assessment/activity	Measure
Vitals	• Blood oxygen saturation level (SpO_2) • Resting heart rate
Exercise tolerance	• 6MWT distance • Modified Borg dyspnea and leg fatigue rating pre and post 6MWT

CVDR	• Waist circumference
	• Framingham Risk Score:
	  ○ age
	  ○ gender
	  ○ smoking status
	  ○ systolic BP
	  ○ self-report use of BP medication
	  ○ self-report diagnosis of diabetes
	  ○ self-report use of diabetic or hypoglycemic medication
	  ○ BMI
	• Blood pressure

Self-report surveys	• General health status (SF-12v2) • Health inventory checklist • Medications • Health care utilization • COPD symptoms (SGRQ-C)

10.2.4.5. Pre-randomization eligibility and safety screening:

A site study investigator or appropriately qualified designee reviews the participant's research enrollment record for eligibility, including adequacy of spirometry and existence of any safety concerns and health-related suitability prior to randomization. If deemed appropriate, the coordinator will randomize the participant via REDCap.

10.3. **Randomization**

All of the baseline assessment measures listed in Tables 5 and 6 must be completed prior to randomization. A site coordinator will randomize the participant using the REDCap randomization function. The unit of randomization will be the participant, performed at a ratio of 1:1. We will stratify each site on smoking status (current smoker vs. non-smoker). In order to maintain blinding of the outcome assessors to the randomization assignment, sites may choose to:

- Have one coordinator conduct the baseline assessment, conduct randomization, and orient those in the intervention arm to the intervention, then have a different trained coordinator conduct 12-month outcome assessments; or
- After baseline assessment, hand-off the participant to a different coordinator who only will conduct randomization and orient participants to the intervention, and who will not conduct outcome assessments.

10.3.1. ***Participants randomized to the intervention***

Intervention introduction: A site coordinator provided the intervention materials (Table 7), set the participant up with MyFitnessPal and Fitbit website accounts, and link the account with the INSIGHT COPD lifestyle coach account. A lifestyle coach will introduce the participant to the intervention materials during the phone orientation with procedures including: reviewing the schedule and process for using the 12-weekly GLB DVDs or online videos and handouts and 10 post-core session materials; providing instruction on how to use the Fitbit activity tracker and weight scale for self-tracking; synchronizing the activity tracker with Fitbit.com or mobile application; logging weight, diet, physical activity, and session completion into MyFitnessPal or on Keeping Track Booklets; checking biweekly messages from the lifestyle coach on MyFitnessPal; and contacting the lifestyle coach via MyFitnessPal and phone, and at the participant's discretion, by email and/or texting.

The INSIGHT COPD trial is using MyFitnessPal instead of Heart360, which was used in E-LITE trial, for the following reasons:

- Ease of use for participants: one login in MyFitnessPal vs. two for Heart360 because the latter requires a HealthVault account as well.
- Availability of dietary self-tracking in MyFitnessPal, but not in Heart360.
- Successful switch from Heart360 to MyFitnessPal in Dr. Ma's R01s (HL119453 and HS022702), funded after the completion of E-LITE.

Intervention Orientation: The lifestyle coach contacts intervention participants via phone within 1 – 2 business days of randomization to schedule a phone orientation session. The orientation session should take place within two weeks of randomization to the extent possible, although deviation from this schedule is permissible to accommodate participants' scheduling needs and preferences. In the orientation session, the coach will review the program, benefits and options for using his/her lifestyle coaching expertise, and answer any questions (see section 9.6.3. "Intervention Format, Structure, and Content" for additional details).

Table 7: Intervention materials

- Group Lifestyle Balance™ DVD or online videos
- Post Core Support Physical Activity DVD
- GLB Binder and participant handouts pertinent to the 12-week core intervention activities and to the post-core activities for the remainder of the 12-month intervention
- Weight scale
- Fitbit activity tracker/ instructions/batteries
- The Calorie King™ Calorie, Fat and Carbohydrate Counter book
- Keeping Track Booklets and postage-paid return envelopes (alternative or complement to tracking via MyFitnessPal and Fitbit)
- MyFitnessPal and Fitbit Account Setup Instructions
- Lifestyle coach contact information/options

*10.3.2. **Participants randomized to the control***

These participants are instructed to continue their usual diet and exercise activities and weight management practices as desired. Control participants will be given a Fitbit activity tracker at their 12-month visit to approximate the weight and activity aids the intervention group received.

*10.3.3. **All participants***

All participants receive a tote bag, water bottle, and refrigerator magnet that display the INSIGHT COPD logo. The PTC supplies these items to sites.

10.4. Time Commitment

*10.4.1. **Control group***

- Total time for the coordinator is approximately 3.5 hours.
- Total time for the participants is approximately 2.5 hours.

*10.4.2. **Intervention group***

- Total time for the coordinator is approximately 4.0 hours.
- Total time for the participants is approximately 3.0 hours.

10.5. **Follow-up Visit and Data Collection**

Participants complete a follow-up visit at 12 months post enrollment. The target time window for completion is +/-2 weeks of the index post-randomization date; however, events outside the influence of the site may prevent this; therefore, it is acceptable to conduct the visit within +/-4 weeks. Visits that occur outside of the acceptable window must be accompanied by justification. Acceptable reasons include participant illness, or inability to reach the participant, participant not able to travel to the site, or suspended visits because of the COVID-19 pandemic. The site is expected to schedule and complete a follow-up site whenever possible even if it falls outside the acceptable window. The staff person conducting these assessments must be different from the person who conducted and oriented the participant to the randomization assignment. The coordinator will assess the measures summarized in Table 8.

