LOTT MOP

Long-term Oxygen Treatment Trial
Manual of Operations: Part I Patient Procedures and Clinical Center Operations
25 March 2013

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1 Design overview

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1.1 Data collection tiers

General

- The LOTT protocol incorporates three tiers of data collection: Core, Expanded, and Substudy. Core data collection (both Core Baseline and Core Followup) are required on every randomized patient, regardless of enrolling site. Expanded data collection (both Expanded Baseline and Expanded Followup) are additional to Core data and will be collected on a subset of patients, depending on the capabilities of the site that enrolls the patient and consent of patient. Patients will be identified as Core or Expanded data collection patients at baseline. Substudy data collection is anticipated but currently not determined.

Core data collection

- Required on all patients, regardless of enrolling site
- Elements of Core Baseline:
  - Demographics and baseline history
  - Room air resting oximetry
  - Room air 6 minute walk with oximetry
  - Spirometry (pre and post bronchodilator)
  - Limited physical exam
  - Hemoglobin and hematocrit
  - Cotinine (if not smoking and not using nicotine products)
  - Epworth Sleepiness Scale
  - Modified Medical Research Council Scale
  - St George's Respiratory Questionnaire
  - Quality of Well-Being Scale
  - DNA and plasma banking (patient may opt out of DNA and/or plasma banking and still enroll in Core data collection)
- Elements of Core Followup:
  - Interim history
  - Room air resting oximetry
  - Room air 6 minute walk with oximetry
  - Limited physical exam
  - Hemoglobin and hematocrit
  - Cotinine (if not smoking and not using nicotine products)
  - Modified Medical Research Council Scale
  - St George's Respiratory Questionnaire
  - Quality of Well-Being Scale

Expanded data collection

- Additional to Core data collection
- Collected on a subset of patients, depending on capabilities of enrolling site and consent of patient
- Patient is identified at baseline as Expanded or Core and if patient is identified as an Expanded data collection patient, then all Expanded data collection elements are required for that patient except that the patient may opt out of serum collection and still be an Expanded data collection patient
- Elements of Expanded Baseline:
  - SF-36v2 questionnaire
  - Pittsburgh Sleep Quality Scale
  - Hospital Anxiety and Depression Scale

- A1AT testing
- Serum banking (patient may opt out of serum banking and still enroll in Expanded data collection)

• Elements of Expanded Followup:
- SF-36v2 questionnaire
- Pittsburgh Sleep Quality Scale
- Hospital Anxiety and Depression Scale
- Spirometry (pre- and post-bronchodilator)

1.2 Design synopsis

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_2 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_2 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
- 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 (368 per treatment group)
- Expected composite events: 351 (96 all-cause mortality and 255 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)

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

Inclusion criteria (all are required)

- Age at least 40 years
- Dyspnea and lung disease process dominated by COPD in judgment of the study physician
- Post-bronchodilator FEV_1 percent predicted ≤ 70%
- Post-bronchodilator $FEV_1/FVC < 0.70$
- 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)
  - 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

1.2. Design synopsis

Mode of support

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

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

1.3 In person and telephone visit data collection schedule (not including contacts for adherence promotion or monitoring)

	BL		Followup																						
			Year 1			Year 2			Year 3			Year 4			Year 5			Year 6			Year 7		
Months from RZ	-2	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72	76	80	
[C]linic or [T]elephone visit	C	C	T	T	C	T	T	C	T	T	C	T	T	C	T	T	C	T	T	C	T	T	
Core data (all patients)																							
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^R	.	.	X^R	.	.	X^R	.	.	X^R	.	.	X^R	.	.	X^R	.	.	X^R	.	.	
FEV_1, 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	.	.	
Expanded data (selected sites)																							
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_1, FVC†	.	.	.	.	X	.	.	X	.	.	X	.	.	X	.	.	X	.	.	X	.	.	
A1AT	X	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	
Serum banking	X	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	
Substudy data collection (on an as yet unspecified number of patients)																							
(To be determined)																							

*B = Baseline history, S = short interim history, L = long interim history, M = by mail, RA = room air

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

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

1.4 Whole blood (venous; mL) draw schedule

Months from RZ	Screening/ baseline[1] -2	0	Followup 12	24	36	48	60	72
Core								
Hemoglobin, hematocrit[2]	3	.	.	.	.	.	.	.
Cotinine[3]	10	.	10	.	.	.	.	.
DNA/plasma banking[4]	18.5	.	.	.	.	.	.	.
Total for Core	**31.5**	.	**10**	.	.	.	.	.
Expanded								
A1AT[5]	3	.	.	.	.	.	.	.
Serum banking[6]	10	.	.	.	.	.	.	.
Total for Expanded[7]	**44.5**	.	**10**	.	.	.	.	.

[1]Note: Blood is to be drawn before randomization.

[2]Hemoglobin, hematocrit: One 3 mL purple top tube (tests done by local lab).

[3]Cotinine: One 10 mL red top tube (not serum separator). Test is done by local lab.

[4]DNA/plasma banking: 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.

[5]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.

[6]Serum banking: One 10 mL red top serum separator tube. Serum is sent to Biosample Repository at the Channing Laboratory.

[7]Expanded data collection is additional to Core data collection, so total for Expanded is sum of amounts collected for Core and amounts collected for Expanded.

1.5 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 grp	CC	T	T	T	T	T	T	T*	T	T	T*	T	C	C	C	C	C	C
No supplemental oxygen grp	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 1st 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)

1.6 Post randomization contact schedule (summary)

	RWZ	Yr 1: Mos						Yr 2: Mos						Yr 3: Mos						Yr 4: Mos						Yr 5: Mos						Yr 6: Mos						Yr 7: Mos					
	01	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	4
All patients																																											
Visit	C	.	.	T	.	T	.	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[1]	.	C	A	A	A	A	A	A	.	.	.	.	.	A	.	.	.	.	.	A	.	.	.	.	.	A	.	.	.	.	.	.	.	.	.	.	.	A	.	.	.	.	.
Diary[2]	.	.	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	D	D	D	D	D	D
Additional contacts for control patients																																											
Visit	.	T	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.

T=telephone visit with interview, C=clinic visit, M=mailed questionnaire, A=adherence promotion contact, D=adherence monitoring diary

[1] Adherence promotion telephone contacts are weekly for 1st month and monthly for 2nd - 6th months, every 2 months for 7th - 12th, in person at annual visits (part of the intervention).

[2] Patients are to complete and return diaries indicating oxygen usage every 2 months through all followup.

2 Consent

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2.1 Consent overview

- The **goals of the consent process** are to inform the prospective patient as much as possible and as accurately as possible about the procedures involved, what is expected of patients who consent to participate, what the study can and cannot provide to the patient, what are the reasonable risks and benefits, and what are the alternatives to participation. Patient questions should be answered as consistently and as completely as possible, both before and after consent is requested.

- **When to obtain:** Signed consent to participate in LOTT must be obtained before any data collection is initiated; the first item on the first LOTT data collection form to be completed (the Registration or RG form) queries signature of the LOTT consent statement; if the patient has not signed the LOTT consent, the form instructs you to STOP – you may not proceed with LOTT screening until signed consent is obtained

- You should **verify Medicare coverage** or availability of other resources (other insurance, other funds) to cover the costs of study treatment and procedures before asking the patient to sign the LOTT consent

- You should **identify the level of data collection** that the patient will participate in (eg, Core or Expanded) and be sure that the patient signs the consent for that level of data collection; Expanded data collection requires consent for the extra procedures included in Expanded data collection (24-hour oximetry at baseline, additional questionnaires at baseline and annual visits, serum collection at baseline, A1AT testing at baseline, and spirometry at annual visits)

- **The LOTT consent statement covers screening, randomization, and followup**; signature of the LOTT consent provides consent for all three phases of LOTT participation; the patient will be asked to affirm consent to randomization to either treatment orally at the randomization visit before the treatment assignment is generated

- **If the patient is using home oxygen when screening starts**, make sure that the patient understands as that he/she must give up the home oxygen if randomized to the no oxygen group; before randomization, the patient must abstain from using the oxygen for at least 4 days prior to randomization and the prescribing physician must agree in writing that he/she will cancel the prescription if the patient is randomized to the no oxygen group; the patient should understand that the LOTT staff will contact his/her physician to obtain this agreement. The patient must understand that if he/she is randomized to the no oxygen group in LOTT, then he/she will not use home oxygen until and unless he/she develops severe hypoxemia at rest (SpO_2 of 88% or less at rest)

- Signature of the LOTT consent also covers **consent to access the patient's Medicare claims** for the year prior to screening and thereafter for the duration of the trial and to providing the DCC with the patient's HIC and social security numbers to allow tracking the patient in Medicare databases and other electronic databases for vital status.

- **Consent for biospecimen collection** (DNA, plasma, and serum) may be included in the LOTT consent for screening, randomization, and treatment or may be covered in a separate biospecimen consent or separate consents for DNA and plasma and serum, as required by the local IRB; a patient may opt out of some or all of the biospecimen collection and still be randomized in LOTT and participate in Core or Expanded data collection

2.1. Consent overview

- The **LOTT consent statement is an "all or none" form except with regard to biospecimen collection**. The patient either accepts it in its entirety and signs it, or does not. The patient must consent to the evaluation procedures, treatment procedures, and follow-up evaluations. If the patient refuses any part (other than biospecimen collection), the patient may not enroll in LOTT.

- The consent should include **HIPAA authorization** to disclose protected health information or a separate HIPAA authorization should be signed

- The **DCC posts the most recent IRB notice of protocol approval and IRB approved consent documents for each participating site on the LOTT website (www.lottsite.org)**; click on Documents and scroll down to "IRB approvals and consent statements" and then click on the RCC of interest and then click on the site and document of interest

2.2 Contract not to smoke

- All patients, not just current smokers, are required to sign the contract not to smoke prior to randomization

- The contract not to smoke is an agreement that the patient will not smoke while using supplemental oxygen; the contract does not assume that the patient is a smoker nor that the patient is a nonsmoker, it is simply an agreement that the patient will not smoke while using supplemental oxygen

  - If the patient doesn't smoke now, then the patient will have no problem not smoking while using oxygen
  - If a non smoking patient relapses, the agreement becomes something that the patient will actively need to abide by
  - If the patient is assigned to the control (no oxygen) group, the agreement becomes applicable if the patient develops severe hypoxemia or otherwise is prescribed oxygen after randomization

- Signature of the contract is a criterion for randomization; refusal to sign renders the patient ineligible for LOTT

2.3 Release of medical records

- All patients will be asked to sign a release of medical records form prior to randomization and at each annual visit thereafter; this can be the LOTT prototype release or your standard institutional medical records release form

- LOTT may ask for medical records in the following situations
  - After a patient's death
  - In relation to investigation of an adverse event or an unanticipated problem

- The Study Physician may seek medical records in relation to local institutional review board queries or other local requirements

- Do not gather medical records for sending to the DCC nor send medical records to the DCC until requested to do so

2.4 Consent for DNA, plasma, and serum collection and use

- Patients will be asked to consent to DNA, plasma and serum collection and banking
  - A patient may opt out of all or some of this collection and still enroll in LOTT
  - A site can have one comprehensive consent or have separate consents for each of these collections, as required by the local IRB

- Patients may consent to how the specimens provided may be used
  - Used for research on COPD and smoking-related illness
  - Used for research unrelated to COPD and smoking-related illness

- Patients may consent to who may use their specimens
  - Specimens may be used by LOTT investigators
  - Specimens may be used by investigators not participating in LOTT

- The mechanism for tracking (and being able to honor) these consent options is the Consent Documentation for DNA, Serum, and Plasma Banking (DC) form
  - The DC form is completed initially during screening when the consent for specimens is first obtained; the form is keyed to the web-based data management system
  - Complete and key an additional DC form if the patient changes their mind about any aspect of the biospecimen consent
  - Contact the DCC if the patient is making a request that does not seem to be covered by the DC form
  - If the site does not have IRB approval for specimen banking:
    - Complete the DC form by checking "No" to each of items 7, 8, and 9 (No, the patient does not consent to DNA banking, No the patient does not consent to plasma banking, No the patient does not consent to serum banking); then check Yes to item 10 and that will skip you to the Administrative Information section of the form
    - Key the completed DC form

- Patients should understand that changes to their consent for specimens can be implemented for specimens remaining at the time the change is implemented and will not affect specimens that have already been used

- The DNA, plasma, and serum are obtained from three tubes of whole blood collected at baseline:
  - DNA is obtained from the Paxgene tube
  - DNA and plasma are obtained from the EDTA tube (the EDTA tube is a backup source of DNA as well as plasma)
  - Serum is obtained from the serum separator tube

2.5 HIPAA considerations

LOTT study staff have access to patient health information and to patient identifiers, such as name, address, and telephone number. Study records are to be kept in a secure place. Only people working on LOTT should have access to these records. However, these records could be reviewed to make sure that the study is being done as it should. People who may see medical records supporting study records are:

- Officials of your institution
- Your institution's research ethics committee
- Officials of your RCC's institution
- Your RCC's research ethics committee
- Monitors from the LOTT Data Coordinating Center at the Johns Hopkins University, or other individuals selected by the LOTT Steering Committee to monitor the trial
- Members of the LOTT Data and Safety Monitoring Board (DSMB) to monitor overall progress of the trial
- Government officials from the Office of Human Research Protections or the National Institutes of Health or the Food and Drug Administration

Each clinical center should take steps to protect patient privacy. The assigned patient ID number and code are used to identify the patient. Personal information such as name, address, and telephone number should be kept only at the clinical center where a patient completes visits and its RCC, if applicable.

People outside the clinical center who will receive LOTT study data include:

- The LOTT Data Coordinating Center at the Johns Hopkins University in Baltimore, Maryland (or its successor) to maintain the central study database
- The LOTT Data and Safety Monitoring Board to review the LOTT data for performance and safety
- The Channing Laboratory of the Brigham and Women's Hospital in Boston, Massachusetts (or its successor) will receive and bank patients' DNA, plasma and serum; the blood samples for a particular patient will be identified by the patient's study ID number and code, not by name
- The LOTT investigators, as well as outside researchers, to analyze and report LOTT data. Patient identity will not be disclosed in any reports or publications resulting from the study. While LOTT is ongoing, the use of LOTT data and samples must be approved by the LOTT Steering Committee.
- At the end of LOTT, the LOTT data and remaining biospecimens will be turned over to the NHLBI. NHLBI will provide data and/or samples to requesting applicants who meet their approval requirements. The data provided to NHLBI at the end of the study will not include name, address, or HIC or social security numbers.

Patient agreement to join the LOTT indicates that the patient also agrees to the use of study data as described above. If a patient does not agree to the described uses of study data, the patient may not participate in LOTT. The only exception is refusal to provide blood for DNA, plasma, and/or serum; patients may refuse to provide blood for DNA, plasma and/or serum samples and still enroll in LOTT.

The HIPAA authorization form will be prepared by each clinical center according to local clinical center institutional requirements and guidelines. Sites may include the HIPAA authorization in the consent for enrollment and randomization or may prepare a separate HIPAA authorization form for LOTT.

2.6 Institutional review board process

Prototype consent materials prepared for the LOTT include:

- Consent for enrollment, randomization, and specimen banking and HIPAA authorization
- Contract agreement not to smoke while using oxygen
- Authorization for release of medical records

Clinical centers are expected to use these materials in their submissions to their institutional review boards (IRBs) for approval to participate in LOTT. Each clinical center must send copies of their IRB's notice of protocol approval and their IRB approved consent documents to be used at their site, stamped or otherwise marked with their IRB's approval, to the DCC prior to initiating patient activities in LOTT. DCC staff will review and compare the approved local documents to the prototype documents. Additions and reformatting of material to meet local institutional requirements are permitted, but deletion of information considered necessary for informed consent is not permitted. If the materials are approved by the DCC, the DCC will request the NHLBI to authorize the site to begin patient activities (Phase 2). The DCC posts the most recent IRB notice of protocol approval and IRB approved consent documents for each participating site on the LOTT website (www.lottsite.org); click on Documents and scroll down to "IRB approvals and consent statements" and then click on the RCC of interest and then click on the site and document of interest.

Additionally, each clinical center will submit to their IRB any recruitment materials to be used at their site.

A clinical center may not initiate any patient activities in LOTT until the site has IRB approval for LOTT and the DCC has certified the site for initiation of LOTT patient activities and the NHLBI has authorized initiation of Phase 2 of LOTT.

2.7 Consent administration

Overview

Patients referred to a clinical center for screening may have heard about LOTT, but their level of knowledge and expectations may well differ. We wish to standardize the consent administration across clinical centers as much as possible. Administration of the LOTT consent involves two tasks:

(1) A LOTT staff member must sit down with the patient and review the contents of the consent documents; explain the risks, benefits, and responsibilities of participation; review the alternatives to participation; and answer questions. The LOTT staff member must sign the consent dcouments as the person obtaining consent.

(2) A LOTT investigator must sign the consent documents, taking overall responsibility for the patient's informed and voluntary consent.

Consent, HIPAA authoirzation, and contract not to smoke while using oxygen

The consent statement, HIPAA authorization, and contract not to smoke may be sent to the patient in advance of the initial visit. These materials will then be reviewed with the patient by the staff member designated to obtain consent; the consenter may opt to read the statements to the patient, pausing to explain issues as needed. This activity should take place in a quiet, private and relaxed setting in the clinical center.

The patient should sign the consent statement, HIPAA authorization, and the contract not to smoke in the presence of the LOTT staff member after all questions have been answered and when the patient has asserted orally that he/she is ready to sign the consent. After the patient has signed and dated the consent, HIPAA authorization, and contract not to smoke, the patient should meet with a LOTT investigator for the investigator to sign the documents; ordinarily this meeting should take place on the same day that the patient signed the documents. The investigator should ask the patient to confirm his/her voluntary consent and query the patient about any questions or concerns the patient may have about participation. All signatures on the documents must be in a non-erasable ink pen. If the investigator cannot meet with the patient on the same day that the patient signs the documents, the investigator may sign on another day.

Medical records release form

The medical records release form should be signed prior to randomization. Clinical center staff may decide whether to obtain the patient’s signature during the screening visit or whether to wait until the day of randomization.

2.8 Time considerations for obtaining consent

- The **LOTT consent and HIPAA authorization must be obtained at the start of the initial visit** (visit sb). Signature of the consent is required prior to sending the patient for any LOTT tests. A check for signature of the consent statement occurs on the Registration (RG) form. Signature of the contract not to smoke is checked on the Eligibility Review (RR) form at the randomization visit.

- **Consent for biospecimen collection and banking must be obtained prior to drawing blood for DNA, plasma, or serum collection**; a check for signature of this consent statement occurs on the Blood Collection for DNA, Serum and Plasma Banking (BC) form. Consent for biospecimen banking is not required for randomization in LOTT (i.e., the patient may choose not to participate in the biospecimen component of LOTT) but documentation of consent or lack of consent is required for randomization. The Documentation of Consent for DNA, Plasma, and Serum Banking (DC) form must be completed for every patient prior to randomization. It will document lack of consent for those patients who refuse one or more of the elements of biospecimen banking and for patients who are enrolled at a site which does not have IRB approval for biospecimen banking.

- **The patient may be given the consent documents to review prior to the initiation of visit sb** to meet patient needs with respect to review time. Whenever the consent documents are first given to a patient for review, it should be made clear to the patient that the consent documents should not be signed until requested by a LOTT staff member. The consent documents may be mailed to the patient prior to LOTT visit sb. Whatever timing is used by a clinic, the patient should be allowed enough time to reflect about the proposed LOTT procedures, pose questions, and consult with other individuals that he/she considers relevant to their participation in LOTT. Patients may request and should be given time to "think it over" at home and come back at a later time.

- **Oral affirmation of consent is required at the randomization visit, prior to generation of the treatment assignment**; the Clinical Coordinator or Study Physician must ask the patient if he/she still consents to randomization; a check for this is included on the Eligibility Review (RR) form.

2.9 Handling consent documents

- Signed consent documents are legal documents. These signed documents should be kept in the patient's LOTT clinical center file together with his/her other LOTT forms and documents. These forms are not part of the individual's institutional medical record, but part of his/her study record in the LOTT. Consent documents may be examined during site visits.

- Consent documents should be annotated with the patient's study identifiers (ID number and code).

2.10 Informing patients of changes to the consent statement

As new data become available during the conduct of LOTT, the consent statement may need to be changed to reflect the current assessment of risks and benefits to participants in the study.

Procedures for dissemination of revisions of consent statements from the DCC

- Changes deemed necessary will be made to the prototype consent statement
- Revisions of the prototype consent statement will be distributed to sites via a numbered Policy and Procedure Memorandum (PPM) with instructions to submit the revised consent to their IRB
- The revised prototype consent will be posted to the Documents page of the LOTT website (www.lottsite.org)

Procedures for reviewing changes to consent statements with patients

- Clinical center personnel will develop a chronology of IRB approved changes to the consent statement used at their site
- At each followup visit, staff will use the chronology of consent changes to review with the patient any changes to the consent since the last visit. This review does not require obtaining the patient's signature on a new consent statement, unless the local IRB requires obtaining a signature.
- This review process is not intended to be a reaffirmation of consent – eg., the clinical center, if required by their local IRB, may develop procedures for reaffirmation of consent on a yearly schedule.

3 Eligibility and enrollment

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3.1 Eligibility criteria

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?
- Dyspnea and lung disease process dominated by COPD in judgment of the study physician
- Post-bronchodilator FEV_1 percent predicted less than or equal to 70% predicted (reference equations of Hankinson et al, 1999 will be used)
- Post-bronchodilator FEV_1/FVC less then 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
- 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

3.1. Eligibility criteria

- 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.

