

*Long-Term Oxygen Treatment Trial*

LOTT

**Protocol**

25 March 2013

# Long-term Oxygen Treatment Trial Protocol (25 March 2013)

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# LOTT Protocol

## Abstract

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The Long-term Oxygen Treatment Trial (LOTT) is a multi-center, randomized clinical trial of supplemental oxygen therapy versus no supplemental oxygen therapy for patients with chronic obstructive pulmonary disease (COPD), moderate resting hypoxemia or severe hypoxemia during exercise, and increased risk of mortality. Seven hundred and thirty-seven participants will be randomized to one of the two treatment groups in a 1:1 ratio. Participants with moderate resting hypoxemia who are assigned to supplemental oxygen will be instructed to use the oxygen 24 hours per day; participants with normal resting saturation who have severe hypoxemia during exercise who are assigned to supplemental oxygen will be instructed to use oxygen during physical activity and sleep. Participants assigned to the no supplemental oxygen group are expected not to use supplemental oxygen unless the participant develops severe resting hypoxemia. Participant randomization is expected to be completed by December 2014; each randomized participant will be followed for at least 1 year and up to 7 years, depending on the date of enrollment. The target accrual rate for each of the 14 Regional Clinical Centers is 0.7 participants per month.

The trial is designed to determine if supplemental oxygen therapy results in increased time to the first occurrence of the primary composite outcome of either all-cause mortality or all-cause hospitalization. Secondary outcomes are the two components of the composite primary outcome, all-cause mortality and all-cause hospitalization. Other outcomes to be evaluated are disease-specific quality of life (St George's Respiratory Questionnaire) and preference-weighted health-related quality of life (Quality of Well-Being Scale), as well as exacerbation rate, dyspnea, six minute walk distance, nutritional status, and health care utilization. Additional outcomes to be collected in a subset of participants include spirometry, general quality of life, sleep quality, depression symptoms, and anxiety symptoms. In addition, substudies investigating treatment adherence and sleep, neurocognition, and oxidative stress are planned at selected sites and will include subsets of LOTT participants. A substudy on cost effectiveness that will include all LOTT participants is also planned.

Fourteen Regional Clinical Centers, a Data Coordinating Center, the National Heart, Lung, and Blood Institute, and the Centers for Medicare and Medicaid Services will conduct the trial. Each Regional Clinical Center will work with a network of major affiliates and satellite centers to evaluate, randomize, and follow participants.

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# LOTT Protocol

## 1. Background and rationale

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Chronic Obstructive Pulmonary Disease (COPD) is currently the fourth leading cause of death in the United States and, of the top ten causes of death, COPD is the only one that continues to increase (Mannino et al, 2002). The primary cause of COPD is cigarette smoking, but even as the smoking rate has declined, both the prevalence of COPD and the mortality due to COPD have increased. These increases are related to several factors, but probably the most important is that increasing age is a risk factor for COPD and the United States is experiencing a significant increase in the aging of its population.

Few interventions for COPD are known to be effective in decreasing mortality. Two clinical trials reported in 1980 and 1981, the Nocturnal Oxygen Therapy Trial (NOTT) and Medical Research Council (MRC) studies, demonstrated that long-term oxygen therapy (LTOT) substantially decreases mortality in COPD with severe resting hypoxemia (NOTT Group, 1980; MRC Working Party, 1981). Very little new knowledge has been obtained since these publications. The importance of smoking cessation in both preventing COPD and reducing the mortality of existing COPD is well established (Anthonisen et al, 2005). There are retrospective studies suggesting mortality reduction from pneumococcal and, perhaps more definitively, influenza vaccinations (Nichol et al, 1999; Nichol et al, 1999). There seems to be a mortality reduction from non-invasive positive pressure ventilation in patients with respiratory failure (Ram et al, 2004). Recently, lung volume reduction surgery has been shown to improve survival in selected patients with severe emphysema (NETT Research Group, 2003).

Of all the approaches, LTOT seems the most likely candidate strategy for increasing survival in large numbers of COPD patients, if LTOT increases survival in COPD patients with moderate resting hypoxemia, as it does in those with severe resting hypoxemia. The United States has a nationwide network for delivery of home oxygen which is efficient and relatively cost-effective. There are well-established payment systems for home oxygen therapy and the potential of thousands of patients who may benefit.

Oxygen therapy has been tested in only two randomized clinical trials since the NOTT and MRC studies. Both Gorecka et al in 1997 (Gorecka et al, 1997) and Chaouat et al in 1999 (Chaouat et al, 1999) reported no survival advantage for LTOT in COPD with moderate resting hypoxemia. Unfortunately, neither of these studies was sufficiently powered to be able to rule out a survival advantage.

The combined total enrollment for all four randomized clinical trials (NOTT, MRC, Gorecka et al, Chaouat et al) was 501 patients. Very few women were enrolled in any of these trials, and the only trials adequate to give definitive results began over 30 years ago and were reported over 25 years ago. Much has changed since that time, with great improvements in the therapy of a number of

diseases. Decrease in COPD mortality, however, has been an elusive goal, and oxygen therapy is one of the most well recognized approaches that has produced substantive benefits. It is hoped that the group of patients for whom LTOT is beneficial can be expanded.

Data from the NOTT suggests that supplemental oxygen may reduce hospitalizations. The NOTT patients in the continuous oxygen group had fewer hospitalizations than the patients in the nocturnal oxygen group, but the difference was not statistically significant (NOTT Group, 1980). Additionally, several observational studies suggest that hospitalization decreases after the initiation of oxygen therapy. Stewart et al (1975) found that hospitalization days for respiratory illness were reduced by 42% in the year after starting LTOT when compared with the year prior to LTOT for 10 American patients. Comparing the year before starting oxygen to the year after starting oxygen, 26 Australian COPD patients experienced 30% fewer hospital admissions and 35% fewer hospital days (Crockett et al, 1993). In 30 Belgian patients who had been followed at least one year prior to starting LTOT, hospital days were reduced by 51% in the year following LTOT initiation (Buyse et al, 1995). In a Danish cohort of 256 COPD patients started on oxygen therapy, hospitalizations were compared in the 10 months before and the 10 months after beginning therapy (Ringbaek et al, 2002). In the period after starting LTOT, hospital days were reduced by 44%, admission rates were reduced by 24%, and the number of patients with at least one hospitalization was reduced by 31%.

In May 2004, the National Heart, Lung, and Blood Institute convened a working group entitled “Long-term Oxygen Treatment in COPD” in Bethesda, Maryland (Croxtton and Bailey, 2006). Two other components of the Department of Health and Human Services, the Centers for Medicare and Medicaid Services (CMS) and the Agency for Healthcare Research and Quality (AHRQ), cooperated with the NHLBI in planning this meeting. CMS also commissioned AHRQ to perform a technical review of prior research. The working group was charged with evaluating the current state of knowledge regarding LTOT, identifying research questions of clinical importance, and discussing technical issues that might influence the feasibility and design of LTOT trials.

The working group identified three clear reasons for patients with COPD to receive LTOT. Two carefully conducted randomized control trials (the NOTT and MRC studies) demonstrated survival benefits for those with severe resting hypoxemia, and, when considered together, showed a relationship between survival and the average daily duration of oxygen use. Median survival for patients receiving supplemental oxygen for 18 hours a day was approximately twice that of those receiving no supplemental oxygen at all. In addition, there is a biological rationale in that severe COPD produces an oxygen deficit impairing the transfer of oxygen from the atmosphere to the blood. This can be corrected by increasing the fraction of oxygen in the inspired air. There may, of course, be additional biological advantages, in that oxygen has been shown to regulate pulmonary blood flow, control ventilation, and modulate gene expression in cellular phenotype throughout the body (Mitchell et al, 2001; Raj and Shimoda, 2002; Semenza, 1999). Some of these benefits may occur through mechanisms other than the simple metabolic effects of increased oxygen delivery, e.g., from a pharmacologic effect that involves remodeling or repair of the lung.

There are also reasons not to give LTOT to COPD patients. Two clinical trials showed no benefit (Gorecka et al, 1997 and Chaouat et al, 1999). Even though these trials were under powered statistically, there was so little difference in mortality between the control and the treated groups that we cannot be confident of an effect in these less severe patients. Also, there is at least a theoretical possibility of toxicity. There is no evidence that the current clinical application of LTOT produces a risk, but we know that hyperoxia can produce severe retinopathy in pre-term infants and newborn rodents (Chow et al, 2003; McColm et al, 2004). Oxidative stress may contribute to COPD progression through the molecular pathways believed to be involved in its pathogenesis (MacNee, 2002). Together, these observations require that toxic effects of oxygen must be considered. It is possible that toxic effects may be limited to individuals who have impaired upregulating oxidant defense mechanisms or those who sporadically use oxygen.

Another reason not to use oxygen unnecessarily is the cost. Currently, Medicare reimbursements for oxygen-related costs for COPD exceed two billion dollars per year and are increasing at an annual rate of 12-13% (unpublished CMS data). It is estimated that approximately one million patients annually receive oxygen through the Medicaid programs (unpublished CMS data).

Finally, both inconvenience and embarrassment are legitimate patient-centered reasons not to give oxygen to those who do not clearly benefit from the treatment. Nasal prongs are uncomfortable, and stationary sources often permanently limit the patient's activity. While a number of more portable devices are beginning to be used, there is much to be learned about their relative benefits. Also, patients may feel uncomfortable using supplemental oxygen in public because of the stigma of smoking-related diseases.

In addition to these reasons to use or not to use oxygen, there are also a number of uncertainties regarding oxygen use. Currently, all therapeutic guidelines are based more or less on the NOTT and MRC studies, and yet the eligibility requirements for these studies were arbitrary, originating from reasonable, prospective choices made during design of the NOTT and MRC trials and not from analysis of results from these trials. Hence, the precision and detail of therapeutic guidelines based on these inclusion criteria overstate their scientific basis. We know from these studies that, in general, patients with severe resting hypoxemia benefit from LTOT and mortality is reduced, but we truly do not know if these criteria include all individuals who would benefit from LTOT. In fact, there are potential significant differences between the patients selected for the NOTT trial and those eligible for LTOT under current Medicare regulations. The NOTT protocol required candidate participants to meet the arterial oxygen criterion twice during a three-week period before randomization. About 50% of candidates were eliminated on the second oxygen saturation assessment. Additional uncertainty arises from the small number of patients ever formally studied. Billions of dollars are spent each year based on data from only a few hundred subjects.

There are also uncertainties regarding the specifics for the duration and timing of oxygen use. Both the NOTT and MRC trials showed that survival appears to depend on the daily duration of treatment. Is this because the total time that oxygen is inspired is the key to benefit, making 24-hour oxygen treatment the optimal goal? Or is it because prolonged oxygen use prevents periods of deleterious desaturation? If it is the latter case, focused use of oxygen therapy, e.g., during times of exercise or sleep, might provide a more beneficial, more cost-effective result. Another area of uncertainty is which oxygen delivery device to use. There are many varieties of stationary and portable devices which currently are not distinguished by Medicare reimbursement, but differ in cost to the supplier and in restrictions on mobility and activities of the patients. As devices become more sophisticated, it is probable that the cost variation will be greater. There is little science to guide physicians on which device to use.

The working group identified seven important issues that should be investigated. The first was long-term efficacy of LTOT in patients with moderate resting hypoxemia, the same group of patients that had been examined by both Gorecka and Chaouat (Gorecka et al, 1997; Chaouat et al, 1999). Neither the study by Gorecka et al nor that by Chaouat et al was sufficiently powered to rule out the benefits of oxygen, and Gorecka and colleagues studied patients who received oxygen for 13.5 hours per day on average. It may be that 24 hours a day is necessary to see a survival effect in patients with moderate resting hypoxemia. There may be other benefits from LTOT such as decreased frequency of COPD exacerbations, improved exercise capacity, improved quality of life, and improved neuropsychological function. There also may be subgroups at greater risk of mortality who would benefit from LTOT even if the entire population did not; subgroups that might benefit include those with co-morbid heart disease, frequent exacerbations, decreased exercise capacity, low body mass index, or pulmonary hypertension.

Another issue of great importance is the efficacy of LTOT in patients who have normal oxygen saturation at rest but who desaturate with physical activity. We know that exercise desaturation in subjects with interstitial lung disease who are normoxic at rest is associated with decreased survival (Lama et al, 2003). The dyspnea associated with hypoxemia during activity may discourage exercise, promote deconditioning, and thereby decrease quality of life and increase mortality. This has not been formally studied, but we know that acute supplemental oxygen improves ventilatory function and exercise endurance in patients with advanced COPD (O'Donnell et al, 2001). Both of these situations would dictate the use of oxygen during activity but not necessarily at rest.

The effect of LTOT on individuals who are normoxic when awake but who desaturate during sleep was also identified as an important issue. It has been shown that supplemental oxygen prevents transient hypoxemia in most COPD patients with nocturnal desaturation (Fletcher and Levin, 1984). One observational study suggested a survival benefit in these patients from supplemental oxygen (Fletcher et al, 1992). It is felt that this issue is separate from oxygen desaturation secondary to sleep apnea where continuous positive airway pressure ventilatory support is indicated.



Other important issues that need to be answered include the optimal timing and duration of oxygen supplementation, the mechanism by which oxygen mediates the beneficial effects, clinical and biochemical predictors of responses to LTOT, and methods for enhancing adherence to LTOT.

The working group recommended to NHLBI that four trials are needed regarding LTOT: Study 1, Oxygen supplementation during ambulation (very high priority); Study 2, Continuous oxygen supplementation in patients with moderate hypoxemia (very high priority); Study 3, Nocturnal oxygen treatment of desaturation during sleep (high priority); and Study 4, Detailed, individualized prescriptions for long-term oxygen supplementation (high priority).

In March 2006, NHLBI and CMS announced their intention to work together to conduct a trial to assess the efficacy of around-the-clock, supplemental oxygen therapy in patients with COPD and moderately severe hypoxemia. By agreement, NHLBI has responsibility for all activities related to negotiating, awarding, directing, and terminating of the contracts; monitoring and evaluating program progress from a technical, legal, and financial standpoint; appointing the Data and Safety Monitoring Board (DSMB); and receiving and making decisions based on the advice from the DSMB. All data produced under the performance of these contracts are the property of the NHLBI, and the NHLBI reserves the right to use, release, distribute, and publish the data. CMS is responsible for providing reimbursement directly to clinics in compliance with studywide goals for protocol-related allowable clinical services for its beneficiaries who participate in the trial.

The solicitations requesting proposals for regional clinical centers and the data coordinating center were released on 8 November 2005 and 24 November 2005, respectively. Proposals were due at the NHLBI on 24 January 2006. The proposals were evaluated by independent scientific peer review groups convened by the NHLBI; these groups evaluated the merits of each proposal using the review criteria contained in the solicitations. On the basis of this scientific peer review, contract awards were made to fourteen Regional Clinical Centers and one Data Coordinating Center on 31 October 2006. Investigators from these centers were charged with the design and conduct of a randomized clinical trial of supplemental oxygen therapy versus no supplemental oxygen therapy for COPD patients with moderately severe resting hypoxemia. This research effort is the Long-term Oxygen Treatment Trial (LOTT).

The LOTT opened for patient recruitment in January 2009. As initially planned, LOTT focused on patients with moderate hypoxemia at rest. By spring 2009, it was evident that patients meeting the eligibility criteria were very few, were likely to be using oxygen already, or were reluctant to commit to 24-hour oxygen use for up to 4.5 years. It also was evident that pulmonary physicians were looking for a solution about what to do with the patient who desaturates during exercise but has normal saturation at rest. The LOTT Steering Committee considered these issues and agreed to expand the current trial to include patients who are normoxic at rest but desaturate during exercise and to revise the treatment plan to be supplemental oxygen during the periods of hypoxemia (patients who desaturate at rest or during exercise are judged likely to desaturate during sleep as well).

Patients with moderate resting hypoxemia who are assigned to supplemental oxygen will be instructed to use it 24 hours per day, and patients with normal resting saturation who desaturate during exercise who are assigned to supplemental oxygen will be instructed to use it during physical activity and sleep.

Under this plan, the LOTT combines elements of Study 1 (continuous oxygen supplementation versus no supplementation in patients with moderate hypoxemia where the hypothesis to be tested is whether survival and quality of life differ between the two treatment groups with regular monitoring of arterial oxygenation) and Study 2 (oxygen supplementation during ambulation) as proposed by the working group convened by NHLBI. LOTT investigators decided to substitute the measurement of oxygen saturation for arterial oxygenation for practical reasons (see chapter 3). Through subgroup analysis, LOTT should provide information about individuals who desaturate during sleep, the subject of Study 3 proposed by the NHLBI working group.

By 2012 it had become evident that the original assumptions about treatment group dropins and dropouts were very different from the observed dropin and dropout rates; therefore, the required sample size was lower than the original target sample size of 1134. In March 2012, the LOTT DSMB approved a revised sample size calculation of 737 patients based on the observed dropin and dropout rates. In March 2013, the NHLBI approved extension of recruitment to 31 December 2014 and followup to 31 December 2015.

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# LOTT Protocol

## 2. Objectives and hypotheses

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### 2.1. Primary objective

Previous studies have shown that there is a substantial survival benefit in providing continuous supplemental oxygen to COPD patients who have severe resting hypoxemia (PaO<sub>2</sub> at or below 55 mmHg) while in a stable state of health and suggest that supplemental oxygen may reduce hospitalization rate. The primary objective of LOTT is to determine whether treatment with supplemental oxygen increases time to a composite outcome of all-cause mortality or all-cause hospitalization in patients who have more moderate degrees of resting hypoxemia (SpO<sub>2</sub> 89-93%) or normal resting saturation and severe desaturation during exercise.

### 2.2. Hypotheses

Hypotheses are stated as alternative hypotheses (versus null hypotheses):

#### • Primary

H<sub>a</sub> 1: COPD patients with moderate resting hypoxemia or normal resting saturation and severe hypoxemia during exercise will have increased time to all-cause mortality or all-cause hospitalization if they are treated with supplemental oxygen tailored to their periods of hypoxemia.