Table 8: 12-month measures

Assessment/activity	Measure
Weight	Measure weight
Vitals	• Blood oxygen saturation level (SpO_2) • Resting heart rate
Exercise tolerance	• 6MWT distance • Modified Borg dyspnea and leg fatigue rating pre and post 6MWT

CVDR	• Waist Circumference
	• Framingham Risk Score:
	  ○ age
	  ○ gender
	  ○ smoking status
	  ○ systolic BP
	  ○ self-report use of BP medication
	  ○ self-report diagnosis of diabetes
	  ○ self-report use of diabetic or hypoglycemic medication
	  ○ BMI
	• Blood pressure

Self-report surveys	• General health status (SF-12v2) • Health inventory checklist • Medications • Health care utilization • COPD symptoms (SGRQ-C)
Spirometry	Measure pre and post bronchodilator: • FEV1/FVC • FEV1 • FVC
Intervention adherence	• Self-report DVD viewing: number of sessions viewed self-tracked by participants via MyFitnessPal or paper booklets)

10.5.1. ***Time Commitment:***

- Total time for the coordinator is approximately 2.25 hours for all participants;
- Total time for the patients is approximately 1.25 hour for the 12-month follow-up

10.6. **Intervention**

For patient safety and generalizability, participants in both the control and intervention arms will continue to receive standard medical care from their usual providers. We chose UC only for our control group because pragmatic RCTs are most useful in testing interventions in real-world settings and addressing the question "how does the intervention compare to what we are doing now?". The study is also designed not interfere with ongoing patient care. To control for changes in medical practice and secular trends and to protect external validity, no participant will be restricted from seeking weight loss treatment once enrolled.

10.6.1. ***Theoretical Basis***

The self-directed lifestyle intervention approach is grounded in Social Cognitive Theory[75] and uses time-tested self-regulation strategies (goal setting, self-monitoring, action planning, and problem-solving) to achieve and maintain realistic intervention goals: 5-10% of baseline weight and at least 150 minutes per week of moderate-intensity physical activity. It stresses a triadic, reciprocally deterministic relationship between the individual, environment, and behavior, and it recognizes that self-efficacy is enhanced through social support and gradual mastery of self-regulation skills. Further, it builds on the premise that long-term changes in diet and exercise and sustained motivation to maintain behavior changes are most likely to occur when the strategies used to motivate and support behavior change are flexible, sensitive to cultural and individual differences, and broadly acceptable to those in the target population. The program promotes the following goals.

10.6.2. ***Evidence-based Intervention Goals***

Weight: The intervention is designed to achieve and maintain a weight loss of 5-10% of baseline body weight in a gradual stepwise fashion. This amount of weight loss is safe, feasible and associated with clinically significant reductions in the risk of diabetes and CVRFs. To help achieve and maintain the weight goal, participants are advised to reduce their calorie intake by 500-1000 kcal/day, as recommended in adult obesity guidelines. Participants will gradually achieve the calorie goals through portion control, choices of low-energy nutrient-dense meals and snacks (e.g., whole fruit, vegetables, whole grains, and low-fat, unsweetened dairy products), reduced consumption of refined and/or added carbohydrates/sugars, healthy food preparation techniques, and careful selection of restaurant items.

Physical Activity: The physical activity goal is to achieve and maintain a minimum of 150 minutes per week of moderate-intensity physical activity (such as brisk walking). This goal is consistent with the 2008 Physical Activity Guidelines for Americans, and is deemed safe and attainable for most adults, including those with chronic conditions such as COPD. Participants will gradually and steadily increase daily walking with a goal of achieving 150 minutes of brisk walking per week by the end of the 12-week DVD program. They may also choose to adopt regular activities of moderate intensity other than brisk walking. After attaining the minimum goal of 150 minutes per week, participants may choose to be more active; or if participants reach the 150-minute goal but are not achieving the weight goal, they should further gradually increase to 60 minutes/day of moderate physical activity.

10.6.3. ***Intervention Format, Structure, and Content***

There is a national call for the provision and coverage of multicomponent lifestyle interventions for obesity in primary care settings.[76-78] The challenge historically with such interventions is that they are often too intensive to implement in the real world. The Centers for Medicare and Medicaid Services (CMS) reimbursement policy promotes brief (15 minutes), lower-intensity (compared with efficacy studies), face-to-face behavioral counseling within a limited timeframe (i.e., 6-12 months).[77] The E-LITE interventions[48], upon which INSIGHT COPD is modeled, fit this general pragmatic framework with likely better efficiency due to use of technology. The INSIGHT COPD trial will contribute to the evidence base needed to inform and guide policy change, in the context of growing interest and evidence in technology-based interventions.

INSIGHT COPD consists of a 12-month intervention that will have 2 distinct stages: core curriculum (months 1-3) and post core (months 4-12). The core curriculum will be delivered using the GLB DVD or on-line viewing option, with supplementary remote lifestyle coaching at the participant's discretion. The intervention orientation is described in Section 9.3.1. The coach will contact intervention participants within two weeks of randomization for phone orientation, to review the coach role in the intervention, and describe how participants may request coaching if desired. Also, the coach will send biweekly standardized messages via MyFitnessPal as reminders and/or to reinforce the lifestyle change recommendations in the videos.

The lifestyle coach will monitor intervention adherence by downloading participants' self-monitored data from MyFitnessPal and Fitbit web and mobile technologies. For participants who do not use these tools, they will be instructed to mail their booklets every month. The coach will also document the number and content of contacts with participants in a REDCap database.