3.2 Use of oxygen during screening

Home oxygen use during screening

- Patients using home oxygen may screen for LOTT while using the oxygen
- Patients using home oxygen must stop the oxygen for the room air resting oximetry session and room air 6 minute walk
- If a patient screens for LOTT while using oxygen, the following conditions must be met before the patient may be randomized in LOTT:
  - The patient must stop the oxygen for at least the 4 days prior to randomization
  - The patient must agree that the oxygen will be stopped and equipment removed from the home if the patient is randomized to the no oxygen group
  - The prescribing physician must agree in writing that he/she will cancel the prescription if the patient is randomized to the no oxygen group
- All home oxygen is subject to these rules – home oxygen with CPAP would have to be stopped prior to randomization and permanently stopped if the patient is randomized to the no oxygen group
- New prescription of oxygen during screening prior to randomization is exclusionary

Other oxygen

- Patients may use non home oxygen – eg, patients may use oxygen during pulmonary rehab sessions

3.3 Patients found to be ineligible

- If initiated, the Registration (RG) form must be keyed regardless of eligibility status of patient
- If the patient is ineligible upon completion of the Registration (RG) form, key the form and file it in the file for ineligible patients; no other forms need to be completed for the patient
- Patients found to be ineligible subsequent to completion of the Registration (RG) form:
  - The Eligibility Review (RR) form must be keyed; this form closes out the patient and indicates the reason for ineligibility; answer the questions that you can answer, mark the ones you cannot answer with "m"; if you check an Ineligibility condition, you can skip to the item where you check the reason for ineligibility (item 27 on RR2)
  - All other forms completed for the patient prior to finding the patient to be ineligible may be keyed to the database but are not required to be keyed
  - Forms (other than the Registration (RG) and Eligibility Review (RR) forms) that indicate ineligibility (ie, have an ineligible response checked) cannot be keyed to the data system
- Forms for patients found to be ineligible should be retained but may be filed separately from forms for eligible patients
- Patients found ineligible because of a temporary ineligibility may be rescreened; all screening procedures and baseline data collection will need to be repeated

3.4 Repeating testing sessions within a screening cycle

A patient may repeat screening tests during a single screening cycle and a patient may have more than one screening cycle.

By "repeat screening tests" we mean that you may do more than one resting oximetry session, or more than one 6 minute walk or more than one spirometry session.

By "screening cycle", we mean the set of tests between the most recent registration of the patient and completion of the Eligibility Review (RR) form declaring the patient ready for randomization (eligible patient) or declaring the patient ineligible and specifying the reason(s) for ineligibility.

The basic rule is that the patient must meet the LOTT selection criteria and have a complete set of required baseline data within the required time window to be randomized. The patient can be retested as needed per the discretion of the Study Physician. Retesting of eligibility is not monitored; clinic staff are expected to use good medical judgment and good research sense regarding repeating testing sessions within a screening cycle. Suggested guidelines for retesting are:

- **Ineligibility based on room air resting oximetry** – do not test more than 3 times on 1 calendar day and if the patient fails more than 4 times, stop testing and rescreen in 6 months
- **Ineligibility based on room air 6 minute walk** – do not test more than 2 times on 1 calendar day and if the patient fails more than 3 times, stop testing and rescreen in 6 months
- **Unwilling to participate** – the patient may be rescreened after 3 months

If you repeat screening tests and the patient ultimately is eligible, key the data for the test that meets the LOTT eligibility criteria. Mark the form and report that relate to the initial (ineligible) session as "not keyed due to ineligibility" attach to the back of the eligible form and report.

3.5 Assignment of study identifiers

What

- The LOTT uses 2 identifiers for each patient
  - ID number (2 letters and 3 digits): the 1st letter identifies the RCC and the 2nd letter identifies the satellite site; each RCC is its own "a" satellite
  - ID code (4 alphabetic characters)
- These identifiers help assure confidentiality of patient identity

Materials

- RG form ID number and code label (in upper left corner of the screening visit label page received from the DCC; there is one page/patient - see figure below; each page also includes the labels used with visit sb questionnaire forms and blood tubes)
- Registration (RG) form

When

- Visit sb

By whom

- Clinical Coordinator

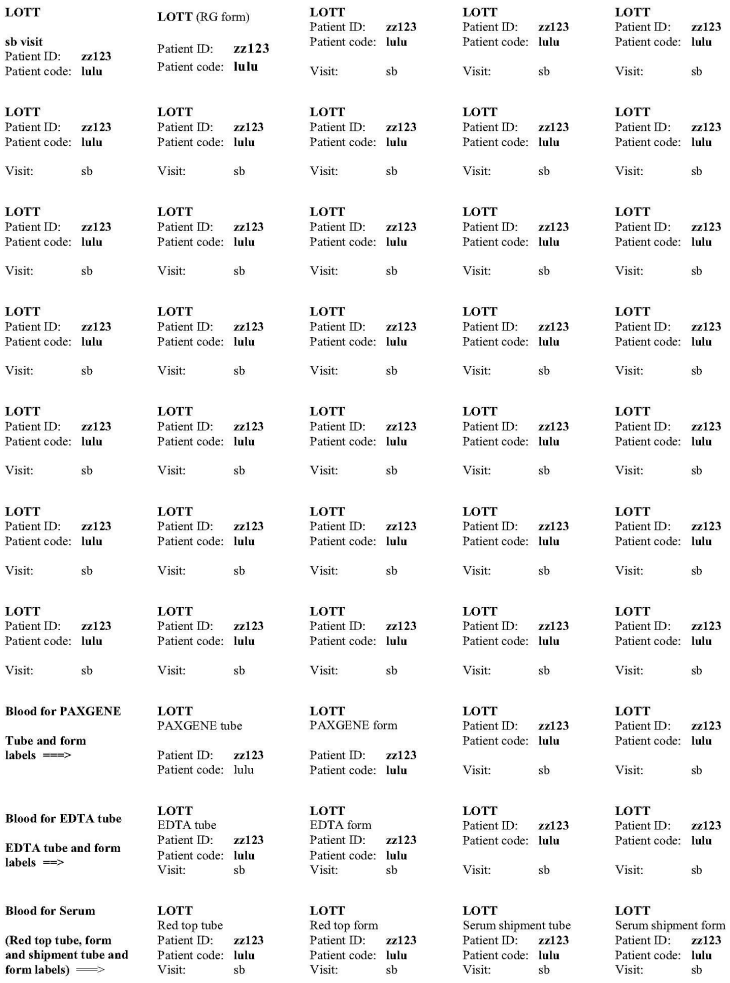
Procedures

- Complete the Registration (RG) form; once the patient has signed the LOTT consent and insurance coverage is verified, the RG form instructs the Clinical Coordinator to assign an ID number and code by peeling the RG form label off the visit sb label sheet and affixing it to the specified item on form RG
- Key the Registration (RG) form into LOTT data system; this must be the first form keyed
- The Registration (RG) form must be keyed for each patient for whom it is initiated, regardless of eligibility status at the end of the form
- If you are rescreening a patient for whom a LOTT ID was previously assigned, you will assign a new ID and new code for this new screening cycle and you will note the ID and code used in the previous screening cycle on the newly completed Registration (RG) form

Comments

- If the patient is found to be ineligible or refuses enrollment, DO NOT reassign or reuse that patient's ID
- If you need additional visit sb label pages, contact the DCC

3.5. Assignment of study identifiers



3.6 Process for rescreening patients

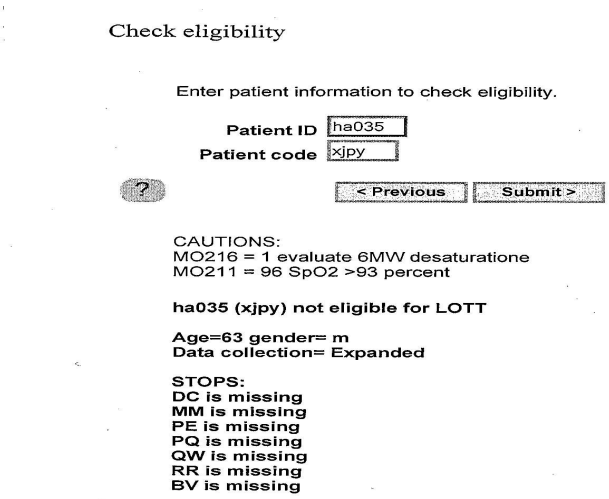
- **Patient ID assignment:** When rescreening a patient for LOTT, you will assign a new ID and start the re-screening with the Registration (RG) form – you will record the ID number and code used in the previous screening on the Registration form and then assign a new ID number and code

- **Repeat all screening and baseline data collection:** For randomization, you will need a complete set of screening forms, all completed after the new RG form and within 60 days of randomization

3.7 Randomization and eligibility checking

Randomization steps

- Complete collection of screening and baseline data and key screening and baseline data forms
- Run electronic check on eligibility (i.e., run the Randomize task)
  - The task will list any CAUTION conditions identified during the check
  - CAUTIONS are warnings or reminders, primarily relating to administrative issues given the data keyed for the patient; they are not meant to indicate any dubiousness about the patient's eligibility for LOTT and they will not stop randomization
  - Examples of CAUTIONS are patient is using oxygen during screening (you need to be sure you are ready to remove the equipment), patient has resting saturation above 93% (you need to be sure desaturation on 6 minute walk was detected), blood value levels are keyed as pending (keyed as ?; you need to key those values when you receive the lab reports), etc
  - The task will list any STOP conditions identified during the check
    - STOPS are ineligibility conditions; STOPS stop the treatment assignment from being generated
    - Examples of STOPS are missing forms or form items keyed with a "?" (Other than blood test values), dates out of window (date of review on RR must be the date you randomize), value out of range for eligibility, etc; for example:



  - If the patient passes the eligibility checks, the data system will ask if the patient is to be randomized now; if the Data Entry Technician keys "yes", the assignment will be generated
- An assignment will be generated only if:
  - The database shows that all data keyed for the patient are consistent with eligibility for LOTT
  - The database shows that the patient has signed the LOTT consent statement for the data collection level specified for the patient
  - The database shows that all required baseline data have been keyed
  - The database shows that all baseline data were obtained within the required time window (60 days from initiating screening)
  - The Data Entry Technician keys that the patient is to be randomized "now"

- Once the Randomize task is run and the Data Entry Technician confirms that the patient is to be randomized "now", the task will officially randomize the patient in LOTT, and the randomization assignment and the visit time window guide will be generated; this task will assign each patient to one of two treatment groups:
  - Supplemental oxygen
  - No supplemental oxygen (control)

Overriding eligibility criteria

- Requests to override eligibility criteria must be made in writing to the DCC (direct the request to Alice Sternberg at asternbe@jhsph.edu); the request must specify the eligibility criteria for which override is requested and the request must be justified
- The DCC may require agreement to the override from the Principal Investigator of the RCC and/or the Satellite Center Director and/or the LOTT Steering Committee
- Override requests require time to review and the review process will not be shortened

Randomization

- The date of randomization is the date that the clinic runs the Randomize task and confirms that the patient is to be randomized "now" and the treatment group is assigned
- The date of randomization is the "time zero" for reckoning the time windows specified on the patient's LOTT visit time window guide
- The Randomize task should not be run unless:
  - The site affirms that they are ready to schedule delivery of oxygen equipment and the patient affirms that he/she is ready to receive delivery of equipment if the patient is assigned to supplemental oxygen – delivery should occur within 24 hours of randomization; if either the site or the patient is not ready for this, delay randomization
  - The site, patient and prescribing physician are ready to have oxygen equipment removed if the patient has home oxygen equipment and the patient is assigned to the no supplemental oxygen group

3.8 Form completion issues related to screening, rescreening, and enrollment

- The very first form to be completed for a LOTT candidate patient must be the Registration (RG) form – this form documents that consent has been obtained and that the patient has Medicare or other insurance or resources that will pay the costs of screening and treatment

- If you check a response with a STOP sign on it, you must resolve the condition so that there is no STOP before you may continue with the form; for example, the first STOP item on the Registration (RG) form relates to consent; if the patient has not signed the LOTT consent statement, you cannot proceed with screening until the patient has signed the consent statement

- If you check a response with an Ineligibility sign, the patient is ineligible and screening should stop; stop completing the form and skip to the Administrative Information section

- The Registration (RG) form must be keyed for all patients for which it is initiated, including those found ineligible during completion of it

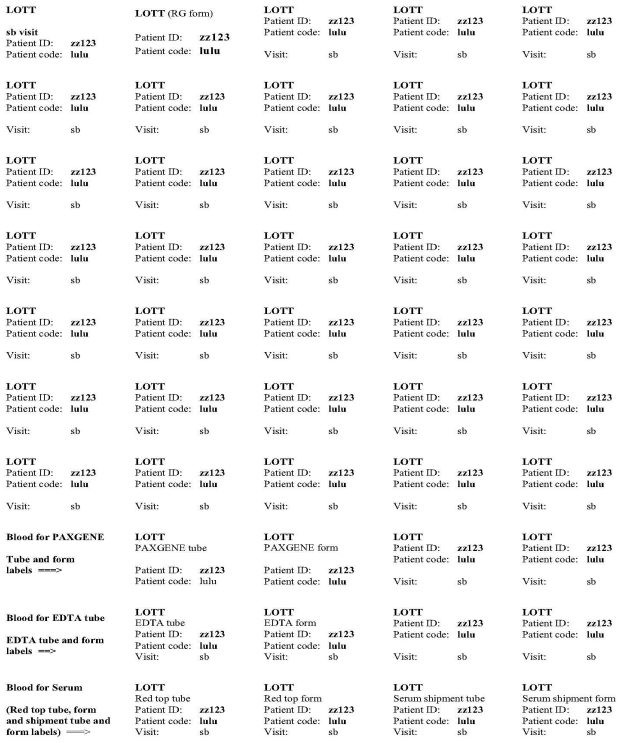
- If you get to the end of the Registration (RG) form without checking a STOP or an ineligibility condition, you must:
  - Continue screening and collecting baseline data until either the patient is found ineligible or screening and baseline data collection are completed
  - You may stop data collection as soon as the patient is found ineligible; you do not key forms for ineligible patients except that you must key the Registration (RG) form and if the RG form was completed without encountering an ineligibility, you must complete and key the Eligibility Review (RR) form
  - Complete and key the Eligibility Review (RR) form – if the patient is eligible, this form will direct you to randomization, and if the patient is ineligible, this form will direct you to specify the reason for ineligibility – the RR form closes out the patient's screening for LOTT with either randomization or a record of the reason(s) why the patient was not randomized

- You cannot delete the Registration (RG) form once keyed

3.9 Screening window duration and labels used in screening

- **Duration of screening window**
  - You must complete screening within 60 days of initiating the Registration (RG) form
  - Data cannot be collected and forms cannot be completed prior to the RG form – other forms for a patient may not predate the patient's RG form

- **Patient labels used in screening**
  - The labels used in screening (ID number and code label, labels used with questionnaires, and labels used with blood tubes) are preprinted at the DCC and provided to the site
  - Each patient ID number will have its own sheet of labels for use in screening
  - Store unused labels in a safe place and remember where you put them
  - Do not manufacture your own screening labels - if you need more, contact the DCC



3.10 Guidelines for recruitment materials prepared by sites

- Recruitment materials include materials directed at:
  - Potential patients
  - Medical community referral sources (e.g., physicians, lung associations, rehab sites)
  - Public relations within the lay community or scientific community
  - Scientific community in general

- Recruitment materials can be local or central: Local materials are materials produced by a site and intended for use by the site alone or by the sites comprising a Regional Clinical Center; central materials are materials produced for studywide use

- Materials directed at potential patients or referral sources or produced for public relations purposes
  - Must not be advertisements for oxygen therapy
  - Must be limited to efforts to enhance recruitment of patients into the study

- All recruitment materials should include a statement about the study sponsors, eg, "The National Heart, Lung, and Blood Institute oversees and administers the LOTT. Medicare covers the costs of items and medical services that are generally available through that program to beneficiaries enrolled in the trial."

- Recruitment materials should include only information about LOTT that is in the public domain; all information about the study is considered privileged until released into the public domain by the NHLBI and the study leadership

- Other characteristics of LOTT to be noted as appropriate to the specific material:
  - The study represents a collaborative effort involving multiple centers
  - The local center works as part of the xxx Regional Clinical Center (RCC), which is one of 14 RCCs that operate nationwide in the study
  - The trial is ongoing and will take a period of time (about 7 years) to address the question
  - We don't know which treatment is better
  - Results will not be available until released by the NHLBI

- Recruitment materials prepared by sites and sent to the DCC are posted on the LOTT website (www.lottsite.org, click on Documents, scroll down to Recruitment and retention aids and then click on Materials prepared by sites)

- Review and approval process for recruitment materials
  - DCC staff members are available to review local materials for accuracy of statements about LOTT if such review is wanted
  - NHLBI would like to review all materials prior to IRB submission – send copies to the DCC; the DCC will forward materials to NHLBI and will post materials to the LOTT website following review by NHLBI
  - Local sites are responsible for obtaining any required local IRB approval of local and central recruitment materials
  - Send copies of IRB approved local materials to the DCC for posting to the LOTT website; materials are accessible from the Documents page; scroll down to Recruitment and retention aids and click on Materials prepared by sites
  - Central materials require review and approval of the Steering Committee

- Each site must keep a record and copies of local publicity (letters, press releases, flyers, scripts for radio or TV advertisements, etc) for review if requested

4 Study visits

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4.1 Overview of visit schedule

- **Screening and baseline data collection** (60 days maximum duration)
  - Procedures may be completed over 1 or more visits depending on patient's and clinic's schedule
  - Randomization must occur within 60 days of initiating screening
  - Patient must be present at the clinic for randomization

- **Randomization to treatment** (1 week)
  - Patient must be present at the clinic when the treatment assignment is generated (visit rz)
  - **Control group:** randomization visit (when treatment assignment is generated) and one phone visit 1 week later
  - **Oxygen group:** randomization visit (when treatment assignment is generated) and ambulatory oxygen dosing visit as soon as patient has ambulatory system and as soon after randomization as possible

- **Treatment and followup** (minimum duration of 1 year and maximum of 7 years)
  - **Everyone:** 2 telephone interview visits and 1 annual visit per year (contacts every 4 months); mailed quality of life questionnaires at 4 months and 16 months
  - **Additional for oxygen group:**
    - Adherence promotion: telephone contacts weekly for the 1st month, monthly from 1 month to 6 months, and every other month from 6 months to 12 months and then annually in person adherence contacts at the annual followup visits
    - Adherence monitoring: collection of oxygen equipment usage log every 2 months throughout followup

4.2 Visits, data forms, and procedures

Visit code	Form abbr	Procedures to be done
Eligibility check and baseline assessments		
sb	RG	Documentation of consent for enrollment and registration interview; done before initiating any testing
	ID	Documentation of patient identifiers for Medicare/vital status followup
	PL	Documentation of patient location information
	DC	Documentation of consent for DNA, plasma, serum banking and use of banked samples
	HB	Baseline history: symptoms, exposures, co morbidities, treatment history, health care utilization
	MO	Room air resting oximetry
	MM	Room air 6 minute walk with oximetry
	SP	Spirometry: pre and post BD FEV_1 and FVC
	PE	Physical examination
	BV	Blood tests results: hematocrit, hemoglobin, cotinine (all patients); A1AT (Expanded data collection)
	BC	Document collection of blood for DNA and plasma banking (all patients) and serum banking (Expanded data collection)
	EP	Epworth Sleepiness Scale
	QG	St George's Respiratory Questionnaire
	QW	Quality of Well-Being Scale
	QF	SF-36v2 (Expanded data collection)
	PQ	Pittsburgh Sleep Quality Index (Expanded data collection)
	HA	Hospital Anxiety and Depression Scale (HADS; Expanded data collection)
Randomization activities		
rz	RR	Eligibility review and randomization request
	XZ	Documentation of randomization and adherence contacts
	OE	Document specific oxygen equipment provided to patient (manufacturer, model, specifications needed for adherence measures; initiated at visit rz) (oxygen group)
	PL	Check for updates to patient location information

4.2. Visits, data forms, and procedures

Visit code	Form abbr	Procedures to be done
rx	MP	Ambulatory oxygen dose (visit shortly after randomization when patient has personal oxygen equipment; oxygen group)
	AE	Adherence promotion contact during visit for dosing using personal equipment and further education about equipment (oxygen group)
	OE	Document specific oxygen equipment provided to patient (manufacturer, model, specifications needed for adherence measures; finish filling out) (oxygen group)
AS,AQ,AP		Oxygen equipment usage log appropriate to patient's equipment choice – provide to patient and educate about use (oxygen group)
	PL	Check for updates to patient location information
Followup		
w01	AH	Adherence promotion contact (oxygen group)
	OF	Oxygen equipment printout – check for updates (oxygen group)
	AC	Adherence promotion contact (control group)
w02	AH	Adherence promotion contact (oxygen group)
	OF	Oxygen equipment printout – check for updates (oxygen group)
w03	AH	Adherence promotion contact (oxygen group)
	OF	Oxygen equipment printout – check for updates (oxygen group)
w04	AH	Adherence promotion contact (oxygen group)
	OF	Oxygen equipment printout – check for updates (oxygen group)
a02	AH	Adherence promotion contact (oxygen group)
	OF	Oxygen equipment printout – check for updates (oxygen group)
a03	AH	Adherence promotion contact (oxygen group)
	OF	Oxygen equipment printout – check for updates (oxygen group)
f04	HT	Telephone interim history
	QG	St George's Respiratory Questionnaire
	QW	Quality of Well-Being Scale
	OF	Oxygen equipment printout – check for updates (oxygen group)
a04	AH	Adherence promotion contact (oxygen group)
	OF	Oxygen equipment printout – check for updates (oxygen group)
a05	AH	Adherence promotion contact (oxygen group)
	OF	Oxygen equipment printout – check for updates (oxygen group)
a06	AH	Adherence promotion contact (oxygen group)
	OF	Oxygen equipment printout – check for updates (oxygen group)