#### • Secondary

H<sub>a</sub> 2: COPD patients with moderate resting hypoxemia or normal resting saturation and severe hypoxemia during exercise will have increased time to all-cause mortality if they are treated with supplemental oxygen tailored to their periods of hypoxemia.

H<sub>a</sub> 3: COPD patients with moderate resting hypoxemia or normal resting saturation and severe hypoxemia during exercise will have increased time to all-cause hospitalization if they are treated with supplemental oxygen tailored to their periods of hypoxemia.

#### • Other

H<sub>a</sub> 4: COPD patients with moderate resting hypoxemia or normal resting saturation and severe hypoxemia during exercise will have improved disease-specific quality of life if they are treated with supplemental oxygen tailored to their periods of hypoxemia.

**2.2. Hypotheses**

- H<sub>a</sub> 5: COPD patients with moderate resting hypoxemia or normal resting saturation and severe hypoxemia during exercise will have improved preference-weighted health-related quality of life if they are treated with supplemental oxygen tailored to their periods of hypoxemia.
- H<sub>a</sub> 6: COPD patients with moderate resting hypoxemia or normal resting saturation and severe hypoxemia during exercise will have decreased disease impact (e.g., reduced dyspnea, longer 6 minute walk distance, reduced COPD exacerbation rate) if they are treated with supplemental oxygen tailored to their periods of hypoxemia.
- H<sub>a</sub> 7: COPD patients with moderate resting hypoxemia or normal resting saturation and severe hypoxemia during exercise will have improved quality-adjusted survival if they are treated with supplemental oxygen tailored to their periods of hypoxemia.
- H<sub>a</sub> 8: COPD patients with moderate resting hypoxemia or normal resting saturation and severe hypoxemia during exercise will have lower health care utilization if they are treated with supplemental oxygen tailored to their periods of hypoxemia.
- H<sub>a</sub> 9: COPD patients with moderate resting hypoxemia or normal resting saturation and severe hypoxemia during exercise will have better maintenance of nutritional status (e.g., body mass index) if they are treated with supplemental oxygen tailored to their periods of hypoxemia.
- H<sub>a</sub> 10: COPD patients with moderate resting hypoxemia or normal resting saturation and severe hypoxemia during exercise will have improved general quality of life if they are treated with supplemental oxygen tailored to their periods of hypoxemia.
- H<sub>a</sub> 11: COPD patients with moderate resting hypoxemia or normal resting saturation and severe hypoxemia during exercise will have better sleep quality if they are treated with supplemental oxygen tailored to their periods of hypoxemia.
- H<sub>a</sub> 12: COPD patients with moderate resting hypoxemia or normal resting saturation and severe hypoxemia during exercise will have less depression and less anxiety if they are treated with supplemental oxygen tailored to their periods of hypoxemia.
- H<sub>a</sub> 13: COPD patients with moderate hypoxemia or normal resting saturation and severe hypoxemia during exercise will have delayed onset of severe hypoxemia (defined as room air SpO<sub>2</sub> less than or equal to 88%) if they are treated with supplemental oxygen tailored to their periods of hypoxemia.

**2.2. Hypotheses**

- H<sub>a</sub> 14: COPD patients with moderate hypoxemia or normal resting saturation and severe hypoxemia during exercise will have improved neurocognitive function if they are treated with supplemental oxygen tailored to their periods of hypoxemia.
- H<sub>a</sub> 15: COPD patients with moderate hypoxemia or normal resting saturation and severe hypoxemia during exercise with greater adherence to supplemental oxygen tailored to their periods of hypoxemia will have longer survival and better outcomes than those with lesser adherence.
- H<sub>a</sub> 16: COPD patients with moderate hypoxemia or normal resting saturation and severe hypoxemia during exercise will have lower risk of cardiovascular disease outcomes (e.g., acute coronary syndrome, chronic heart failure exacerbation, mortality secondary to these outcomes) if they are treated with supplemental oxygen tailored to their periods of hypoxemia.
- H<sub>a</sub> 17: In COPD patients with moderate hypoxemia or normal resting saturation and severe hypoxemia during exercise, treatment with supplemental oxygen tailored to their periods of hypoxemia will be more cost effective than no supplemental oxygen.

**• Exploratory**

Analyses will be performed to test the consistency of treatment effects across subgroups defined by baseline demographic and clinical characteristics. Subgroups to be examined include but are not limited to those defined by age, race/ethnicity, gender, oxygen saturation during exercise, oxygen saturation during sleep, lung function (e.g., FEV<sub>1</sub>), and smoking status.

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# LOTT Protocol

## 3. Study design

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The LOTT is a randomized clinical trial of supplemental oxygen versus no supplemental oxygen for COPD with moderate resting hypoxemia or normal resting saturation but severe hypoxemia on exercise and increased risk of mortality. The primary outcome is time from randomization to the first occurrence of either hospitalization from any cause or death from any cause. Because Medicare is paying the costs of treatment and the clinical procedures for the trial, only participants who are Medicare beneficiaries or whose insurance is willing (or who are personally willing) to cover the costs of participation may enroll in the LOTT. CMS issued a National Coverage Determination that extended coverage for home oxygen use to Medicare beneficiaries participating in LOTT ([www.cms.hhs.gov/MedicareApprovedFacilitie/02\\_o2trial.asp](http://www.cms.hhs.gov/MedicareApprovedFacilitie/02_o2trial.asp)).

Presence of moderate resting hypoxemia or severe exercise hypoxemia will be assessed by pulse oximetry while the participant is breathing room air. The rationale for choosing pulse oximetry over measuring the partial pressure of oxygen in arterial blood is that (1) in the United States pulse oximetry is the standard method for assessing oxygenation in an outpatient clinic setting, (2) the pain associated with obtaining arterial blood could adversely affect participant enrollment (a major consideration given the large enrollment number planned) and follow-up, (3) many potential enrollment sites do not have blood gas analyzers readily available and this would also adversely affect participant enrollment, (4) pulse oximetry is currently permitted by CMS as a criterion for demonstrating need for home oxygen, and (5) pulse oximetry is thought to be the most practical way of monitoring patients over time. To limit the variability and reduced precision of pulse oximetry compared with arterial blood gas analysis for assessing the degree of hypoxemia, the same model and brand of oximeter will be used by all LOTT sites for all participants, and all measurements will be obtained using a standard algorithm. All of the measurements during the testing period will be retained for analysis and may be used to further characterize the participant. The goal is for the LOTT algorithms for assessment of resting hypoxemia and assessment of exercise desaturation to be reproducible, robust to artifact, and processes that could readily be applied in physician offices after the trial.

Participants with SpO<sub>2</sub> of 89-93% will be considered to have moderate resting hypoxemia. Participants with SpO<sub>2</sub> of 94% or greater who desaturate below 90% for at least 10 seconds during the 6 minute walk will be considered to have normal resting saturation but severe hypoxemia on exercise. A single demonstration of this degree of resting hypoxemia or hypoxemia on exercise (under the required conditions and techniques) will be sufficient for eligibility. The rationale for requiring only a single demonstration is that (1) the participant must be in a stable or improving state of health and be at least 30 days post acute care hospital discharge for COPD exacerbation when eligibility assessment is performed and (2) in the United States the standard of care or usual practice for evaluating a patient for prescription of oxygen is a single demonstration of hypoxemia.

Participants who are not severely hypoxemic at rest but who desaturate below 90% during exercise or during sleep and who consent to enrollment will be eligible for randomization in the trial, although such participants could be prescribed oxygen for use during exercise or sleep outside of the trial under conventional Medicare guidelines. The rationale for allowing such participants to be randomized to no supplemental oxygen is the lack of evidence of benefit and the possibility of harm – it is unknown if oxygen treatment helps these patients and it is possible that oxygen treatment is harmful to these patients.

COPD patients at least age 40, with moderate resting hypoxemia or normal resting saturation and severe hypoxemia during exercise, dyspnea, and reduced lung function, currently in a stable state of health, and who are judged able to comply with the trial procedures, tests, and therapy for at least 6 months will be enrolled (eligibility criteria are detailed in Chapter 4). Participants will be randomized to supplemental oxygen or no supplemental oxygen in a 1:1 ratio. The oxygen prescription will be tailored to alleviate the participant's periods of desaturation. Participants who are moderately hypoxemic at rest will be instructed to use oxygen continuously (i.e., 24-hour oxygen). Participants who have normal saturation at rest but are eligible under the exercise desaturation criterion will be instructed to use oxygen during physical activity and during sleep. The oxygen equipment will be provided through Medicare-approved home oxygen suppliers.

The recruitment goal for the trial is 737 participants, of whom 9% (66 participants) are expected to be of minority background and 50% (368 participants) female. Recruitment is expected to be accomplished by within 6 years of initiation (target accrual rate is 0.7 participants/month/regional clinical center) and each participant is expected to be followed for at least 1 year and up to 7 years. Regularly scheduled followup on participants in both treatment groups includes 2 telephone visits per year (for vital status and interim history) and 1 in person clinic visit per year and collection of quality of life questionnaires by mail 4 and 16 months after randomization, as well as at each yearly clinic visit.

The LOTT will include an adherence promotion program for participants assigned to supplemental oxygen. The program will emphasize educating the participant about use of their equipment and finding strategies to overcome barriers to adherence as identified through motivational interviews with the participant. There will be discussions at the randomization visit to address any issues with the treatment assignment, an in person visit shortly after randomization after the participant has received his/her oxygen equipment to educate the participant about use of the specific equipment provided and to determine the participant's ambulatory prescription, weekly contacts by telephone for the next 3 weeks after this visit, monthly telephone contacts for the next 5 months after that, and then contacts every other month through 12 months. Additional adherence promotion contacts may be added after year 1 as needed if the participant appears receptive to encouragement.

The randomization visit for participants assigned to no supplemental oxygen will include a session with the coordinator to address any disappointment in the assignment and to review the importance of keeping the LOTT staff informed about any prescription for oxygen that the participant receives outside of LOTT. Participants in the no supplemental oxygen group need to understand the importance of staying off supplemental oxygen while they are in a stable state (as they are at baseline) but also should have a clear understanding that LOTT will not ignore a need for supplemental oxygen if the participant has an exacerbation or change in health that makes oxygen appropriate. The participant needs to understand that LOTT wants them to use oxygen if they need it and to stop oxygen when they no longer need it. Participants in the no supplemental oxygen group will have a followup telephone contact 1 week after the randomization visit to address any remaining issues related to their treatment assignment.

Because there appears to be a dose-response relationship between daily duration of oxygen use and survival benefit, LOTT will monitor adherence with oxygen use. For supplemental oxygen participants, the goal will be to be able to estimate oxygen use on a daily basis for each participant for the duration of the trial. The primary mode of obtaining this daily use information will be mailed self-reports of oxygen use measures every two months. For the no oxygen group, information on oxygen use will be obtained during interviews at regularly scheduled followup contacts. A more precise estimate of adherence will be obtained in a subset of participants through a substudy using recording devices attached to their oxygen equipment.

In summary, contacts with participants subsequent to randomization will include:

- (1) Treatment assignment adjustment telephone contact 1 week after randomization (no oxygen group)
- (2) Oxygen education and ambulatory prescription visit 1 week after randomization (supplemental oxygen group)
- (3) Telephone visit for vital status and interim history every 4 months between yearly in person visits (both groups)
- (4) In person clinic visits at yearly anniversaries after randomization (both groups)
- (5) Adherence promotion contacts by telephone weekly for 1 month, monthly for 5 months after randomization, every other month through 12 months, and annually (at in person visits) thereafter (supplemental oxygen group)
- (6) Adherence monitoring contacts by mail every 2 months after randomization for the duration of the trial (supplemental group)
- (7) Mailed collection of 2 quality of life questionnaires at 4 and 16 months

Fourteen Regional Clinical Centers (RCC), a Data Coordinating Center, the National Heart, Lung, and Blood Institute, and the Centers for Medicare and Medicaid Services are conducting the trial. Each RCC may work with and manage a network of associated sites to evaluate, randomize,



and follow participants. It is expected that the associated sites may have varying capability for data collection for the trial, and the LOTT Steering Committee has tried to construct the LOTT protocol to permit these differing levels of participation while still requiring high quality data collection and patient care. Partnering with the pulmonary community will facilitate recruiting the very large sample size required for the primary outcome (survival) analysis in LOTT. Partnering with the pulmonary community will also yield insight into how to make the trial clinically relevant, and in the future, will facilitate introduction, acceptance, and use of the results in clinical practice.

Hence the LOTT protocol incorporates three tiers of data collection: Core, Expanded, and Substudy (to be determined). Core data collection (both Core Baseline and Core Followup) are required on every randomized participant, regardless of enrolling site, and will provide the basis for determining eligibility for randomization, the primary outcome analysis, and assessment of hypotheses related to dyspnea, respiratory symptoms, preference-weighted health-related quality of life, functional status (six minute walk distance), nutritional status (body mass index; BMI), and health care utilization. Core data collection also includes some of the demographic and clinical characteristics which will be used for subgroup analyses testing the consistency of treatment effects (e.g., exercise desaturation). Core data collection includes all of the elements needed for a cost-effectiveness analysis of supplemental oxygen versus no supplemental oxygen, should funding be obtained for this analysis.

Expanded data collection (both Expanded Baseline and Expanded Followup) are additional to Core data and will be collected on a subset of participants, depending on the capabilities of the site which enrolls the participant. Expanded data collection permits assessment of treatment effects on additional outcomes (such as general quality of life, depression, anxiety) and also permits assessment of treatment effects in additional subgroups of participants (e.g., nocturnal desaturation).

Participants will be identified as Core or Expanded data collection participants at enrollment. Participants identified as participating in Expanded data collection are expected to complete all elements of Expanded data collection.

A synopsis of the LOTT design is shown in Table 11.1.

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# LOTT Protocol

## 4. Eligibility, baseline data collection, and randomization

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### 4.1. Overview

Participants will be evaluated for eligibility under the supervision of a LOTT Regional Clinical Center (RCC), either at the RCC or at a satellite site of the RCC. All participants must meet all of the inclusion criteria and none of the exclusion criteria. All participants will have a standard set of assessments at baseline (Core Baseline data collection). A subset of participants (as many as possible) will have a standard set of additional baseline data collected (Expanded Baseline data collection). Another subset of participants, those who enroll in LOTT substudies, will have additional baseline data collection related to the substudies in which the participant enrolls.

Because Medicare is paying the costs of treatment and the clinical procedures for the trial, the trial is open only to patients who are Medicare beneficiaries with both Part A and Part B coverage or whose insurance is willing to cover the costs covered by Medicare or who are personally willing to cover the costs covered by Medicare. Participants with Medicare Advantage coverage (Medicare HMOs, PPOs, etc) have Medicare Part A and Part B coverage as part of the Medicare Advantage coverage.

The major steps in eligibility evaluation are:

- Step 1: Information obtained from the referring physician is reviewed by LOTT staff (RCC or satellite) and insurance coverage is reviewed; this step establishes that the participant is not obviously ineligible for the trial and that the costs of procedures will be covered.
- Step 2: The participant is asked to consent to evaluation and enrollment in the trial, retention of data in the study database, and for access to the participant's Medicare claims for the year prior to enrollment and for the duration of the trial.
- Step 3: Testing for eligibility is ordered and completed: baseline history, dyspnea assessment, Modified Medical Research Council (MMRC) questionnaire, room air resting oximetry, room air six minute walk with oximetry, pre- and post-bronchodilator spirometry, Epworth Sleepiness Scale.
- Step 4: Review of eligibility for LOTT; participants found to be eligible and willing proceed with baseline assessments, while those found to be ineligible will return to the referring physician.
- Step 5a: Core Baseline assessments (all participants): limited physical exam, blood draw for hemoglobin and hematocrit, blood draw for DNA and plasma banking (participant may refuse DNA and plasma banking and still be randomized in LOTT), St. George's Respiratory Questionnaire, Quality of Well-Being Scale.

**4.1. Overview**

- Step 5b: Expanded Baseline assessments (selected participants): SF-36 Questionnaire, Pittsburgh Sleep Quality Index, the Hospital Anxiety and Depression Scale, blood draw for A1AT, blood draw for serum banking (participant may refuse serum banking and still be randomized in LOTT).
- Step 5c: Substudy baseline assessments (selected participants): to be determined; likely to relate to sleep quality and quantity, neurocognitive status, and oxidative stress.
- Step 6: Review of eligibility for randomization.
- Step 7: Affirm consent for randomization.
- Step 8: Randomization.

The maximum duration between initiation of eligibility evaluation and randomization is 60 days. How a clinic chooses to combine the steps outlined above into visits is at the clinic's discretion; however, the trial's data collection aims must be met. These aims are:

- To determine that the participant meets the eligibility criteria for the trial before randomization.
- To have in the database at the time of randomization a complete set of Core Baseline assessments for all participants and a complete set of Expanded Baseline assessments for participants identified as Expanded data collection participants and a complete set of Substudy Baseline assessments for participants identified as Substudy participants; the only exception to the completion requirements is that a participant may opt out of DNA, plasma, and/or serum banking and still be considered a Core or Expanded data collection participant in LOTT.
- The eligibility and baseline assessments must have been made near in time to randomization; near is defined as within 60 days.

The database established in Step 2 includes all participants who initiate eligibility evaluation at a LOTT site. Reason for ineligibility will be recorded if the participant is found to be ineligible. Followup data collection on ineligible participants will be limited to vital status searches of the Social Security Administration Death File, the National Death Index, and/or the Veteran's Administration Beneficiary Identification and Records Locator System (BIRLS) death file.

**4.2. Eligibility criteria**

The eligibility criteria for randomization in the LOTT are:

**Inclusion criteria (all must be met)**

- Age at least 40 years at initial eligibility evaluation
- Participant must respond Yes to at least one of the following questions:
  - Are you short of breath when hurrying on the level?
  - Are you short of breath when walking up a slight hill?

