Online Data Supplement

The Long-term Oxygen Treatment Trial (LOTT) for Chronic Obstructive Pulmonary Disease: Rationale, Design, and Lessons Learned

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Appendix 1: Additional LOTT methodology

This appendix provides additional details regarding participant eligibility, oxyhemoglobin saturation by pulse oximetry (**SpO_2**) assessment, Expanded and Core data collection, adherence assessment, outcome verification, and study assumptions. The Long-term Oxygen Treatment Trial (**LOTT**) protocol (**Appendix 2**) provides additional study methodology information.

Patients and Eligibility

During the conduct of the trial, the investigators recognized that some patients did not meet the LOTT eligibility criteria, though they clearly met the spirit of the eligibility requirements of the protocol. Thus, the Steering Committee decided to allow exemptions from study eligibility criteria if approved by the LOTT Eligibility Review Committee. The Eligibility Review Committee consisted of 5 physicians, the Data Coordinating Center (**DCC**) project manager, and the DCC principal investigator. Allowance of an exemption required at least 3 physicians and either the DCC project manager or the DCC principal investigator to approve it. If a site had a patient whom they felt was appropriate for LOTT but who did not meet the stated eligibility criteria, the site was permitted to appeal to the Committee by submitting a written justification for an exemption and relevant records (e.g., spirometry, medical history details) as requested by the Committee. For example, a patient whose spirometry was just outside the eligibility range who had COPD, emphysema on chest computed tomography scan, and hypoxemia associated with COPD, could undergo review by the Committee and potentially be allowed to enroll. Of the 38 requests for an eligibility exemption, the

Committee approved 24 (24/738 [3.2%] randomized), declined 8, and did not make a determination on 6 that the submitting investigators withdrew. Periodic review of the submissions and decisions by the Steering Committee eventually led to alteration of the FEV_1 eligibility criterion in December 2010 to include patients with FEV_1 above 70% of the predicted normal value[1] if the site investigator confirmed that the patient had radiologic evidence of emphysema.

SpO_2 Assessment

LOTT participants underwent SpO_2 assessment with the Masimo Radical 7® pulse oximeter and Masimo Rainbow® DCI-dc3 finger or LNCS® TF-1 forehead sensor. For the resting SpO_2 assessment, the participant was required to breathe room air for the 15 consecutive minutes just prior to the assessment. With SpO_2 sampling occurring every second, resting SpO_2 was determined as the mean of the acceptable quality SpO_2 data points obtained in the last 5 minutes of a 6 minute test session. The coefficient of variation of the data points included in the mean calculation had to be 2.5% or less. If more than 100 of the data points in the last 5 minutes of the test session had unacceptable quality, the test session was considered unacceptable and the mean saturation was not calculated. The oximeter was connected to a laptop during the test session; custom software developed by the LOTT DCC implemented this algorithm during the test session and provided an assessment of eligibility with respect to resting desaturation. During follow-up, this same methodology was used to identify occurrences of *severe* resting desaturation (i.e., 88% or below) that required prescription of round-the-clock supplemental oxygen.

For the exercise desaturation assessment, the participant was required to breathe room air for the 15 consecutive minutes just prior to the assessment. Oximetry data collected during the 6-minute walk were assessed for desaturation during exercise; a LOTT staff member carrying the oximeter trailed the participant during the walk or the oximeter was placed in a fanny pack worn by the participant. Exercise desaturation was defined as desaturation below 90% for at least 10 consecutive seconds during the 6 minute walk. For this eligibility criterion, in terms of the 180 data points obtained during the 6 minutes of walking (sampling occurred every 2 seconds), the participant had to have at least 5 consecutive good quality data points with saturation below 90%. To assure that the exercise desaturation was *moderate* and was not *severe*, every rolling average of 30 consecutive data points had to have a mean saturation of 80% or greater. At least 20 of the 30 points in each rolling average had to have acceptable quality. A LOTT staff member downloaded the oximetry data collected during the 6-minute walk to the LOTT laptop. Custom software developed by the LOTT DCC was used to analyze the data and implement the LOTT eligibility algorithm for determination of exercise desaturation sufficient for eligibility and to implement the LOTT criterion for determination of *severe* exercise desaturation during follow-up.

Expanded and Core Data Collection

To increase the acceptance of the LOTT program to both participants and satellite sites, the LOTT installed a two tier level of data collection requirements defined as Core and Expanded (**Table 3**).[2-11] Expanded data collection included all Core data collection plus three additional questionnaires (i.e., Hospital Anxiety and Depression Scale

[HADS],[10] SF-36 Health Survey,[8] Pittsburgh Sleep Quality Index [PSQI][9]) at the baseline and annual follow-up evaluations, additional procedures at baseline (collection of serum for banking and alpha 1-antitrypsin (**A1AT**) testing[11]), and an additional procedure in follow-up (spirometry). All regional clinical centers were expected to complete Expanded data collection; satellite sites could choose to complete Core or Expanded data collection. The Core baseline data provided the basis for determining eligibility for randomization, and the Core follow-up data provided the necessary information for the primary outcome analysis and assessment of secondary hypotheses related to dyspnea, respiratory symptoms, preference-weighted health-related quality of life and disease-specific quality of life, functional status (e.g., six minute walk distance), nutritional status (e.g., body mass index), and health care utilization (**Table 1**). Core data collection also included some of the demographic and clinical characteristics that allowed for additional subgroup analyses and testing the consistency of treatment effects (e.g., exercise desaturation). Expanded data collection permitted the assessment of treatment effects on additional secondary outcomes (such as general quality of life, depression, anxiety, spirometry) and in additional patient subgroups.

Adherence Assessment

Participants who used stationary concentrators provided meter readings periodically, which yielded the operating hours of the concentrator during a given recording interval. The number of compressed gas tanks used, tank liter contents, and oxygen flow setting (with correction for oxygen conservation if a conserver device was used) allowed for calculation of ambulatory oxygen use. For participants using liquid oxygen, pounds of

liquid oxygen delivered to the home, numbers of portable liquid gas tanks used, flow rate used for stationary and ambulatory use, and corrections for oxygen conserver use and for evaporation rate allowed for estimates of stationary and ambulatory supplemental oxygen use. Also, during telephone and clinic visit interviews, study personnel queried participants in both treatment groups about average hours of supplemental oxygen use per day for the past week.

Outcome Verification

Primary outcome events and specific secondary outcomes underwent verification. For the all-cause mortality component, the protocol required study investigators to complete a death report form when notified of a participant's death. The DCC compared the vital status as reported by clinic staff to the vital status as indicated by the Social Security Death Master File.[12] Discrepancies underwent resolution. Study coordinators queried the incidence of hospitalization at each annual visit and during each telephone interview (a total of 3 times per year); the study coordinators attempted to verify hospitalization dates and diagnoses by acquiring the discharge summary or other supporting documents. Coordinators also queried the incidence of COPD exacerbation at each interview and sought medical record documentation for each reported COPD exacerbation. Study participants could report outcome events between scheduled contacts.

At each interview, coordinators queried participants in both treatment groups regarding the incidence of fires, burns, falls, and trips associated with oxygen equipment, and the presence of nasal symptoms, and other health problems.

Assumptions

Regarding target patient mix, we expected 25% of participants to enter the study with moderate resting hypoxemia and 75% to have a normal resting saturation associated with oxyhemoglobin desaturation during exercise. We estimated that 50% of randomized patients would have had a hospitalization for COPD in the year prior to screening.

APPENDIX-1 REFERENCES

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Appendix 2: LOTT Protocol