The main objective of the core stage is to facilitate gradual weight loss through progressive healthful changes in diet quality and physical activity and behavioral skills training. The post core stage is focused on continued gradual weight loss as well as maintenance through participants' self-directed continued dietary and activity changes, and implementation of self-regulation skills through an iterative self-guided mastery process.[79] The intervention components of the core curriculum stage include:

- the 12-session GLB-DVD or on-line session;
- goal setting and self-monitoring via the MyFitnessPal web and mobile technologies (to include: www.MyFitnessPal.com);
- use of the Fitbit activity tracker and Fitbit.com web and mobile technologies;
- use of a weight scale;
- lifestyle coaching, available at patient request, by phone or by MyFitnessPal secure messaging. Option for personalized lifestyle coaching will continue throughout the post core stage. Lifestyle coaches in Dr. Ma's team will be available by phone or by secure messaging that is embedded in the free MyFitnessPal web and mobile technologies.

Self-monitoring is key to success in behavioral weight-loss interventions.[67] E-LITE results supported a hypothesized positive relationship between the frequency of self-monitoring on Heart360 and the amount of weight loss.[62] At the start of the intervention, sites will provide each participant in the treatment arm with a Fitbit activity tracker and a standard bathroom weight scale. Participants will be strongly encouraged to self-monitor diet, activity, weight, and session completion through MyFitnessPal and the Fitbit throughout, and beyond the 12-month intervention. Participants will also connect their Fitbit device with their Fitbit.com account, which enables synchronized transfer of their Fitbit daily steps. These features greatly enhance the intervention's reach and adoption potential given that use of the internet and mobile technology is ubiquitous in the U.S.

10.7. **Payments/Remuneration**

Recommended study participant remuneration (depending on local IRB requirements) is $40 for completing the baseline visit and being randomized. For randomized participants, the recommended remuneration is $110 for completing the 12-month follow-up. Table 9 summarizes recommended participant payments. Control patients will receive a Fitbit and the end of the 12-month visit. Because of the June 2018 protocol change eliminating the 18-month visit, sites should ask participants who have already completed the 12-month visit to return to complete spirometry, receive a Fitbit if they were in the control group, and receive final remuneration.

Table 9: Recommended participant payments

	Baseline, randomized	12-month
Screen fail	--	--
Randomized, either group	$40	$110

11.0. **MEASUREMENTS**

Table 10 summarizes measurement and timing of data collection:

Table 10: Timing of measurements and data collection

	Source	Baseline	12-month
Primary outcome			
Six-minute walk distance	Measured	x	x
Secondary outcomes			
Weight	Measured	x	x
Modified Borg Dyspnea scale	Questionnaire	x	x
12-Item Short Form (SF-12v2)	Questionnaire	x	x
St. George's Respiratory Questionnaire-C	Questionnaire	x	x
CVD risk			
Framingham Risk Score	Measured/ Calculated	x	x
Waist circumference	Measured	x	x
Blood pressure	Measured	x	x
BMI	Calculated	x	x
Other measures			
Height	Measured	x	
Leg fatigue	Questionnaire		
Spirometry	Measured	x	x
Health inventory checklist	Questionnaire	x	x
Medications	Questionnaire	x	x
Health care utilization	Questionnaire	x	x
Demographics	Questionnaire	x	
Intervention: self-monitoring; coach communications	MyFitnessPal; Keeping Track Booklets; REDCap	Throughout 12-month intervention period	

11.1. **Anthropometric measures**

Height, weight, and waist circumference[80-82], are measured with participants wearing light indoor clothes without shoes, using a stadiometer, digital or balance beam scale, and tape measure, respectively. We will use standardized protocols published by the *PhenX Toolkit*[81] and the *National Health and Nutrition Examination Survey (NHANES) Anthropometry Procedures Manual*.[83] BMI will be calculated.

11.2. **Exercise tolerance**

Exercise tolerance is assessed with the 6MWT, a widely used assessment of functional exercise capacity in subjects with COPD. The test has been shown to be reliable, safe and valid for measuring functional status in COPD. A coordinator will measure how far an individual can walk in six minutes breathing room air using ATS guidelines.[84] Participants that use walking aids will use them while completing the 6MWT. Participants that use supplemental oxygen are allowed to use supplemental oxygen during the 6MWT.

11.3. **Spirometry**

Lung function is assessed with spirometry which is considered the gold standard for assigning the diagnosis of COPD. We will conduct the testing according to the American Thoracic Society (ATS) recommendations[85], and ask participants to refrain from taking inhaled medications for breathing during the six hours prior to their visit, unless they are having trouble with their breathing. Spirometry is a routine clinical measure that requires the patient to blow forcefully into a tube for at least six seconds for three-to-eight times until three acceptable results show repeatability. Coordinators will administer this test both before and after the participant inhales a bronchodilator, and measure forced vial capacity (FVC) and forced expiratory volume in one second (FEV1).

These measurements will allow us to determine the presence of COPD by calculating the FEV1/FVC and FEV1 percent predicted using each subject's age, height, weight, and ethnicity. Participants are eligible to participate in INSIGHT COPD if their FEV1/FVC is less than 0.70 and FEV1% predicted >30.

11.4. **Dyspnea and fatigue**

Modified Medical Research Council (mMRC) dyspnea score:[73] Used to assess study eligibility. The mMRC asks patients to recall the degree to which every-day activities elicit dyspnea, scored on a 5-point scale with higher scores indicating greater dyspnea. Participants are eligible to participate in INSIGHT COPD if they score 1 or higher ("I get short of breath when hurrying on the level or walking up a slight hill").