4.2. Visits, data forms, and procedures

Visit code	Form abbr	Procedures to be done
f08	HT	Telephone interim history
	OF	Oxygen equipment printout – check for updates (oxygen group)
a08	AH	Adherence promotion contact (oxygen group)
	OF	Oxygen equipment printout – check for updates (oxygen group)
a10	AH	Adherence promotion contact (oxygen group)
	OF	Oxygen equipment printout – check for updates (oxygen group)
f12	HI	Interim history at annual visit: MMRC, exposures, co morbidities, treatment history, health care utilization
	PL	Check for updates to patient location information
	OF	Oxygen equipment printout – check for updates (oxygen group)
	MO	Room air resting oximetry
	MM	Room air 6 minute walk with oximetry
	MP	Ambulatory oxygen dose (oxygen group)
	SP	Spirometry: pre and post BD FEV_1 and FVC (Expanded data collection)
	PE	Physical examination
	BV	Documentation of blood test results: Cotinine
	QG	St George's Respiratory Questionnaire
	QW	Quality of Well-Being Scale
	QF	SF-36v2 (Expanded data collection)
	PQ	Pittsburgh Sleep Quality Index (Expanded data collection)
	HA	Hospital Anxiety and Depression Scale (HADS; Expanded data collection)
	AH	Adherence promotion contact (oxygen group)
	OF	Oxygen equipment printout – check for updates (oxygen group)
f16	HT	Telephone interim history
	QG	St George's Respiratory Questionnaire
	QW	Quality of Well-Being Scale
	OF	Oxygen equipment printout – check for updates (oxygen group)
f20	HT	Telephone interim history
	OF	Oxygen equipment printout – check for updates (oxygen group)

4.2. Visits, data forms, and procedures

Visit code	Form abbr	Procedures to be done
f24	HI	Interim history at annual visit: MMRC, exposures, co morbidities, treatment history, health care utilization
	PL	Check for updates to patient location information
	OF	Oxygen equipment printout – check for updates (oxygen group)
	MO	Room air resting oximetry
	MM	Room air 6 minute walk with oximetry
	MP	Ambulatory oxygen dose (oxygen group)
	SP	Spirometry: pre and post BD FEV_1 and FVC (Expanded data collection)
	PE	Physical examination
	QG	St George's Respiratory Questionnaire
	QW	Quality of Well-Being Scale
	QF	SF-36v2 (Expanded data collection)
	PQ	Pittsburgh Sleep Quality Index (Expanded data collection)
	HA	Hospital Anxiety and Depression Scale (HADS; Expanded data collection)
	AH	Adherence promotion contact (oxygen group)
	OF	Oxygen equipment printout – check for updates (oxygen group)
f28	HT	Telephone interim history
	OF	Oxygen equipment printout – check for updates (oxygen group)
f32	HT	Telephone interim history
	OF	Oxygen equipment printout – check for updates (oxygen group)
f36	HI	Interim history at annual visit – MMRC, exposures, co morbidities, treatment history, health care utilization
	PL	Check for updates to patient location information
	OF	Oxygen equipment printout – check for updates (oxygen group)
	MO	Room air resting oximetry
	MM	Room air 6 minute walk with oximetry
	MP	Ambulatory oxygen dose (oxygen group)
	SP	Spirometry: pre and post BD FEV_1 and FVC (Expanded data collection)
	PE	Physical examination
	QG	St George's Respiratory Questionnaire
	QW	Quality of Well-Being Scale
	QF	SF-36v2 (Expanded data collection)
	PQ	Pittsburgh Sleep Quality Index (Expanded data collection)
	HA	Hospital Anxiety and Depression Scale (HADS; Expanded data collection)
	AH	Adherence promotion contact (oxygen group)
	OF	Oxygen equipment printout – check for updates (oxygen group)
f40	HT	Telephone interim history
	OF	Oxygen equipment printout – check for updates (oxygen group)
f44	HT	Telephone interim history
	OF	Oxygen equipment printout – check for updates (oxygen group)

4.2. Visits, data forms, and procedures

Visit code	Form abbr	Procedures to be done
f48	HI	Interim history at annual visit – MMRC, exposures, co morbidities, treatment history, health care utilization
	PL	Check for updates to patient location information
	OF	Oxygen equipment printout – check for updates (oxygen group)
	MO	Room air resting oximetry
	MM	Room air 6 minute walk with oximetry
	MP	Ambulatory oxygen dose (oxygen group)
	SP	Spirometry – pre and post BD FEV_1 and FVC (Expanded data)
	PE	Physical examination
	QG	St George's Respiratory Questionnaire
	QW	Quality of Well-Being Scale
	QF	SF-36v2 (Expanded data collection)
	PQ	Pittsburgh Sleep Quality Index (Expanded data collection)
	HA	Hospital Anxiety and Depression Scale (HADS; Expanded data collection)
	AH	oxygen group adherence promotion contact
	OF	Oxygen equipment printout – check for updates (oxygen group)
f52	HT	Telephone interim history
	OF	Oxygen equipment printout – check for updates (oxygen group)
f56	HT	Telephone interim history
	OF	Oxygen equipment printout – check for updates (oxygen group)
f60	HI	Interim history at annual visit – MMRC, exposures, co morbidities, treatment history, health care utilization
	PL	Check for updates to patient location information
	OF	Oxygen equipment printout – check for updates (oxygen group)
	MO	Room air resting oximetry
	MM	Room air 6 minute walk with oximetry
	MP	Ambulatory oxygen dose (oxygen group)
	SP	Spirometry – pre and post BD FEV_1 and FVC (Expanded data)
	PE	Physical examination
	QG	St George's Respiratory Questionnaire
	QW	Quality of Well-Being Scale
	QF	SF-36v2 (Expanded data collection)
	PQ	Pittsburgh Sleep Quality Index (Expanded data collection)
	HA	Hospital Anxiety and Depression Scale (HADS; Expanded data collection)
	AH	oxygen group adherence promotion contact
	OF	Oxygen equipment printout – check for updates (oxygen group)
f64	HT	Telephone interim history
	OF	Oxygen equipment printout – check for updates (oxygen group)
f68	HT	Telephone interim history
	OF	Oxygen equipment printout – check for updates (oxygen group)

4.2. Visits, data forms, and procedures

Visit code	Form abbr	Procedures to be done
f72	HI	Interim history at annual visit – MMRC, exposures, co morbidities, treatment history, health care utilization
	PL	Check for updates to patient location information
	OF	Oxygen equipment printout – check for updates (oxygen group)
	MO	Room air resting oximetry
	MM	Room air 6 minute walk with oximetry
	MP	Ambulatory oxygen dose (oxygen group)
	SP	Spirometry – pre and post BD FEV_1 and FVC (Expanded data)
	PE	Physical examination
	QG	St George's Respiratory Questionnaire
	QW	Quality of Well-Being Scale
	QF	SF-36v2 (Expanded data collection)
	PQ	Pittsburgh Sleep Quality Index (Expanded data collection)
	HA	Hospital Anxiety and Depression Scale (HADS; Expanded data collection)
	AH	oxygen group adherence promotion contact
	OF	Oxygen equipment printout – check for updates (oxygen group)
f76	HT	Telephone interim history
	OF	Oxygen equipment printout – check for updates (oxygen group)
f80	HT	Telephone interim history
	OF	Oxygen equipment printout – check for updates (oxygen group)

Note: The oxygen group also has adherence monitoring contacts (check on changes to equipment and collection of oxygen usage information (via the Oxygen Equipment Usage Log (AP, AQ, AS form) appropriate to the patient's choice of oxygen equipment) throughout followup at 2 month intervals from randomization. These contacts by mail use visit code n.

4.3 Visit and contact time windows

Screening and randomization visits (all patients unless otherwise noted)

- **sb (screening; takes place at clinic):** Must occur within 2 months (60 days) of randomization
- **rz (randomization to treatment; takes place at clinic):** Must occur within 2 months (60 days) of initiating screening (date of RG form)
- **rx (ambulatory dose determination; takes place at clinic; oxygen patients only):** Should occur as soon as patient has his/her ambulatory system, within a week of randomization but may occur at longer durations from randomization under extraordinary circumstances; durations longer than 1 week must be explained. Ideal date is the day after randomization.

Clinic and telephone followup visits (all patients)

- **f04 (telephone and mail):** Window opens 2 months + 1 day (62 days) after randomization and closes 6 months (183 days) after randomization; ideal date is 4 months (122 days) after randomization.
- **f08 (telephone):** Window opens 6 months + 1 day (184 days) after randomization and closes 10 months (304 days) after randomization; ideal date is 8 months (244 days) after randomization.
- **f12 (clinic):** Window opens 10 months + 1 day (305 days) after randomization and closes 14 months (426 days) after randomization; ideal date is 1 year (365 days) after randomization.
- **f16 (telephone and mail):** Window opens 14 months + 1 day (427 days) after randomization and closes 18 months (548 days) after randomization; ideal date is 1 year + 4 months (487 days) after randomization.
- **f20 (telephone):** Window opens 18 months + 1 day (549 days) after randomization and closes 22 months (670 days) after randomization; ideal date is 1 year + 8 months (609 days) after randomization.
- **f24 (clinic):** Window opens 22 months + 1 day (671 days) after randomization and closes 26 months (791 days) after randomization; ideal date is 2 years (730 days) after randomization.
- **f28 (telephone):** Window opens 26 months + 1 day (792 days) after randomization and closes 30 months (913 days) after randomization; ideal date is 2 years + 4 months (852 days) after randomization.
- **f32 (telephone):** Window opens 30 months + 1 day (914 days) after randomization and closes 34 months (1035 days) after randomization; ideal date is 2 years + 8 months (974 days) after randomization.
- **f36 (clinic):** Window opens 34 months + 1 day (1036 days) after randomization and closes 38 months (1157 days) after randomization; ideal date is 3 years (1096 days) after randomization.
- **f40 (telephone):** Window opens 38 months and 1 day (1158 days) after randomization and closes 42 months (1278 days) after randomization; ideal date is 3 years + 4 months (1218 days) after randomization.
- **f44 (telephone):** Window opens 42 months + 1 day (1279 days) after randomization and closes 46 months (1400 days) after randomization; ideal date is 3 years + 8 months (1339 days) after randomization.
- **f48 (clinic):** Window 46 months + 1 day (1401 days) after randomization and closes 50 months (1522 days) after randomization; ideal date is 4 years (1461 days) after randomization.
- **f52 (telephone):** Window opens 50 months + 1 day (1523 days) after randomization and closes 54 months (1644 days) after randomization; ideal date is 4 years + 4 months (1583 days) after randomization.
- **f56 (telephone):** Window opens 54 months + 1 day (1645 days) after randomization and closes 58 months (1765 days) after randomization; ideal date is 4 years and 8 months (1705 days) after randomization
- **f60 (clinic):** Window opens 58 months + 1 day (1766 days) after randomization and closes 62 months (1887 days) after randomization; ideal date is 5 years (1826 days) after randomization
- **f64 (telephone):** Window opens 62 months + 1 day (1888 days) after randomization and closes 66 months (2009 days) after randomization; ideal date is 5 years and 4 months (1948 days) after randomization

- **f68 (telephone):** Window opens 66 months + 1 day (2010 days) after randomization and closes 70 months (2131 days) after randomization; ideal date is 5 years and 8 months (2070 days) after randomization
- **f72 (clinic):** Window opens 70 months + 1 day (2132 days) after randomization and closes 74 months (2252 days) after randomization; ideal date is 6 years (2192 days) after randomization
- **f76 (telephone):** Window opens 74 months + 1 day (2253 days) after randomization and closes 78 months (2374 days) after randomization; ideal date is 6 years and 4 months (2313 days) after randomization
- **f80 (telephone):** Window opens 78 months + 1 day (2375 days) after randomization and closes 82 months (2496 days) after randomization; ideal date is 6 years and 8 months (2435 days) after randomization

Adherence promotion visits (oxygen group only, except for visit w01)

- **w01 (telephone; both groups):** Window opens 1 day after randomization and closes 10 days after randomization, ideal date is 7 days after randomization. Oxygen group patients may skip visit w01 if visit rx is completed within 4 days of the closing date for visit w01 – check the footnote at the end of the patient's visit windows listing; it specifies the date requirements for skipping w01 for the patient.
- **w02 (telephone):** Window opens 11 days after randomization and closes 17 days after randomization; ideal date is 14 days (2 weeks) after randomization.
- **w03 (telephone):** Window opens 18 days after randomization and closes 24 days after randomization; ideal date is 21 days (3 weeks) after randomization.
- **w04 (telephone):** Window opens 25 days after randomization and closes 42 days after randomization; ideal date is 28 days (4 weeks) after randomization.
- **a02 (telephone):** Window opens 43 days after randomization and closes 76 days after randomization; ideal date is 61 days (2 months) after randomization.
- **a03 (telephone):** Window opens 77 days after randomization and closes 106 days after randomization; ideal date is 91 days (3 months) after randomization.
- **a04 (telephone):** Window opens 107 days after randomization and closes 137 days after randomization; ideal date is 122 days (4 months) after randomization.
- **a05 (telephone):** Window opens 138 days after randomization and closes 167 days after randomization; ideal date is 152 days (5 months) after randomization.
- **a06 (telephone):** Window opens 168 days after randomization and closes 213 days (7 months) after randomization; ideal date is 183 days (6 months) after randomization.
- **a08 (telephone):** Window opens 214 days (7 months +1 day) after randomization and closes 274 days (9 months) after randomization; ideal date is 244 days (8 months) after randomization.
- **a10 (telephone):** Window opens 275 days (9 months + 1 day) after randomization and closes 335 days (11 months) after randomization; ideal date is 304 days (10 months) after randomization.
- **f12 (clinic):** Same window as followup visit f12; visit procedures include an adherence promotion contact for oxygen group patients.
- **f24 (clinic):** Same window as followup visit f24; visit procedures include an adherence promotion contact for oxygen group patients.
- **f36 (clinic):** Same window as followup visit f36; visit procedures include an adherence promotion contact for oxygen group patients.
- **f48 (clinic):** Same window as followup visit f48; visit procedures include an adherence promotion contact for oxygen group patients.
- **f60 (clinic):** Same window as followup visit f60; visit procedures include an adherence promotion contact for oxygen group patients.
- **f72 (clinic):** Same window as followup visit f72; visit procedures include an adherence promotion contact for oxygen group patients.

4.3. Visit and contact time windows

Adherence monitoring contacts (oxygen patients; by mail)

- Should occur every 2 months after randomization: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, and 80 months
- Time windows are not imposed since these data are collected throughout followup
- Visit code n is used with these data; a listing of mail dates for materials will be printed for each oxygen patient at randomization

Missed or incomplete visits

- Once a window has closed, the visit cannot be done; visits can only be done on calendar days on or between the opening date and closing date for the window for the visit
- If none of the procedures for a visit is done, then the visit is missed
- If at least one, but not all, of the procedures for a visit is done, then the visit is incomplete

4.4 Guide for visit sb

When

- The 60-day clock on randomization starts ticking on the date screening (or re-screening) is initiated

Type

- In person

Staff

- Clinical Coordinator
- Study Physician
- Oximetry Technician
- Six Minute Walk Tester
- Spirometry Technician

Before the patient arrives for the visit

- Locate ID and screening visit labels and have ready for use
- Gather specimen collection tubes and mailing materials (PaxGene, EDTA, red top serum separator, and serum shipment tubes from the DCC and shipper from Channing Lab)
- Alert phlebotomy lab staff of need to draw blood and, if applicable, need to process whole blood to serum shipment tube

Procedures

- Obtain signed consent for enrollment and randomization and signed contract not to smoke (all patients, not just current smokers)
- Verify coverage by Medicare or other resources to cover clinical costs
- Initiate data collection for registration and initial eligibility screen; complete the Registration (RG) form which includes height and weight measurement
- Continue with data collection if patient is not excluded by the Registration (RG) form interview
  - Collect insurance number and social security number
  - Complete clinical assessments
    - Room air resting oximetry
    - Spirometry
    - Room air 6 minute walk
    - Physical exam
    - Blood draw for hemoglobin (all patients), hematocrit (all patients), and serum cotinine (patients who are not smoking and not using nicotine products) and A1AT concentration and phenotype (if not available from chart review and if Expanded data collection patient)
    - Blood draw for DNA and plasma banking (if consent obtained)
    - Blood draw for serum banking (if consent obtained and if Expanded data collection patient)
  - Interview for baseline history
  - Administer Epworth Sleepiness Scale, St George's Respiratory, and Quality of Well-Being Scale questionnaires
  - Administer SF-36, HADS, and Pittsburgh Sleep Quality Index questionnaires (Expanded data collection patients only)
- Obtain patient location information
- Check eligibility (hand/eyeball review of unkeyed data)
- Obtain signed medical records release
- Explain to the patient that you will electronically check eligibility after keying the data collected at the visit and that you will contact him/her with the eligibility results and if eligible, you will ask to schedule the randomization visit

Data collection forms

- Forms completed for all patients
  - RG - Registration
  - BC - Blood Collection for DNA, Serum, and Plasma Banking
  - BV - Blood Values
  - DC - Consent Documentation for DNA, Serum, and Plasma Banking
  - EP - Epworth Sleepiness Scale
  - HB - Baseline History
  - ID - Patient Identifiers
  - MM - Room Air 6 Minute Walk
  - MO - Room Air Resting Oximetry
  - PE - Physical Examination
  - QG - St George's Respiratory Questionnaire
  - QW - Quality of Well-Being Scale
  - SP - Spirometry
- Additional forms required for Expanded data collection
  - HA - Hospital Anxiety and Depression Scale
  - PQ - Pittsburgh Sleep Quality Index
  - QF - SF-36 v2 Health Survey

Forms for clinical center use only (not keyed)

- PL - Patient Location

Flash Cards

- #1 - Ethnicity Category (NIH)
- #2 - Racial Category (NIH)
- #3 - Highest Educational Level Achieved
- #4 - Marital Status
- #5 - Total Annual Household Income Before Taxes
- #6 - Instructions for Patient During 6 Minute Walk
- #7 - Perceived Symptoms (Borg) scale
- #8 - Degree of Breathlessness (MMRC Dyspnea Scale)
- #9 - Race/Ethnicity (Pulmonary Function)

After the patient leaves the clinical center

- Register patient on clinic data system by keying the Registration (RG) form
- Set up LOTT chart for patient
- Process serum to serum shipment tube (if applicable)
- Package blood samples for sending to the Channing Laboratory (Paxgene tube, EDTA tube, serum shipment tube) and send by overnight delivery service
- Key remaining data forms
- Upload resting and 6 minute walk oximetry data to the LOTT data system
- Check eligibility (run Randomize task on web-based data system)

4.5 Guide for visit rz

When
- Within 60 days of initiating screening

Type
- In person

Staff
- Clinical Coordinator
- Study Physician
- Adherence Educator

Procedures
- If the patient has home oxygen equipment
  - Check that the patient did not use the equipment for at least the previous 4 days and that the patient managed Ok without the oxygen
  - Check that the patient agrees to have the equipment removed if randomized to no oxygen
  - Make sure that you have written agreement to removal from the prescribing physician
- Complete the Eligibility Review (RR) form; this form queries interim history, asks the patient to affirm consent to randomization, checks that the patient is ready to receive oxygen equipment if assigned to oxygen, and asks the Study Physician to approve randomization of the patient to either treatment group
- Check for updates to patient location information
- Key the completed RR form while the patient is at the clinic and then run the Randomize task on the web-based data system
- Patient should be present in the clinic when the treatment assignment is generated
- A treatment assignment will be issued only if the database shows that the patient is eligible, has signed the consent statement and smoker's contract, and has had all required baseline data keyed to the database
- If all checks indicate eligibility, patient will be randomized to supplemental oxygen or no supplemental oxygen (control treatment)
- Every patient must meet with the Adherence Educator following treatment assignment to be counseled about their feelings regarding their treatment assignment
- Oxygen group patients
  - Clinical Coordinator or Adherence Educator must call the oxygen supplier and arrange for equipment delivery for patients assigned to oxygen and start to gather the required information about the equipment (i.e., start to complete the Oxygen Equipment (OE) form; form may not be able to be finished until visit rx)
  - Schedule visit rx (ambulatory dosing visit)
  - If the patient has home oxygen equipment: make arrangements for waiver of copayments and deductibles if possible
- No oxygen (control) group patients
  - If patient was using home oxygen, arrange for removal of the equipment
  - Schedule 1 week adherence promotion contact (visit w01)
- Schedule visit f12

Data collection forms
- RR - Eligibility Review
- XZ - Documentation of Randomization and Randomization Day Adherence Promotion Contact
- OE - Oxygen Equipment (oxygen patients only; start form at visit rz and finish by the end of visit rx)

Comment
- The date of randomization visit is the zero date for reckoning time windows for all followup visits and contacts

4.6 Guide for visit rx

Who
- All patients assigned to supplemental oxygen

When
- As soon as possible after the patient receives his/her oxygen equipment
- Ideally, this visit occurs the day after randomization
- Visit rx may be combined with visit rz if the patient has his/her portable equipment already (eg, already has it or oxygen company can deliver it to the LOTT office during the rz visit)

Type
- In person

Staff
- Clinical Coordinator
- Study Physician
- Oximetry Technician
- Adherence Educator