### 4.2. Eligibility criteria

- Dyspnea and lung disease process dominated by COPD in judgment of the study physician
- One of the following must be true:
  - Post-bronchodilator FEV<sub>1</sub> percent predicted less than or equal to 70% (reference equations of Hankinson et al, 1999 will be used)
  - or
  - Post-bronchodilator FEV<sub>1</sub> percent predicted greater than 70% (reference equations of Hankinson et al, 1999 will be used) and LOTT Study Physician determines that there is radiologic evidence of emphysema (e.g., by chest CT scan or chest X-ray)
- Post-bronchodilator FEV<sub>1</sub>/FVC less than 0.70
- Participant must meet either of the following oxygen saturation criteria
  - Oxygen saturation at least 89% and no greater than 93% after sitting quietly on room air, without hyperventilation and without pursed lips breathing
  - Resting oxygen saturation 94% or greater and desaturation during exercise defined as saturation below 90% for at least 10 seconds during the 6 minute walk test
- If participant is on supplemental oxygen (i.e., is prescribed a stationary or portable oxygen system) at the start of screening, all of the following must be met prior to randomization:
  - Participant agrees to stop using oxygen if randomized to no oxygen
  - Participant's physician agrees in writing to rescind order for oxygen if participant is randomized to no oxygen
  - Participant must report not using oxygen on the day of randomization and must report not using oxygen for the 4 calendar days prior to randomization (run in period where participant tries living without oxygen)
  - Satisfactory resolution of logistics of continuation with same oxygen company with waiver of cost sharing obligations or switch to new company that will waive cost sharing obligations if participant is randomized to oxygen
- At least 10 pack-years of tobacco cigarette smoking in the past
- Agreement not to smoke while using supplemental oxygen
- Medicare beneficiary with both Part A and Part B coverage or insurance or personally willing to cover costs covered by Medicare
- Approval of study physician for randomization to either treatment group
- Completion of all required pre-randomization assessments within 60 days of initiating eligibility evaluation
- Randomization within 60 days of initiating eligibility evaluation
- Consent

#### Exclusion criteria (none may be met)

- Less than 30 days post treatment for an acute exacerbation of COPD as of initiating eligibility evaluation (less than 30 days from last dose of antibiotics or since a new or increased dose of systemic corticosteroids was initiated); chronic use of systemic corticosteroids while health is stable is not exclusionary

**4.2. Eligibility criteria**

- COPD exacerbation requiring antibiotics, new or increased dose of systemic corticosteroids, or oxygen treatment after screening starts and prior to randomization (chronic use of corticosteroids while health is stable is not exclusionary)
- Less than 30 days post discharge from an acute care hospital after acute care hospitalization for COPD or other condition, as of initiating eligibility evaluation (participant may be in a rehab hospital at time of screening)
- New prescription of supplemental oxygen after screening starts and before randomization
- Thoracotomy, sternotomy, major cardiopulmonary intervention (lung resection, open heart surgery, etc), or other procedure in the 6 months prior to evaluation likely to cause instability of pulmonary status
- Non COPD lung disease that affects oxygenation or survival
- Epworth Sleepiness Scale score greater than 15
- Desaturation below 80% for at least 1 minute during the 6 minute walk
- Disease or condition expected to cause death or inability to perform procedures for the trial or inability to comply with therapy within 6 months of randomization, as judged by study physician
- Participation in another intervention study

All participants must sign a written contract agreeing not to smoke while using supplemental oxygen.

**4.3. Baseline data collection**

The assessments comprising Core Baseline and Expanded Baseline data collection are specified in Table 11.2. These assessments establish eligibility and further characterize the population and provide data that may be used in subgroup analyses. All baseline data must be collected prior to randomization; with the exception of collection of whole blood for DNA banking, assessments collected after randomization may not be used as baseline data of any kind. Whole blood draw will occur at baseline and 1 year. Table 11.3 indicates the amounts needed for specific purposes.

**4.4. Randomization**

Participants will be assigned to the two treatment groups in a 1:1 ratio. Separate randomization schedules will be used for each RCC, and assignments within each RCC will be balanced over time. The randomization process for the LOTT is designed for remote administration by LOTT-certified staff via the web-based LOTT data system. The steps are:

- Site determines if candidate qualifies for randomization through form-driven eligibility checks on completion of required procedures, collection of required data, conformance with eligibility criteria, and provision of consent
- Site requests an assignment using a special purpose, password-protected randomization program designed by the Data Coordinating Center

**4.4. Randomization**

- If eligibility and completion of required baseline procedures are confirmed by the randomization program, a treatment assignment is issued; the participant will be analyzed in the assigned treatment group regardless of the subsequent course of treatment or the willingness of the participant to accept the assigned treatment
- Data system prints treatment assignment sheet, visit time windows guide, and other materials related to randomization
- For participants assigned to supplemental oxygen: site talks with participant about any dissatisfaction with assignment and discusses importance of adhering to oxygen treatment, site arranges for delivery of oxygen equipment if needed and arranges for collection of equipment information if equipment is already in the home, arranges for in person visit for education and determination of ambulatory oxygen prescription, schedules 12 months in person followup visit, and reminds participant of mail and telephone contact schedule.
- For participants assigned to no supplemental oxygen: site talks with participant about any dissatisfaction with assignment and discusses importance of adhering to no supplemental oxygen while health is stable and not ignoring a need for oxygen if prescription of oxygen becomes appropriate, arranges for removal of any oxygen equipment previously prescribed, schedules 12 months in person followup visit, and reminds participant of telephone contact schedule.

As a check on site use of the randomization program, every attempt at randomization (and the data used in the eligibility checks) will be logged electronically. Hence, changes to data that lead to a change in eligibility status will be identifiable, and staff may be queried for explanations.

The followup visit schedule will be reckoned from the date of randomization for participants in both treatment groups. Participants in the supplemental oxygen group who refuse oxygen and participants in the no supplemental oxygen group who are prescribed oxygen after randomization remain in the trial and are required to return for all followup visits, just as if their course of treatment had not deviated from the protocol.

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# LOTT Protocol

## 5. Treatments

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The two treatments to be compared are supplemental oxygen and no supplemental oxygen.

### 5.1. Supplemental oxygen

Participants randomized to supplemental oxygen will be prescribed oxygen in accordance with the type of hypoxemia observed during screening (and under which the participant was found eligible for LOTT). Participants enrolled under the resting desaturation criterion will be instructed to use oxygen continuously, 24 hours/day. Participants enrolled under the normal resting saturation with desaturation on exercise criterion will be instructed to use oxygen during physical activity and sleep.

All participants randomized to supplemental oxygen will be prescribed a stationary oxygen system and a portable oxygen system (participants with normal resting saturation and desaturation on exercise need a stationary system to use during sleep). If the device uses electricity, an estimate of the device's power consumption will be provided to the participant. Each participant will be offered an ambulatory/portable/wearable system weighing 6 pounds or less, and the system must be able to be configured to provide with regulator for at least 3 hours before needing to be refilled or recharged. Participants may choose a heavier system if that is preferred by the participant. E cylinders may not be used as the primary ambulatory system in LOTT. E cylinders may be provided to participants as backup systems for use during power failures.

The dose at rest and during sleep will be 2 L/min via nasal cannula. The dose of supplemental oxygen used while walking will be individually prescribed; the participant will use his/her portable oxygen system during the assessment to determine walking dose. The dose of oxygen used while walking will be increased above a setting of 2 as needed to keep saturation at least 90% for at least 2 consecutive minutes while walking. This walking dose will be determined shortly after randomization (within 10 days) when the participant has his/her portable system, and then will be rechecked annually.

All participants assigned to supplemental oxygen will be instructed not to use their oxygen when within 5 feet of an open flame (e.g., candles, when cooking with a gas stove), a burning cigarette, or an appliance that sparks during operation, or when being assessed off oxygen for health outcomes. Participants also will be allowed to stop oxygen while traveling by airplane so that participants will not be burdened by having to pay for in flight oxygen. Stopping oxygen during air travel is considered safe for LOTT participants as they will be resting in their seats.

**5.1. Supplemental oxygen**

Participants randomized to supplemental oxygen who already have oxygen equipment in the home may continue to use that equipment. If this is the case, the clinic staff will need to work with the oxygen supplier to obtain the needed equipment information (initial readings and parameters) and to start billing under the LOTT billing arrangements, including any waiver of cost sharing obligations promised by the site in the consent signed by the participant. Participants who already have an ambulatory oxygen system will bring the ambulatory system to the clinic and ambulatory dose determination will be performed.

**5.2. No supplemental oxygen**

Participants randomized to no supplemental oxygen are expected not to use supplemental oxygen unless the participant becomes severely hypoxemic at rest (i.e., meets conventional Medicare criteria for 24-hour supplemental oxygen due to severe hypoxemia at rest). LOTT participants who meet the conventional Medicare criteria for oxygen during sleep or exercise but do not meet conventional Medical criteria for oxygen at rest are expected not to be prescribed oxygen by any of their physicians unless randomly assigned to supplemental oxygen in LOTT. There is no evidence that such patients benefit from supplemental oxygen and the supplemental oxygen may be harmful.

Participants randomized to no supplemental oxygen who have oxygen equipment in the home at the time of randomization are expected to return that equipment to the supplier. Clinic staff will work with the prescribing physician to rescind the prescription and will work with the participant, supplier, and physician to have the equipment removed from the home. The prescribing physician must have agreed in writing prior to randomization to rescission of the prescription if the patient is randomized to the no oxygen group.

**5.3. Oxygen prescription changes during follow-up**

During follow-up, participants in either treatment group may develop severe resting hypoxemia. The LOTT Steering Committee believes it will be unusual for LOTT participants to manifest isolated severe oxygen desaturation during ambulation that is outside of the LOTT exclusion criterion (SpO<sub>2</sub> less than 80% for at least 1 minute during the room air 6 minute walk is exclusionary). However, if that does develop during follow-up, the exercise desaturation will be treated as described below. Also, participants in the supplemental oxygen group may require higher oxygen flow rates during COPD exacerbations, and participants in the no supplemental oxygen group may require newly prescribed oxygen during COPD exacerbations.

It is recognized that supplemental oxygen group participants may have their LOTT oxygen prescription changed by a health care provider external to LOTT, and participants in the no supplemental oxygen group may be prescribed oxygen by a provider external to LOTT who uses different oxygen dosing algorithms than those used in LOTT. Participants will be instructed to



**5.3. Oxygen prescription changes during follow-up**

communicate such changes to their LOTT site. If such changes occur, the aims of the LOTT protocol will be: (1) to return participants to their LOTT assigned treatment/dose as quickly as possible, if safe to do so; (2) if the participant has become severely hypoxemic at rest (i.e.,  $SpO_2 \leq 88\%$  while on room air), to inform the participant of that event and prescribe the lowest dose at or above 2 L/min that relieves that hypoxemia (dose for use during rest and sleep) and prescribe the lowest dose at or above a setting of 2 that keeps the participant at or above 90% for at least 2 consecutive minutes while walking (exercise dose); (3) if the participant remains moderately hypoxemic at rest but has developed severe isolated hypoxemia during exercise (i.e., meets the LOTT exclusionary criteria related to desaturation during exercise,  $SpO_2$  below 80% for at least 1 minute during room air 6 minute walk), to inform the participant of that event and prescribe the lowest dose at or above a setting of 2 that keeps the participant above 90% for at least 2 consecutive minutes while walking; and (4) if prescribing a dose that deviates from the LOTT standard dose, to check the participant after 30 days to see if the dose can be reduced or oxygen can be stopped.

All participants will be evaluated with room air resting oximetry and room air 6 minute walk at every annual LOTT follow-up visit. Evaluations may also include resting and/or 6 minute walk oximetry while the participant is using oxygen, as needed per protocol. Procedures for dealing with supplemental oxygen group participants are described first, followed by procedures for participants in the no supplemental oxygen group.

If a participant assigned to supplemental oxygen has severe resting hypoxemia during follow-up (i.e.,  $SpO_2 \leq 88\%$  while on room air), the participant will be informed of this event and the adequacy of 2 L/min to correct that resting hypoxemia will be checked. The participant will undergo resting oximetry while using 2 L/min. If resting oxygen saturation is 89% or greater while using 2 L/min, the participant will continue on 2 L/min. If resting oxygen saturation is below 89%, then the testing process will be repeated using 3 L/min. The process will repeat, with oxygen dose increases of 1 L/min, until an oxygen dose is reached that achieves a resting saturation at least 89%. After 30 days, if the participant has  $SpO_2 \geq 89\%$  while breathing room air, the participant will resume 2 L/min oxygen at rest and sleep and their individualized prescription of oxygen supplementation during walking. If the participant continues to require a higher dose of oxygen than 2 L/min to maintain resting  $SpO_2 \geq 89\%$ , the participant will be rechecked in 30 more days. If the participant still does not meet criteria for lowering the dose of supplemental oxygen, the participant will be continued on the higher dose of oxygen until the participant's next annual LOTT follow-up visit.

A participant assigned to supplemental oxygen who has exercise desaturation below the LOTT eligibility criterion ( $SpO_2$  below 80% for at least 1 minute during room air 6 minute walk) when tested on room air will be informed of this event and reminded that use of their LOTT ambulatory prescription will protect the participant against desaturation during exercise (that prescription maintains  $SpO_2$  at least 90% for 2 consecutive minutes while walking).

**5.3. Oxygen prescription changes during follow-up**

Participants assigned to the no supplemental oxygen group who develop severe resting hypoxemia will be informed that they now meet conventional Medicare criteria for starting 24-hour oxygen and will be prescribed 2 L/min oxygen during rest and sleep and will be provided a personalized prescription for physical activity, similar to the protocol for supplemental oxygen participants. After 30 days, if the participant has  $SpO_2 \geq 89\%$  while breathing room air at rest, the oxygen will be stopped. If the participant continues to require 2 L/min to maintain resting  $SpO_2 \geq 89\%$ , the participant will be rechecked in 30 more days and if the participant still does not meet criteria for stopping supplemental oxygen, the participant will continue on oxygen until the participant's next annual LOTT follow-up visit when retesting would next occur.

A participant assigned to the no supplemental oxygen group who has moderate resting hypoxemia or normal resting saturation but has developed exercise desaturation below the LOTT eligibility criterion when tested on room air will be treated by the LOTT study physician (if participant and primary MD agree). The LOTT study physician will prescribe oxygen during ambulation (setting of 2 or greater, as needed to maintain saturation at 90% or higher for 2 consecutive minutes while walking). The participant will be retested in 30 days. If the participant no longer has saturation below 80% for more than 1 minute during the room air 6 minute walk and continues to have moderate resting hypoxemia or normal resting saturation, then the oxygen will be stopped. If the participant continues to have exercise desaturation and moderate resting hypoxemia or normal resting saturation, the oxygen prescription for physical activity will be continued for 30 more days and the participant will then be retested. If the participant still has isolated severe oxygen desaturation during ambulation, the participant will be continued on oxygen for physical activity for the duration of the trial.

Participants in either treatment group who become normoxic at rest (94% or greater) or normoxic during exercise (saturation at least 90% at all times or below 90% for less than 10 seconds during the 6 minute walk) during follow-up will be informed of the event and will continue on the LOTT prescribed oxygen dose (supplemental oxygen participants) without change or recheck or will continue on no supplemental oxygen (control participants). The rationale for this is that participants will have intermittent fluctuation in their oxygen saturation.

All subjects, those randomized to supplemental oxygen and those randomized to no supplemental oxygen, will be instructed to call the study coordinator if changes are made to their oxygen prescription, or if prescribed oxygen by their primary care physician. Changes to the subject's oxygen prescription will be noted on the case report forms in either scenario. Settings used by subjects are to be collected on adherence logs collected every 2 months, and participants will be asked about use and prescription of oxygen during telephone visits every 4 months.

**5.4. Safety issues**

Risks of supplemental oxygen treatment include:

- More rapid onset of severe resting hypoxemia if supplemental oxygen therapy leads to oxidative stress and oxidative stress contributes to COPD progression
- Burns from combustion of oxygen (personal burns to participant, burns to people in the participant's area, burns to objects in the participant's area)
- Burns from frost buildup on liquid oxygen tanks (if using liquid oxygen); these could be burns to the participant or to someone assisting with tank fills
- Nosebleed or dry nose
- Musculoskeletal injury (e.g., sprain or fracture) from tripping over equipment; this could be to the participant or people in the participant's area
- Increased personal expense due to copayments for oxygen treatment and increased use of electricity

Precautions to minimize these risks will include educational materials for the participant and the participant's family that teach the safe and proper use and care of oxygen equipment. Participants who remain active smokers will be encouraged to quit smoking. All participants must sign a written contract with LOTT staff promising not to smoke while using oxygen. Smoking status at baseline and during followup will be obtained by interview, and cotinine level will be measured at baseline and 12 months in participants who do not report tobacco chewing, current smoking, or use of any nicotine product. Participants assigned to supplemental oxygen will be given \$350 each year to help defray the cost of the oxygen treatment prescribed by LOTT.

Risks associated with assignment to the no supplemental oxygen group include:

- More rapid onset of severe resting hypoxemia if supplemental oxygen therapy slows or stops the progression of COPD
- Loss of benefits of supplemental oxygen treatment during exercise if such treatment is beneficial and participant qualifies for such treatment under conventional Medicare criteria and does not receive this treatment due to participation in LOTT
- Loss of benefits of supplemental oxygen treatment during sleep if such treatment is beneficial and participant qualifies for such treatment under conventional Medicare criteria and does not receive this treatment due to participation in LOTT

Precautions to minimize these risks will include annual monitoring of oxygen saturation at rest and during exercise.