Modified Borg Scale: [86-88] Used to assess dyspnea and leg fatigue level before and after the 6MWT. This scale assesses symptoms at the time of exercise and does not require patient recall. Scores on the modified scale range from 0 (nothing at all) to 10 (very, very severe).

11.5. **Cardiovascular risk factors (CVR)**

CVR is assessed by waist circumference, the Framingham Risk Score (FRS),[89] blood pressure and BMI. The INSIGHT COPD trial will use the FRS non-laboratory predictors to estimate participants' 10-year risk of myocardial infarction and coronary mortality using age, BMI, systolic blood pressure, smoking status, presence of diabetes assessed by self-report diabetes diagnosis or use of diabetes medication , and self-report use of medication for high blood pressure.

11.6. **Vital signs**

Pulse: Measured in conjunction with the 6MWT according to standardized procedures.

Blood pressure (BP): Measured in conjunction with the 6MWT and used as part of the FRS. Measured using an automatic or manual blood pressure cuff that meets the recommendations of the American Heart Association.[90]

Blood oxygen saturation (SpO_2): Measured with an oximeter in conjunction with the 6MWT using standardized procedures.

11.7. **Self-administered instruments**

Demographic and health inventory: Sites ask participants about their socio-demographic characteristics, health behaviors (e.g., smoking, use of personal trainer), comorbid conditions, family history of lung disease, respiratory symptoms, supplemental oxygen, sleep disturbance, COPD exacerbations, medications, and health care utilization.

Generic HRQoL:[91] Assessed using the 12-Item Short form Health Survey (SF-12v2),[91] which is well validated and has physical and mental health component scores.

COPD symptom QoL: Assessed using the St George's Respiratory Questionnaire-C (SGRQ-C). The SGRQ-C, specifically for COPD patients, is a 40-item survey designed to measure health status for chronic airflow limitation. It has two parts that produce Symptom scores and Activity and Impacts scores, as well as a Total score. The SGRQ-C was derived from the original version following detailed analysis of data from large studies in COPD. The intention was to remove the items with the weakest measurement properties in the original instrument, but at the same time ensure that its scores were directly comparable with the original SGRQ.[92]

11.8. **Additional Process Measures**

Data on the proportion and representativeness of patients willing to participate, as well as reasons for declining to participate, are used to assess the potential reach and the likelihood of adoption of the INSIGHT COPD intervention.

12.0. **SAFETY**

This trial has minimal risk, as demonstrated by the excellent safety data in E-LITE.[48] To ensure unbiased determination across treatment arms, the PLG will train clinical center staff to systematically query participants about possible adverse events (AEs) and serious AEs (SAEs) at each scheduled data collection time-point using a body system-based approach. A clinical site clinician (MD, nurse, or other appropriately qualified personnel) will perform safety monitoring based on the AE query forms completed by their center staff, and then make a determination regarding event seriousness, expectedness, and study relatedness. Events rated as serious and unexpected are reviewed by a PTC medical monitor. Sites will report events to their local IRB, the NEMO, Data Safety and Monitoring Board (DSMB), and/or the NHLBI according to all timelines required by these entities.

The PLG will summarize on a semi-annual basis the number of AEs and SAEs for each unidentified treatment group as specified by the NEMO DSMB.

AEs and SAEs will be reported to the IRB, DSMB, and Sponsor. Summaries will also be included in the annual progress reports to the sponsor. At the discretion of the DSMB, the Chair may request unblinded results in order to determine the nature and extent of effect of the experimental intervention. Should the DSMB make this request, it will be fulfilled following a procedure which will maintain blinding of the investigators and the staff involved in follow-up data collection and analysis. If, at any time, the investigators believe they are seeing an unexpected increase in SAEs or in AEs that are a cause for concern, this will be specifically brought to the attention of the DSMB and their advice will be sought.

Sites will also follow and comply with their own local institution's adverse event reporting requirements. These reporting requirements may be more stringent than those adopted by INSIGHT COPD. Regardless of what INSIGHT COPD requires, each site must comply with their local IRB's requirements. Depending on the local requirements, a site may report events locally that are not reported to INSIGHT COPD.

Stopping rules. Given that the follow-up period is are 12-months, and that the intervention is considered feasible for not only healthy adults, but also older adults and adults with chronic conditions or functional limitations, formal stopping rules for safety, efficacy, and futility are not proposed. Interim monitoring of study outcomes for evidence of efficacy or futility is not planned. Evidence of extremely low rates of patient accrual, extremely high rates of patient drop-out, and/or a marked preponderance in the rates of SAEs in the either study arm will trigger further consideration of both statistical and clinical evidence by the DSMB to decide whether the trial should continue. The DSMB will carefully weigh the risk of completing the trial as planned against the risk of prematurely stopping the trial for safety or futility.

DSMB recommendations. At the end of each meeting, DSMB members will make a recommendation regarding the continuation of the trial and the date and format of the next meeting. In addition, there will be an evaluative statement regarding AE/SAEs, protocol exceptions, and other matters of data quality, integrity of the trial, and timeliness. The DSMB's findings and recommendations will be documented in the meeting minutes and transmitted to the Investigators for their information and action. They also will be incorporated into the annual Progress Reports to the sponsor.