Before the patient arrives for the visit
- Remind the patient to bring his/her ambulatory system to the visit

Procedures
- Determine walking dose
- Educate patient about his/her specific oxygen systems
  - How to set and check flow rate
  - How to change tanks (if applicable)
  - How to maneuver the equipment
  - Maintenance and cleaning of equipment
  - How to obtain a meter reading (if using a concentrator)
- Educate the patient about oxygen safety
- Educate patient about oxygen usage log (AP, AQ, AS depending on patient's choice of system)
- Educate patient about oxygen equipment in use printout (OF form printout)
- Remind patient about adherence promotion call schedule
- Check for updates to patient location information
- Schedule first telephone adherence promotion contact (visit w01)
  - You may start the telephone adherence promotion contacts with w02 if visit rx is done within 4 days of the close of the window for visit w01; see the footnote on the patient's visit time window guide)

Data collection forms
- AE - Oxygen Group Adherence Promotion Contact - Initial Walking Dose Determination (if visit rx is done on the same day as visit rz, complete both the XZ form and the AE form; the responses on the AE form will be the same as those on the XZ form)
- AP, AQ, AS - Oxygen Usage Log (show patient how to complete this form)
  - AP is used with a portable concentrator
  - AQ is used with a liquid oxygen system
  - AS is used with a stationary concentrator and cylinders of compressed oxygen gas
- OE - Oxygen Equipment (finish completing if applicable)
- MP - Ambulatory Oxygen Dose
- PL - Patient Location Information (check for updates)

4.7 Guide for visit w01

Who
- All patients

When
- Ideally, this visit occurs 1 week after randomization
- Permissible dates are 1 to 10 days after randomization
- Oxygen group patients may skip this contact if visit rx is done within 4 days of the close of the window for visit w01 (check the footnote on the patient's visit time windows listing); oxygen group patients then start the telephone adherence promotion contacts with visit w02

Type
- Adherence promotion
- Telephone

Staff
- Adherence Educator

Before contacting the patient
- Assemble notes from previous visits with patient
- Obtain current oxygen equipment in use (OF) form printout for patient (oxygen group)

Procedures
- **Oxygen group**: Ask about questions or problems with completion of oxygen equipment usage log; intent is to help assure that patients understand how to keep the log and to problem solve about keeping the log, not to query adherence)
- **No oxygen (control) group**: Ask about questions and problems with treatment assignment; check patient's level of understanding of protocol
- Conduct adherence promotion contact: See Adherence Educator's Training Manual

Data collection forms
- **Oxygen group**
  AH - Oxygen Group Adherence Promotion Contact - Telephone or Annual Visit
  AP, AQ, AS - Oxygen Equipment Usage Log appropriate for patient's choice of system (remind patient about keeping it, answer questions about use, do not ask for adherence data)
  - AP is used with a portable concentrator
  - AQ is used with a liquid oxygen system
  - AS is used with a stationary concentrator and cylinders of compressed oxygen gas
- **No oxygen (control) group**
  AC - Control Group Adherence Promotion Contact - Visit w01

4.8 Guide for visits w02, w03, w04, a02, a03, a04, a05, a06, a08, and a10

Who
- All patients assigned to supplemental oxygen

When
- w02 - Ideally, this visit occurs 2 weeks after randomization
- w03 - Ideally, this visit occurs 3 weeks after randomization
- w04 - Ideally, this visit occurs 4 weeks after randomization
- a02 - Ideally, this visit occurs 2 months after randomization
- a03 - Ideally, this visit occurs 3 months after randomization
- a04 - Ideally, this visit occurs 4 months after randomization
- a05 - Ideally, this visit occurs 5 months after randomization
- a06 - Ideally, this visit occurs 6 months after randomization
- a08 - Ideally, this visit occurs 8 months after randomization
- a10 - Ideally, this visit occurs 10 months after randomization

Type
- Adherence promotion
- Telephone

Staff
- Adherence Educator

Before contacting the patient
- Assemble notes from previous visits/contacts with patient
- Obtain current oxygen equipment in use (OF) form printout for patient

Procedures
- Ask about equipment changes
- Through visit w04: Ask about questions or problems with completion of oxygen equipment usage log (after that LOTT is trying to keep adherence monitoring separate from adherence promotion)
- Conduct adherence promotion contact: See Adherence Educator's Training Manual

Data collection forms
- AH - Oxygen Group Adherence Promotion Contact - Telephone or Annual Visit
- AP, AQ, AS - Oxygen Equipment Usage Log appropriate to patient's choice of system (remind patient about keeping it, answer questions about use, do not ask for adherence data)
  - AP is used with a portable concentrator
  - AQ is used with a liquid oxygen system
  - AS is used with a stationary concentrator and cylinders of compressed oxygen gas
- OF form printout

4.9 Guide for visits f04, f08, f16, f20, f28, f32, f40, f44, f52, f56, f64, f68, f76, f80

Who
- All patients

When
- f04 - Ideally, 4 months after randomization
- f08 - Ideally, 8 months after randomization
- f16 - Ideally, 16 months (1 year and 4 months) after randomization
- f20 - Ideally, 20 months (1 year and 8 months) after randomization
- f28 - Ideally, 28 months (2 years and 4 months) after randomization
- f32 - Ideally, 32 months (2 years and 8 months) after randomization
- f40 - Ideally, 40 months (3 years and 4 months) after randomization
- f44 - Ideally, 44 months (3 years and 8 months) after randomization
- f52 - Ideally, 52 months (4 years and 4 months) after randomization
- f56 - Ideally, 56 months (4 years and 8 months) after randomization
- f64 - Ideally, 64 months (5 years and 4 months) after randomization
- f68 - Ideally, 68 months (5 years and 8 months) after randomization
- f76 - Ideally, 76 months (6 years and 4 months) after randomization
- f80 - Ideally, 80 months (6 years and 8 months) after randomization

Type
- Telephone and mail (f04, f16)
- Telephone (f08, f20, f28, f32, f40, f44, f52, f56, f64, f68, f76, f80)

Staff
- Clinical Coordinator

Before contacting the patient
- Print oxygen equipment in use (OF) form printout (oxygen patients only)

Procedures
- Obtain interim history (HT form) by interview of patient
- f04 and f16 only – mail the St George's Respiratory Questionnaire (QG) and Quality of Well-Being Scale (QW) forms to the patient and ask for return within 2 weeks
  - Ideally, mail the patient the forms 2 weeks prior to the target date for the visit, but it is permissible to mail at any time once the window is open
  - Complete Section A on page 1 of each form except for item 4 and set page 1 aside
  - Affix a Patient ID, code, and visit label to each of pages 2 and up of each questionnaire
  - Send the patient pages 2 and up of the QG and QW forms with a self-addressed, stamped return envelope and ask patient to complete and return the questionnaires within 2 weeks
  - When the questionnaires are returned:
    - Re-attach page 1 to each questionnaire and complete Section B on page 1
    - If the questionnaires are returned within the window for the visit:
      - For the QG form: Enter the date that the patient wrote in item 60 into item 4; enter the date the form was mailed to the patient if item 60 was left blank
      - For the QW form: Enter the date the patient wrote in item 71 into item 4; use the date the form was mailed to the patient if item 71 was left blank
    - If the patient returns the forms after the window closed and the patient wrote in a date of completion that is within the window, the form was completed within the window and you should enter the date in item 60 (QG)/item 71 (QW) in item 4
    - If the patient returned the forms after the window closed and the patient wrote in a date of completion that is outside the window, the form was completed outside the window and the data cannot be keyed to the data system; mark the form with a note that it was completed

4.9. Guide for visits f04, f08, f16, f20, f28, f32, f40, f44, f52, f56, f64, f68, f76, and f80

outside the window and file the form without keying it; complete a Missed or Incomplete Visit (MV) form to document the missed questionnaires

- If the patient returned the forms 10 or fewer days after the window closed and the patient did not write in a date of completion then, enter the date the window closed in item 4
- If the patient returned the forms 11 or more days after the window closed and the patient did not write in a date of completion then, the forms are considered to have been completed outside of the window and the data cannot be keyed to the data system; mark each form with a note that it was returned 11 or more days after the window closed and file the forms without keying them; complete a Missed or Incomplete Visit (MV) form to document the missed questionnaires

• Ask about changes to patient's oxygen equipment (oxygen patients only)

Data collection forms

• HT - Interim History at 4-Month Telephone Visit (f04, f08, f16, f20, f28, f32, f40, f44, f52, f56, f64, f68, f76, f80)
• QG - St George's Respiratory Questionnaire (f04, f16)
• QW - Quality of Well-Being Scale (f04, f16)

4.10 Guide for visits f12, f24, f36, f48, f60, and f72

Who
- All patients

When
- Visit f12 - Ideally, 12 months (1 year) after randomization
- Visit f24 - Ideally, 24 months (2 years) after randomization
- Visit f36 - Ideally, 36 months (3 years) after randomization
- Visit f48 - Ideally, 48 months (4 years) after randomization
- Visit f60 - Ideally, 60 months (5 years) after randomization
- Visit f72 - Ideally, 72 months (6 years) after randomization

Type
- In person

Staff
- Clinical Coordinator
- Oximetry Technician
- Six Minute Walk Tester
- Spirometry Technician (Expanded data collection patients)
- Adherence Educator (oxygen patients)
- Study Physician

Before the patient arrives for the visit
- Print oxygen equipment in use (OF) form printout (oxygen patients only)
- Schedule phlebotomy for serum cotinine (visit f12 only and non smokers who are not using nicotine products)
- You may mail the patient the QG, QW, QF, PQ, and HA questionnaires 2 weeks prior to the scheduled visit and ask the patient to complete them at home and bring them to the visit; if the patient does not bring the completed questionnaires to the visit, then ask the patient to complete them during the visit

Procedures
- Interim history
- Questionnaires
- Limited physical exam
- Room air oximetry
- Room air 6 minute walk
- Spirometry (Expanded patients)
- Blood draw for serum cotinine (visit f12 only; nonsmokers who are not using nicotine products)
- Ambulatory dosing check (oxygen group)
- Adherence promotion contact (oxygen group)
- Ask about updates to oxygen equipment (oxygen group)
- Check for updates to patient location information
- Obtain signed current medical records release form

Data collection forms
- HI - Interim History at Annual Visit
- PE - Physical Examination
- BV - Blood Values (visit f12 only)
- MO - Resting Room Air Oximetry

4.10. Guide for visits f12, f24, f36, f48, f60, and f72

- MM - Room Air 6 Minute Walk with Oximetry
- SP - Spirometry (Expanded patients)
- MP - Ambulatory Oxygen Dose (oxygen patients only)
- QG - St George's Respiratory Questionnaire
- QW - Quality of Well-Being Scale
- HA - Hospital Anxiety and Depression Scale (Expanded data collection patients)
- QF - SF-36 v2 Health Survey (Expanded data collection patients)
- PQ - Pittsburgh Sleep Quality Index (Expanded data collection patients)
- AH - Oxygen Group Adherence Promotion Contact - Telephone or Annual Visit (oxygen patients only)

Flash Cards

- #6 - Instructions for Patient During 6 Minute Walk
- #7 - Perceived Symptoms (Borg) scale
- #8 - Degree of Breathlessness (MMRC Dyspnea Scale)
- #9 - Race/Ethnicity (Pulmonary Function)

4.11 Missed or incomplete visits

Definitions

- **Missed visit:** A visit is missed if none of the forms comprising the visit is completed within the time window for the visit
- **Incomplete visit:** A visit is incomplete if at least one, but not all, of the forms comprising the visit is completed within the time window for the visit

Forms

- The Missed or Incomplete Visit (MV) form is used with 4-month telephone or annual followup visits: f04, f08, f12, f16, f20, f24, f28, f32, f36, f40, f44, f48, f52, f56, f60, f64, f68, f72, f76, f80
- Missed adherence promotion contacts (rx, w01, w02, w03, w04, a02, a03, a04, a05, a06, a08, a10, f12, f24, f36, f48, f60, f72) are documented on the interview form (AC, AE, or AH) for the specific visit
- The MV, AC, AE, and AH forms include items to document the reason(s) for missing or not completing the visit or contact and to document efforts made to complete the visit or contact

When

- Complete the MV, or AC, AE or AH form at the close of the visit window for the missed or incomplete visit or contact

Procedures

- For a completely missed visit or contact:
  - Item 4 on the MV or AC, AE, or AH form is the closing date of the visit window
- For an incomplete visit (partially completed visit):
  - Item 4 on the MV or AC, AE, or AH form is the closing date of the visit window
- Adherence contacts (except for visit rx) consist of one procedure (one form) and hence either are completely missed or completed

4.12 Follow-up compliance problems

- LOTT wants all patients to continue to complete visits regardless of course of treatment. Patients assigned to oxygen who stop oxygen should continue to complete visits. Patients assigned to no oxygen who start oxygen should continue to complete visits.

- If a patient cannot attend an annual visit in person, try to complete the Interim History (HI) form by telephone and try to complete questionnaires (QG, QW, QF, HA, PQ) by mail or by phone

- If a patient wants to drop out of LOTT:
  - Consider if the patient would be open to negotiating – would the patient be willing to do one visit per year, only phone contacts, etc
  - Try to negotiate permission to contact the patient after 3 months, after 1 year – the idea is to give the patient a break from LOTT and try to resume some level of participation after the break
  - Try to find out what about LOTT they object to and negotiate participation in the parts of LOTT that the patient doesn't object to
  - Remind the patient of the patient stipend payable upon completion of the annual visit in person

- If you cannot reach a patient by mail or telephone:
  - Contact the alternate contacts the patient provided on the Patient Location (PL) form at the start of screening
  - Search for obituaries, search online versions of the social security death index
  - Can you find any new contact information if you search the web for the patient
  - If you have permission, search your institution's electronic records for evidence of vital status and hospitalization
  - Contact the referring physician; he/she might be willing to pass on a message from LOTT or provide contact information

5 Patient assessment procedures

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5.1 Height, weight, and physical exam

Data collection level
- Core

When
- Visit sb (no more than 60 days prior to randomization)
- Visits f12, f24, f36, f48, f60, and f72

Who
- All patients (Core data collection)
- Exam may be done by Study Physician, Clinical Coordinator, or Physical Exam Assessor at discretion of site

Equipment
- Stadiometer
- Tape measure
- Scale
- Sphygmomanometer
- Stethoscope

Form
- Physical Examination (PE) form
- Registration (RG) form: Height is collected only during screening and is recorded on the RG form

Exam elements
- **Height**
  - Height may be measured in inches or centimeters
  - Use a stadiometer
  - Follow the manufacturer's recommendations regarding method and frequency of calibration
  - Raise the stadiometer platform
  - Patient removes shoes
  - Patient stands erect on the stadiometer base with his/her back parallel to the vertical mounted measure scale (but not touching the wall), looking straight ahead and not raising the chin; the middle of the ear and the corner of the eye should be in a straight line
  - Lower the stadiometer platform snugly, but not tightly, against the top of the head
  - Record the height to the nearest tenth of the unit of measurement
  - If height cannot be measured, then arm span should be measured
- **Arm span**
  - Measure only if height cannot be measured.
  - Arm span may be measured in inches or centimeters
  - Patient should stand or sit against a wall with arms outspread as far as possible
  - Measure distance between tips of right and left middle fingers using a tape measure
  - Height is calculated from arm span as:
    - Black or African-American men: Height = arm span/1.06
    - All other men: Height = arm span/1.03
    - Women (regardless of race/ethnicity): Height = arm span/1.01
- **Weight**
  - Weight may be measured in pounds or kilograms
  - Use a scale
  - Follow the manufacturer's recommendation regarding method and frequency of calibration

- Zero the scale before obtaining weight
- Patient should remove shoes and remove items from pockets
- Patient should be wearing light clothing
- Patient should stand in center of scale platform with head erect and staring straight ahead
- A patient who has a limb amputation or who is wearing a cast should have weight measured, but note the amputation and/or cast on the form in the margin and be sure that the note is keyed to the General Comments area of the keying

• **Blood pressure**
- Patient should relax for 5 minutes before measurement
- Blood pressure may be measured with the patient supine or sitting

• **Resting radial pulse**
- Patient should sit quietly for 5 minutes
- Count the pulse for 30 seconds and multiply by 2 to obtain beats per minute.

• **Pretibial pitting edema**
- Patient should roll down socks; clear hose do not need to be removed
- Press on each leg with moderate pressure; assess edema as:
  ◦ None or trace
  ◦ More than trace
- Report edema of worst leg

• **Auscultation of chest and lungs:** Assess presence of decreased intensity of breath sounds, prolongation of expiration, rales, crackles, rhonchi, and wheezes.

Reference

• Hepper NGG et al: Relationship of lung volume to height and arm span in normal subjects and patients with spinal deformity. Am Rev Respir Dis 1965;91:356-362.

5.2 Baseline history

Data collection level
- Core

When
- Visit sb (no more than 60 days prior to randomization)

Form
- Registration (RG) form
- Baseline History (HB) form

Flash cards (used with the RG form)
- #1 - Ethnicity Category (NIH categories)
- #2 - Racial Category (NIH categories)
- #3 - Highest Educational Level
- #4 - Marital Status
- #5 - Total Annual Household Income before Taxes for Last Year
- #8 - Degree of Breathlessness (MMRC Dyspnea Scale)

Who/How
- Clinical Coordinator should interview the patient; the patient's spouse or family may assist with questions about history, medications, and other factual subjects
- Clinical Coordinator may review medical records as needed to confirm or explore the patient's responses

History elements
- **Registration (RG) form**
  - Demographics and residence
  - MMRC dyspnea scale
  - Tobacco cigarette smoking
  - Selected exclusion criteria related to: recent hospitalization, medications and treatment for COPD, willingness to stop home oxygen use, and recent procedure likely to cause pulmonary instability
- **Baseline History (HB) form**
  - Family history
  - Symptoms
  - Weight loss
  - Smoking and alcohol use
  - Medical conditions
  - Thoracic surgery and pulmonary rehabilitation experience
  - Current medications
  - COPD exacerbation history
  - Supplemental oxygen history
  - Healthcare utilization
  - Selected exclusion criteria related to medical history

5.3 Interim history at annual visit

Data collection level
- Core

When
- Visits f12, f24, f36, f48, f60, and f72

Form
- Interim History at Annual Visit (HI) form

Flash card
- #8 - Degree of Breathlessness (MMRC Dyspnea Scale)

Who/How
- Clinical Coordinator should interview the patient. The patient's spouse or family may assist with questions about history, medications, and other factual subjects.
- Clinical Coordinator may review medical records as needed to confirm or explore the patient's responses

History elements
- Residence
- MMRC dyspnea scale
- Symptoms
- Smoking and alcohol use
- Medical conditions, lung volume reduction surgery, pulmonary rehabilitation, use of a positive pressure device
- Current medications
- COPD exacerbations and interim use of oxygen
- Adverse events related to oxygen equipment
- Other serious health problem (eg, health problem requiring doctor visit or treatment or otherwise reported by the patient when asked the form question)
- Acute care hospitalization
- General healthcare utilization

5.4 Interim history at 4-month telephone visit

Data collection level
- Core

When
- 4-month telephone visits (f04, f08, f16, f20, f28, f32, f40, f44, f52, f56, f64, f68, f76, f80)

Form
- Interim History at 4-Month Telephone Visit (HT) form

Who/How
- Clinical Coordinator should interview the patient; the patient's spouse or family may assist with questions about history, medications, and other factual subjects
- Clinical Coordinator may review medical records as needed to confirm or explore the patient's responses

History elements
- Nasal symptoms
- Smoking
- COPD exacerbations and interim use of oxygen
- Adverse events related to oxygen equipment
- Other serious health problem (eg, health problem requiring doctor visit or treatment or otherwise reported by the patient when asked the form question)
- Acute care hospitalization

5.5 Hemoglobin, hematocrit, A1AT, cotinine

Hemoglobin and hematocrit

- All patients (Core data collection)
- Visit sb only
- Covered by Medicare
- Follow your usual local protocol for obtaining these values
- If your lab returns results electronically, print a copy of the lab report
- Attach lab report or printout to back of the Blood Values (BV) form
- Record results on the Blood Values (BV) form
  - Hemaglobin is recorded in g/dL
  - Hematocrit is recorded as a %

Alpha-1 antitrypsin (A1AT) testing

- Part of Expanded data collection
- Visit sb only
- Covered by Medicare
- What to do:
  - Results may be obtained by chart review if available
  - If concentration is not available, draw blood for A1AT testing
  - If concentration is available and concentration is greater than 100 mg/dL (greater than 100 mg% , greater than 1 mg/mL, or greater than 19 µM), then phenotype is not required and not reported
  - If concentration is available and is 100 mg/dL or less (100 mg% or less, 1 mg/mL or less, or 19 µM or less), then phenotype is required
    - ▸ If phenotype is not available, draw blood for A1AT testing
    - ▸ If phenotype is available, do not draw blood for A1AT testing
- Follow your usual local protocol for A1AT testing
- If your lab returns results electronically, print a copy of the lab report
- Attach lab report or printout to back of the Blood Values (BV) form
- Record results on the Blood Values (BV) form
  - If your lab reports the concentration as >xxx or <xxx where xxx is some level, specify the appropriate prefix (> or <) in the form item for this information and specify the level (xxx) in the form item for level
  - If your lab reports the specific concentration (eg, 103 mg/dL), leave the prefix item blank and specify the level in the form item for level
  - If the concentration is greater than 100 mg/dL (greater than 100 mg% , greater than 1 mg/mL, or greater than 19 µM), then check choice 1 in the phenotype item on the Blood Values (BV) form (choice 1=concentration >100 mg/dL); otherwise phenotype is specified as ZZ, MZ, MM, SS, SZ, Null or other. If you specify the phenotype as other, be sure to hand write the phenotype carefully so that S, Z, 2 and other similar characters are not confused