**5.5. Adherence promotion**

Study staff trained in active listening and strategies for motivational enhancement for long-term oxygen therapy will engage participants assigned to supplemental oxygen in motivational discussions of issues related to adherence. The initial discussion will take place at a face-to-face interview at the randomization visit after the participant's treatment assignment has been generated. A second face-to-face interview will take place after the participant has received his/her oxygen equipment and has been assessed for the walking dose, about 1 week after randomization. Each of these visits is expected to take approximately 45 minutes. Study staff will review the mechanics of using the portable and stationary oxygen systems prescribed for the participant and will model use of the portable system. Participants will then demonstrate their ability to use the portable system properly to ensure that the physical use of the system is not a barrier to using supplemental oxygen. Follow-up discussions of approximately 10-15 minutes will be by telephone, weekly for the first month, then monthly for the following 5 months, then every other month to 12 months. Discussions will also occur at in person visits. These contacts will focus on the same issues as the initial interview: the participant's readiness for, importance of, and confidence in oxygen use; identifying barriers to, and solutions for, using oxygen; and exploring the participant's ambivalence towards oxygen use in such a manner as to elicit their motivation for adhering to using it.

Participants assigned to the no oxygen group will also be engaged in discussion with study staff to explore their feelings about living with COPD without supplemental oxygen. The initial discussion, held during the randomization visit, is expected to take approximately 20 minutes and will be conducted in a similar manner by the same person as with the supplemental oxygen participants. One follow-up phone discussion will be held one week later. Some of the strategies used with the supplemental oxygen group, particularly active listening, will be used with these participants. As well, discussions will explore ambivalence, barriers and solutions to living with breathing difficulties without supplemental oxygen.

**5.6. Adherence monitoring**

Adherence monitoring in LOTT will proceed in three formats:

(1) Self-report by interview (both groups): Participants will be queried about their use of supplemental oxygen since the prior interview. Participants assigned to supplemental oxygen will be asked to estimate their daily hourly use in the past 7 days. Participants assigned to no supplemental oxygen will be asked if they have used supplemental oxygen since the prior visit and if yes, details will be recorded (dose, duration of use, adherence with prescription).

**5.6. Adherence monitoring**

(2) Self-report of oxygen equipment, use and settings by mail (supplemental oxygen group) every 2 months: Participants in the supplemental oxygen group will be asked to report changes to their equipment, meter readings on concentrators, counts of tanks used, weight of liquid oxygen delivered, and conserver settings.

(3) Automated monitor report: 200 participants in the supplemental oxygen group will participate in a substudy that will monitor adherence via recording monitors attached to their stationary and ambulatory oxygen sources. The monitor will record minute by minute oxygen use. The more precise estimate of adherence gained by this substudy will be used to adjust the cruder estimate of adherence obtained on all supplemental oxygen group participants in format (2).

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# LOTT Protocol

## 6. Followup data collection

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### 6.1. Regularly scheduled followup contacts for data collection

Table 11.2 displays the data collection schedule for Core and Expanded followup at in person clinic, telephone, and mail visits completed by participants in both treatment groups. Table 11.3 displays the whole blood draw schedule for Core and Expanded followup. In person Core Followup visits occur at yearly intervals after randomization and include interim history; room air resting oximetry; room air six minute walk with oximetry; measurement of height, weight, blood pressure, and heart rate; assessment for edema; and completion of questionnaires (MMRC dyspnea scale, St. George's Respiratory, Quality of Well-Being Scale). Participants randomized to supplemental oxygen will also be assessed for any needed changes to their current ambulatory oxygen dose. Telephone Core Followup visits occur at 4-month intervals between in person visits and include a short interview about interim history. Quality of life questionnaires (St George's Respiratory, Quality of Well-Being Scale) will be mailed to participants for completion at 4 and 16 months after randomization.

Expanded Followup data collection, collected on a subset of randomized participants, adds a general quality of life questionnaire (SF-36), a sleep quality questionnaire (Pittsburgh Sleep Quality Index), an assessment of depression and anxiety (Hospital Anxiety and Depression Scale), and pre- and post- bronchodilator spirometry to each annual in person visit.

Visit windows (i.e., calendar intervals during which the visit may take place) will be constructed to be contiguous. Visit windows will be reckoned from the day of randomization.

Quality of life and respiratory symptom questionnaires will be mailed to participants 2 weeks prior to the scheduled date of the annual visit so that participants may complete the questionnaires at home; the questionnaires will be collected during the visit and reviewed for completeness prior to the conclusion of the visit at the clinical center.

### 6.2. Adherence promotion contacts

Table 11.4 displays the schedule of contacts for adherence promotion. Adherence promotion begins at the randomization visit. At that visit all participants will be counseled about their treatment assignment. Participants assigned to oxygen who do not already have oxygen equipment in the home will have arrangements made for delivery of the equipment. All participants randomized to oxygen will bring their ambulatory system to the clinic for a visit shortly after randomization (within 10 days) to teach the participant about their equipment and to determine their exercise oxygen prescription. Participants in the no supplemental oxygen group will receive a call from the

**6.2. Adherence promotion contacts**

coordinator at 1 week after randomization. After the in person visit after randomization, participants in the supplemental oxygen group will receive weekly calls for the next 3 weeks, monthly calls for 5 months after the call at 4 weeks, and calls every 2 months after that to 12 months. After 1 year, adherence promotion contacts will occur at in person followup visits. The primary purpose of the contacts is to trouble shoot problems with equipment and adherence to continuous oxygen. Additional telephone adherence promotion contacts may be scheduled after 1 year if the participant appears receptive to the contacts.

**6.3. Adherence monitoring contacts**

Participants assigned to supplemental oxygen will be asked to report changes to their equipment, meter readings on concentrators, numbers of tanks emptied, weight of liquid oxygen delivered, and flow settings every 2 months. Participants will be provided with log forms to record interim use (e.g., tanks emptied) and will receive a personalized form in the mail that shows their current equipment (as last reported to the clinic). Participants will be asked to mark the form with any updates, record use since the last report, and return the form in the stamped envelope provided by the clinic.

**6.4. Detection of severe depression**

The LOTT will use the Hospital Anxiety and Depression Scale (HADS) questionnaire in Expanded data collection. The depression domain of the HADS consists of 7 questions scaled from 0-3; total depression domain score ranges from 0-21 with higher score indicating greater depressive symptoms. A total depression domain score of 11 or greater is suggestive of clinical depression. With permission from the participant with a total depression domain score of 11 or greater, the LOTT staff will (1) inform the participant's healthcare provider that the questionnaire is suggestive of the presence of clinical depression, and (2) suggest that the participant undergo timely evaluation and appropriate treatment.

**6.5. Vital status monitoring**

Clinics will be required to complete and key a death report form upon notification of a participant's death. Vital status as reported by clinic staff will be compared to vital status as indicated by the Social Security Administration Death File, the National Death Index, and/or the Veteran's Administration Beneficiary Identification and Record Locator Subsystem (BIRLS) Death File (which includes vital status information on veterans). Discrepancies will be returned to clinical sites for resolution.

**6.6. Cause of death determination****6.6. Cause of death determination**

Determining of cause of death for LOTT decedents will be the responsibility of the RCC principal investigator or his/her designee. Death is usually the result of a complex sequence of events and processes acting along a causal pathway. Thus, adjudication of a single proximate cause of death is usually neither possible nor a complete descriptor of the terminal disease process. However, within the context of a COPD treatment trial, it is possible to classify stereotypical terminal illnesses in such a way that the classification will capture all information that is relevant to interpretation of the treatment effects of the intervention. Cause of death information will be important to know if supplemental oxygen is found to be harmful. In this event, cause of death information may be useful in understanding why or how the oxygen treatment was harmful to the participant.

It is common practice in multicenter clinical trials for cause of death to be adjudicated by an independent mortality review board. Because of the expected number of deaths (400-500) and the logistics and cost of managing this, LOTT will have the RCC principal investigator or his/her designee adjudicate the cause of death using a standard conceptual framework. Reliability of this method will be determined by having a sample of deaths adjudicated by a second independent reviewer.

The framework will be constructed to provide a probable cause of death (COPD, Cardiovascular, Cerebrovascular, Cancer, Other, Unknown) in a standard way. All cases will have a secondary classification to determine whether the death is related to COPD (Yes, No, Possible, Probable, Unknown).

**6.7. Hospitalization**

When a site determines that a participant has been hospitalized for any reason, the location, admission date, discharge date, and the reason for the hospitalization should be acquired by the site based on interview with the participant or their family. If possible, the hospitalization dates and diagnosis will be verified by acquisition of the discharge summary or a copy of the insurance explanation of benefits. Cause of hospitalization will be determined in the same way that cause of death will be determined – the RCC principal investigator or his/her designee will review the available records and witnesses, and categorize the cause per written guidelines. Relationship of the hospitalization with COPD will be assessed. Central review of a subset of events may be carried out for quality control. Searches of CMS claims databases and VA records for hospitalizations may also be carried out.



**6.8. COPD exacerbation****6.8. COPD exacerbation**

Every COPD exacerbation occurring during LOTT followup will be documented. Information to be recorded includes: characteristics of the exacerbation (i.e., increased shortness of breath, increased volume of sputum, increased sputum purulence, wheezing, chest tightness, increased cough, increased nasal congestion), other medical conditions that significantly impact the participant's LOTT treatment regimen, morbidity or mortality), treatment for the exacerbation, healthcare utilization for the exacerbation, requirement for ICU and/or mechanical ventilation, new or changed prescription of oxygen). Events that do not include any of the characteristics listed above should be reviewed by the study physician to consider if the event is truly a COPD exacerbation.

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# LOTT Protocol

## 7. Biostatistical considerations

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### 7.1. Study design

The LOTT is an unmasked, multicenter, randomized clinical trial with a planned sample size of 737 patients prospectively randomized to receive either supplemental oxygen or no supplemental oxygen. Patients will be allocated in equal proportions to each of the two treatment groups, and will be stratified by regional clinical center, with randomly permuted blocks of varying sizes within each stratum. Each regional clinical center is expected to recruit approximately 53 patients.

The primary objective of the trial is to determine the direction and magnitude of the difference in a composite outcome, time to first occurrence of either all-cause mortality or all-cause hospitalization, during the period of followup between the group assigned to receive supplemental oxygen compared to the group assigned to receive no supplemental oxygen.

The size and structure of the trial will also permit assessment of treatment group differences in the two secondary outcomes derived from the primary composite outcome, all-cause mortality and all-cause hospitalizations, but with less power than for the primary composite outcome. Other outcomes to be assessed for difference by treatment group include change in disease-specific quality of life at 1 year and change in preference-weighted health-related quality of life at 1 year, as well as exacerbation rate, dyspnea, six minute walk distance, nutritional status, and healthcare utilization; treatment group differences in these outcomes will be assessed with power equal to or greater than the power for the primary outcome. Analyses to determine if there are subsets of patients with differential risk or benefit from oxygen supplementation will be assessed with lower power than the comparisons using all patients, but should permit clinically important differences to be detected or suggested, especially if such differences are large.

### 7.2. Sample size considerations

Since the primary outcome measure for this trial is the time to first occurrence of either all-cause mortality or all-cause hospitalization, assumptions are needed to specify the complexities and contingencies of the LOTT design for the purposes of estimating sample size. Since there were no published data that relate to the target population with moderate hypoxemia, we used a web-based survey (see section 12.2 for the survey instrument), followed by an in-person discussion, to solicit expert opinions about design assumptions from LOTT investigators who were familiar with the available literature and with the target population of the LOTT. By 2012, it was clear that the assumptions made in 2007 about treatment group dropin and dropout rates were very different from the observed dropin and dropout rates; therefore, the required sample size was lower than the original target sample size of 1134. In March 2012, the LOTT DSMB approved a revised sample size calculation of 737 patients based on the observed dropin and dropout rates. The assumptions used in the sample size justification for the purpose of comparing the time to occurrence of the primary

## LOTT Protocol

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### 7.2. Sample size considerations

composite outcome measure between the supplemental oxygen and no supplemental oxygen groups are the following:

- The two-sided Type I error is  $\alpha = 0.05$ .
- The statistical power is  $1 - \beta = 0.90$ .
- The smallest clinically meaningful reduction in the composite event rate in the supplemental oxygen group = 40% (hazard ratio = 0.6).
- Enrollment will occur at a constant rate until December 2014 and will be staggered over time, with each patient having at least 1 year and up to 7 years of followup depending on the date of enrollment (common closeout date).
- The percent of patients in the group assigned to no supplemental oxygen who will crossover to oxygen treatment at some point during the trial is estimated to be 11.7% overall, 13.3% in year 1, 19.6% in year 2, and 25% per year thereafter.
- The percent of patients in the group assigned to supplemental oxygen who become crossovers by virtue of nonadherence with the tailored oxygen prescription, defined as not receiving at least 75% of the tailored oxygen prescription during a given year, is estimated to be 3.1% overall, 3.9% in year 1, 8.7% in year 2, and 15% per year thereafter.
- Crossovers of either type are assumed to experience the risk for the composite of mortality or hospitalization in the opposite group after crossover.
- Patients who become nonadherent (i.e., crossovers) are assumed to assume the risk in the opposite group as of the time of the crossover.
- Target patient mix:
  - 25% with moderate resting hypoxemia
  - 75% with normal resting saturation, who desaturate during exercise
  - 50% hospitalized for COPD within the year prior to screening
- Assumed event rates in the no supplemental oxygen group:
  - 33% hospitalization/yr in those with recent COPD hospitalization
  - 10% hospitalization/yr in those without recent COPD hospitalization
  - 7% mortality/yr in those with recent COPD hospitalization
  - 6% mortality/yr in those without recent COPD hospitalization
- 28% composite event rate/yr in the no supplemental oxygen group
- Time to composite events for patients assigned to the group with no supplemental oxygen is assumed to follow an exponential distribution over the period of followup.
- The loss to composite event followup rate is assumed to be only 1%, since direct mortality and hospitalization ascertainment will be supplemented by searches of the Social Security Master Death File, the National Death Index, and/or the BIRLS system for mortality and similar systems which record hospitalizations at CMS and the VA.
- Test statistic: logrank test.

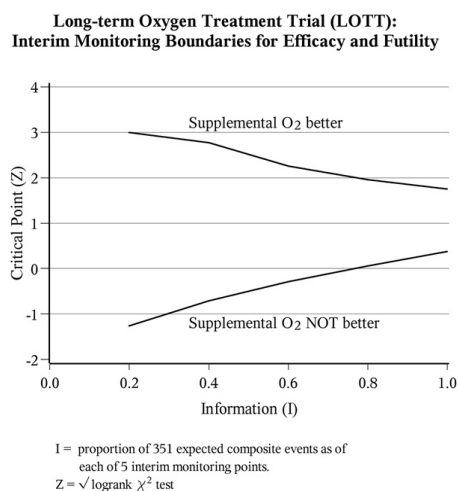
The above assumptions have been incorporated into SIZE, a sample size computer program (Shih, 1995) and yield a sample size estimate of  $n = 737$  patients (368 per group) with 351 expected composite events. The accrual rate required to reach the target of 737 patients by December 2014 is 0.7 patients per regional clinical center per month.

## 7.2. Sample size considerations

Secondary objectives of the trial are to assess treatment group differences with respect to the components of the primary outcome: all-cause mortality (power = 0.39) and all-cause hospitalization (power = 0.82). Other objectives include comparison of the treatment groups with respect to disease-specific quality of life assessments and preference-weighted health-related quality of life assessments, as well as other outcomes of interest. Overall, the trial will have exceptionally high power to meet these other objectives, since they involve continuous or semi-continuous outcome measures, rather than time-to-event outcomes.

## 7.3. Interim monitoring

A multidisciplinary, independent Data and Safety Monitoring Board (DSMB), appointed by the NHLBI, has responsibility for the protection of the safety of patients enrolled in the LOTT. The responsibilities and operating characteristics of the board are outlined in the template LOTT DSMB charter in Section 12.1 which follows the NHLBI guidelines for charters for DSMBs (<http://www.nhlbi.nih.gov/crg/word-templates/dsmb-charter-template-final.doc>). The charter will be reviewed at regular intervals by the DSMB and may be modified according to the needs of the trial. Briefly, the DSMB is charged with making recommendations to the NHLBI about starting, continuing, and stopping the LOTT. During the trial, the DSMB will meet periodically to review interim reports and analyses derived from the accumulating data or related findings from sources external to the LOTT that may be needed to make recommendations to the NHLBI. These reports and analyses will focus on three major areas: 1) overall efficacy and benefit/risk ratio, 2) efficacy and benefit/risk ratios within defined subsets of patients, and 3) overall and clinic-specific performance and data quality. To assist in the interpretation of the primary survival outcome, the spending function approach (see Figure for LOTT monitoring) of Lan and DeMets (Lan and DeMets, 1989) with boundaries chosen so that the boundaries approximately follow those of O'Brien and Fleming (O'Brien and Fleming, 1979) will be used to construct asymmetric stopping guidelines (DeMets and Ware, 1982) based on the normalized Z scores from interim logrank statistics comparing time to the composite outcome (mortality or hospitalization) in the supplemental oxygen group versus no supplemental oxygen to indicate consideration of (1) early termination or modification of the trial due to demonstrated benefit when the upper boundary in the figure is crossed, (2) early termination or modification of the trial due to demonstrated futility of continuing the trial (harm for oxygen or lack of a clinically meaningful survival benefit) when the lower boundary in the figure is crossed, or (3) unmodified continuation of



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### 7.3. Interim monitoring

the trial. The  $\alpha$ -spending function approach permits flexibility in timing of interim analyses. Monitoring of longitudinal continuous variables will be assisted, if needed, using the methods of Lee and DeMets (Lee and DeMets, 1995). The  $\alpha$ -spending function will be also chosen so that the boundaries approximately follow those of O'Brien and Fleming (O'Brien and Fleming, 1979).

### 7.4. Analysis plan

**Initial analyses.** Treatment group comparisons will be made assuming statistical significance at the 0.05 level. Analyses will be conducted to assess whether treatment effects are differential across subsets of patients, using appropriate methods for detecting effect modification (interaction).