13.0. **RETENTION**

Retention of participants is an essential component of conducting clinical trials so that the investigators can detect differences in outcomes between the intervention and control groups, and so that they can generalize study findings. Sites will use the following strategies to maximize participant retention, including contacting participants at regular intervals between the baseline and 12-month visit to thank them for participating and remind them of their commitment to complete the 12-month visit. At least one of the contacts must be by telephone four-to-eight months after randomization:

Table 1. Retention strategies by timepoint
(apply to ALL participants, regardless of randomized group)

	Strategy	Baseline	Between visit	12-month visit
Participant Experience	Careful staff selection & standardized training in rapport building, interviewing techniques, trial-specific protocols, and problem-solving techniques as appropriate to study roles	x	x	x
	Maintain atmosphere that allows participants to feel comfortable and valued, and is professional and efficient	x	x	x
	Contacts by same staff member for continuity as possible while maintaining blinding	x	x	x
	Careful eligibility screening	x		
	Consider clinical no-show rate when determining eligibility*	x		
	Careful explanation of study requirements and random assignment, including importance of attending follow-up visit (even if not adhering to treatment assignment); assurance ppt fully understands expectations	x	x	
	Give clear instructions for completing questionnaires and measurements	x		x
	Keep visits running on time • modified shortened visit to obtain primary outcome data as necessary	x		x
	Snacks or meal vouchers as appropriate*	x		x
	Schedule follow-up at baseline	x		
	Flexible scheduling to accommodate participant's needs	x		x
	Participant incentives, as appropriate, e.g.: • Free parking and/or transportation* • Sufficient remuneration	x		x
Participant Engagement	Promote study identity, e.g.: • refrigerator magnet • water bottle	x	x	
	Maintain current contact information, including a secondary contact as appropriate	x	x	x
	Maintain regular contact (at least every 4 months), e.g.: • at least one contact by phone four-to-eight months after randomization • holiday or birthday cards/calls • regular participation reminder letter/calls • greet at clinic visits		x	x
	Begin process of scheduling follow-up visit 2-3 months prior to 12-month date			x
	Confirmation letter at least 1 week before appointment			x
	Appointment confirmation call ~3 days before visit			x
	Coordinate study visit with clinic visit to reduce trips	x		x
	Mechanism for monitoring visit cancellations and timely re-scheduling	x	x	x
	Ongoing monitoring of recruitment and retention	x	x	x
	Diligent efforts to re-engage inactive participants • multiple methods of contact (phone, text, email, letters)	x	x	x

We use systematic quality control, adherence to high quality practices, and regular reporting to clinical centers to maintain subject participation in this trial. Examples of training that facilitate retention include thorough and fully informed roles and responsibilities of staff and participants, conveying an appreciation of participation and study identification, nominal remuneration for study visits and parking, and reasonable accommodations to participant schedules. As part of our monthly clinic site calls, we will review retention rates, making comparisons between sites, and re-reviewing high quality practices. We will also work individually with sites that have high participant attrition.

14.0. **ANALYSIS**

14.1. **Sample size**

The primary endpoint is 6MWT distance at 12 months, a continuous scale outcome. An overall sample size of 680, with 340 in each treatment group, will allow detection of a standardized mean difference (Cohen's *d*) of 0.28 between the intervention and UC groups with a power of 90%, two-sided α = 0.05, and assuming at least 80% retention at 12 months. The decision to use a Cohen's *d* of 0.28 is based on based on 30m as the MID for 6MWT distance.[93] In the CONCERT study[94], the Cohen's d effect size was approximately 0.39 for 6MWT distance between the overweight and obese groups. A two-sample t-test is used to estimate power (**Table 11**). No multiplicity adjustment will be made for secondary analyses, which are intended to complement the primary findings and to inform future research. They will be interpreted within that context, considering the totality of evidence available.[95,96]

Table 11 Continuous Outcome: 6MWT distance

6MW (m)	Cohen's d	α	β	$power$	Sample size for each group	Sample size for each group assuming 20% attrition rate
24.8	.23	.05	0.10	0.90	499	399
30.2	.28	.05	0.10	0.90	336	268
35.6	.33	.05	0.10	0.90	242	193

14.2. **Overview of analysis plan**

This is a patient-randomized trial with patients nested within site and repeated measures within patient. This type of design makes it invalid to use standard approaches to assess a patient-level randomized trial because of the correlation between patients within site and repeated measures within patient. For the primary analysis, we will be evaluating the effect of the intervention at the primary endpoint (12 months through modeling of baseline and 12-month outcomes. It is reasonable to expect that patients within a site are not independent of one another and that repeated measures within patient are not independent from one another. These effects, depending on the correlations within and across sites and patients, may lead to decreased variance at the outcome measurement level and increase the probability of a type I error. The primary research hypothesis to be tested is that the intervention will lead to net improvement in 6MWT distance at 12 months. A linear mixed-effects model (LMM) will be necessary to assess the effect of the treatment. The statistical test will be two-sided because it is possible that the control group is superior to the intervention in either outcome measure. In other words, the statistical alternative hypothesis is two-sided, namely, the two study groups will result in significantly different 6MWT distances at 12 months.

Statistical analysis will occur in two phases. First, preliminary analyses will be performed to examine the suitability and feasibility of assumptions required to conduct more complex analysis including distributional assumptions (e.g., variance homogeneity, normality, etc.), collinearity and independence will be carried out. Second, we will conduct hypothesis testing analyses for the specific aims as described below.

14.3. **Baseline Analysis and Descriptive Statistics**

Equivalence of participants in the intervention and control arms will be assessed on demographic and clinical variables, including outcomes, health status, co-morbidity, and utilization variables. Because this is a randomized controlled trial, no systematic bias is anticipated. However, we will conduct sensitivity analyses that adjust for the covariates that are thought a priori to be related to the primary and secondary outcomes (e.g., age, sex). We will report summary statistics for all baseline covariates and outcomes (means, standard deviations, and quartiles for continuous variables; frequencies and percentages for binary variables) by randomized treatment group.