Serum cotinine

- Part of Core data collection
- Visits sb and f12
- Covered by Medicare
- Omit cotinine testing if:
  - Patient reports smoking tobacco products
  - Patient reports chewing tobacco
  - Patient reports using nicotine products (e.g., gum, lozenge, patch, inhaler, nasal spray)
- Follow your usual local protocol for serum cotinine testing
- If your lab returns results electronically, print a copy of the lab report

5.5. Hemoglobin, hematocrit, A1AT, cotinine

- Attach lab report or printout to back of the Blood Values (BV) form
- Record results on the Blood Values (BV) form
  - If your lab reports the cotinine as >xxx or <xxx where xxx is some level, specify the appropriate prefix (> or <) in the form item for this information and specify the level (xxx) in the form item for level
  - If your lab reports the specific level (eg, 14 ng/mL), leave the prefix item blank and specify the level in the form item for level

5.6 DNA, plasma, and serum banking

Purpose
- Obtain whole blood sample from which DNA will be obtained and banked for use later in LOTT or in approved LOTT ancillary studies
- Obtain whole blood sample from which plasma and DNA will be obtained and banked for use later in LOTT or in approved LOTT ancillary studies
- Obtain whole blood sample from which serum will be obtained and banked for use later in LOTT or in approved LOTT ancillary studies

Data collection level
- DNA – Core
- Plasma – Core
- Serum – Expanded

When
- Visit sb
- Blood may be redrawn during followup for DNA banking if the yield from the initial draw was inadequate – use the extra labels at the bottom of the f12 visit label page
- Ship blood daily to the Channing Laboratory, except when it is collected on a Friday or the day before a holiday; in that case, refrigerate at 4°C and ship on the next business day; if you cannot refrigerate at 4°C, then store the Paxgene and EDTA tubes in the shipper with a frozen cold pak (be sure to put the egg foam cushion between the tubes and pak; we do not want the Paxgene and EDTA tubes to freeze since that will result in hemolysis) or at room temperature; the serum shipment tube may be stored in a -19°C freezer until the next business day

Who
- Clinical Coordinator
- Local site phlebotomist
- Person preparing shipment must have DOT/IATA training in the shipping of Biological Substances, Category B

Forms and Flash Cards
- Flash Card #11 (to determine tubes to draw in accordance with patient's consent for specimen banking)
- Blood Collection for DNA, Plasma, and Serum Banking (BC) form (to document collection)
- Specimen Shipment Log (SS) form

Tubes, labels, and equipment
- 8.5 mL PAXgene tube (provided by the DCC; QIAGEN Cat# 761115)
- 10 mL purple top EDTA tube (provided by the DCC, Fisher Cat # 02-657-32, BD 366643)
- 10 mL red top tube (provided by the DCC, Fisher Cat # 02-685-112, BD 367820)
- 4.5 mL cryovial serum shipment tube (provided by the DCC, Nunc Cat # 337516)
- Foam sleeves for tubes (provided by the DCC; UFP Technologies, Foam Pouches/Sleeves, 5 x 1½", 978-352-2200, info@ufpt.com)
- Tube and form labels for each patient (provided by the DCC)
- Swinging bucket centrifuge or centrifuge with fixed angle rotor heads and capacity to refrigerate specimens during processing. If a site does not have a refrigerated centrifuge, it is preferable to spin with a non refrigerated centrifuge than to leave the specimen unspun. (provided by the site)
- Shipper (provided by the Channing Lab) consisting of:
  - Cardboard shipper box with appropriate IATA labels printed on the sides of the shipper

- Polystyrene cooler
- U-tek cold pack
- Eggshell foam
- Sealing plastic biohazard specimen bag with 3 DriMop dessicant envelopes

Procedure

- Determine the tubes to collect for the patient based on their consent for specimen collection and Flash Card #11
- Label the PAXgene, EDTA, red top, and/or serum shipment tubes with the patient's tube labels.
- Fill one labeled 8.5 mL PAXgene tube with whole blood, invert 6 times to mix blood and additives, and refrigerate at 4°C until ready to pack specimen in shipper.
- Fill one labeled 10 mL EDTA tube with whole blood, invert 6 times to mix blood and additives, and refrigerate at 4°C until ready to pack specimen in shipper.
- Fill one labeled 10 mL red top tube with whole blood and let clot for 2-4 hours at room temperature. Spin for 10 minutes at 2000 rpm using either a swinging bucket centrifuge or centrifuge with fixed angle rotor heads and capacity to refrigerate specimen to 4°C during processing. Pour off serum into the labeled 4.5 mL serum shipment tube. Refrigerate serum specimen at 4°C until ready to pack specimen in shipper.

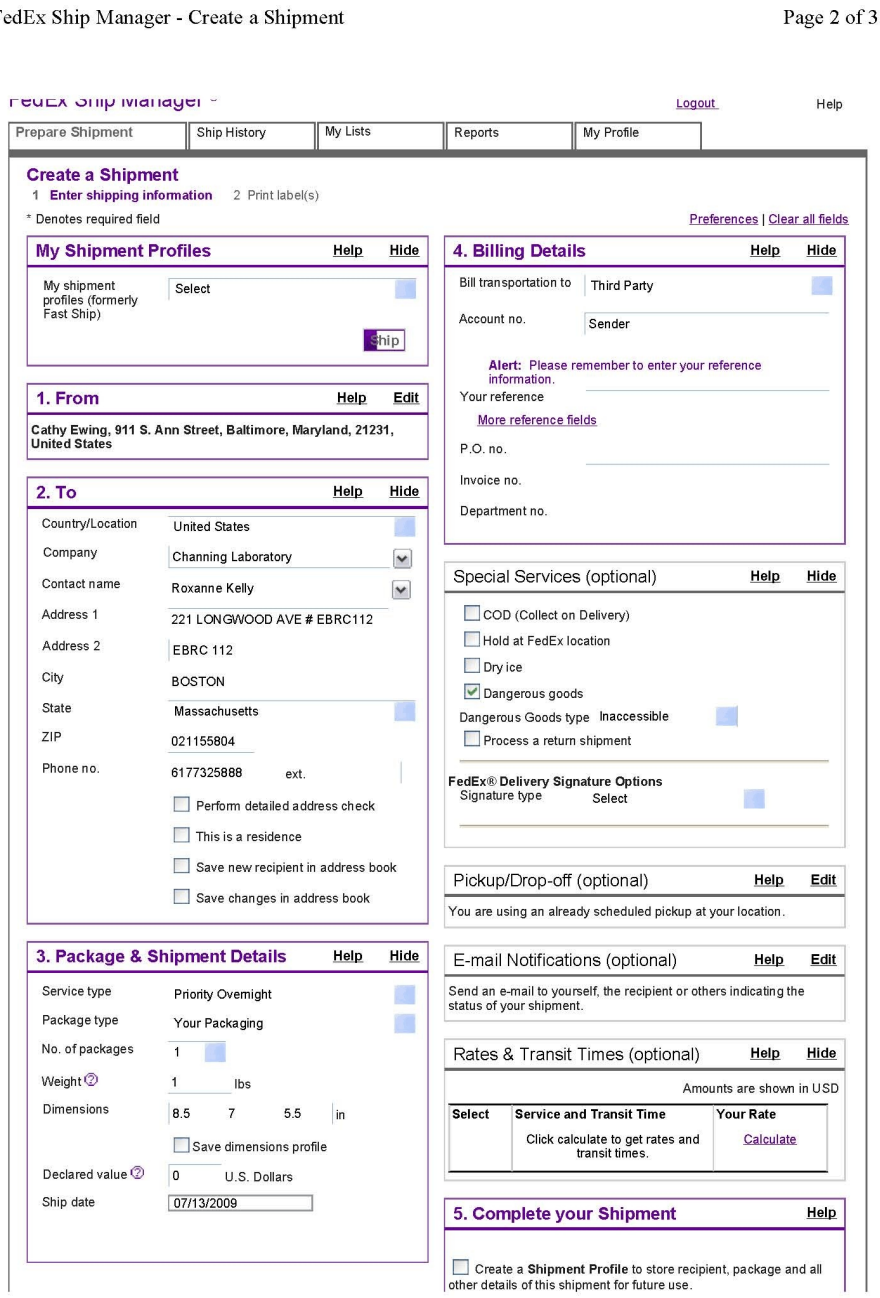
  Note: If the site does not have a refrigerated centrifuge, it is acceptable to spin the red top tube with an unrefrigerated centrifuge.
- Packing and shipping instructions:
  - Person preparing shipment must have DOT/IATA training in the shipping of Biological Substances, Category B
  - Each shipper can hold up to 9 tubes. Ship tubes daily Monday through Thursday. Hold specimens collected on Friday until the following Monday (refrigerate specimens at 4°C until shipment). Complete one Specimen Shipment Log (SS) form per shipper shipped.
  - Make sure the cold pak that came with the shipper has been frozen overnight at -20°C.
  - Make sure the plastic biohazard specimen bag contains 3 dessicant Dri Mop envelopes.
  - Load each tube into a foam sleeve, and place tubes inside the plastic bag provided with the shipper. Press out any air and press the seal on the bag closed. You may ship tubes for more than one patient in the same plastic bag.
  - Place the frozen U-tek cold pack in the bottom of the polystyrene cooler, place the eggshell foam on top of the cold pack, egg shell side up, and place the plastic bag of tubes on top of the cold pack. Place the lid on the polystyrene cooler. Tape the cooler shut.
  - Place the shipment log on top of the polystyrene cooler and slide both into the cardboard shipper box. Lock the box shut with the tabs.
  - Prepare an **overnight, next am (no later than 10:30 am) delivery** airbill for the shipment:
    - Address the shipment to:

      Roxanne Kelly
      Channing Laboratory
      221 Longwood Avenue, EBRC 112
      Boston, MA 02115-5804
      617-732-5888
    - The airbill should indicate Priority delivery (next am delivery), Other packaging (ie, Federal Express or other courier service's own packaging is not being used), Dangerous goods, shipper declaration not required, and Accessible goods (this checkoff is used on the online Federal Express airbill). Declared value is $0. Shipping charges are billed to the sender and are paid out of the site's LOTT funds. Sample airbills for Federal Express shipment are shown below.
    - Affix the airbill pouch to the top side of the shipper box, making sure that the UN3373, Biohazard, and Biological Substance Category B labels on the box are all fully visible.
  - Contact overnight delivery service for pickup of shipper.
  - Ship daily except do not ship on Fridays or the day before national holidays. If specimens are

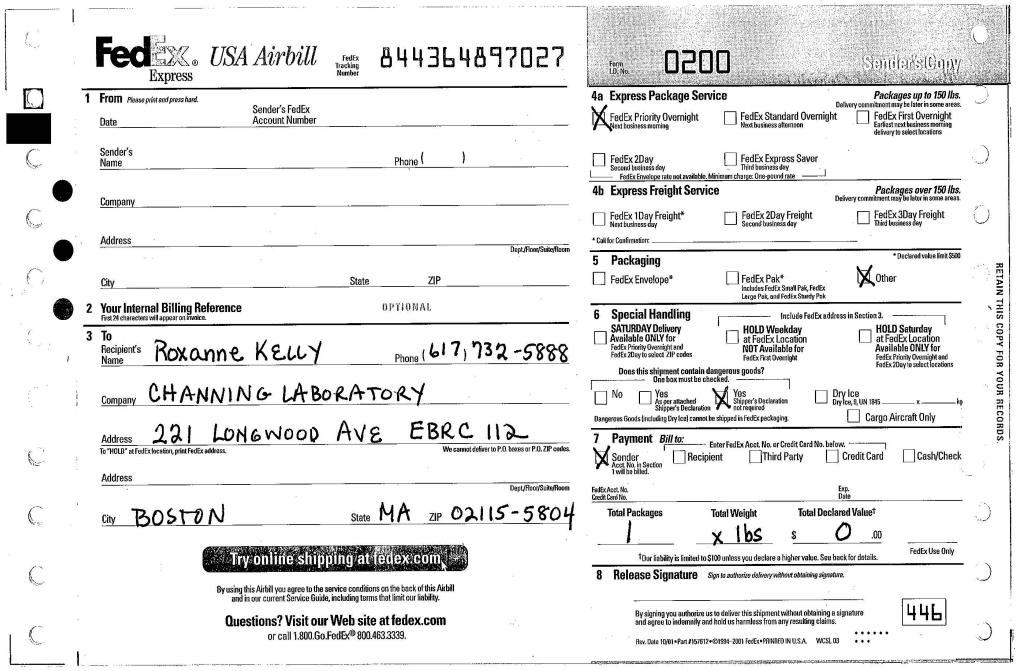
collected on Friday or the day before a national holiday, refrigerate the tubes at 4°C until shipment on the next business day; if you cannot refrigerate at 4°C, then store the Paxgene and EDTA tubes in the shipper with a frozen cold pak (be sure to put the egg foam cushion between the tubes and pak; we do not want the Paxgene and EDTA tubes to freeze since that will result in hemolysis) or at room temperature; the serum shipment tube may be stored in a -19°C freezer until the next business day.

If a patient changes their consent after specimens have been sent to the Channing Laboratory

- Complete a new Consent Documentation for DNA, Serum, and Plasma Banking (DC) form and key it to the data system
- The DCC will transmit the permissions for the patient's samples to the Channing Laboratory; any specimens remaining at the time consent for a specimen is withdrawn (via the newly keyed DC form) will be destroyed by the Channing Lab



https://www.fedex.com/shipping/shipEntryAction.do?method=doEntry&locale=en_us&url... 7/12/2009



FedEx Express USA Airbill FedEx Tracking Number 844364897027

Form I.D. No. 0200 Sender's Copy

1 From Please print and press hard.
Date
Sender's FedEx Account Number
Sender's Name
Phone ( )
Company
Address
Dept./Floor/Suite/Room
City State ZIP

2 Your Internal Billing Reference
First 24 characters will appear on invoice. OPTIONAL

3 To
Recipient's Name Roxanne KELLY Phone (617) 732-5888
Company CHANNING LABORATORY
Address 221 LONGWOOD AVE EBRC 112
To "HOLD" at FedEx location, print FedEx address. We cannot deliver to P.O. boxes or P.O. ZIP codes.
Address
Dept./Floor/Suite/Room
City BOSTON State MA ZIP 02115-5804

Try online shipping at fedex.com

By using this Airbill you agree to the service conditions on the back of this Airbill and in our current Service Guide, including terms that limit our liability.

Questions? Visit our Web site at fedex.com or call 1.800.Go.FedEx® 800.463.3339.

4a Express Package Service — Packages up to 150 lbs. Delivery commitment may be later in some areas.
[X] FedEx Priority Overnight Next business morning
[ ] FedEx Standard Overnight Next business afternoon
[ ] FedEx First Overnight Earliest next business morning delivery to select locations
[ ] FedEx 2Day Second business day
[ ] FedEx Express Saver Third business day
FedEx Envelope rate not available. Minimum charge: One-pound rate

4b Express Freight Service — Packages over 150 lbs. Delivery commitment may be later in some areas.
[ ] FedEx 1Day Freight* Next business day
[ ] FedEx 2Day Freight Second business day
[ ] FedEx 3Day Freight Third business day
* Call for Confirmation:

5 Packaging * Declared value limit $500
[ ] FedEx Envelope*
[ ] FedEx Pak* Includes FedEx Small Pak, FedEx Large Pak, and FedEx Sturdy Pak
[X] Other

6 Special Handling — Include FedEx address in Section 3.
[ ] SATURDAY Delivery Available ONLY for FedEx Priority Overnight and FedEx 2Day to select ZIP codes
[ ] HOLD Weekday at FedEx Location NOT Available for FedEx First Overnight
[ ] HOLD Saturday at FedEx Location Available ONLY for FedEx Priority Overnight and FedEx 2Day to select locations

Does this shipment contain dangerous goods? One box must be checked.
[ ] No
[ ] Yes As per attached Shipper's Declaration
[X] Yes Shipper's Declaration not required
[ ] Dry Ice Dry Ice, 9, UN 1845 ____ x ____ kg
Dangerous Goods (including Dry Ice) cannot be shipped in FedEx packaging.
[ ] Cargo Aircraft Only

7 Payment Bill to: Enter FedEx Acct. No. or Credit Card No. below.
[X] Sender Acct. No. in Section 1 will be billed.
[ ] Recipient
[ ] Third Party
[ ] Credit Card
[ ] Cash/Check
FedEx Acct. No. / Credit Card No. Exp. Date

Total Packages: 1 Total Weight: x lbs Total Declared Value†: $ 0 .00
†Our liability is limited to $100 unless you declare a higher value. See back for details.
FedEx Use Only

8 Release Signature Sign to authorize delivery without obtaining signature.
By signing you authorize us to deliver this shipment without obtaining a signature and agree to indemnify and hold us harmless from any resulting claims.

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5.7 Room air resting oximetry

Data collection level
- Core

When
- Visit sb (no more than 60 days prior to randomization)
- Visits f12, f24, f36, f48, f60, and f72
- Visit code n if checking resting saturation between annual visits
- Room air resting oximetry must be done before the room air 6 minute walk.
- Room air resting oximetry must be done before the patient has their resting or ambulatory oxygen prescription checked.
- Clinics may use their discretion with respect to sequencing of other procedures except that patient must rest at least 15 minutes off oxygen immediately prior to room air resting oximetry.

Who
- All patients (Core data collection)
- Oximetry Technician

Equipment
- Masimo Radical 7 oximeter (handheld and docking station)
- Reusable DCI adult finger sensor
- Reusable TFI forehead sensor, single use adhesive pad, and headband (use if you cannot get a good reading with the finger sensor)
- LOTT laptop computer (Dell D630 or E6400) with mouse and printer
- Serial cable (LOTT R7-to-PC cable) and, if applicable, USB2.0 to RS232 serial adapter
  - For D630 laptops: This cable connects the oximeter to the laptop
  - For E6400 laptops: This cable connects the oximeter to the serial adapter which connects to the laptop

Forms
- Room Air Resting Oximetry (MO) form

Patient preparation
- Explain that the test will measure the level of oxygen in the blood while the patient is breathing room air and sitting quietly; the sensor is placed on a finger and uses light beams to measure the oxygen level, not a needle
- All fingernail polish (including clear polish) must be removed from the finger on which the sensor will be placed.
- The finger should be washed clean of ink stains, paint, or other substances that could impede the sensor.
- Instruct patient that he/she is to rest quietly with minimal talking for 15 minutes prior to the test and should not talk during the test and should not hyperventilate or used pursed lips breathing

Oximeter/computer system preparation
- Unless you are sure that the laptop is adequately charged, plug the laptop into an outlet using the power supply cord
- Insert the Radical 7 handheld into the docking station and connect the docking station to the laptop using the serial cable (LOTT R7 to PC cable) and, if applicable, serial adapter.
  - On the D630 laptop, the serial port on the laptop is in the middle of the back edge.

- The E6400 laptop does not have a serial port and you need to plug the USB2.0 to RS232 adapter into the Serial-to-USB port on the laptop (top left USB port)
- The serial port on the back of the docking station is labeled RS232
- The cable ends are different, so there is only one way that the end match up with these ports; if you can plug in the cable, it is plugged in correctly.

• Plug the docking station power cord into the back of the docking station and into an outlet.
• Insert the DCI finger sensor directly into the handheld; the forehead sensor plugs into the DC10 cable which plugs into the handheld.
• The printer connects to the laptop using the HP USB cable and plugs into the laptop USB port labeled "Printer" and the back of the printer. The printer power supply will need to be plugged into an outlet.
• The mouse plugs into the laptop USB port labeled "Mouse".
• Power up the laptop and enter passwords; start the LOTT oximetry program by clicking on the LOTT Oximetry icon on the laptop desktop
• Note the oximeter handheld ID number and docking station number on the MO form

Procedure

• **Rest period:** The patient should be off oxygen and sitting in a chair and breathing room air for 15 minutes. During the rest period the patient should be seated and quiet (not chatting), but does not need to be isolated from his/her family.
• **From the Pulse Oximetry screen, click on Resting Evaluation** and enter the patient/session identification information: select your RCC code (note: each satellite will select their RCC's code) and enter the patient ID number and patient code, testing date in ddmmmyy format, visit code (sb, f12, f24, f36, f48, f60, f72 or n), and Radical 7 handheld ID number. Upper or lower case can be used. Be very careful to enter the information correctly as there are few checks on the information keyed on this screen.
• **The patient should be seated and the reusable DCI probe should be placed on one of the patient's fingers**. The finger should be free of nail polish, paint, and other substances that could interfere with testing. The patient should rest his/her hand on a table or his/her lap.
• Click "Begin" to begin the Stabilization Phase; readings should appear on the handheld display and on the Current data bar of the laptop screen and in the Incoming raw data window of the laptop screen
• **If the oximeter is unable to detect an adequate signal using a finger probe**, check for common problems (such as a clenched fist, poorly placed probe, fingernail polish, etc). If the oximeter still does not detect an adequate signal, other fingers should be tried. If the oximeter is unable to detect an adequate signal on any finger, the forehead sensor may be used. Using a forehead sensor should be a last resort effort for obtaining an adequate signal.
• **When patient and Oximetry Technician are ready and the oximetry reading on the laptop screen is stable, note the time on the handheld screen and click on the "Begin Evaluation" button on the Stabilization Phase screen**. The Evaluation Phase screen will appear. The time remaining for the evaluation will be displayed (ie, counting down from 6 minutes). The Current data bar will show the current reading and the Incoming raw data window will show the raw readings. The Technician should record the time noted on the handheld display as the test start time on Form MO.
• During the session, the Oximetry Technician should monitor the patient, oximeter, and laptop screen for problems. The Oximetry Technician should remain alert to sensor malfunction and reposition the sensor as needed.
• **Early termination of session:** If saturation remains below 85% for more than 2 minutes, the session should be stopped. A warning in large red font will appear on the laptop screen in above the Current data bar.