The analysis of the primary outcome measure will focus on comparisons between the two treatment groups with respect to the relative rate of occurrence of the composite event (all-cause mortality or all-cause hospitalization) to identify adverse or beneficial effects that might be attributable to supplemental oxygen therapy. Key secondary analyses will focus on comparisons between the two treatment groups with respect to each of the components of the primary composite outcome measure, i.e., all-cause mortality and all-cause hospitalizations. The primary analysis will be carried out according to original treatment assignment (“intention to treat” principle). Analyses of the primary composite outcome reported in the publication of primary results will use the Kaplan-Meier product-limit estimator and associated logrank test for comparing the two treatment groups. The same analyses for the components of the composite outcome will also be included in the publication of the primary results. The Cox proportional hazards model will be used for confirmatory analyses, accounting for potential confounding variables that may arise. As noted earlier, we expect nearly 99% followup for mortality and hospitalization, given availability of mortality status on enrolled patients from Social Security and other databases and availability of hospitalization claim data from Medicare and the VA.

Other outcomes are disease-specific quality of life (St George’s Respiratory Questionnaire, SGRQ) score and preference-weighted health-related quality life (Quality of Well-Being Scale, QWB) score (scored 0 if the patient is deceased) at 1 year. LOTT will categorize the change in SGRQ total score from baseline to 1 year and define an outcome for each patient. A patient with an increase from baseline in total SGRQ score of 4 units or more or who misses the assessment or who dies during the time window for the assessment will be considered deteriorated at 1 year and a patient with any other outcome at 1 year (i.e., an increase in score of 1-3 or no change in score or a decrease in score) will be considered not deteriorated. A change in SGRQ score of less than 4 units is not considered clinically significant. Additional outcomes identified in the protocol include MMRC dyspnea score, six minute walk distance, exacerbation rate, health care utilization rates, nutritional status, general quality of life, sleep quality, depression and anxiety scores, and incidence of severe resting hypoxemia.

**7.4. Analysis plan**

Patients with missing measures at a particular time of followup will be excluded from analyses that require those measures, but will not be excluded from other analyses for which data are available. Baseline characteristics of patients with missing measures will be compared between treatment groups.

Exploration of measurements and other responses collected will emphasize robust statistical methods (Hoaglin et al 1983, Huber 1981); stem and leaf charts and letter value displays (5-value summary) will be used to explore the primary measures, to identify outliers, and to suggest transformations of scale, if needed.

The generalized linear model approach to regression analysis of repeated measures data (Liang and Zeger, 1986) applies to discrete responses as well as measurements and appears well suited for analyses of secondary outcomes from the LOTT data. In this approach, the marginal expectations of the response are expressed as a function of treatment group and other baseline covariates, taking correlations among the repeated measurements into account. The model can also accommodate time-varying covariates such as treatment crossovers, but this approach, which amounts to adjustment for post-randomization variables, is not recommended for primary comparisons among treatment groups in a randomized trial. Generalized estimating equations (GEE) are used to obtain parameter and standard error estimates that are consistent. If missing data become an issue and the probability distribution of missing data varies by treatment group, the GEE methodology is inappropriate. If this should occur, mixed random effects models will be employed.

Much is known about the problems in modeling respiratory function and related variables such as the 6 minute walk test distance (Buist and Vollmer, 1988). Methods for dealing with repeated measures with variable followup times, missing data, non-linear age effects, and transformations of scale are available (D'Agostino et al 1995; Wypig et al 1993).

Primary analyses according to original treatment group are unbiased but may suffer from loss of statistical power. Barlow and Azen (1990) showed that if complete information on the crossover history is available and if certain strong assumptions hold, some of the statistical power may be regained. This approach would be explored for the LOTT, as a confirmatory analysis. Other approaches that would supplement the "intention to treat" analyses would include 1) censoring measurements such as the 6 minute walk distance as of the crossover, 2) censoring event times as of the time of crossover, and 3) analyses with treatment status as a time dependent covariate.

Another analytic complication relates to the analysis of functional outcomes in the presence of possibly non-trivial intercurrent mortality. Patients who die early will not have the required, longer term outcome measures available, and these losses have the potential to bias treatment comparisons if they occur differentially by treatment group (ie, informative censoring). This problem, which was present in the NETT, can be addressed by including a functional outcome defined for all patients, such as deterioration at 1 year – patients who die before 1 year are considered deteriorated and given the lowest score, patients who are still alive at 1 year but miss the assessment are assigned a score above death but lower than the observed scores (sensitivity analyses will also be carried out that assign these patients the best or average score), and patients who complete the measure are assigned

## 7.4. Analysis plan

a score based on their performance. These scores can be analyzed using methods appropriate for ordered data (proportional odds models), or may be categorized as “significantly improved” or not and then analyzed with methods appropriate for binary outcomes (Fisher’s Exact Test or logistic regression). These analyses, which include all patients, will be supplemented by analyses that look at observed functional changes among survivors, but these must be interpreted with care.

## 7.5. Stopping guidelines

**Safety outcomes.** The primary safety outcome, total mortality, is also a component of the primary efficacy outcome and the boundaries for interim monitoring account for both efficacy and safety. Other safety outcomes will be identified, and trends across clinics and time will be quantitatively monitored as part of the DSMB data reviews, employing methodology for quality improvement given in Statistical Process Control (Oakland JS, 6<sup>th</sup> edition, Elsevier, 2008) and Statistical Process Control for Health Care (Hart MK and Hart RF, Brooks-Cole, 2001). The DSMB will also assess safety-related events quantitatively, and qualitative judgments will be made as to whether an event constitutes a sentinel event that requires investigation and actions by the clinics and whether the event carries sufficient concern to suspend the trial.

**Efficacy outcome.** The principal efficacy outcome is the intent-to-treat, randomized, between group comparison of the relative rate of occurrence (RR) of the composite outcome (all-cause mortality or all-cause hospitalization). We will employ a schedule of interim analyses that depends on information time, as indicated by the proportion of expected events (N=351) that have occurred (see Table below):

| Analysis time<br>(at proportions of<br>information time) | LOWER BOUNDARY<br>(supplemental O <sub>2</sub> worse<br>or not different) |                            | UPPER BOUNDARY<br>(favors supplemental O <sub>2</sub> ) |                            |
|--|---|----------------------------|---|----------------------------|
|  | Critical<br>point (Z)   | Observed RR<br>at boundary | Critical<br>point (Z)                                   | Observed RR<br>at boundary |
| 0.20   | -1.26   | 1.35                       | 3.00  | 0.49                       |
| 0.40   | -0.71   | 1.13                       | 2.77  | 0.63                       |
| 0.60   | -0.29   | 1.04                       | 2.26  | 0.73                       |
| 0.80   | 0.06  | 0.99                       | 1.96  | 0.79                       |
| 1.00   | 0.38  | 0.96                       | 1.75  | 0.83                       |

The critical points (Z) relate to the sequence of normalized logrank statistics comparing the two treatment groups. The planned total number of patients is 737, and the 5 interim analyses are to be conducted at roughly equally spaced information time, where information time is defined as the

**7.5. Stopping guidelines**

proportion of the 351 expected composite events that have occurred. The smallest clinically meaningful relative rate of occurrence (RR) of composite events (all-cause deaths or all-cause hospitalizations), comparing the supplemental oxygen group to the no oxygen group, is 0.60. The lower boundaries indicate guidelines for declaring the futility of continuing the trial (oxygen worse or not different from no oxygen) corresponding to repeated testing of the alternative hypothesis of a 0.60 RR favoring the supplemental oxygen group at the  $P = 0.005$  level, as suggested by Fleming, Harrington, and O'Brien (1984) and discussed by Freidlin B and Korn EL (2002). The upper boundaries indicate guidelines for early termination of the trial due to demonstrated mortality benefit of the oxygen treatment derived from 1-sided O'Brien-Fleming limits capped at  $Z=3.0$  to avoid extreme boundaries for benefit in early analyses as recommended by Fleming TR, Harrington DP and O'Brien PC (1984). For reference, the table also shows, at each analysis time, the corresponding observed relative rate (oxygen vs. no oxygen) at both the lower and upper stopping boundaries.

The approach to the interim analyses and the quantitative guidelines presented are not intended to replace multidisciplinary good judgment, examination of critical secondary outcomes, information from outside the trial, or unforeseen circumstances. Approximate adherence to these guidelines will assure desirable statistical properties for decisions and an objective spirit, but cannot substitute for the experience and judgment of the Data and Safety Monitoring Board. Therefore, we emphasize that the plans discussed here are necessarily incomplete. Therefore, it is possible or even likely that final decisions will not match these guidelines exactly.

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# LOTT Protocol

## 8. Quality assurance and performance monitoring

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### 8.1. Introduction

Quality assurance strategies for the LOTT include design strategies and specific activities. Design strategies include use of randomization to assign participants to treatment groups, requirement of certification of staff and sites, and formal training of staff in LOTT procedures. Activities to assure quality include range checks of data during keying, computerized checks on eligibility and completeness of data, written edit messages from batch editing of records at the Data Coordinating Center with followup on unreturned edit messages, comparison of forms reporting the data to keyed records and source documents (audits), and feedback on and peer review of performance via distribution of studywide reports to all centers and review of performance data at group meetings. Frequent, as needed in person contact between DCC and site staff is also a key quality assurance activity.

### 8.2. Certification of RCCs and satellites

The Data Coordinating Center will certify sites for data collection in LOTT. The NHLBI will authorize certified sites to start the participant activities phase of LOTT. Each RCC will be required to complete a certification form for their RCC that provides detailed information with regard to the plans for carrying out LOTT at that RCC and specifies any associated satellite sites. Items requested on the form include copies of the IRB notice of approval for LOTT and IRB approved LOTT consent statement, HIPAA authorization, contract not to smoke, and medical records release form. Each satellite site will be required to complete a similar certification form for their satellite and to provide copies of their IRB notice of approval for LOTT and IRB approved LOTT consent statement, HIPAA authorization, contract not to smoke, and medical records release form. Each form serves as a checklist for the site staff for the resources that need to be in place when participant activities begin (e.g., needed space, equipment, documents, personnel). The information provided will be reviewed by Data Coordinating Center staff prior to certification.

### 8.3. Certification of RCC and satellite staff

The purpose of the staff certification program is twofold. It identifies to the Data Coordinating Center and to the study group the staff who will collect and/or record certain items of data for LOTT and who will make decisions relating to eligibility for LOTT. Secondly, it makes the data collector aware that he/she is a part of LOTT and has a responsible and identifiable role in it.

### 8.3. Certification of RCC and satellite staff

Functions for which LOTT will certify staff include study physician, principal clinical coordinator, clinical coordinator, principal adherence educator, adherence educator, oximetry technician, six minute walk tester, spirometry technician, physical exam assessor, and data entry technician:

- **Study physician:** Signs off on eligibility, prescribes LOTT treatment, can assign cause of death; study physician must be an MD or DO. There may be multiple study physicians per site.
- **Principal clinical coordinator:** Only one per site; this individual is the chief liaison for the DCC at the site. Otherwise description of clinical coordinator applies – signs off on all (or almost all) forms, administers interviews and self-report questionnaires.
- **Clinical coordinator:** Signs off on all (or almost all) forms; administers interviews and self-report questionnaires. There may be multiple clinical coordinators per site.
- **Principal adherence educator:** Only one per site; this individual is the chief liaison for the DCC at the site with regard to adherence promotion issues. Otherwise description of adherence educator applies.
- **Adherence educator:** Carries out the adherence education and contacts. Is trained in adherence promotion protocol. Does not carry out adherence monitoring contacts. There may be multiple adherence educators per site.
- **Oximetry technician:** Carries out the resting oximetry assessments and signs off on those forms. Is trained to manage, read, and deal with the LOTT oximeter. There may be multiple oximetry technicians per site.
- **Six minute walk tester:** Does the six minute walk and oximetry procedure and signs off on that form. Is trained to manage, read, and deal with the LOTT oximeter. There may be multiple six minute walk testers per site.
- **Spirometry technician:** Assures that the spirometry session meets ATS standards and LOTT protocol requirements and signs off on spirometry form. There may be multiple spirometry technicians per site.
- **Physical exam assessor:** Completes the physical exam for LOTT participants (physical exams may also be completed by a study physician or clinical coordinator). There may be multiple physical exam assessors per site.

### 8.3. Certification of RCC and satellite staff

- **Data entry technician:** Has access to web based data system, keys forms, and provides clinic staff with the resources they need from the web based data system. There may be multiple data entry technicians per site.

This listing of certified functions results from recognition that some data for LOTT will be collected by LOTT staff in the LOTT office, while other data will be collected at LOTT certified sites and under the LOTT protocol but the staff will not be directly employed or trained by LOTT. It also results from the belief that individuals who make decisions about eligibility for LOTT should be identifiable and accountable for decisions about specific participants and the belief that adherence promotion staff and tasks should be separate from adherence monitoring staff and tasks.

All certified staff will be required to read the participant consent and information materials, to complete a form identifying the functions for which they are applying for certification in LOTT, and to sign a statement acknowledging that they have read these materials; that they understand that LOTT is a collaborative activity and that results will not be available until the study is terminated; that they will adhere to high standards of integrity in the data collection, recording, and editing processes; and that they will treat all LOTT data as privileged information and thereby protect the confidentiality of the study participants and the collaborative research team. Additional requirements may be implemented for some functions. Each staff member certified for one or more functions for LOTT will be issued a personal identification number; this number will be recorded as requested when completing data collection forms.

### 8.4. Quality control for outcomes

- **Mortality:** Clinic staff will be in touch with participants on a regular basis and will be the primary source of reports of participant deaths. Vital status as assessed by clinic staff will be confirmed by searches of electronic databases such as the Social Security Administration Death file.
- **Cause of death:** Cause of death will be ascertained using a standard framework (see section 6.6); a sample of deaths will be assessed by a pulmonologist independent of the sites and agreement with the original assessment will be determined.
- **Hospitalization:** Occurrence of hospitalization will be queried in a standard way at each of the telephone and clinic visits (every 4 months). In addition, the participant or a family member may report hospitalization between visits. Participant or family report of acute care hospitalization will be confirmed through acquisition and review of the discharge summary or a copy of the insurance company explanation of benefits.

### 8.4. Quality control for outcomes

- **COPD exacerbation:** Occurrence of COPD exacerbation will be queried in a standard way at each of the telephone and clinic visits (every 4 months) and information about the exacerbation will be recorded on a structured, standard form.
- **Oxygen saturation:** Use of same model and brand oximeter at all sites for all assessments of the same type (LOTT may decide that different models are needed for different types of assessment); training and certification of staff in use of the oximeter; customized programming of oximeter to generate LOTT specific eligibility and followup assessments and summary reports of testing sessions.
- **Quality of life, dyspnea, sleepiness, sleep quality, depression, and anxiety:** Use of standardized questionnaires; training of coordinators in administration; checks for completeness and consistency of responses within and across forms and visits.
- **Six minute walk test:** Use of standard script to encourage participant at standard times (each minute); requirement for indoor, flat, and unobstructed course with traffic control.
- **Spirometry:** Sessions must meet the American Thoracic Society standards for equipment, quality and repeatability.

### 8.5. Performance monitoring

Performance monitoring will begin with the initiation of participant evaluation and will continue throughout the duration of the trial. Reports of the numbers of participants evaluated and randomized will be available through the LOTT website. Other performance measures to be monitored and reported include numbers of completed visits, missed visits and unaccounted for visits; number of incomplete visits; number and type of procedures missed; number of data queries from batch edits of keyed data; and time from form completion to keying. Review of performance data will be an agenda item for all Steering Committee meetings.

Shortly after initiation of data collection, a program of records audits will be instituted. Copies of forms and source documents selected by Data Coordinating Center staff will be requested from RCCs. The information on these documents will be compared to the database keyings of this information, and discrepancies will be noted and reported. The electronic log of attempted randomizations will be reviewed periodically at the DCC, and RCCs will be questioned about unusual occurrences.

ID numbers assigned to participants and certification numbers assigned to staff will allow identification of both RCC and satellite enrolling the participant, allowing performance monitoring at both the RCC and satellite levels.

# LOTT Protocol

## 9. Human subjects issues

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### 9.1. Consent process

The consent process for LOTT is perceived as a dialogue between the participant and LOTT staff, supported by discussions and written materials. Opportunities for discussions about participation will arise during the assessment appointments and during meetings with the participant to review the results of the participant's tests.

The written materials include consent for the trial and specimen banking, the HIPAA authorization, the contract not to smoke, and the release of medical records. The consent statement is to be signed at the first face-to-face visit at the LOTT clinic, after the participant has been judged not known to be ineligible and coverage of costs by Medicare, willing insurance company, or other resource has been established. This consent statement describes the evaluation, treatment assignment, and followup processes for the trial and requests consent for testing and consent for inclusion in the study database. Unless otherwise requested by the participant or unless the consent is mailed to the participant prior to the initial visit to the LOTT clinic, the participant will be asked to sign this statement at the same visit at which he/she first sees the statement. The testing for LOTT is routinely done for COPD. Consent to be included in the study database does commit the participant to having his/her Medicare HIC number and Social Security number transmitted to the Data Coordinating Center. Signature of the consent also gives permission to LOTT to access the participant's Medicare claims records for the year prior to enrollment and thereafter for the duration of the trial.

A prototype consent, HIPAA authorization, contract not to smoke, and medical records release form will be developed and approved by the LOTT Steering Committee. RCCs and satellites may add information and reformat information to conform with their local requirements, but in general, deletion of information material to informed consent will not be permitted. DCC staff will review all consents (RCCs and satellites) and check for inclusion of required material.

### 9.2. IRB approval monitoring

One of the requirements for certification of a site to begin participant activities at the site will be submission to the Data Coordinating Center of the site's notice of IRB approval and a copy of the consent, HIPAA authorization, contract not to smoke, and medical records release form to be used at the site. These materials will be reviewed by Data Coordinating Center staff for conformance with the prototype materials and deviations will be questioned as appropriate. Renewal of IRB approval will be monitored by the DCC, and copies of renewal notices will be collected by the DCC.