14.4. **Drop Outs and Missing Data**

We will make every effort to obtain complete data on each study participant at all data collection points. However, some missing data is inevitable and creates a risk for selection bias that can skew results. We will document and evaluate the extent, pattern, and reasons for missing data. Our primary analysis model will

handle missing data using restricted maximum likelihood (REML) estimation which relies on the assumption that the data is missing at random (MAR). ML has been shown to yield similar results to its alternative multiple imputation (MI).[97-99] ML is a powerful alternative to MI and valid for our data as we will collect all patient demographics prior to randomization. This means that we expect to have no missing values in our explanatory variables, which is a necessary criterion for REML. For the MAR assumption to hold, it must be believed that the probability the outcome is missing depends only on the information available. In the case of this study, this assumption should be acceptable as the missing outcome variables should be explained by the available variables. However, should the MAR assumption appear to be violated, we will conduct sensitivity analyses that instead assume the data are missing not at random. In this case, it is necessary to account for the missing data mechanism in the model.

14.5. **Primary Analysis for Aim 1**

The primary analysis will use intention-to-treat and all available data in model fitting. Our continuous primary outcomes and important secondary outcomes – 6MWT distance (primary), weight (secondary), and post-walk modified Borg dyspnea scale (secondary) – will be modeled via mixed-effects linear regression of the following form[100-102]:

$$y_{ijk} = \beta_0 + \beta_1 k + \beta_2(\text{Intervention}_i * k) + \beta_3 \text{COVID}_{ik} + \beta_4 \text{BaselineSmoker}_i + \alpha_i + \gamma_j + e_{ijk}$$

Where y_{ijk} stands for the outcome measurement for patient i of site j at time point k (k is equal to 0 at baseline and is equal to 1 at 12-month follow-up). Intervention_i is an indicator variable equal to 1 for patients randomized to the intervention arm and is equal to 0 otherwise. COVID_{ik} is an indicator equal to 1 if y_{ijk} was measured on or after March 19, 2020 and is equal to 0 otherwise. BaselineSmoker_i is equal to 1 if patient *i* reported smoking within one month prior to baseline self-report and is equal to 0 otherwise. The α_i are random patient-level intercepts assumed independently distributed Normal$(0, \sigma_\alpha^2)$, the γ_j are random site-level intercepts assumed independently distributed Normal$(0, \sigma_\gamma^2)$, and the e_{ijk} are outcome-level errors assumed independently distributed Normal$(0, \sigma^2)$.

To compare the intervention arm to the control arm at significance level α = 0.05 with respect to each outcome, an adjusted difference in means estimate, 95% confidence interval, and p-value for testing whether the adjusted difference in means at 12-month follow-up is unequal to zero will be generated based on each primary analysis model's β_2 parameter.

We will verify that the linear mixed effects model-based results are not sensitive to violations of model assumptions with permutation and bootstrap resampling tests.[103,104]

14.6. **Sensitivity Analyses**

We will summarize and visualize our outcomes based on missingness patterns across time. If this investigation produces evidences of missingness not at random, a multiple imputation using chained equations (MICE) approach will be implemented as a sensitivity analysis for each primary analysis model, with Rubin's rules employed to pool inference across analyses of completed datasets.[98,105-107]

We will also investigate whether the distribution of follow-up measurement time differs across treatment arm. If a difference is evidenced, each primary analysis model and MICE sensitivity analysis model, if using, will be re-fit with a continuous covariate that counts the number of days from 12-months post-randomization date to actual follow-up measurement date.

Additional covariates (e.g., age, sex) will be included to elucidate the primary intention-to-treat findings regarding treatment arm difference in our outcomes at 12-month follow-up. Further sensitivity analyses will be conducted using Generalized Estimating Equations (GEEs) if the distributional assumption of normality is not met within the LMM framework. GEEs do not rely on this distributional assumption and will allow for an evaluation of the intervention in this scenario.

14.7. **Secondary Analysis for Aim 1**

Dichotomized secondary outcomes for 6MWT distance, weight, and post-walk modified Borg dyspnea scale will be generated based on whether the respective, continuously measured primary outcome meets or exceeds the minimal important difference, as described below:

- 6MWT distance: 30m
  - Dichotomous outcome is equal to 1 if (follow-up 6MWT distance - baseline 6MWT distance) ≥ 30m, and it is equal to 0 otherwise.
- Weight: (Multiple)
  - Dichotomous outcome is equal to 1 if (follow-up weight – baseline weight)/(baseline weight)*100% ≥ 5%, and it is equal to 0 otherwise.
  - Dichotomous outcome is equal to 1 if (follow-up weight – baseline weight)/(baseline weight)*100% ≥ 3%, and it is equal to 0 otherwise.
- Post-walk modified Borg dyspnea scale (i.e., shortness of breath): 1 unit
  - Dichotomous outcome is equal to 1 if (baseline shortness of breath - follow-up shortness of breath) ≥ 1 unit, and it is equal to 0 otherwise.

Mixed-effects logistic regression models of the following form will be fit to these secondary outcomes and used to estimate a treatment arm standardized risk difference:

$$y_{ij} = \beta_0 + \beta_1 \text{Intervention}_i + \beta_3 \text{COVID}_i + \beta_4 \text{BaselineSmoker}_i + \gamma_j + e_{ij}$$

Where y_{ij} stands for the dichotomized outcome for patient i of site j. Intervention_i is an indicator variable equal to 1 for patients randomized to the intervention arm and is equal to 0 otherwise. COVID_i is an indicator equal to 1 for patients whose follow-up outcome was measured on or after March 19, 2020 and is equal to 0 otherwise. BaselineSmoker_i is equal to 1 if patient *i* reported smoking within one month prior to baseline self-report and is equal to 0 otherwise. The γ_j are random site-level intercepts assumed independently distributed Normal$(0, \sigma_\gamma^2)$, and the e_{ijk} are outcome-level errors assumed independently distributed Normal$(0, \sigma^2)$.