- **When the testing session is complete, the Results screen will show on the laptop.** This screen includes 4 components: identification information for the patient and test session, the test results, summary statistics for the session and its readings, and a graph of the SpO_2 over time. The Results component includes 3 assessments: Evaluation, SpO_2, and Result. Evaluation is an assessment of the quality of the session readings (Quality Acceptable or Quality Not Acceptable). SpO_2 is the summary oxygen saturation for the session. For visit sb sessions, Result will be Eligible for LOTT or Ineligible for LOTT. For visit fxx sessions, the Result will be Meets Conventional Medicare Criteria for Oxygen or Does Not Meet Conventional Medicare Criteria for Oxygen. Print the report as instructed by the program and remove the probe from the patient's finger and attach it to the back of the MO form.
- **Click OK and then click Quit to exit the program and to be able to start a new session for the same patient or a different patient.** You must exit to the desktop and click on the LOTT Oximetry icon to start a new session, even if this is a repeat session for the same patient or if you want now to do a different type of session for the same patient.

Retesting if session has unacceptable quality

- **During screening:** If the session has unacceptable quality, the patient may be retested up to 2 more times that day. If 3 sessions on one day are all unacceptable, the Study Physician should review the printed reports and any other information available about the patient and decide if the patient may be retested on another day.
- **During followup:** If the session has unacceptable quality, the patient may be retested up to 2 more times that day. If 3 sessions on one day are all unacceptable, then indicate that on Form MO; additional retesting is not required; however, the Study Physician should use best medical judgment to determine if the patient has become severely hypoxemic at rest and should be started on 24-hour oxygen if not already using 24-hour oxygen.

Eligibility criterion related to resting oxygenation

- If the session is acceptable in quality and is a screening session, the summary oxygenation value is compared to the eligibility criterion (89-93%) to determine eligibility with respect to resting oxygenation.

Followup criterion for meeting conventional Medicare criteria for 24-hour oxygen

- If the session is acceptable in quality and is a followup session, the summary oxygenation value is compared to the Medicare criterion for starting 24-hour oxygen at rest (88% or less). If resting saturation is 88% or less, the patient should be informed of this finding and the patient should be prescribed 24-hour oxygen (by the study physician or patient's pulmonary care provider).

Algorithm incorporated into computerized determination of acceptability and summary value from resting room air oximetry

- Test sessions must last 6 minutes; a test session that lasts less than 6 minutes is unacceptable.
- The sampling rate is once every second.
- The first 60 readings are ignored.
- Poor quality data points in the remaining 5 minutes of testing (300 readings) are ignored. If more than 100 of the remaining 300 data points are of poor quality, the session is unacceptable.
- The mean and standard deviation of the acceptable quality data points are calculated
- The coefficient of variation, expressed as a percent ((standard deviation divided by the mean) x 100) is calculated.

- If the coefficient of variation for the session is greater than 2.5%, the session is considered to be of unacceptable quality. If the coefficient of variation is 2.5% or less, the session is considered acceptable and the mean saturation is the summary saturation for the session.

Oximetry analysis notes

- Resting data are sampled every second (60/minute)
- SpO2 on the resting report is the lowest one-minute average, selected out of all the one-minute periods with at least 20 valid data points; if data quality for the resting session is unacceptable, SpO2 prints as -1

Practice oximetry sessions

- Use ID number xx000 (where xx is your site's ID number prefix) for all practice sessions
- You may use any 4 character alphabetic code for the practice patient code

5.8 Room air six minute walk with oximetry

Data collection level
- Core.

When
- Visit sb (no more than 60 days prior to randomization).
- Visits f12, f24, f36, f48, f60, and f72
- Visit code n if checking exercise saturation between annual visits
- Room air resting oximetry must be done before the room air 6 minute walk.
- Clinics may use their discretion with respect to sequencing of other procedures except that patient must rest at least 10 minutes off oxygen immediately prior to the room air six minute walk.

Who
- Core (all patients).
- Six Minute Walk Tester (must be certified in cardiopulmonary resuscitation with a minimum of Basic Life Support by an American Health Association-approved cardiopulmonary resuscitation course).
- Physician attendance is not required, but a physician needs to be available (the physician does not need to be a LOTT Study Physician).
- If physician review of 6 minute walk data is required or if the walk has an abnormal termination, only the LOTT Study Physician may rule the patient eligible

Contraindications for doing the 6 minute walk in LOTT
- **Absolute contraindications**
  - Resting room air oxygen saturation less than 80%.
  - Unstable angina in previous month.
  - Myocardial infarction in previous month.
  - Pulmonary limitation that precludes walking
  - Non pulmonary limitation that precludes walking
- **Relative contraindications (Study Physician must approve proceeding with walk)**
  - Resting heart rate greater than 120 beats/minute (Study Physician must review an EKG done in the previous 6 months).
  - Systolic blood pressure greater than 180 mm Hg (Study Physician must review an EKG done in the previous 6 months).
  - Diastolic blood pressure greater than 100 mm Hg (Study Physician must review an EKG done in the previous 6 months).
  - Resting room air oximetry test did not have a normal termination by the Oximetry Technician.
- **Patients with exertional angina**
  - May not complete the 6 minute walk if the angina is not stable (consult the supervising physician if you are unsure of the patient's angina status)
  - If the patient takes medication regularly for angina, the patient must have taken his/her usual medication; otherwise the patient may not complete the walk
  - The patient should not take any rescue angina medication before the walk, but the rescue angina medication must be available; if not available, the walk may not be completed
- If the patient has an absolute contraindication to doing the 6 minute walk or the Study Physician disapproves a patient with a relative contraindication doing the 6 minute walk, the MM form must still be completed to document the reason for missing the 6 minute walk
- Patient safety is paramount; the walk should not be done if there is any concern that completing the walk or collection of the walk data would endanger the patient

Use of aids during testing
- Patients should use their usual walking aids (e.g., cane, walker, crutches) during the walk.

5.8. Room air six minute walk with oximetry

Walk course

- To the extent possible, the conditions of the course should be identical on serial tests; if the site changes location, the site should try to replicate the layout and conditions of the original 6 minute walk course at the new location.
- The path should be unobstructed, flat, indoors, and at least 100 feet (30 meters) long.
- If a public corridor is used, ability to control traffic should be assured so that conditions are not changed between serial tests.
- At time of site certification, each site is asked to diagram each course that they will use.
- If the patient has to change direction on the course (e.g., a straight course versus a round course), small cones should be placed at those points to alert the patient to the need to turn.

Equipment

- Masimo Radical 7 handheld oximeter.
- DCI reusable finger sensor or TF1 forehead sensor and adhesive pad.
- Adhesive tape.
- Waist pack to hold the oximeter.
- External clock (eg, wall clock or Tester's watch)
- Timer or stopwatch.
- Ruler or measuring tape.
- Small cones to mark turn around points (if applicable).
- Chair that can be easily moved along the course.
- A source of oxygen.
- Sphygmomanometer.
- Telephone.
- Automated electronic defibrillator and/or access to crash cart.
- Rescue medications including oxygen, sublingual nitroglycerine, aspirin, and albuterol (metered dose inhaler or nebulizer).
- Radical 7 docking station
- LOTT Dell D630 or E6400 laptop computer with mouse and printer
- Serial cable (LOTT R7-to-PC cable) and, if applicable, USB2.0 to RS232 serial adapter
  - For D630 laptops: This cable connects the oximeter to the laptop
  - For E6400 laptops: This cable connects the oximeter to the serial adapter which connects to the laptop

Forms/Flash cards

- LOTT Room Air 6 Minute Walk (MM) form.
- LOTT Flash Card #6, Instructions for Patients During 6 Minute Walk Test.
- LOTT Flash Card #7, Perceived Symptom (Borg) Scale.

Patient preparation

- Explain that the test will measure the level of oxygen in the blood while the patient is breathing room air and walking; the sensor is placed on a finger and uses light beams to measure the oxygen level, not a needle
- All fingernail polish (including clear polish) must be removed from the finger on which the sensor will be placed.
- The finger should be washed clean of ink stains, paint, or other substances that could impede the sensor.
- The patient should wear comfortable clothing and shoes appropriate for walking.
- The patient should continue his/her usual medication regimen on the day of the walk.
- The patient should not have exercised vigorously within 2 hours of starting the test.
- A light meal at least 2 hours and no more than 4 hours prior to testing is advised.

5.8. Room air six minute walk with oximetry

Walking behind the patient

- In most circumstances, it is appropriate for the Six Minute Walk Tester to stand at one end of the course or on the side of the course so that the patient can be observed at all times; in this situation the oximeter is carried by the patient in the fanny pack
- In some very breathless or frail patients or those with particular difficulty with ambulation, it is permissible for the Tester to walk behind the patient and hold the oximeter. In these circumstances, the tester should be sure not to pace the patient nor to coach the patient except as specified in the LOT T script for 6 minute walks

Procedure

- Charge the Radical 7 handheld if you are not sure of its charge lasting the duration of the session.
- Clear the Radical 7 memory (if all walks in memory have been transferred and processed)
- Verify that the Radical 7 handheld is showing the correct date and time.
- Make sure handheld has been turned off after the resting session - the off, on cycle is a marker between sessions
- The patient should rest in a chair near the starting point of the walk and breathing room air for 10 minutes immediately before starting the test. During this time, the Six Minute Walk Tester should check for contraindications, measure blood pressure and pulse, and check patient preparation conditions.
- Simultaneously note the time on the oximeter display and the time on the clock with which you will time the patient's walk (eg, your watch or a wall clock); write down both times. This will identify any discrepancy in the oximeter's internal clock and the clock on which you will note the time that the patient started walking
- Plug the sensor cable into the handheld. Place the sensor on the patient's finger and check that the oximeter is detecting the saturaiton. Tape the sensor in place if necessary to get a consistently good signal.
- If the oximeter is unable to detect an adequate signal using a finger sensor, check for common problems (such as a clenched fist, poorly placed sensor, fingernail polish, etc). If the oximeter still does not detect an adequate signal, other fingers should be tried. If the oximeter is unable to detect an adequate signal on any finger, a forehead sensor may be used.
- When you are sure the handheld is operating properly, place the handheld in the waist pack, and put the waist pack around the patient's waist.
- Explain that although we want the patient to walk as far as the patient can in 6 minutes, the patient may stop and rest as needed during the walk
- Have the patient stand and rate their baseline shortness of breath and overall fatigue using the Borg Scale (Flash Card #7). Show the patient Flash Card #7 and ask the patient: "Please grade your level of shortness of breath using this scale. Zero means no shortness of breath, 10 means the most breathless you have ever felt." Then ask the patient: "Please grade your level of fatigue using this scale. Zero means no fatigue, 10 means the most fatigue you have ever felt." Inform the patient that they will be asked to describe their shortness of breath and fatigue in a similar fashion at the end of the test.
- Set the timer/stopwatch and set the lap counter. Assemble all equipment (lap counter, timer/stopwatch, Flash Cards, forms, tape or bean bag, chair).
- Move the patient to the start of the course and instruct the patient as follows (outlined on LOTT Flash Card #6):

  "The object of this test is to walk as far as possible for 6 minutes. You will walk back and forth in this hallway [or around and around this course if applicable]. Six minutes is a long time to walk, so you will be exerting yourself. You are permitted to slow down, to stop, and to rest as necessary. You may lean against the wall while resting, but resume walking as soon as you are able.

You will be walking back and forth around the cones [or around and around]. You should pivot briskly around the cones and continue back the other way without hesitation. Now I'm going to show you. Please watch the way I walk without hesitation."

Demonstrate by walking one lap yourself. Walk and pivot around a cone briskly.

"Are you ready to do that? I am going to use this counter to keep track of the number of laps that you complete. I will click it each time you turn around at [cross] this starting line. Remember that the object is to walk as far as possible for 6 minutes, but don't run or jog."

- Tell the patient: "Start now or whenever you are ready."
- As soon as the patient starts walking, start the timer or stop watch and note and write down the time on the same clock that you used in the previous step when you noted the time on the oximeter display and a separate clock.
- Stand near the starting line during the test. Do not walk with the patient.
- Each time the patient returns to the starting line, click the lap counter once (or mark the lap on the worksheet area of Form MM). Let the patient see you do it.
- At the end of each minute and using an even tone of voice, give the patient the following standard statements:

End of minute 1(timer shows 5 minutes left):	"You are doing well. You have 5 minutes to go."
End of minute 2 (timer shows 4 minutes left):	"Keep up the good work. You have 4 minutes to go."
End of minute 3 (timer shows 3 minutes left):	"You are doing well. You are halfway done."
End of minute 4 (timer shows 2 minutes left):	"Keep up the good work. You have only 2 minutes left."
End of minute 5 (timer shows 1 minute left):	"You are doing well. You have only 1 minute to go."

When the timer is 15 seconds from completion, tell the patient "In a moment I'm going to tell you to stop. When I do, just stop right where you are and I will come to you".

When the timer rings or buzzes, tell the patient: "Stop!" and walk over to the patient. Take the chair if the patient looks exhausted. Mark the spot where they stopped by placing a bean bag or piece of tape on the floor.

If the patient stops walking during the test and needs a rest, tell the patient: "You can lean against the wall if you would like; then continue walking whenever you feel able." Do not stop the timer.

If the patient stops before the 6 minutes are up and refuses to continue (or you decide that they should not continue), move the chair over for the patient to sit on, discontinue the walk, mark the spot where the patient stopped, and record the reason for stopping prematurely.

- Borg scale ratings of shortness of breath and fatigue are obtained if the 6 minute walk test terminates normally (i.e., the patient is on the course for 6 minutes, regardless of rest periods). Remind the patient of the shortness of breath rating that they chose before the walk and ask the patient to grade their shortness of breath level again. Remind the patient of their overall fatigue rating before the walk and ask the patient to grade their level of fatigue again. Showing the patient the Borg Scale (Flash Card #7), say: "Please grade your level of shortness of breath using this scale. Zero means no shortness of breath, 10 means the most breathless you have ever felt." Then ask the patient: "Please grade your level of fatigue using this scale. Zero means no fatigue, 10 means the most fatigue you have ever felt."

- Congratulate the patient on good effort and offer a drink of water.
- Record the additional distance completed in the final partial lap in the worksheet area of Form MM, compute the total distance walked, and finish completing Form MM regardless of normal or abnormal termination of the walk.
- Rest periods are not recorded; a test lasts 6 minutes if the patient is on the course for 6 minutes; the patient need not walk continuously for 6 minutes for the walk to be considered to have a normal termination.
- If the walk is terminated before 6 minutes have elapsed, clinic staff may use their judgment whether to retest the patient on another day or whether to declare the data missing. Ordinarily, it would be inappropriate to attempt to complete a 6 minute walk more than 3 times.
- Download the oximetry data to the LOTT laptop.

Stopping a walk early

- Reasons for stopping a walk immediately
  - Chest pain
  - Intolerable dyspnea
  - Leg cramps
  - Staggering
  - Diaphoresis
  - Pale or ashen appearance
  - Tester's judgment that it is unsafe to continue
- There are no specific limits of oxygen saturation or heart rate that automatically mandate cessation of the test; the Tester is to observe the patient throughout the walk for clinical signs of severe desaturation or tachycardia.
- If there is doubt whether a test should be stopped early because of patient symptoms, it is better to err on the side of safety and stop the test early
- Have a chair available near the course for the patient to sit in and recover
- If a severe prolonged desaturation occurs, consult with the supervising physician as needed and treat the patient as needed, eg, provide supplemental oxygen

Transfer data to LOTT laptop

- Unless you are sure that the laptop is adequately charged, plug the laptop into an outlet using the power supply cord
- Insert the Radical 7 handheld into the docking station and connect the docking station to the laptop using the serial cable (LOTT R7 to PC cable) and, if applicable, serial adapter.
  - On the D630 laptop, the serial port on the laptop is in the middle of the back edge.
  - The E6400 laptop does not have a serial port and you need to plug the USB2.0 to RS232 adapter into the Serial-to-USB port on the laptop (top left USB port)
  - The serial port on the back of the docking station is labeled RS232
  - The cable ends are different, so there is only one way that the end match up with these ports; if you can plug in the cable, it is plugged in correctly.
- Plug the docking station power cord into the back of the docking station and into an outlet.
- The printer connects to the laptop using the HP USB cable; the cable plugs into the USB port labeled "Printer" and the back of the printer. The printer power supply will need to be plugged into an outlet.
- The mouse plugs into the USB port labeled "Mouse".
- Power up the laptop and enter passwords; start the LOTT oximetry program by clicking on the LOTT Oximetry icon on the laptop desktop

- **From the Pulse Oximetry screen, click on Transfer 6MW Data** and enter the patient/session identification information: select your RCC code (note: each satellite will select their RCC's code) and enter the patient ID number and patient code, testing date in ddmmmyy format, visit code (sb, f12, f24, f36, f48, f60, f72, or n), and Radical 7 handheld ID number. Upper or lower case can be used. Be very careful to enter the information correctly as there are few checks on the information keyed on this screen. Click OK.
- After checking that the oximeter handheld and docking station and laptop are properly connected and the handheld is turned on and the handheld data screen has appeared, click "Begin". Data should immediately begin streaming and showing up in the Incoming Raw Data window.
- The yellow "Transfer Completed, Press Continue Button to Proceed" bar will appear when transfer is complete. Note that if there are a lot of data to transfer, the Incoming Raw Data may stop filling before transfer is complete. Just let transfer continue until the yellow Transfer Completed bar appears. Click Continue to proceed.
- Enter the date and approximate start time of this 6 minute walk. Enter the date in ddmmmyy format and the time (hours and minutes) in 24-hour clock format.
- The next screen will show the streams of data transferred (a stream is a set of data between powering the handheld on and off). Note that the date of collection, the duration of the stream, and the number of data points in each stream are specified to help you select the one that you want to evaluate. The graphical display on the right of the screen is the display for the highlighted stream. Click on the stream that includes the 6 minute walk data that you want to evaluate.
- On the next screen, slide the gray box to select the 6 minutes of actual walking. You can use the mouse to slide the box, or hold the left button of the touch pad down while dragging with the large button of the touch pad. The time of the starting data point for the gray box shows in the lower left corner of the screen. Using your knowledge of the discrepancy between the oximeter's internal clock and the clock that you used to note the time when the patient started walking (recorded on the MM form), calculate what the oximeter clock's equivalent to the time the patient started walking and move the gray box as needed until that time is displayed in the lower left corner of the screen. For example:

    - The oximeter's display (oximeter's internal clock) shows 08:30:20 at the same time as your watch says 08:31:10
    - Your watch says 08:35:15 when the patient starts walking
    - You move the gray box so that 08:34:25 shows in the lower left corner:
        - Oximeter is 50 seconds slower than your watch (08:31:10 - 50 seconds = 08:30:20)
        - 08:35:15 - 50 seconds = 08:35:00 - 35 seconds = 08:34:25

  Click Done when finished.
- The Results screen will show on the laptop. This screen includes 4 components: identification information for the patient and test session, the test results, summary statistics for the session and its readings, and a graph of the SpO_2 during the duration of the data stream with 2 vertical bars delineating the 6 minutes of walking. The Results component includes 3 assessments: Evaluation, Min SpO_2, and Result. Evaluation is an assessment of the quality of the session readings (Quality Acceptable or Quality Not Acceptable). Min SpO_2 is the lowest 1 minute average saturation. For visit sb, the Result will be 6MW Eligible for LOTT, Not 6MW Eligible for LOTT, Ineligible for LOTT, or Physician Review Needed to Determine Eligibility. For visit fxx sessions, the Result will be No Change in Exercise O2 Indicated, May Require Exercise O2, or Physician Review Required to Assess for Exercise O2. Print the report as instructed by the program and attach it to the back of the MM form.
- **Click OK and then click Quit to exit the program.** You must exit to the desktop and click on the LOTT Oximetry icon to start a new evaluation, even if you want to evaluate another of the streams of data just transferred. When data are transferred, only one test or evaluation can be processed, even if the laptop shows the data for other evaluations. If you want to process another evaluation, you will have to retransfer the oximeter's stored data. Do not clear trend memory until you have processed (and printed reports) for all tests performed on that handheld.

- **If the walk terminates abnormally but desaturation below 80% for at least 1 minute is not detected but desaturation below 90% for more than 10 seconds is detected and you want to enroll the patient,** the Study Physician must explain why the patient should not be considered to have exercise desaturation meeting the LOTT exclusion criterion

Eligibility evaluation with respect to the room air 6 minute walk: The patient must not have desaturated below 80% for at least 1 minute and must have desaturated below 90% for more than 10 seconds.

- The patient will be determined to have desaturated below 80% for at least 1 minute if any rolling average of 30 consecutive data points is less than 80% (that is, the data stream represents samples taken every 2 seconds; thus any 30 consecutive points represents 1 minute of continuous data; over 6 minutes, there will be 151 different sets of 30 data points [ie, points 1-30, 2-31, 3-32, ..., 151-180]; if anyone of those 151 means is below 80, the patient has desaturated). Unacceptable quality data points in the 30 points are discarded and the average is calculated from the good quality points remaining in the 30 data point stream; at least 20 of the 30 points in the stream have to be of good quality or the average calculated is ignored.
- The patient will be determined to have desaturated below 90% for more than 10 seconds if 5 consecutive, valid data points with saturation below 90% are observed; poor quality points may not be present in the stream of 5 consecutive, valid data points below 90%
- If desaturation below 80% for at least 1 minute is detected, the patient is ruled ineligible regardless of the quality of the remainder of the test session.
- The results of the assessment will be available only after the data from the 6 minute walk have been transferred from the handheld to the LOTT laptop.