**9.3. Adverse event reporting**

The LOTT will follow the NHLBI guidelines for reporting adverse events (<http://www.nhlbi.nih.gov/funding/policies/adverse.htm>) and the OHRP guidelines for reporting unanticipated problems (<http://www.hhs.gov/ohrp/policy/AdvEvtGuid.htm>). An adverse event is defined as any untoward or unfavorable medical occurrence in a human subject, including abnormal sign (e.g., abnormal physical exam or laboratory finding), symptom or disease temporally associated with the subject's participation in LOTT, whether or not considered related to the subject's participation in LOTT. OHRP defines an unanticipated problem as any incident, experience, or outcome that meets all of the following criteria: (1) is unexpected, in terms of nature, severity, or frequency, given the research procedures that are described in the LOTT protocol and informed consent document and the characteristics of the participants with COPD and moderate resting hypoxemia; (2) is related or possibly related to participation in LOTT; possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by LOTT procedures; and (3) suggests that the participation in LOTT places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Deciding how to classify an event is the responsibility of the study physician and Principal Investigator (PI) of the Regional Clinical Center. The study chair, the NHLBI project officer, and staff at the Data Coordinating Center will be available to study staff for consultation. Study staff will determine if an event is an adverse event or an unanticipated problem and will classify the event as to severity, seriousness, relatedness to LOTT participation, and expectedness in the context of LOTT.

Unexpected serious adverse events possibly, probably or definitely related to LOTT participation and all unanticipated problems will be reported individually to the DCC (LOTT will have a specific form for such reports) and these reports will be forwarded to the DSMB, OHRP, NHLBI, CMS, study chair, and Steering Committee in real time (those that are fatal or life threatening will be reported to the DCC within 7 days of when the clinic learned of the event; other unexpected serious adverse events thought related or possibly related or other unanticipated problems will be reported within 14 days of when the clinic learned of the event). Clinics will be instructed to forward the report to their IRB.

Other adverse events (eg, unexpected related adverse events of lesser severity or expected adverse events of any severity) will be reported to LOTT on an interim event form or a regular interview form and, in general, will be reported in aggregate form to the DSMB at the time of regular data reports. However, clinics will have the option of bringing any event to the immediate attention of the DCC (via faxing the interim event report form to the DCC who will forward all such forms to the Safety Officer) for review and discussion by the Steering Committee and for consideration of immediate reporting to the DSMB. Similarly, the DCC will have the option of bringing any event to the attention of the Steering Committee.

**9.3. Adverse event reporting**

Adverse events that are expected in LOTT include risks associated with the LOTT treatment and risks associated with LOTT procedures. These include:

- COPD exacerbation.
- Worsening of COPD (worsening of lung function, development of severe resting hypoxemia, death from COPD).
- Burns (from smoking while using oxygen, from using oxygen around an open flame or equipment that sparks, from frost buildup on liquid oxygen systems).
- Nosebleed or dry nose.
- Musculoskeletal injury from tripping over oxygen cords.
- Bruising or infection at blood draw site.
- Fainting related to blood draw.
- Side effects of albuterol – throat irritation, palpitations, nervousness, shakiness, stomach upset, headache, dizziness, weakness, sweating, chest pain.
- Fainting or dizziness related to spirometry.
- Fainting, dizziness, chest pain, ataxic gait, lower extremity claudication, or mental confusion related to 6 minute walk testing.

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

**9.4. Confidentiality of data**

In general, participants will be known by LOTT identification number and a 4-character alphabetic code. Participant name will be known only at the site(s) enrolling and seeing the participant (RCC and/or satellite). Medicare HIC number and social security number will be sent to the Data Coordinating Center; this information is needed for accessing Medicare claim information and for vital status searches of national databases. These data will be kept in a password protected computer file, separate from the rest of the database on a different server. In correspondence between the RCC and Data Coordinating Center and in internal study reports that require identification of individual participants, participants will be referred to and known by their ID number and 4-character code. RCCs and satellites will be required to store study data in a secure location. There will be discussions at study meetings about the need to protect the confidentiality of participant information.

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# LOTT Protocol

## 10. Organization

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The investigators at the centers participating in the LOTT collaborate through a study organization which is designed to maintain continuity of operations, to facilitate effective communication and cooperation among the participating units, and to monitor and maintain the operations of the trial.

### 10.1. Study administration

The officers for LOTT are the study chair (William Bailey, MD), the study vice chair (James Tonascia, PhD), and the NHLBI project officer (Antonello Punturieri, MD, PhD).

Currently, the study operates with the following committees and subcommittees:

- Steering Committee – comprised of the study chair, the NHLBI project officer, the CMS representative, and the principal investigators from the 14 RCCs and the Data Coordinating Center
- Subcommittees on ancillary studies and publications and presentations are likely to be formed
- Data and Safety Monitoring Board (DSMB) – appointed by the NHLBI and advisory to the NHLBI; charged with review and approval of the trial protocol prior to the start of patient activities, review of the accumulating study data for evidence of adverse or beneficial treatment effects, and review of the conduct of the trial; membership is composed of individuals with expertise in biostatistics, pulmonary and critical care medicine, quality of life assessment, and clinical trials who are independent of all LOTT centers.

### 10.2. Contracting centers

The 14 Regional Clinical Centers (RCCs) and Data Coordinating Center are supported by contracts from the NHLBI. The 14 RCCs may establish a network of satellite centers which will carry out some of the trial functions. The 14 RCCs are:

- Brigham and Women's Hospital, Harvard Medical School
- Cleveland Clinic Foundation
- Denver Health and Hospital Authority
- Duke University
- Kaiser Foundation Hospital
- Los Angeles Biomedical Research Institute at Harbor - UCLA Medical Center
- Ohio State University



**10.2. Contracting centers**

- Temple University
- University of Alabama at Birmingham
- University of Michigan, Ann Arbor
- University of Pittsburgh
- University of Utah
- University of Washington
- Washington University

Four types of satellites are expected to participate in LOTT, per the plans of the RCCs. The possible satellite levels are:

- **Major Affiliate:** Similar facilities to contractual RCCs; able to perform all Core and Expanded Baseline and Core and Expanded Followup data collection; likely to collect substudy and ancillary study data
- **Level A Satellite:** Able to perform all Core (Baseline and Followup) data collection; likely to be quality pulmonary practice, rehab program, or primary care practice involved in clinical trials with appreciation for quality data collection
- **Level B Satellite:** Able to obtain informed consent and some but not all Core data (i.e., a patient who sees a Level B site and initiates data collection there will have to travel to the RCC or another satellite site for another visit to complete the Core data collection)
- **Level C Satellite:** Able to identify potential patients but must refer patients to another site for LOTT data collection

Some RCCs do not plan on using any satellites.

The Data Coordinating Center is located in The Johns Hopkins University.

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# LOTT Protocol

## 11. Tables

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## 11.1. Design synopsis

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### Study name (abbreviation)

- Long-term Oxygen Treatment Trial (LOTT)

### Treatment groups

- Supplemental oxygen therapy tailored to patient's hypoxemia
  - If patient is moderately hypoxemic at rest, prescription is 2 L/min at rest and during sleep and dose is increased as needed to achieve at least 90% SpO<sub>2</sub> during ambulation
  - If patient is normoxic at rest, but desaturates on exercise, prescription is 2 L/min during sleep and dose is increased as needed to achieve at least 90% SpO<sub>2</sub> during ambulation
- No supplemental oxygen
- 1:1 treatment assignment ratio

### Sample size calculation assumptions

- Composite outcome variable: time from randomization to the first occurrence of either hospitalization from any cause or death from any cause
- Minimum clinically significant reduction in the composite event rate (composite of either death or hospitalization) in the supplemental oxygen group vs. the no supplemental oxygen group: 40% (hazard ratio = 0.60)
- 5% Type I error
- 90% power
- The percent of patients in the group assigned to no supplemental oxygen who will crossover to oxygen treatment at some point during the trial is estimated to be 11.7% overall, 13.3% in year 1, 19.6% in year 2, and 25% per year thereafter
- The percent of patients in the group assigned to supplemental oxygen who become crossovers by virtue of nonadherence with the tailored oxygen prescription, defined as not receiving at least 75% of the tailored oxygen prescription during a given year, is estimated to be 3.1% overall, 3.9% in year 1, 8.7% in year 2, and 15% per year thereafter
- Crossovers of either type are assumed to experience the risk for the composite of mortality or hospitalization in the opposite group after crossover.
- Patients who become nonadherent (i.e., crossovers) are assumed to assume the risk in the opposite group as of the time of the crossover
- Target patient mix
  - 25% with moderate resting hypoxemia
  - 75% with normal resting saturation, who desaturate during exercise
  - 50% with hospitalization for COPD within the year prior to screening
- Assumed event rates in the no supplemental oxygen group:
  - 33% hospitalization/yr in those with recent COPD hospitalization
  - 10% hospitalization/yr in those without recent COPD hospitalization
  - 7% mortality/yr in those with recent COPD hospitalization
  - 6% mortality/yr in those without recent COPD hospitalization

## 11.1. Design synopsis

- 28% composite event rate/yr in the no supplemental oxygen group
- Time to composite events for patients assigned to the group with no supplemental oxygen is assumed to follow an exponential distribution over the period of followup
- The loss to composite event followup rate is assumed to be only 1%, since both direct mortality and hospitalization ascertainment will be supplemented by searches of the Social Security Master Death File, the National Death Index, and/or the BIRLS system for mortality and similar systems which record hospitalizations at CMS and the VA
- Logrank test statistic
- Calculated sample size: 737 patients (368 per treatment group)
- Expected composite events: 351 (90 all-cause mortality and 261 all-cause hospitalizations)
- Power (N=737): Composite outcome, 90%; all-cause mortality, 39%; all-cause hospitalization, 82%

### Recruitment goals

- 737 patients (53 per RCC)
- 50% female
- 9% minority

### Outcome measures

- Core
  - PRIMARY OUTCOME: Time to the composite event, all-cause mortality or all-cause hospitalization
  - Time to all-cause mortality
  - Time to all-cause hospitalization
  - Disease-specific quality of life (change in St. George's Respiratory Questionnaire)
  - Preference-weighted health-related quality of life (Quality of Well-Being Scale)
  - Exacerbation rate
  - Dyspnea (change in MMRC dyspnea score)
  - Nutrition (body mass index)
  - Exercise capacity (six minute walk distance)
  - Health resource utilization
  - Time till onset of severe resting hypoxemia
- Expanded
  - General quality of life (SF-36)
  - Sleep quality (Pittsburgh Sleep Quality Scale)
  - Anxiety and depression (Hospital Anxiety and Depression Scale)
  - Spirometry
- Substudy (to be determined)

## 11.1. Design synopsis

### Data collection schedule

- Eligibility evaluation and baseline data collection visit
- Randomization visit
- Followup: Mix of in person, telephone, and mail contacts
  - Treatment adjustment visit shortly after randomization
    - Clinic visit for ambulatory dosing (oxygen group)
    - Telephone visit (no oxygen group)
  - Yearly in person visits (both groups)
  - Telephone visits at 4-month intervals between in person visits (both groups)
  - Quality of life questionnaires collected by mail at 4 and 16 months (both groups)
  - Adherence promotion contacts: weekly for 1 month, monthly for 5 months, then every 2 months to 12 months, and yearly thereafter at annual visits (oxygen group)
  - Adherence monitoring by mailed diary every 2 months (oxygen group)

### Expected duration of recruitment and followup

- Recruitment completed by December 2014
- Followup: at least 1 year on every randomized patient and followup on all randomized patients to a common closeout date (maximum followup of 7 years)

### Inclusion criteria (all are required)

- Age at least 40 years
- Dyspnea and lung disease process dominated by COPD in the judgment of the study physician
- One of the following must be true:
  - Post-bronchodilator FEV<sub>1</sub> percent predicted  $\leq$  70%
  - or
  - Post-bronchodilator FEV<sub>1</sub> percent predicted  $>$  70% and LOTT Study Physician determines that there is radiologic evidence of emphysema
- Post-bronchodilator FEV<sub>1</sub>/FVC  $<$  0.70
- Desaturation during rest or exercise per one of the following:
  - Resting oxygen saturation 89-93%
  - Desaturation below 90% for at least 10 seconds during 6 minute walk
- Response of Yes to at least one of the following questions:
  - Are you short of breath when hurrying on the level?
  - Are you short of breath when walking up a slight hill?
- If patient is using oxygen at the start of screening, all of the following must be met:
  - Patient agrees to stop using oxygen if randomized to no oxygen
  - Patient's physician agrees in writing to rescind order for oxygen if patient is randomized to no oxygen
  - Patient must report not using oxygen on the day of randomization and must report not using oxygen for the 4 calendar days prior to randomization (run in period where patient tries living without oxygen)

## 11.1. Design synopsis

- Satisfactory resolution of logistics of continuation with same oxygen company with waiver of cost sharing obligations or switch to new company that will waive cost sharing obligations if patient is randomized to oxygen
- At least 10 pack-years of tobacco cigarette smoking in past
- Agreement not to smoke while using oxygen
- Medicare Part A and Part B beneficiary or insurance or other resource willing to pay costs of treatment and costs of study procedures and visits
- Approval by study physician for randomization to either treatment group
- Completion of all required pre-randomization assessments within 60 days of initiating eligibility evaluation
- Randomization within 60 days of initiating eligibility evaluation
- Consent

### **Exclusion criteria (any disqualifies a patient from randomization)**

- Less than 30 days post treatment for an acute exacerbation of COPD as of initiating eligibility evaluation (less than 30 days from last dose of antibiotics or since a new or increased dose of systemic corticosteroids was initiated); chronic use of systemic corticosteroids while health is stable is not exclusionary
- COPD exacerbation requiring antibiotics, new or increased dose of systemic corticosteroids, or oxygen treatment after screening starts and prior to randomization (chronic use of corticosteroids while health is stable is not exclusionary)
- Less than 30 days post discharge from an acute care hospital after acute care hospitalization for COPD or other condition, as of initiating eligibility evaluation (patient may be in a rehabilitation hospital at time of screening)
- New prescription of supplemental oxygen after screening starts and before randomization
- Thoracotomy, sternotomy, major cardiopulmonary intervention (lung resection, open heart surgery, etc), or other procedure in the 6 months prior to eligibility evaluation likely to cause instability of pulmonary status
- Non COPD lung disease that affects oxygenation or survival
- Epworth Sleepiness Scale score greater than 15
- Desaturation below 80% for at least 1 minute during the six minute walk
- Disease or condition expected to cause death or inability to perform trial procedures or inability to comply with therapy within 6 months of randomization, as judged by study physician
- Participation in another intervention study

### **Mode of support**

- Contracts from NHLBI
- Reimbursement by CMS for allowable clinical services for its beneficiaries conducted as part of the study protocol

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**11.1. Design synopsis****Participating centers**

- 14 Regional Clinical Centers
    - Major affiliates
    - Satellite sites of varying levels of participation in the trial
  - Data Coordinating Center
  - Chairman's Office
  - NHLBI
  - CMS
-

# LOTT Protocol

# 11. Tables

## 11.2. Clinic and telephone visit data collection schedule (not including contacts for adherence promotion or monitoring)

| Months from RZ<br>[C]linic or [T]elephone visit   | BL |                | Year 1 |   |                | Year 2 |    |                | Year 3 |    |                | Year 4 |    |                | Year 5 |    |                | Year 6 |    |                | Year 7 |    |
|---|----|----------------|--------|---|----------------|--------|----|----------------|--------|----|----------------|--------|----|----------------|--------|----|----------------|--------|----|----------------|--------|----|
|   | -2 | 0              | 4      | 8 | 12             | 16     | 20 | 24             | 28     | 32 | 36             | 40     | 44 | 48             | 52     | 56 | 60             | 64     | 68 | 72             | 76     | 80 |
|   | C  | C              | T      | T | C              | T      | T  | C              | T      | T  | C              | T      | T  | C              | T      | T  | C              | T      | T  | C              | T      | T  |
| <b>Core data (all patients)</b>   |    |                |        |   |                |        |    |                |        |    |                |        |    |                |        |    |                |        |    |                |        |    |
| Consent   | X  | X              | .      | . | .              | .      | .  | .              | .      | .  | .              | .      | .  | .              | .      | .  | .              | .      | .  | .              | .      | .  |
| History*  | B  | S              | S      | S | L              | S      | S  | L              | S      | S  | L              | S      | S  | L              | S      | S  | L              | S      | S  | L              | S      | S  |
| RA resting oximetry   | X  | .              | .      | . | X              | .      | .  | X              | .      | .  | X              | .      | .  | X              | .      | .  | X              | .      | .  | X              | .      | .  |
| RA 6MW w/oximetry   | X  | .              | .      | . | X              | .      | .  | X              | .      | .  | X              | .      | .  | X              | .      | .  | X              | .      | .  | X              | .      | .  |
| Ambulatory oxygen dose  | .  | X <sup>R</sup> | .      | . | X <sup>R</sup> | .      | .  | X <sup>R</sup> | .      | .  | X <sup>R</sup> | .      | .  | X <sup>R</sup> | .      | .  | X <sup>R</sup> | .      | .  | X <sup>R</sup> | .      | .  |
| FEV <sub>1</sub> , FVC†   | X  | .              | .      | . | .              | .      | .  | .              | .      | .  | .              | .      | .  | .              | .      | .  | .              | .      | .  | .              | .      | .  |
| Height, arm span  | X  | .              | .      | . | .              | .      | .  | .              | .      | .  | .              | .      | .  | .              | .      | .  | .              | .      | .  | .              | .      | .  |
| Weight, edema   | X  | .              | .      | . | X              | .      | .  | X              | .      | .  | X              | .      | .  | X              | .      | .  | X              | .      | .  | X              | .      | .  |
| Hemoglobin, hematocrit  | X  | .              | .      | . | .              | .      | .  | .              | .      | .  | .              | .      | .  | .              | .      | .  | .              | .      | .  | .              | .      | .  |
| Cotinine  | X  | .              | .      | . | X              | .      | .  | .              | .      | .  | .              | .      | .  | .              | .      | .  | .              | .      | .  | .              | .      | .  |
| DNA and plasma banking  | X  | .              | .      | . | .              | .      | .  | .              | .      | .  | .              | .      | .  | .              | .      | .  | .              | .      | .  | .              | .      | .  |
| Epworth Sleepiness  | X  | .              | .      | . | .              | .      | .  | .              | .      | .  | .              | .      | .  | .              | .      | .  | .              | .      | .  | .              | .      | .  |
| MMRC  | X  | .              | .      | . | X              | .      | .  | X              | .      | .  | X              | .      | .  | X              | .      | .  | X              | .      | .  | X              | .      | .  |
| SGRQ  | X  | .              | M      | . | X              | M      | .  | X              | .      | .  | X              | .      | .  | X              | .      | .  | X              | .      | .  | X              | .      | .  |
| QWB-SA  | X  | .              | M      | . | X              | M      | .  | X              | .      | .  | X              | .      | .  | X              | .      | .  | X              | .      | .  | X              | .      | .  |
| <b>Expanded data (selected sites)</b>   |    |                |        |   |                |        |    |                |        |    |                |        |    |                |        |    |                |        |    |                |        |    |
| SF-36   | X  | .              | .      | . | X              | .      | .  | X              | .      | .  | X              | .      | .  | X              | .      | .  | X              | .      | .  | X              | .      | .  |
| Pitts. Sleep Qual. Index  | X  | .              | .      | . | X              | .      | .  | X              | .      | .  | X              | .      | .  | X              | .      | .  | X              | .      | .  | X              | .      | .  |
| Hosp. Anx. & Depr. Scale  | X  | .              | .      | . | X              | .      | .  | X              | .      | .  | X              | .      | .  | X              | .      | .  | X              | .      | .  | X              | .      | .  |
| FEV <sub>1</sub> , FVC†   | .  | .              | .      | . | X              | .      | .  | X              | .      | .  | X              | .      | .  | X              | .      | .  | X              | .      | .  | X              | .      | .  |
| A1AT  | X  | .              | .      | . | .              | .      | .  | .              | .      | .  | .              | .      | .  | .              | .      | .  | .              | .      | .  | .              | .      | .  |
| Serum banking   | X  | .              | .      | . | .              | .      | .  | .              | .      | .  | .              | .      | .  | .              | .      | .  | .              | .      | .  | .              | .      | .  |
| <b>Substudy data collection (on an as yet unspecified number of patients)</b><br>(To be determined) |    |                |        |   |                |        |    |                |        |    |                |        |    |                |        |    |                |        |    |                |        |    |