Additional secondary outcomes – generic HRQoL, Framingham CVD Risk Score, waist circumference, blood pressure, and BMI – will be analyzed similarly as in the primary and secondary analyses of 6MWT distance, weight, and post-walk modified Borg dyspnea scale.

14.8. **Interim Analyses**

The purpose of sequential trial design is to permit assessment of early termination of a trial because of either major harms or benefits. Interim analyses also are considered when the recruitment period is lengthy, or when there might be an opportunity to intervene during the trial experience to either remove the potential of a harmful intervention or to allow all participants to benefit from the intervention.

The DSMB requested rationale for not proposing interim analyses for a trial as large as INSIGHT COPD. The INSIGHT COPD trial seeks to test whether a behavioral intervention based on the diabetes prevention program (DPP) will reduce weight and improve exercise tolerance among overweight and obese patients with COPD.

Conducting an interim analysis prior to the intended completion of data collection would be advisable if there were uncertainty regarding whether the intervention will effect an increase in adverse outcomes such as mortality or medical complication rates. If, during an interim analysis, there were evidence that the treatment is causing major harm, the application of the intervention could be immediately terminated.

An interim analysis could also show evidence of an intervention effect based on data already collected. If we were satisfied in having shown evidence of an intervention effect at the interim analysis, we could consider early termination of the study to save time and resources.

We do not propose conducting an interim analysis in the current trial because we do not anticipate evidence of major harm or substantial benefit that would warrant early stopping. First, the behavioral weight loss intervention under study involves minimum risk and has demonstrated good safety profiles in the original Diabetes Prevention Program multicenter efficacy trial and in numerous subsequent studies in which the intervention was adapted and evaluated for diverse populations and settings. Second, we hypothesize a modest, clinically relevant effect of the intervention on the primary outcome as shown in our power analysis. This is reasonable on the basis of a large body of literature showing modest benefits of behavioral interventions in general for a wide range of health outcomes in different populations. The likelihood is low that we would have convincing evidence of an intervention effect on the primary outcome prior to the planned completion of the trial. Moreover, early termination would adversely affect our ability to fully assess the intervention's impact on secondary outcomes, which are parsimonious and clinically important.

15.0. **DATA MANAGEMENT**

Sites enter data coded with a confidential Participant ID into the REDCap hosted by the University of Washington. REDCap is a free web application tailored for research studies to build and manage online surveys and databases. REDCap has sophisticated customizable capabilities important for quality and security including flexible form creation, granular user privileging, password management, user authentication, auto logout, logging and audit trails, data export and de-identification, and protective security measures. Additional information about the REDCap system may be found at the following websites.
https://redcap.vanderbilt.edu/consortium/REDCapTechnicalOverview.pdf
https://www.iths.org/wp-content/uploads/REDCap_System_Security_Statement_29032013.pdf

Data is either directly entered into REDCap by a site coordinator, or by the participant for self-report surveys (if the participant so chooses), or completed on paper with subsequent entry into REDCap by the site coordinator. The REDCap database employs automatic, real-time range, logic, and missing value checks. Research coordinators (blinded to treatment assignment) review participant responses on questionnaires with participants present, and skipped or incorrectly addressed items will be brought to the participant to verify and correct as appropriate.

Participants may enter their diet and physical activity information into MyFitnessPal, or log information into paper tracking booklets identified only by the study ID. These data are entered onto REDCap by the lifestyle coach.

REDCap data are cleaned and verified, then downloaded into appropriate analysis software housed on the VA Center of Innovation for Veteran-Centered and Value-Driven Care (COIN) secure computer network servers, and handled in accordance with the COIN's extensive data security policy. The study data is backed up daily and maintained by the COIN. One official copy of all study data and a master data dictionary are maintained and updated regularly by the study data manager. Data crosswalks are maintained by the clinical sites and kept separately from all other study data. Paper forms are stored in locked file cabinets per local site security standards.

The PLG takes numerous steps to maintain the integrity and security of the data system. First and foremost among these are the NEMO's provision of careful training, certification, and guidance to all staff at the PLG and the clinical sites. Study sites are expected to provide a secure, monitored location for their data storage. All involved sites are expected to use password-protected data systems. All personnel are expected to follow strict procedures to protect confidentiality of information and for guarding privacy of participants enrolled in the study. Users access REDCap via a user specific login and password provided by the University of Washington. The PLG restricts specific access to the REDCap INSIGHT COPD project to individuals who have demonstrated proficiency with the data system by correctly entering training data forms into a "certification data system." This certification process is designed to highlight all important features of the data system. The PLG conducts additional "back-end" quality control including review of the REDCap audit trail for all data entries and revisions, checks for missing data, logical inconsistencies, and other anomalous entries.

The PLG closely monitors: a) participant accrual and follow-up in relation to goals and timeline; b) the randomization process and group comparability on the balancing variables; c) key baseline characteristics of the sample, by group, on the primary and secondary outcome variables and proposed effect moderators and mediators; d) intervention adherence; and e) protocol violations. Problems identified are addressed swiftly.

All study information is accessible only by IRB approved study staff on a need-to-know basis. Limited analytic datasets are shared between authorized study personnel via secure transmission and/or via a secure virtual private network employing industry-standard password protection and data encryption. Study information is not disclosed to any third party except as required by law. A de-identified dataset will be shared with NHLBI's data repository. Only aggregate data will be used to report study results. Patient identifiers will be retained per IRB permissions.