Oximetry analysis notes

- 6 minute walk data are sampled every 2 seconds (30/minute)
- Min SpO2 on the 6MW report is the assessment for desaturation below 80%

Practice oximetry sessions

- Use ID number xx000 (where xx is your site's ID number prefix) for all practice sessions
- You may use any 4 character alphabetic code for the practice patient code

Reference

- ATS Statement: Guidelines for the Six-Minute Walk Test. *Am J Respir Crit Care Med* 2002;166:111-117.

5.9 Use, setup, maintenance, and operation of the LOTT oximetry system

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Appropriate use of the LOTT oximetry system

- In keeping with the security requirements in the LOTT contracts, the LOTT oximeters, the LOTT laptop, and the LOTT flash drive are to be used **only for LOTT oximetry practice, real LOTT oximetry sessions, and upload of data to the LOTT data system**. No other use is allowed. You may not use the laptop for other LOTT functions – you may not load other software onto the laptop.
- The LOTT oximetry files are designed not to allow input of name or identifying information other than LOTT ID number. The LOTT oximetry files on the laptop and flash drive are encrypted. Any other use of the LOTT laptop could compromise the confidentiality of patient identity and data. If you use the LOTT equipment properly and the laptop or flash drive is stolen, you will be able to report to the DCC and NHLBI that the only data on it are LOTT oximetry data which are encrypted and so are inaccessible to the thief. **It is extremely important that all LOTT staff adhere to the appropriate use guidelines specified above.**

Oximetry system components

- Dell D630 or E6400 laptop
- Printer
- HP ink cartridges 74 or 74XL and 75 or 75XL
- Radical 7 handheld
- Radical 7 docking station and power cord
- Serial RS232 cable (labeled "LOTT R7-to-PC cable") for connecting Radical 7 to D630 laptop directly and for connecting Radical 7 to E6400 laptop via the USB2.0 to RS232 serial adapter
- DCI sensor
- TF1 forehead sensor, adhesive pad, and headband
- LNCS patient cable LNC-10
- HP USB cable
- Wired mouse
- Flash drive
- Laptop lock
- Waist pack for holding Radical 7 handheld during 6 minute walk

Setup

- The D630 laptop latch opens by sliding it to the right; the E6400 laptop opens by pressing on the latch
- The laptop can be powered off by holding down the power button for 10 seconds – but be careful to let go of the power button when the laptop powers off or it will start powering up
- The laptop cover has labels for where the different cables and devices should be attached.
- The Radical 7 docking station connects to the laptop using the RS232 serial cable labeled "LOTT R7-to-PC cable"; plug one end into the RS232 port on the back of the docking station and plug the other end into the laptop port labeled "Serial" (D630 laptop) or into the serial cable adapter which then plugs into the laptop port labeled Serial to USB (E6400 laptop).
- The printer connects to the laptop using the HP USB cable; the cable plugs into the laptop port labeled "Printer" and the back of the printer.
- The flash drive plugs into the laptop port labeled "Flash drive".
- The mouse plugs into the laptop port labeled "Mouse".
- The DCI sensor plugs directly into the Radical 7 handheld
- The TF1 forehead sensor plugs into the LNCS 10' cable which plugs into the handheld

5.9. Use, setup, maintenance, and operation of the LOTT oximetry system

Passwords

- The passwords are case sensitive.
- When you boot the laptop, you will first be asked for the laptop userid and password.
- You are next asked for the TrueCrypt password.
- If the LOTT flash drive is plugged in, you will have to enter the TrueCrypt password a second time.
- The system userid and passwords should be kept confidential and shared only with LOTT staff who complete oximetry tasks.

Oximeter and laptop settings

- The Radical 7 handheld is set to ASCII 2 output mode.
- The Radical 7 handheld clock display is set to "on".
- Both the Radical 7 and laptop clocks and calendar are set to the current local time and date.
- Averaging time on the Radical 7 handheld is set to 8.

Practice sessions

- Use patient ID number xx000 (where xx is your site prefix) for all practices sessions
- You may use any 4 character alpha code for patient code
- Use visit code sb or one of the followup visit codes (f12, f24, f36, f48, n) for the practice sessions; try both types of visit code out to become familiar with the screening and followup report formats and messages.

Clearing trend memory on the Radical 7 handheld

- Power on the handheld (this gets you to the screen that works with the buttons mentioned below)
- **If the handheld is inserted into the docking station and the docking station is standing vertically (tall and narrow)**
  - Press the 4th button from the left and then press the 3rd button from the left to view the trend screen (the display will go sideways, as if docking station were short and fat, but leave it standing tall and narrow); let screen stabilize
  - Press the 4th button from the left twice until a trash can is displayed at the far left above the 1st button
  - Press the 1st button on the left to select the trash can and click the ✓button (1st button on left) to confirm that you want to clear memory
  - To get back to the upright vertical display, press the 4th button on the left and then press the 3rd button on the left; navigate to Rotate Screen and press the 3rd button on the left to select that menu; use the arrow keys to select Vertical1; the screen will reset to the vertical, upright display
- **If the handheld is inserted into the docking station and the docking station is standing horizontally (short and wide)**
  - Press the 4th button from the left and then press the 3rd button from the left to view the trend screen (the display will go sideways, as if docking station were short and fat, but leave it standing tall and narrow); let screen stabilize
  - Press the 4th button from the left twice until a trash can is displayed at the far left above the 1st button
  - Press the 1st button on the left to select the trash can and click the ✓button (1st button on left) to confirm that you want to clear memory
  - To get back to the upright vertical display, press the 4th button on the left and then press the 3rd button on the left; navigate to Rotate Screen and press the 3rd button on the left to select that menu; use the arrow keys to select Vertical1; the screen will reset to the vertical, upright display

5.9. Use, setup, maintenance, and operation of the LOTT oximetry system

Setting the clock and date on the Radical 7 handheld

- **Note: changing the clock or date on the handheld will clear trend data – do not do this if there are data on the handheld that need to be evaluated (and reports printed)**
- Power on the handheld (this gets you to the screen that works with the buttons mentioned below)
- **If the handheld is inserted into the docking station and the docking station is standing vertically (tall and narrow)**
  - Press the 3rd button from the left and then use the Down Arrow button to scroll to "Clock" and press the 3rd button from the left to select Clock
  - Use the Down Arrow button to navigate to the field of interest and use the 3rd button from the left to select the field and then use the Up and Down Arrow buttons to set the field to the desired setting (note: specify pm times as if using a 24-hour clock despite screen notation that we are using a 12-hour clock; display will be based on 12 hours, but you specify settings as if using a 24-hour display)
  - Press the ✓ button to select settings
  - Press the ⊠ button to exit
  - Press the ✓ button to confirm that trend data may be cleared
  - Press the ⊠ button to exit the Menu screen
- **If the handheld is inserted into the docking station and the docking station is standing horizontally (short and wide)**
  - Press the 3rd button from the left and then use the Down Arrow button to scroll to "Clock" and press the 3rd button from the left to select Clock
  - Use the Down Arrow button to navigate to the field of interest and use the 3rd button from the left to select the field and then use the Up and Down Arrow buttons to set the field to the desired setting (note: specify pm times as if using a 24-hour clock despite screen notation that we are using a 12-hour clock; display will be based on 12 hours, but you specify settings as if using a 24-hour display)
  - Press the ✓ button to select settings
  - Press the ⊠ button to exit
  - Press the ✓ button to confirm that trend data may be cleared
  - Press the ⊠ button to exit the Menu screen

Setting Clock display to On

- Power on the handheld (this gets you to the screen that works with the buttons mentioned below)
- **If the handheld is inserted into the docking station and the docking station is standing vertically (tall and narrow):**
  - Press the 3rd button from the left and then use the Down Arrow button to scroll to "Clock" and press the 3rd button from the left to select Clock
  - Use the Down Arrow button to navigate to Display Clock and use the 3rd button from the left to select the field and then use the Up and Down Arrow buttons to set the field to Yes
  - Press the ✓ button to select settings
  - Press the ⊠ button twice to exit

- **If the handheld is inserted into the docking station and the docking station is standing horizontally (short and wide):**
  - Press the 3rd button from the left and then use the Down Arrow button to scroll to "Clock" and press the 3rd button from the left to select Clock
  - Use the Down Arrow button to navigate to Display Clock and use the 3rd button from the left to select the field and then use the Up and Down Arrow buttons to set the field to Yes
  - Press the ✓ button to select settings
  - Press the ⊠ button twice to exit

Setting Output to ASCII 2

- Power on the handheld (this gets you to the screen that works with the buttons mentioned below)
- **If the handheld inserted into the docking station and the docking station is standing vertically (tall and narrow):**
  - Press the 3rd button from the left and then use the Down Arrow button to scroll to "Output" and press the 3rd button from the left to select Output
  - Use the Up/Down Arrow buttons to change the setting to ASCII 2 and press the 3rd button from the left to confirm the setting
  - Press the ⊠ button to exit
- **If the handheld inserted into the docking station and the docking station is standing horizontally (short and wide):**
  - Press the 3rd button from the left and then use the Down Arrow button to scroll to "Output" and press the 3rd button from the left to select Output
  - Use the Up/Down Arrow buttons to change the setting to ASCII 2 and press the 3rd button from the left to confirm the setting
  - Press the ⊠ button to exit

Setting averaging time to 8

- Power on the handheld (this gets you to the screen that works with the buttons mentioned below)
- **If the handheld is inserted into the docking station and the docking station is standing vertically (tall and narrow):**
  - Press the 3rd button from the left and then use the Down Arrow button to scroll to "General" and press the 3rd button from the left to select General
  - Averaging time is the first entry; use the Up/Down Arrow buttons to change the setting to 8 and press the 3rd button from the left to confirm the setting
  - Press the ⊠ button to exit
- **If the handheld is inserted into the docking station and the docking station is standing horizontally (short and wide):**
  - Press the 3rd button from the left and then use the Down Arrow button to scroll to "General" and press the 3rd button from the left to select General
  - Averaging time is the first entry; use the Up/Down Arrow buttons to change the setting to 8 and press the 3rd button from the left to confirm the setting
  - Press the ⊠ button to exit

Service

- If an oximeter needs service, please contact Alice Sternberg at the DCC (asternbe@jhsph.edu) with a description of the problem.
- If the laptop or printer needs service, contact Alice Sternberg at the DCC (asternbe@jhsph.edu) with a description of the problem, and the DCC will make a determination of the next step.

5.9. Use, setup, maintenance, and operation of the LOTT oximetry system

Additional supplies

- Oximeter cables, sensors, serial cables, adhesive pads for forehead sensor: These will be supplied by the DCC; contact Alice Sternberg (asternbe@jhsph.edu).
- Additional paper or ink cartridges: These will be supplied by your site. The printer takes HP cartridges 74 or 74XL and 75 or 75XL.

5.10 Oximetry tips and explanations

• Power off the handheld when not collecting data on a patient
- Power off when the sensor is not on a patient's finger – data accumulate in memory if the power is on; the data will be nonsense if the handheld is not being used with the patient, but the nonsense readings are in memory
- Power off between resting and 6MW sessions
- Try to make each power off interval last at least 60 seconds

• Resting oximetry report features
- The information that prints at the top of the report (RCC ID, Patient ID, Patient code, Date, Visit code, Handheld ID) is the information that you key to the LOTT Oximetry program when you initiate a resting evaluation session; be sure to key the information correctly; the LOTTOx software constructs a name for the data file from the information you key and prints the name on the report; all resting evaluations have a file name extension of .xro
- All saturation values less than 80% are plotted in red, regardless of the quality of the data point
- The SpO2 value printed under RESULTS is the resting saturation value for the test and is the value that is compared to the LOTT eligibility criterion; transcribe this value to item 11 on the MO form
- If the session quality is unacceptable, no value will print in the RESULTS section for SpO2
- Resting sessions can be labeled "Quality Unacceptable" because of:
  - Too many data points flagged as poor quality
  - Coefficient of variation too large
- The Result under RESULTS gives you the eligibility evaluation for the patient-session with regard to resting saturation
- The values printed in the INFORMATION section of the report are printed FYI and are not transcribed to the MO form

• 6MW session tips
- If possible, clear memory before starting the session - but only if all previous 6MW sessions have already been downloaded
- Power off the handheld for at least 60 seconds
- Turn off the oximeter when the patient stops walking
- Select the stream that includes the time when the patient started walking adjusted for any time difference, and slide the gray box so that the string time at the lower-left corner of the screen matches the time you have noted

• What happens when you click the "Begin" button on the LOTT Rad 7 Data Transfer screen?
- All data in the Rad 7 handheld's memory are transferred to the laptop. That bolus of data is segmented into streams which are displayed on a grid on the laptop screen; each line in the grid is the stream of data between "recognized" power on/power off signals
- The date and time each data stream began are shown – use that info to identify which stream of data (which line on the grid) contains the 6MW data that you want to process
- When you click on any stream in the grid, the display becomes a plot of the data in that stream, helping you to identify the correct stream
- To select a stream, click it once so it is highlighted and then click the "OK" button

- You have to find the 6 minutes in that plot that is the 6 minutes of data for the 6MW that you are trying to process; using your knowledge of any time discrepancy between the time on the handheld and the time on the clock you looked at when noting the clock time the walk began, select the 6 minutes that is the 6MW data of interest by moving the gray window to the left until the time in the lower left corner shows the time when the walk began; use the mouse and a mousepad unless you are really facile with the touchpad
- When you identify 6 minutes of data as the data for the walk, the system analyzes those 6 minutes of data and saves the 6 minutes of data under the patient's ID and visit info specified at the start of the 6MW upload task
- The full bolus of data transferred are saved in a raw data file on the laptop but are unavailable for further processing by you
- If you have more than one 6MW data stream stored in the handheld's memory that you want to download, you need to repeat the 6MW upload task for each 6MW data stream that you want to save and each upload session will include retransfer of the all data in memory
- If you have N 6MW sessions in memory, then you have to do the 6MW data upload task N times – do not clear memory until you have completed N data transfers and processings

• **6MW oximetry report features**
- The information that prints at the top of the report (RCC ID, Patient ID, Patient code, Date, Visit code, Handheld ID) is the information that you key to the LOTT Oximetry program when you initiate a 6 minute walk data transfer; be sure to key the information correctly; the LOTTOx software constructs a name for the data file from the information you key and prints the name on the report; all resting evaluations have a file name extension of .x6m
- All points greater than 70% plot in blue; other points plot in red
- Min SpO2 (under RESULTS) is the lowest 1 minute average SpO2 observed
- Evaluation will be "Quality Acceptable" or "Quality Not Acceptable"
- 6MW sessions can be labeled "Quality Unacceptable" because of:
  - Too many data points flagged as poor quality
- Result will be ...; you will check the corresponding response on the MM3 form (item 28)
- The INFORMATION values are printed FYI; you will not transcribe any of these values to the MM form

• **Check the oximeter's clock periodically** – the times that show up on the 6MW "select stream" grid correspond to the oximeter's clock

• **Printing a screen (eg, so you can capture an error message)**
- Use the mouse to click (left click) on the solid blue bar above the message (FYI, there may be no change in its appearance when you click it)
- Press Alt and PrtScn simultaneously
- Click on the Start button
- Click on All programs
- Click on Accessories (plain vanilla Accessories, not Dell Accessories)
- Click on Wordpad
- Hold down Control and press v while holding down Control
- Hold down Control and press p while holding down Control
- X out of Wordpad (say No to save changes caution)
- Click on OK to exit the utility

5.11 Spirometry

Data collection level
- Core (at baseline).
- Expanded (during followup).

When
- Visit sb (no more than 60 days prior to randomization).
- Visits f12, f24, f36, f48, f60, and f72 (if patient is an Expanded data collection patient).

Who
- All patients at baseline, Expanded data collection patients during followup.
- Spirometry Technician.
- Study Physician (if needed to approve spirometry session that does not meet ATS standards for quality and/or repeatability)

Equipment and supplies
- Spirometer meeting ATS standards
- Albuterol MDI (90 mcg/puff; nebulized albuterol may not be substituted)

Form
- Spirometry (SP) form.

Flash card
- Flash Card #9, Race/ethnicity for pulmonary function
  - Patient self selects from:
    - Caucasian
    - African-American
    - Mexican or Mexican-American
    - Other
  - These choices reflect the race/ethnicity choices for the predicted values of Hankinson et al, 1999 ("other" is pooled with Caucasian)

Additional paperwork
- Predicted values are needed at baseline to evaluate eligibility; a chart of predicted values specific to the patient's age and height (see illustration at the end of this section) prints upon keying the patient's Registration (RG) form or upon accessing the already keyed RG form in "Change a form" mode; Hankinson predicted values for a specific patient may also be obtained from the Hankinson's Spirometric Calculator button on the middle right side of the LOTT website home page (www.lottsite.org)
- Attach site's pulmonary function report to back of Spirometry (SP) form.

Procedure
- Patient must self select race/ethnicity from the 4 choices on Flash Card #9
- Patient is not required to hold bronchodilator medication prior to LOTT spirometry.
- Use spirometry equipment and software meeting ATS standards.
- Race/ethnicity for the pulmonary function predicted value is obtained on the Spirometry (SP) form; show the patient Flash Card #9 and ask the patient to select the category that best describes his/her race/ethnicity.
- Noseclips should be worn.
- The patient should be seated.

- If the patient has used 3 or more puffs of a short-acting (4-hour) bronchodilator in the past 4 hours, skip pre bronchodilator testing for LOTT and proceed with post bronchodilator testing but without administration of additional short-acting bronchodilator
- If the patient has used 2 or fewer (0, 1, or 2) puffs of short-acting (4-hour) bronchodilator in the past 4 hours:
  - Complete pre bronchodilator spirometry
  - Once pre bronchodilator spirometry is complete, administer albuterol MDI (90 mcg/puff) for post bronchodilator testing
    - Administer 4 puffs if the patient has not used any short-acting bronchodilator in the past 4 hours
    - Administer 2 puffs otherwise (ie, if the patient has used 1 or 2 puffs in the past 4 hours)
  - Wait 15 minutes and proceed with post bronchodilator spirometry
- Note: Recent use of 12-hour or 24-hour bronchodilator is ignored by this protocol; make the decisions about whether to complete pre bronchodilator testing and how much bronchdilator to administer for post bronchodilator testing on the basis of 4-hour bronchodilator use only.
- Pre- and post-bronchodilator sessions should meet ATS standards for quality and repeatability
  - For each session, apply the following tests after 3 acceptable spirograms have been obtained:
    - The 2 largest values of FVC must be within 0.150 L of each other
    - The 2 largest values of FEV_1 must be within 0.150 L of each other
    - If both of these criteria are met, the test session may be concluded
    - If both of these criteria are not met, continue testing until:
      - Both of the criteria are met with analysis of additional acceptable spirograms, or
      - A total of eight tests have been performed
      - The patient cannot or should not continue
  - If a session does not meet the ATS standards for quality and/or repeatability, the first step is to repeat the session.
  - If repeating is not possible or if the repeat session again does not meet ATS standards, the session may be used for LOTT if the LOTT Study Physician reviews it and judges that it is acceptable and reflective of the patient's condition.
  - The DCC will monitor for enrollment of patients with spirometry sessions that do not meet ATS standards and will provide the Steering Committee with a summary periodically for review and reassessment of the protocol as warranted.
- During followup, patients using oxygen will remove the oxygen cannula while performing maneuvers and then replace it as soon as maneuvers are completed.

Evaluation of spirometry in followup

- Spirometry in followup is collected and included in the LOTT database but is not used to evaluate patient status; you may use your local PFT lab's usual reference equations to evaluate spirometry in followup as needed

References

- Hankinson JL, Odencrantz JR, Fedan KB: Spirometric reference values from a sample of the general U.S. population. Am J Respir Crit Care Med 1999;159:179-187.
- Miller MR , Hankinson J, Brusasco V, et al: Standardisation of spirometry. Eur Respir J 2005;26:319-338.

Illustration of predicted values chart

LOTT Lung Function Predicted Values

1. Patient ID	hh111
2. Patient code:	dwli
3. Birthdate:	10SEP1950
4. Age as of 15AUG08:	57
5. Gender:	Male
6. Arm span (cm):	Not applicable
7. Measured height (cm):	152.4
8. Height from arm span (cm):	Not applicable

Age (yrs)	Height (cm)	Predicted FEV1(L) if race/ethnicity on Spirometry (SP) form is:			
		White or Caucasian	African American	Mexican or Mexican American	Other
57	152.4	2.53	2.09	2.47	2.53
58	152.4	2.49	2.07	2.44	2.49

References:
1. 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.
2. Hepper NGG, Black LF, Fowler WS: Relationships of lung volume to height and arm span in normal subjects and in patients with spinal deformity. Am Rev Respir Dis 1965;91:356-362.