\*B = Baseline history, S = short interim history, L = long interim history, M = mailed

†Pre- and post-bronchodilator (medication will not be held prior to pre-bronchodilator spirometry)

<sup>R</sup>Only for patients randomized to supplemental oxygen; exercise assessment while using oxygen to determine/check their exercise oxygen dose (done 1 week after randomization).



# LOTT Protocol

# 11. Tables

## 11.3. Whole blood (venous; mL) draw schedule

| Months from RZ                        | Baseline <sup>1</sup> |   | Followup  |    |    |    |    |    |
|---------------------------------------|-----------------------|---|-----------|----|----|----|----|----|
|                                       | -2                    | 0 | 12        | 24 | 36 | 48 | 60 | 72 |
| <b>Core</b>                           |                       |   |           |    |    |    |    |    |
| Hemoglobin, hematocrit <sup>2</sup>   | 3                     | . | .         | .  | .  | .  | .  | .  |
| Cotinine <sup>3</sup>                 | 10                    | . | 10        | .  | .  | .  | .  | .  |
| DNA and plasma banking <sup>4</sup>   | 18.5                  | . | .         | .  | .  | .  | .  | .  |
| <b>Total for Core</b>                 | <b>31.5</b>           | . | <b>10</b> | .  | .  | .  | .  | .  |
| <b>Expanded</b>                       |                       |   |           |    |    |    |    |    |
| A1AT <sup>5</sup>                     | 3                     | . | .         | .  | .  | .  | .  | .  |
| Serum banking <sup>6</sup>            | 10                    | . | .         | .  | .  | .  | .  | .  |
| <b>Total for Expanded<sup>7</sup></b> | <b>44.5</b>           | . | <b>10</b> | .  | .  | .  | .  | .  |

<sup>1</sup>Note: Blood is to be drawn before randomization.

<sup>2</sup>Hemoglobin, hematocrit: One 3 mL purple top tube (tests done by local lab).

<sup>3</sup>Cotinine: One 10 mL red top tube (not serum separator). Test is done by local lab.

<sup>4</sup>One 8.5 mL Paxgene tube (primary DNA source) and one 10 mL EDTA tube (backup DNA source and plasma for banking). Tubes are sent to Biosample Repository at the Channing Laboratory.

<sup>5</sup>A1AT concentration and phenotype can be obtained from chart review. If concentration is greater than 100 mg/dL (100 mg%, 1 mg/mL, 19 µM), phenotype is not required. If concentration is not available or if concentration is 100 mg/dL (100 mg%, 1 mg/mL, 19 µM) or less and phenotype is not available, fill one 3 mL red top tube and have tests done by local lab.

<sup>6</sup>Serum banking: One 10 mL red top tube. Serum is sent to Biosample Repository at the Channing Laboratory.

<sup>7</sup>Expanded data collection is additional to Core data collection, so total for Expanded is sum of amounts for tests done for Core data collection and tests done for Expanded data collection.

### 11.4. Adherence promotion contact schedule

|                        | Weeks from randomization |   |   |   |   | Months from randomization |   |    |   |   |    |    |    |    |    |    |    |    |
|------------------------|--------------------------|---|---|---|---|---------------------------|---|----|---|---|----|----|----|----|----|----|----|----|
|                        | 0                        | 1 | 2 | 3 | 4 | 2                         | 3 | 4  | 5 | 6 | 8  | 10 | 12 | 24 | 36 | 48 | 60 | 72 |
| Supplemental oxygen    | C                        | T | T | T | T | T                         | T | T* | T | T | T* | T  | C  | C  | C  | C  | C  | C  |
| No supplemental oxygen | C                        | T | . | . | . | .                         | . | .  | . | . | .  | .  | .  | .  | .  | .  | .  | .  |

Notes:

C = clinic visit

T = telephone call visit (coordinator calls participant)

\* = combined with data collection telephone visit

**For supplemental oxygen group:**

**In person contact at randomization** (0 visit) includes: counseling about any dissatisfaction with treatment assignment, initiation of education about using oxygen, prescription of oxygen equipment and arranging for delivery to participant's home and scheduling in person visit to obtain walking prescription and further educate participant.

**In person contacts in 1<sup>st</sup> week after randomization and at 1, 2, 3, 4, 5, and 6 years** include: education about participant's personal home and ambulatory systems; walk on oxygen with oximetry (to determine patient's ambulatory oxygen prescription); and adherence promotion discussions (address barriers to adherence, encourage adherence)

**Telephone contacts at 1, 2, 3, and 4 weeks and 2, 3, 4, 5, 6, 8 and 10 months** include: adherence promotion discussions (address barriers to adherence, encourage adherence) and trouble shoot any problems with oxygen equipment. Additional telephone contacts may occur in year 2 as needed if the patient seems receptive to encouragement.

**For no supplemental oxygen group:**

**In person contact at randomization** (0 visit) includes: counseling about any dissatisfaction with treatment assignment, confirmation that any oxygen equipment in the home has been removed, discussion about the importance of adhering to the no oxygen regimen, but keeping LOTT site informed about any prescription for oxygen and if prescribed oxygen, the patient should use it as prescribed.

**Telephone contact** includes: adherence promotion discussions (address barriers to adherence, encourage adherence)

# LOTT Protocol

# 11. Tables

## 11.5. Post randomization contact schedule (summary)

| R | W | Yr 1: Mos |   |   |   |   | Yr 2: Mos |   |   |   |   | Yr 3: Mos |   |   |   |   | Yr 4: Mos |   |   |   |   | Yr 5: Mos |   |   |   |   | Yr 6: Mos |   |   |   |   | Yr 7: Mos |   |   |   |   |   |   |   |   |   |   |
|---|---|-----------|---|---|---|---|-----------|---|---|---|---|-----------|---|---|---|---|-----------|---|---|---|---|-----------|---|---|---|---|-----------|---|---|---|---|-----------|---|---|---|---|---|---|---|---|---|---|
| Z | k |           |   | 1 | 1 |   | 1         | 1 | 1 | 2 | 2 | 2         | 2 | 2 | 3 | 3 | 3         | 3 | 3 | 4 | 4 | 4         | 4 | 4 | 5 | 5 | 5         | 5 | 5 | 6 | 6 | 6         | 6 | 6 | 7 | 7 | 7 | 7 | 7 | 8 | 8 |   |
| 0 | 1 | 2         | 4 | 6 | 8 | 0 | 2         | 4 | 6 | 8 | 0 | 2         | 4 | 6 | 8 | 0 | 2         | 4 | 6 | 8 | 0 | 2         | 4 | 6 | 8 | 0 | 2         | 4 | 6 | 8 | 0 | 2         | 4 | 6 | 8 | 0 | 2 | 4 | 6 | 8 | 0 | 2 |

**All patients**

|       |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|-------|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit | C | . | . | T | . | T | . | C | . | T | . | T | . | C | . | T | . | T | . | C | . | T | . | T | . | C | . | T | . | T | . | C | . | T | . | T | . |
| Mail  | . | . | . | M | . | . | . | . | . | M | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |

**Additional contacts for oxygen patients**

|                        |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|------------------------|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Adh promo <sup>1</sup> | . | C | A | A | A | A | A | A | . | . | . | . | . | A | . | . | . | . | . | A | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| Diary <sup>2</sup>     | . | . | D | D | D | D | D | D | D | D | D | D | D | D | D | D | D | D | D | D | D | D | D | D | D | D | D | D | D | D | D | D | D | D | D | D | D |

**Additional contacts for control patients**

|       |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|-------|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit | . | T | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
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T=telephone visit with interview, C=clinic visit, A=adherence promotion contact, D=adherence monitoring diary  
<sup>2</sup>Adherence promotion telephone contacts are weekly for 1<sup>st</sup> month, monthly for 2<sup>nd</sup> - 6<sup>th</sup> months, every 2 months for 7<sup>th</sup> - 12<sup>th</sup> months, in person at annual visits.  
<sup>3</sup>Patients are to complete and return diaries indicating oxygen usage every 2 months through all followup.

# LOTT Protocol

## 12. Appendices

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**Appendix 1 - DSMB charter**

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**1. Introduction**

This Charter is for the Data and Safety Monitoring Board (DSMB) for the Long-term Oxygen Treatment Trial (LOTT).

The Charter is intended to be a living document. The DSMB may wish to review it at regular intervals to determine whether any changes in procedure are needed.

**2. Responsibilities of the DSMB**

The DSMB is responsible for safeguarding the interests of study participants, assessing the safety and efficacy of study procedures, and for monitoring the overall conduct of the study.

The DSMB is an independent group advisory to the Director, NHLBI, and is required to provide recommendations about starting, continuing, and stopping the study. In addition, the DSMB is asked to make recommendations, as appropriate, to the NHLBI about:

- Efficacy of the study intervention
- Benefit/risk ratio of procedures and participant burden
- Selection, recruitment, and retention of participants
- Adherence to protocol requirements
- Completeness, quality, and analysis of measurements
- Amendments to the study protocol and consent forms
- Performance of individual centers and core labs
- Participant safety
- Notification of and referral for abnormal findings

**3. Organization and Interactions**

The following description illustrates the relationship between the DSMB and other entities in this study.

The LOTT is sponsored by the NHLBI and the Centers for Medicare and Medicaid Services (CMS). The NHLBI has responsibility for all activities related to negotiating, awarding, directing, and terminating of the contracts with the centers conducting the LOTT; monitoring and evaluating program progress from a technical, legal, and financial standpoint; and receiving and making decisions based on the advice of the DSMB. All data produced under the performance of the contracts for the LOTT are the property of the NHLBI, and the NHLBI reserves the right to use, release, distribute, and publish the data. CMS is responsible for providing reimbursement directly to clinics in compliance with study wide goals for protocol-related allowable clinical services for its

beneficiaries who participate in the LOTT. The DSMB is appointed by and is advisory to the NHLBI. Fourteen Regional Clinical Centers and their affiliated sites are responsible for evaluating, enrolling, treating and following LOTT patients. The Data Coordinating Center is responsible for coordinating activities of study committees; collaborating on development of the protocol, manual of operations, and data forms; developing and implementing quality assurance programs for recruitment and data collection; and preparing monitoring reports to judge clinic performance and to identify indications for adverse or beneficial effects of the treatments.

Communication with DSMB members will be primarily through the NHLBI Program Office and the Data Coordinating Center (DCC). It is expected that study investigators will not communicate with DSMB members about the study directly, except when making presentations or responding to questions at DSMB meetings or during conference calls.

#### **4. DSMB Members and NHLBI Program Staff**

Consistent with NHLBI policy, each DSMB is assigned an Executive Secretary (ES) to provide an unbiased staff interface for the DSMB, especially during executive sessions. The ES is responsible for assuring the accuracy and timely transmission of the final recommendations and DSMB minutes.

#### **5. Scheduling, Timing, and Organization of Meetings**

DSMB meetings are usually held in the Washington, DC, area. The purpose of the first meeting is to review and discuss this Charter, to provide an overview of study activities, to review and make recommendations about the protocol, and to determine the frequency of interim analyses and whether data will or will not be masked to identity of randomized groups. Enrollment in a study cannot begin until the DSMB's recommendation for approval has been accepted by the Director, NHLBI, and IRB approval has been obtained at each site.

Meetings are held approximately twice a year in person and twice a year by telephone, or as needed. Meetings and conference calls will be scheduled by the DCC in collaboration with the NHLBI Program Office.

The agenda for DSMB meetings and calls may be drafted by the DCC in consultation with NHLBI staff. The ES will finalize the agenda after consultation with the DSMB Chair. The agenda and meeting materials should be distributed by the DCC 2 weeks before each meeting or call.

Before each meeting, when the agenda is sent out, the ES will ask all DSMB members to state whether they have developed any new conflicts of interest since the last formal annual report to NHLBI. If a new conflict is reported, the Chair and staff will determine if the conflict limits the

ability of the DSMB member to participate in the discussion. The DSMB also will review adverse event data, other safety data, quality and completeness of study data, and enrollment data at each meeting to ensure proper trial conduct. At intervals, as noted above, the DSMB will also review formal interim analyses of the primary end point.

It is expected that all DSMB members will attend every meeting and call. However, it is recognized that this may not always be possible. Therefore, the DSMB may wish to discuss whether establishing a quorum for voting is desirable. All standing Monitoring Board members are voting members. The Board may also wish to decide in advance whether *ad hoc* members can vote.

- A quorum of this DSMB will consist of five members, including at least one with expertise in biostatistics and at least one expert in respiratory disease.

### 6. Discussion of Confidential Material

DSMB meetings and calls will be organized into open, closed, and executive sessions.

- During the **open sessions**, information will be presented to the DSMB by the DCC, study investigators and NHLBI staff as appropriate, with time for discussion.
- During the **closed sessions**, the DSMB, DCC, and NHLBI staff will discuss confidential data from the study, including information on efficacy and safety by treatment arm. The DSMB will decide whether to remain masked to the treatment assignments at each meeting. If the closed session occurs on a conference call, steps will be taken to ensure that only the appropriate participants are on the call, and to invite others to re-join the call only at the conclusion of the closed session.

The DSMB may elect to hold an **executive session** in which only the DSMB members and NHLBI Executive Secretary are present in order to discuss study issues independently. Voting on recommendations will follow Roberts' Rules of Order (**Robert's Rules of Order Newly Revised (10th Edition) RONR** by Henry M. Robert III, William J. Evans (Editor), Daniel H. Honemann (Editor), Thomas J. Balch (Editor), Sarah Corbin Robert, Henry M. Robert III, General Henry M. Robert).

If the executive session occurs on a conference call, steps will be taken to ensure that only the appropriate participants are on the call, and to invite others to re-join the call only at the conclusion of the executive session.

At the conclusion of the closed and executive sessions, the participants will be re-convened so that the DSMB Chair can provide a summary of the DSMB's recommendations. This provides an opportunity for study investigators, the DCC, and NHLBI to ask questions to clarify the recommendations. The meeting is then adjourned.

### 7. Reports of DSMB Deliberations

- Initial summary: The NHLBI ES is responsible for assuring the accuracy and transmission of a brief summary of the DSMB's discussion and recommendations for the Director, NHLBI, within 48 hours of the meeting or call. The Director or designee will review this summary and approve or disapprove the recommendation(s), or request additional information. The recommendations will then be sent to the DCC, and the clinical investigators.
- Action plan: If the DSMB's recommendations require significant changes or follow-up, NHLBI staff in collaboration with the DCC will prepare an action plan outlining the steps required to implement the recommendations.
- Formal minutes: The NHLBI ES is responsible for the accuracy and transmission of the formal DSMB minutes for the Director, NHLBI, within 30 days of the meeting or call. These minutes are subject to FOIA requests and are prepared accordingly to summarize the key points of the discussion and debate, requests for additional information, response of the investigators to previous recommendations, and the recommendations from the current meeting. These minutes will be reviewed by NHLBI staff, key study personnel and the DCC before being forwarded to the DSMB Chair for final review and approval. The DSMB Chair may sign the minutes or indicate approval electronically via email. Then, the minutes are sent to Office of the Director, NHLBI, for OD approval. Subsequently, the minutes are sent back to the DCC and the relevant investigators, and included in the materials for the subsequent DSMB meeting to be approved by voice vote at that meeting. Once they have been voted and approved by the Board, they are considered Final.
- Reports to IRBs: Because this DSMB is convened to supervise a multi-center study, the following additional reporting is required by NHLBI policy:

If the DSMB does not identify any safety or other protocol-related concerns, within 30 days after a DSMB meeting, the NHLBI Program Office will prepare a Summary Report that will state that:

- a review of outcome data, adverse events, and information relating to study performance (e.g., data timeliness, completeness, and quality) across all centers took place on a given date;



- the observed frequency of adverse events did not exceed what was expected and indicated in the informed consent;
- a review of recent literature relevant to the research took place and;
- the DSMB recommended that the study continue without modification of the protocol or informed consent.