16.0. **TRIAL MANAGEMENT**

Both PIs (Dr. Au and Dr. Ma) assume overall fiscal and administrative management of the PLG including maintaining communication among co-Investigators and key personnel at the Seattle Institute for Biomedical and Clinical Research, VA Puget Sound Health Care System, University of Illinois at Chicago, NEMO, and the study clinical centers. Although Dr. Au serves as the contact PI for this application, communication requirements with NHLBI, NEMO, and IRB are shared jointly. Because Dr. Ma developed the intervention and has extensive experience with its implementation in prior trials, she leads efforts to finalize the protocol and address issues that arise to ensure the fidelity of the intervention. Dr. Ma's role includes oversight of implementation of the INSIGHT COPD intervention at the clinical sites and trouble-shooting potential issues, as well as hiring and overseeing the lifestyle coach(es). She implements intervention quality assurance procedures to ensure that project activities are standardized across the interventionists and across the sites and that intervention process data are collected accurately. She periodically reviews the protocol with clinical site staff to ensure fidelity and address questions that arise. Assisted by Dr. Barón, Dr. Au has primary responsibility for overseeing study forms, safety monitoring, and the data management system for data collection, processing, storage, and analysis in a manner that ensures data quality and security.

Drs. Au and Ma work together to provide trial oversight to ensure adherence of the protocol at clinical centers. They share the responsibility for overseeing AE reporting to the NEMO and DSMB, ensuring data quality control, guiding data analysis, and writing study manuscripts. Drs. Au and Ma work with the NEMO to ensure all parties involved in the execution of the INSIGHT COPD protocol comply with all applicable policies and regulations, including human subjects' protection. They will cooperate to ensure the timely and broad dissemination of lessons learned. In addition, as Protocol Leadership Group PIs, Drs. Au and Ma each serve on the PTC operations committee (OC), along with representatives from the clinical centers and officials from the NHLBI.

Conflict resolution. If conflict arises, the PIs agree to meet by telephone/teleconference and attempt to resolve the dispute. If the PIs are unable to resolve the conflict, the appropriate Departmental administrators representing the PIs shall meet by phone and attempt in good faith to settle any dispute, claim or controversy. If a PI moves to a new institution, attempts will be made to transfer any relevant portion of the grant to the new institution. In the event that a PI cannot carry out his/her duties, a new PI will be recruited as a replacement.

As noted, the two PIs along with the study team will work closely together throughout this project. During the study period, Dr. Au and Dr. Ma will meet weekly by telephone/teleconference (such as Skype, Microsoft live meeting) to review progress, discuss and address problems and review budget status and scientific direction. Each will be available to one another as needed by phone/teleconferencing. The two PIs will meet in person at least twice per year, usually as part of the annual meeting of the American Thoracic Society or other conference and at the annual OC meeting in Bethesda, MD. Travel costs and distance between Seattle and Chicago are nominal, and if both agree, each PI is willing travel to the other if they are unable to meet at national meetings or as necessary.

17.0. TRAINING AND CERTIFICATION

The staff of the PLG will work with NEMO to develop site training and staff certification procedures to include modules for conducting the protocol and REDCap data management.

18.0. PUBLICATIONS AND ANCILLARY STUDIES

18.1. Publications

The NEMO Operations Committee coordinates, monitors, reviews, and assumes responsibility for arranging the preparation of all study-wide communications (press releases, interviews, presentations, and publications) relating to the scientific aspects of the PTC. For the purposes publications specific to the INSIGHT COPD trial, Drs. Au and Ma will review all plans for publications or presentations.

With respect to publications and presentations from INSIGHT COPD, the goals are to:

- ensure accurate, uniform, timely, and high-quality reporting of the study activities and results;
- preserve the scientific integrity of the study;
- safeguard the rights and confidentiality of participants;
- assure that the timing of publications and presentations serves the right of the public to know the results of the program without jeopardizing its conduct.

Authors who participate in the writing of an INSIGHT COPD study manuscript do so in accordance with the International Committee of Medical Journal Editors (ICMJE) guidelines (http://www.icmje.org/icmje.pdf) and any additional considerations specific to non-medical journals (such as social and behavioral science journals that follow the standards of the American Psychological Association[108]). First authors are expected to remove names from the final list of authors if those individuals who have not participated in the writing and/or analysis of the paper in accordance with the ICMJE guidelines. All papers should also include an "Acknowledgments" section that lists the INSIGHT COPD investigators and key staff, unless journal policy prohibits publication of such a list.

First authorship should be decided before data analysis for the manuscript begins. The first author also determines the order of co-authorship on the manuscript. A key criterion to co-authorship is the individual's contribution to the paper. In general, authors will appear in order of contribution to the writing and analysis of the paper. When contributions to writing and analysis have been similar, priority should be given to those who have contributed to a greater degree to the design and implementation of the trial and to junior investigators.

18.2. Ancillary Studies

Drs. Au and Ma will evaluate proposals for studies that involve INSIGHT COPD participants and that are not a part of the INSIGHT COPD Protocol and Manual of Procedures (MOP). These studies will in general, be done only on a subset of participants INSIGHT COPD. Nevertheless, studies that include all INSIGHT COPD participants and studies that analyze INSIGHT COPD data in ways extracurricular to the INSIGHT COPD Protocol and MOP must be reviewed and approved by the Steering Committee. Ancillary studies will have to obtain funding from outside INSIGHT COPD.

Major factors in approval of ancillary studies will include:

- compatibility of goals with those of INSIGHT COPD;
- should not place undue burden on INSIGHT COPD participants and staff.

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