If concerns are identified, the report to the clinical centers will outline the concerns, the DSMB's discussion of the concerns, and the basis for any recommendations that the DSMB has made in response to the concerns.

The report will be distributed by the DCC to each clinical center. It is the responsibility of each clinical center to forward this information to the local IRB.

#### **8. Reports to the DSMB**

For each meeting, the DCC, with input from NHLBI staff, will prepare summary reports and tables to facilitate the oversight role of the DSMB. The DSMB should discuss at the first or subsequent meetings what data they wish to review and how it should be presented.

#### **9. Statistical Monitoring Guidelines**

At the first meeting, review of the protocol will include review of the statistical analysis plan. The DSMB should discuss the adequacy of that plan. The DSMB should discuss the statistical monitoring procedures they propose to follow to guide their recommendations about termination or continuation of the trial. These procedures could include guidelines for early termination for benefit, termination for futility, and termination for safety reasons.

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## Appendix 2 - Effect size survey



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Lon

Survey: EffectSize(Feb07)

**INTRODUCTION**

The purpose of this survey is to develop consensus on the smallest treatment effect from oxygen that we would

The smaller the treatment effect, the greater the number of patients we will need to enroll in order to be confident t

Treatment effects can be expressed either as absolute or relative improvement in one treatment group compared t the NNT or number of patients needed to treat for a specified time period in order to save one life.

The following survey will ask your opinion using all of these ways of expressing treatment effect.

As background, review the examples in the next section, before answering the questions relating to the LOTT.

The following survey will ask your opinion using all of these ways of expressing treatment effect. Please answer al

**EXAMPLES OF MORTALITY-REDUCING TREATMENTS FOR CHRONIC DISEASES:**Patient Population: Patients with Coronary Heart Disease

Treatment: Simvastatin

Duration: 5 years

Mortality in untreated group: 15%

Mortality in treated group: 13%

Relative Reduction: 13%

NNT: 59

Duration: 5 years

Ref: MRC/BHF trial. Lancet 2002; 360:7-22

Patient Population: Elderly patients with isolated systolic hypertension (>160 mm Hg)

Treatment: Thiazide diuretic +/- Beta-blocker

Duration: 5 years

Death/Stroke in untreated group: 8.2%

Death/Stroke in treated group: 5.2%

Relative Reduction: 36%

NNT: 33

Duration: 5 years

Ref: SHEP trial. JAMA. 1991;265:3255-64.

Patient Population: Patients with coronary heart disease, meta-analysis (n = 45,215)

Treatment: Statins

Duration: 3.2 years (median of trials)

All-cause mortality in control group: 11%

All-cause mortality in treatment group: 9.4%

Relative Reduction in all-cause mortality: 16%

Absolute Risk Reduction: 1.8%

NNT: 56

Ref: Wilt et al. Arch Intern Med. 2004;164:1427-36.

Patient Population: Patients with mild-moderate COPD, asymptomatic (n = 5887)

Treatment: Smoking Cessation Program + Nicotine gum

Duration 14.5 years

All-cause mortality in control group: 10.4%

All-cause mortality in treatment group: 8.8%

Relative Reduction in all-cause mortality: 16%

Absolute Risk Reduction: 1.6%

NNT: 62.5

Ref: LHS. Ann Intern Med. 2005;142:233-9

## Appendix 2 - Effect size survey

**Patient Population:** Patients with CHF or LV Dysfunction after MI (n=12,763)  
**Treatment:** ACE inhibitors  
**Duration:** 35 months  
**All-cause mortality in control group:** 26.8%  
**All-cause mortality in treatment group:** 23.0%  
**Relative Risk Reduction:** 14%  
**Absolute Risk Reduction:** 3.8%  
**NNT:** 26.3  
**Ref:** Flather et al. Lancet. 2000;355(9215):1575-81

**[For Questions 1-3]:** Given the current version of the major inclusion criteria for LOTT:

- COPD with FEV1  $\leq$  66% predicted, post-BD
- Resting oxygen saturation 89-92%
- No current serious illness likely to cause death within 3 years
- Not current smoker

1. Which of the following is closest to your estimate of the annual mortality in the group not treated with oxygen?

- (a) 2% per year  
 (b) 4% per year  
 (c) 8% per year  
 (d) 16% per year

2. Which of the following is closest to your estimate of the percent of control patients who will cross-over to control randomization?

- (a) 2.5% per year  
 (b) 5% per year  
 (c) 10% per year  
 (d) 20% per year  
 (e) 40% per year

3. Which of the following is closest to your estimate of the percent of patients who will be adherent with continuous or more hours per day for 75% or more days over the first year of treatment)?

- (a) 10% will be adherent  
 (b) 20% will be adherent  
 (c) 40% will be adherent  
 (d) 60% will be adherent  
 (e) 80% will be adherent

**[For Questions 4-7]:** Take into account your best estimate of:

- the burdens and costs of using continuous oxygen;
- non-adherence; and
- cross-overs between groups

Which of the following is closest to your best estimate of the smallest difference which you would be willing to miss LOTT, expressed as a relative reduction in annual mortality:

4. For a control group annual mortality of 2%:  
 (a) 10% reduction (RR=0.90)

## Appendix 2 - Effect size survey

- (b) 20% reduction (RR=0.80)  
 (c) 40% reduction (RR=0.60)  
 (d) 80% reduction (RR=0.20)

5. For a control group annual mortality of 4%:

- (a) 10% reduction (RR=0.90)  
 (b) 20% reduction (RR=0.80)  
 (c) 40% reduction (RR=0.60)  
 (d) 80% reduction (RR=0.20)

6. For a control group annual mortality of 8%:

- (a) 10% reduction (RR=0.90)  
 (b) 20% reduction (RR=0.80)  
 (c) 40% reduction (RR=0.60)  
 (d) 80% reduction (RR=0.20)

7. For a control group annual mortality of 16%:

- (a) 10% reduction (RR=0.90)  
 (b) 20% reduction (RR=0.80)  
 (c) 40% reduction (RR=0.60)  
 (d) 80% reduction (RR=0.20)

[For Questions 8-11]: Take into account your best estimate of:

- the burdens and costs of using continuous oxygen;
- non-adherence; and
- cross-overs between groups

Which of the following is closest to your best estimate of the smallest difference which you would be willing to miss LOTT, expressed as a absolute reduction in annual mortality:

8. For a control group annual mortality of 2%:

- (a) 0.2% reduction  
 (b) 0.4% reduction  
 (c) 0.8% reduction  
 (d) 1.6% reduction

9. For a control group annual mortality of 4%:

- (a) 0.4% reduction  
 (b) 0.8% reduction  
 (c) 1.6% reduction  
 (d) 3.2% reduction

10. For a control group annual mortality of 8%:

- (a) 0.8% reduction  
 (b) 1.6% reduction

## Appendix 2 - Effect size survey

- (c) 3.2% reduction
- (d) 6.4% reduction

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11. For a control group annual mortality of 16%:

- (a) 1.6% reduction
- (b) 3.2% reduction
- (c) 6.4% reduction
- (d) 12.8% reduction

---

[For Question 12]: Take into account your best estimate of:

- the burdens and costs of using continuous oxygen;
- non-adherence; and
- cross-overs between groups

Which of the following is closest to your best estimate of the number of patients with moderate hypoxemia needed years in order to save one patient's life that would warrant you to prescribe continuous oxygen:

---

12. Number Needed to Treat (NNT):

- (a) 5 patients x 3 years
- (b) 10 patients x 3 years
- (c) 20 patients x 3 years
- (d) 40 patients x 3 years
- (e) 80 patients x 3 years
- (f) 160 patients x 3 years
- (g) 320 patients x 3 years
- (h) 640 patients x 3 years

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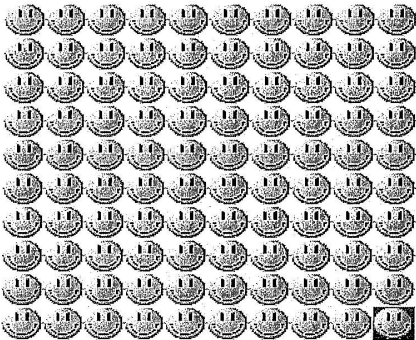
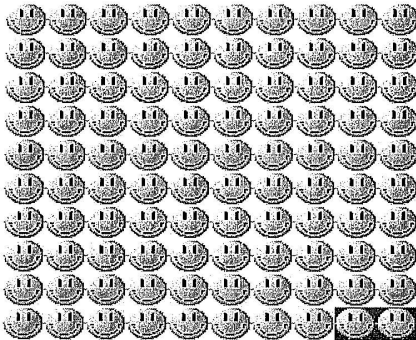

[For Question 13]: Take into account your best estimate of:

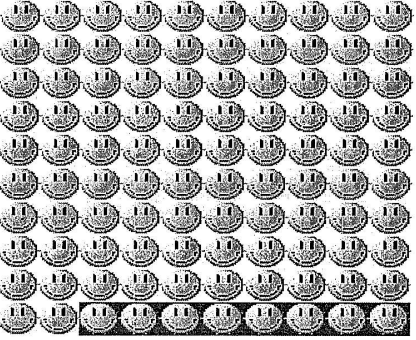
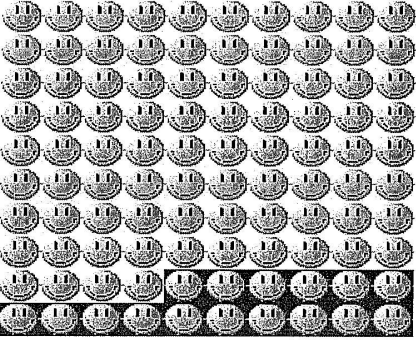

- the burdens and costs of using continuous oxygen;
- non-adherence; and
- cross-overs between groups

---

13. Which figure below best expresses your opinion of the smallest number of additional surviving patients in a thr continuous oxygen to patients with moderate hypoxemia (key: Yellow=treated for 3 years with no survival benefit oxygen treatment):

## Appendix 2 - Effect size survey

**A.**  **B.**  **C.** 

**D.**  **E.**  **F.** 

(a) Figure A  
 (b) Figure B  
 (c) Figure C  
 (d) Figure D  
 (e) Figure E  
 (f) Figure F

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Name:   
Center:

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## References

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- Mannino DM, Homa DM, Akinbami LJ, Ford ES, Redd SC. Chronic obstructive pulmonary disease surveillance: United States, 1971-2000. *MMWR CDC Surveill Summ* 2002;51:1-16.
- Nocturnal Oxygen Therapy Trial Group. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. *Ann Intern Med* 1980;93:391-398.
- Medical Research Council Working Party. Long-term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. *Lancet* 1981;1:681-686.
- Anthonisen NR, Skeans MA, Wise RA, Manfreda J, Kanner RE, Connett JE. The effects of a smoking cessation intervention on 14.5-year mortality. A randomized clinical trial. *Ann Intern Med* 2005;142:233-239.
- Nichol KL, Baken L, Nelson A. Relation between influenza vaccination and outpatient visits, hospitalization, and mortality in elderly persons with chronic lung disease. *Ann Intern Med* 1999;130:397-403.
- Nichol KL, Baken L, Wuorenma J, Nelson A. The health and economic benefits associated with pneumococcal vaccination of elderly persons with chronic lung disease. *Arch Intern Med* 1999;159:2437-2442.
- Ram FSF, Picot J, Lightowler J, Wedzicha JA. Non-invasive positive pressure ventilation for treatment of respiratory failure due to exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2004;1:CD004104.
- National Emphysema Treatment Trial Research Group. A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. *N Engl J Med* 2003;348:2059-2073.
- Gorecka D, Gorselak K, Sliwinski P, Tobiasz M, Zielinski J. Effect of long term oxygen therapy on survival in patients with chronic obstructive pulmonary disease with moderate hypoxaemia. *Thorax* 1997;52:674-679.
- Chaouat A, Weitzenblum E, Kessler R, Charpentier C, Ehrhart M, Schott R, Levi-Valensi P, Zielinski J, Delaunois L, Cornudella R, et al. A randomized trial of nocturnal oxygen therapy in chronic obstructive pulmonary disease patients. *Eur Respir J* 1999;14:1002-1008.

## LOTT Protocol

---

### References

- Stewart BN, Hood CI, Block AJ: Long-term results of continuous oxygen therapy at sea level. *Chest* 1975; 68:486-492.
- Crockett AJ, Moss JR, Cranston JM, Alpers JH: The effects of home oxygen therapy on hospital admission rates in chronic obstructive airways disease. *Monaldi Arch Chest Dis* 1993; 48:445-446.
- Buyse B and Demedts M: Long-term oxygen therapy with concentrators and liquid oxygen. *Acta Clin Belg* 1995; 50:149-157.
- Ringbaek TJ, Viskum K, Lange P: Does long-term oxygen therapy reduce hospitalisation in hypoaemic chronic obstructive pulmonary disease? *Eur Respir J* 2002; 20:38-42.
- Croxtan TL, Bailey WC for the NHLBI Working Group on Long-term Oxygen Treatment in COPD: Long-term oxygen treatment in chronic obstructive pulmonary disease: Recommendations for future research. An NHLBI Workshop Report. *Am J Respir Crit Care Med* 2006; 174:373-378.
- Mitchell GS, Baker TL, Nanda SA, Fuller DD, Zabka AG, Hodgman BA, Bavis RW, Mack KJ, Olson EB Jr. Invited review: intermittent hypoxia and respiratory plasticity. *J Appl Physiol* 2001;90:2466-2475.
- Raj U, Shimoda L. Oxygen-dependent signaling in pulmonary vascular smooth muscle. *Am J Physiol Lung Cell Mol Physiol* 2002;283:L671-L677.
- Semenza GL. Regulation of mammalian O<sub>2</sub> homeostasis by hypoxia-inducible factor 1. *Annu Rev Cell Dev Biol* 1999;15:551-578.
- Chow LC, Wright KW, Sola A; CSMC Oxygen Administration Study Group. Can changes in clinical practice decrease the incidence of severe retinopathy of prematurity in very low birth weight infants? *Pediatrics* 2003;111:339-345.
- McColm JR, Cunningham S, Wade J, Sedowofia K, Gellen B, Sharma T, McIntosh N, Fleck BW. Hypoxic oxygen fluctuations produce less severe retinopathy than hypoxic fluctuations in a rat model of retinopathy of prematurity. *Pediatr Res* 2004;55:107-113.
- MacNee W. Oxidative stress and lung inflammation in airways disease. *Eur J Pharmacol* 2001;429:195-207.



## LOTT Protocol

---

### References

- Lama VN, Flaherty KR, Toews GB, Colby TV, Travis WD, Long Q, Murray S, Kazerooni EA, Gross BH, Lynch JP III, et al. Prognostic value of desaturation during a 6-minute walk test in idiopathic interstitial pneumonia. *Am J Respir Crit Care Med* 2003;168:1084-1090.
- O'Donnell DE, D'Arsigny C, Webb KA. Effects of hyperoxia on ventilatory limitation during exercise in advanced chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001;163:892-898.
- Fletcher EC, Levin DC. Cardiopulmonary hemodynamics during sleep in subjects with chronic obstructive pulmonary disease: the effect of short- and long-term oxygen. *Chest* 1984;85:6-14.
- Fletcher EC, Donner CF, Midgren B, Zielinski J, Levi-Valensi P, Braghiroli A, Rida Z, Miller CC. Survival in COPD patients with a daytime PaO<sub>2</sub> > 60 mm Hg with and without nocturnal oxyhemoglobin desaturation. *Chest* 1992;101:649-655.
- Brooks SM. Surveillance for respiratory hazards. *ATS News* 1982;8:12-16.
- Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general US population. *Am J Respir Crit Care Med* 1999;159:179-187.
- Shih JH. Sample size calculation for complex clinical trials with survival endpoints. *Controlled Clin Trials* 1995;16:395-407.
- Lan KK and DeMets DL. Changing frequency of interim analysis in sequential monitoring. *Biometrics* 1989;45:1017-1020.
- Lee JW and DeMets DL. Group sequential comparisons of changes: ad-hoc versus more exact method. *Biometrics* 1995;51:21-30.
- O'Brien PC and Fleming TR. A multiple testing procedure for clinical trials. *Biometrics* 1979;35:549-556.
- Barlow W, Azen S: The effect of therapeutic treatment crossovers on the power of clinical trials. *Controlled Clin Trials* 1990;11:314-326.
- Buist AS, Vollmer WM: The use of lung function tests in identifying factors that affect lung growth and aging. *Stat Med* 1988: 7:11-18.

## LOTT Protocol

---

### References

D'Agostino RB, Sparrow D, Weiss S, Rosner B: Longitudinal models for analysis of respiratory function. *Stat Med* 1995;14:2205-2216.

Hoaglin DC, Mosteller F, Turkey JW (eds): Understanding Robust and Exploratory Data Analysis John Wiley and Sons, New York, 1983.

Huber PJ: Robust Statistics John Wiley and Sons, New York, 1981.

Liang KY, Zeger SL: Longitudinal data analysis for discrete and continuous outcomes. *Biometrics* 1986;42:121-130.

Wypij D, Pugh M, Ware JH: Modeling pulmonary function growth with regression splines. *Statistica Sinica* 1993;3:329-350.

DeMets DL and Ware JH: Asymmetric group sequential boundaries for monitoring clinical trials. *Biometrika*. 1982; 69:661-663.

Fleming TR, Harrington DP and O'Brien PC: Designs for Group Sequential Tests. *Controlled Clinical Trials*. 1984;5:348-361.

Freidlin B and Korn EL: A comment on futility monitoring. *Controlled Clinical Trials*. 2002;23: 355-366.

---