Calculations:
1. Height (ht) is in cm. Height is calculated from arm span as:
   African American males: height = arm span/1.06
   All other males: height = arm span/1.03
   Females: height = arm span/1.01

2. Age is age at last birthday in years

3. Formulas for predicted lung function values:

   Caucasian:
   Males: FEV1 (L) = 0.5536 - (0.01303*age) - (0.000172*age*age) + (0.00014098*ht*ht)
   Females: FEV1 (L) = 0.4333 - (0.00361*age) - (0.000194*age*age) + (0.00011496*ht*ht)

   African-American:
   Males: FEV1 (L) = 0.3411 - (0.02309*age) + (0.00013194*ht*ht)
   Females: FEV1 (L) = 0.3433 - (0.01283*age) - (0.000097*age*age) + (0.00010846*ht*ht)

   Mexican or Mexican-American:
   Males: FEV1 (L) = 0.6306 - (0.02928*age) + (0.00015104*ht*ht)
   Females: FEV1 (L) = 0.4529 - (0.01178*age) - (0.000113*age*age) + (0.00012154*ht*ht)

   All other race/ethnicities:
   Males: FEV1 (L) =0.5536 - (0.01303*age) - (0.000172*age*age) + (0.00014098*ht*ht)
   Females: FEV1 (L) = 0.4333 - (0.00361*age) - (0.000194*age*age) + (0.00011496*ht*ht)

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5.12 Epworth Sleepiness Scale

Purpose
- To screen for excessive daily sleepiness

Data collection level
- Core

When
- Visit sb (no more than 60 days prior to randomization)

Who
- All patients (Core data collection)
- Clinical Coordinator

Form
- Epworth Sleepiness Scale (EP) form

Procedure
- Clinical Coordinator should detach page 1 from page 2 and attach a label with the patient's ID and code and the visit code to page 2 of the EP form
- Clinical Coordinator should instruct patient in completion of form
- Patient should complete the form
- Clinical Coordinator should review form for missing/incomplete responses and resolve with patient before patient leaves the clinic
- Clinical Coordinator should score the questionnaire

Scoring
- Total score = Sum of scores of the 8 items on the questionnaire

Eligibility
- Total score greater than 15 is exclusionary

Reference
- Johns MW: A new method for measuring daytime sleepiness: The Epworth Sleepiness Scale. Sleep 1991; 14(6):540-545

License to use in LOTT
- The Epworth Sleepiness Scale is in the public domain

5.13 Pittsburgh Sleep Quality Index

Purpose
- To assess sleep quality

Data collection level
- Expanded

When
- Visit sb (no more than 60 days prior to randomization)
- Visits f12, f24, f36, f48, f60, and f72

Who
- Expanded data collection patients
- Clinical Coordinator

Form
- Pittsburgh Sleep Quality Index (PQ) form

Procedure
- Clinical Coordinator should detach page 1 from the remaining pages of the form and attach a label with the patient's ID and code and the visit code to all pages but page 1 of the PQ form
- Clinical Coordinator should instruct patient in completion of form
- Patient should complete the form except item 19; patient's bed partner or roommate should answer item 19 (NOTE: "roommate" is defined as someone living in the same home as the patient, not necessarily sharing a bed or sleeping room with the patient); if this person has not heard or noted any of the activities in item 19 in the past month, that person should check "Not during the past month"
- Clinical Coordinator should review form for missing/incomplete responses and resolve with patient before patient leaves the clinic

Scoring
- Not required at clinics; the DCC will score the questionnaire as needed for analysis

Eligibility
- There are no eligibility criteria related to the PQ form other than completion if patient is an Expanded Data Collection patient

Reference
- Buysse DJ, Reynolds CF III, Monk TH, Berman SR, Kupfer DJ: The Pittsburgh Sleep Quality Index: A new instrument for psychiatric practice and research. Psychiatry Research 1989; 28:193-213

License to use in LOTT
- The Pittsburgh Sleep Quality Index is in the public domain; however, the authors request attribution when it is used

5.14 St. George's Respiratory Questionnaire

Purpose
- To assess respiratory symptoms

Data collection level
- Core

When
- Visit sb (no more than 60 days prior to randomization)
- Visits f04 and f16 (by mail)
- Visits f12, f24, f36, f48, f60, and f72

Who
- All patients (Core data collection)
- Clinical Coordinator

Form
- St George's Respiratory Questionnaire (QG) form

Procedure at sb, f12, f24, f36, f48, f60, and f72
- Clinical Coordinator should detach page 1 from the remaining pages of the form and attach a label with the patient's ID and code and the visit code to all pages but page 1 of the QG form
- Clinical Coordinator should instruct patient in completion of form
- Patient should complete the form independently, without help from spouse or family
- Clinical Coordinator should review form for missing/incomplete responses and resolve with patient before patient leaves the clinic
- During followup, blank questionnaire (with labels) may be mailed to patient 2 weeks before the annual visit for the patient to complete at home and bring to the clinic; if the patient does not bring the completed questionnaire to the clinic, the patient should be given another copy and complete the questionnaire at the clinic

Procedure for mailing at visits f04 and f16
- Ideally, mail the patient the form 2 weeks prior to the target date for the visit, but it is permissible to mail at any time once the window is open; ask for return within 2 weeks
- Complete Section A of page 1 of each form except for item 4 and set page 1 aside
- Affix a Patient ID, code, and visit label to each of pages 2 and up of the questionnaire
- Send the patient pages 2 and up of the QG form with self-addressed, stamped return envelope and ask patient to complete and return the questionnaire within 2 weeks
- When the questionnaire is returned:
  - Re-attach page 1 and complete Section B on page 1
  - If the questionnaire is returned within the window for the visit, enter the date that the patient wrote in item 60 into item 4; enter the date the form was mailed to the patient if item 60 was left blank
  - If the questionnaire is returned after the window closed and the patient wrote in a date of completion that is within the window, the form was completed within the window and you should enter the date in item 60 in item 4
  - If the questionnaire was returned after the window closed and the patient wrote in a date of completion that is outside the window, the form was completed outside the window and the data cannot be keyed to the data system; mark the form with a note that it was completed outside the window and file the form without keying it; complete a Missed or Incomplete Visit (MV) form to document the missed questionnaire
  - If the patient returned the form 10 or fewer days after the window closed and the patient did not

write in a date of completion then, enter the date the window closed in item 4

- If the patient returned the form 11 or more days after the window closed and the patient did not write in a date of completion then, the form is considered to have been completed outside of the window and the data cannot be keyed to the data system; mark it with a note that it was returned 11 or more days after the window closed and file it without keying; complete a Missed or Incomplete Visit (MV) form to document the missed questionnaire

Scoring

- Not required at clinics; the DCC will score the questionnaire as needed for analysis

Eligibility

- There are no eligibility criteria related to the QG form other than completion

References

- Jones PW, Quirk FH, Baveystock: The St. George's Respiratory Questionnaire. Respiratory Medicine 1991; 85:25-31.
- Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure of health status for chronic airflow limitation: The St. George's Respiratory Questionnaire. Am Rev Respir Dis 1992; 145:1321-7.

License to use in LOTT

- Permission to use the SGRQ in LOTT was received from Paul Jones (pjones@sgul.ac.uk)

5.15 Quality of Well-Being Scale

Purpose
- To assess health-related quality of life
- The Quality of Well-Being Scale provides measures of preference-weighted health-related quality of life

Data collection level
- Core

When
- Visit sb (no more than 60 days prior to randomization)
- Visits f04 and f16 (by mail)
- Visits f12, f24, f36, f48, f60, and f72

Who
- All patients (Core data collection)
- Clinical Coordinator

Form
- Quality of Well-Being Scale, Self-Administered (QWB-SA), version 1.04 (QW) form

Procedure at sb, f12, f24, f36, f48, f60, and f72
- Clinical Coordinator should detach page 1 from the remaining pages of the form and attach a label with the patient's ID and code and the visit code to all pages but page 1 of the QW form
- Clinical Coordinator should instruct patient in completion of form
- Patient should complete the form independently, without help from spouse or family
- Clinical Coordinator should review form for missing/incomplete responses and resolve with patient before patient leaves the clinic
- During followup, blank questionnaire (with labels) may be mailed to patient 2 weeks before the annual visit for the patient to complete at home and bring to the clinic; if the patient does not bring the completed questionnaire to the clinic, the patient should be given another copy and complete the questionnaire at the clinic

Procedure for mailing at visits f04 and f16
- Ideally, mail the patient the form 2 weeks prior to the target date for the visit, but it is permissible to mail at any time once the window is open; ask for return within 2 weeks
- Complete Section A of page 1 of the form except for item 4 and set page 1 aside
- Affix a Patient ID, code, and visit label to each of pages 2 and up of the questionnaire
- Send the patient pages 2 and up of the QW form with self-addressed, stamped return envelope and ask patient to complete and return the questionnaire within 2 weeks
- When the questionnaire is returned:
  - Re-attach page 1 and complete Section B on page 1
  - If the questionnaire is returned within the window for the visit, enter the date that the patient wrote in item 71 into item 4; enter the date the form was mailed to the patient if item 71 was left blank
  - If the questionnaire is returned after the window closed and the patient wrote in a date of completion that is within the window, the form was completed within the window and you should enter the date in item 71 in item 4
  - If the questionnaire was returned after the window closed and the patient wrote in a date of completion that is outside the window, the form was completed outside the window and the data cannot be keyed to the data system; mark the form with a note that it was completed outside the window and file the form without keying it; complete a Missed or Incomplete Visit (MV) form to document the missed questionnaire
  - If the patient returned the form 10 or fewer days after the window closed and the patient did not

write in a date of completion then, enter the date the window closed in item 4

- If the patient returned the form 11 or more days after the window closed and the patient did not write in a date of completion then, the form is considered to have been completed outside of the window and the data cannot be keyed to the data system; mark it with a note that it was returned 11 or more days after the window closed and file it without keying; complete a Missed or Incomplete Visit (MV) form to document the missed questionnaire

Scoring

- Not required at clinics; the DCC will score the questionnaire as needed for analysis

Eligibility

- There are no eligibility criteria related to the QW form other than completion

Reference

- Kaplan RM, Atkins CJ, Timms R: Validity of a quality well-being scale as an outcome measure in chronic obstructive pulmonary disease. J Chronic Dis 1984; 37:85-95.

License to use in LOTT

- The DCC has signed a copyright agreement with the creators of the QWB that permits LOTT to reproduce and use the questionnaire for administration to patients in LOTT; investigators should contact qwb@ucsd.edu if they wish to use the QWB in a study other than LOTT.

5.16 SF-36v2 Health Survey

Purpose
- To assess general quality of life

Data collection level
- Expanded

When
- Visit sb (no more than 60 days prior to randomization)
- Visits f12, f24, f36, f48, f60, and f72

Who
- Expanded data collection patients
- Clinical Coordinator

Form
- SF-36v2 (QF) form

Procedure
- Clinical Coordinator should detach page 1 from the remaining pages of the form and attach a label with the patient's ID and code and the visit code to all pages but page 1 of the QF form
- Clinical Coordinator should instruct patient in completion of form
- Patient should complete the form independently, without help from spouse or family
- Clinical Coordinator should review form for missing/incomplete responses and resolve with patient before patient leaves the clinic
- During followup, blank questionnaire (with labels) may be mailed to patient 2 weeks before the annual visit for the patient to complete at home and bring to the clinic; if the patient does not bring the completed questionnaire to the clinic, the patient should be given another copy and complete the questionnaire at the clinic

Scoring
- Not required at clinics; the DCC will score the questionnaire as needed for analysis

Eligibility
- There are no eligibility criteria related to the QF form other than completion (if the patient is an Expanded Data Collection patient)

Reference
- Ware JE Jr and Kosinski M. SF 36 Health Survey (Version 2.0) (Technical note, September 20). Boston: Health Assessment Lab (1996).

License to use in LOTT
- The DCC has purchased permission from the creators of the SF-36v2 that permits LOTT to reproduce and use the questionnaire for administration to patients in LOTT; investigators should contact Quality Metric, Inc. (www.QualityMetric.com) if they wish to use the SF-36v2 in a study other than LOTT.

5.17 Hospital Anxiety and Depression Scale (HADS)

Purpose
- To assess anxiety and depression symptoms

Data collection level
- Expanded

When
- Visit sb (no more than 60 days prior to randomization)
- Visits f12, f24, f36, f48, f60, and f72

Who
- Expanded data collection patients
- Clinical Coordinator

Form
- Hospital Anxiety and Depression Scale (HADS; HA) form

Procedure
- Clinical Coordinator should detach pages 1 and 5 from the remaining pages of the form and attach a label with the patient's ID and code and the visit code to all pages but page 1 of the HA form
- Clinical Coordinator should instruct patient in completion of form
- Patient should complete the form independently, without help from spouse or family
- Clinical Coordinator should review form for missing/incomplete responses and resolve with patient before patient leaves the clinic
- Clinic Coordinator should score the form using the scoring key and weights on page 5 of the HA form

Scoring
- Transcribe responses to the scoring key (page 5 of the HA form)
- Sum the circled scores for each domain
  - Anxiety domain score (range, 0-21) = sum of scoring weights for items 11, 13, 15, 17, 19, 21, 23
  - Depression domain score (range, 0-21) = sum of scoring weights items 12, 14, 16, 18, 20, 22, 24

Eligibility
- There are no eligibility criteria related to the HA form other than completion (if the patient is an Expanded Data Collection patient)

Red flag
- If a patient has a total depression domain score of 11 or greater on any assessment, the LOTT staff will (1) inform the patient's healthcare provider that the questionnaire is suggestive of the presence of clinical depression (if the patient permits the contact), and (2) suggest that the patient undergo timely evaluation and appropriate treatment

Reference
- Zigmund AS and Snaith RP: The Hospital Anxiety and Depression Scale. Acta Psychiatr Scand 1983; 67:361-370.

License to use in LOTT
- The DCC has purchased permission from the copyright holders of the HADS (NFER Nelson) to reproduce and use the questionnaire for administration to patients in LOTT; investigators should email information@nfer-nelson.co.uk if they wish to use the HADS in a study other than LOTT.
- The HADS is available only to registered users approved by NFER Nelson as qualified to use the HADS; for LOTT, the registered person for LOTT is Kathleen Harrington (kharring@uab.edu).

5.18 MMRC Dyspnea Scale

Purpose
- To assess dyspnea

Scoring/scale as used in LOTT

0 = not troubled by breathlessness except during strenuous exercise
1 = troubled by shortness of breath when hurrying on the level OR when walking up a slight hill
2 = walks slower than people of the same age on the level because of breathlessness OR has to stop for breath when walking at own pace on the level
3 = stops for breath after walking about 100 yards OR after a few minutes of walking on the level
4 = too breathless to leave house OR breathless when dressing or undressing

Eligibility
- At baseline, the MMRC score must be at least 1

Data collection level
- Core

When
- Visit sb
- Visits f12, f24, f36, f48, f60, and f72

Form
- At baseline, the MMRC scale is obtained on the Registration (RG) form in two ways
  - First the patient is asked 2 questions comprising the components of a score of 1; the patient must respond "Yes" to at least one of these questions
  - The patient is also shown the MMRC scale (Flash Card #8) and asked to select the score on the scale that best describes his/her breathlessness
- In followup, the MMRC scale is obtained on the Interim History at Annual Visit (HI) form
  - The patient is shown the MMRC scale (Flash Card #8) and asked to select the score on the scale that best describes his/her breathlessness

Flash card
- #8, Degree of breathlessness (MMRC Dyspnea Scale)

References

- Brooks SM (chairman): Task group on surveillance for respiratory hazards in the occupational setting. Surveillance for respiratory hazards. ATS News 1982; 8:12-16
- Mahler DA and Wells CK: Evaluation of clinical methods for rating dyspnea. Chest 1988; 93:580-586

License to use in LOTT
- The MMRC Scale is in the public domain

5.19 Problem responses on self completed questionnaires

- The coordinator should review questionnaires completed by the patient for blank items, multiple responses checked on a check only one item, clearly incorrect answers (eg, blindness checked and patient has sight); it is better to do this while the patient is present
- If the patient has left the clinic and this is visit sb, you can call the patient about the missing or problem items or put the questionnaires aside to address when the patient returns for randomization; just be sure to obtain the corrected responses before randomizing the patient
- If the patient has left the clinic and this is a followup visit, call the patient about the missing or problem items; waiting till the next followup visit is not an option
- Blank items: Ask the patient if he/she intended to leave the item blank; if yes, then stop; if no, ask the patient to respond to the item
- Multiple responses checked and item requires a single response: Read the possible responses to the question and ask the patient which is the correct single response
- Goofy/incorrect response: Re-ask the patient the question as if the patient had left the item blank; record the response as provided by the patient even if it is the same answer as before; add a note to the form and key the note to the general comments area of the keying (eg, patient queried about item XX and gave answers as keyed)

5.20 Patient access to test results and study data

Guidelines for responding to requests from patients for access to test results or study data are:

- In general, there is no plan to provide individual results of LOTT procedures and tests routinely to patients and their providers (except as noted below), but if a patient asks for their results, the patient should be provided those results and if the patient asks that they be forwarded to their primary provider, the LOTT staff should forward those results. These would be results for individual patients, not group results.

- If the LOTT tests or procedures reveal a previously unknown condition, the patient should be informed, just as you would do with a non study patient. If permitted by the patient, the study physician will inform the patient's primary provider. If the patient doesn't permit informing his/her primary provider, the study physician will follow institutional guidelines to refer the patient for appropriate treatment.

- Any patient who develops severe resting hypoxemia (resting saturation below 89%) will be informed of that when it is discovered and then the plan is to prescribe oxygen, either by the Study Physician or the primary provider (whatever arrangement works for the patient, Study Physician and provider – it would be best for LOTT for the Study Physician to prescribe, but that might not be acceptable to the primary provider).

- Any patient who develops severe hypoxemia on exercise (defined as meeting the LOTT exclusion criterion for exercise desaturation, desaturation below 80% for at least one minute) will be informed of that and the plan is to prescribe oxygen for exercise, either by the Study Physician or the primary provider (whatever arrangement works for the patient, Study Physician and provider – it would be best for LOTT for the Study Physician to prescribe, but that might not be acceptable to the primary provider).

- If the HADS depression domain score is 11 or greater, then the patient should be informed that the score is suggestive of the presence of clinical depression and the patient should be advised to undergo timely evaluation and appropriate treatment; if permitted by the patient, the Study Physician will inform the primary provider.

- Alpha 1 anti-trypsin deficiency testing results should be provided to the patient, regardless of the results.

- Serum cotinine level is being obtained as an objective indicator of smoking or non smoking. If a patient who denies smoking and denies using nicotine products has a high cotinine and is prescribed oxygen, the cotinine results should be discussed with the patient, and the patient should be counseled about not smoking. High is defined as cotinine 10 ng/mL or higher.

- There is no plan to provide the results of DNA, plasma, and serum analyses to the patient.

- Group results will not be available until released by the NHLBI, likely at least 6 months after followup on all patients is completed; patients will be informed of the study results just prior to publication of the results.

6 Treatments

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6.1 No supplemental oxygen group

Starting premises

- Patients randomized to the no supplemental oxygen group are expected not to use supplemental oxygen unless the patient becomes severely hypoxemic at rest (i.e., meets conventional Medicare criteria for 24-hour supplemental oxygen due to severe hypoxemia at rest – resting saturation 88% or less).
- Patients randomized to the no supplemental oxygen group who meet conventional Medicare criteria for oxygen during sleep or exercise but do not meet conventional Medicare criteria for oxygen at rest are expected not to be prescribed oxygen for sleep or exercise.

If a patient in the no supplemental oxygen group is prescribed oxygen, the goals will be:

- Stop the oxygen as quickly as it is safe to do so.
- If the patient has become severely hypoxemic at rest (i.e., $SpO_2 \leq 88\%$ while on room air), inform the patient of the finding and prescribe the lowest dose at or above 2 L/min that relieves the resting hypoxemia (dose for use during rest and sleep) and prescribe the lowest dose at or above a setting of 2 that keeps the patient above 90% for at least 2 consecutive minutes while walking (exercise dose).
- If the patient remains moderately hypoxemic at rest but has developed severe isolated hypoxemia during exercise (i.e., $SpO_2 < 80\%$ for at least 1 minute during room air 6 minute walk), inform the patient of the finding and prescribe the lowest dose at or above at setting of 2 that keeps the patient above 90% for at least 2 consecutive minutes while walking.
- Check the patient after 30 days to see if the dose can be reduced or oxygen can be stopped.

Checks for development of severe hypoxemia at rest or isolated severe hypoxemia during exercise

- All patients will undergo room air resting oximetry annually.
- All patients will undergo room air 6 minute walk annually.
- Patients who become severely hypoxemic at rest will undergo resting dose determination and walking dose determination to be sure that the doses prescribed alleviate the hypoxemia.
- Patients who develop severe isolated hypoxemia during exercise will undergo walking dose determination to be sure that the dose prescribed alleviates the exercise hypoxemia.

If the patient develops severe hypoxemia at rest

- Inform the patient that he/she now meets conventional Medicare criteria for starting 24-hour oxygen.
- Prescribe oxygen as needed (setting of 2 or greater) to produce resting saturation $\geq 89\%$; the Study Physician may use his/her discretion regarding the protocol for determining dose greater than 2 L/min and determining adequacy of the dose; the suggested protocol is:
  - Have the patient breathe oxygen at 2 L/min for at least 15 minutes and then assess resting saturation
  - If resting oxygen saturation is 89% or greater while using 2 L/min, the patient will continue on 2 L/min
  - If the resting oxygen saturation is below 89%, increase the dose by 1 L/min (to 3 L/min) and assess afer 1 minute
  - If saturation remains below 89%, repeat the process increasing dose by 1 L/min and assessing each minute, until an oxygen dose is reached that achieves a resting saturation of at least 89% for at least 2 minutes.
- Determine the walking dose using the LOTT protocol for determining walking dose for patients randomized to supplemental oxygen (starting dose should be the newly determined resting dose).
- Check the room air resting oxygenation after 30 days.
  - If the patient has $SpO_2 \geq 89\%$ while breathing room air, stop the oxygen.
  - If the patient continues to require oxygen to maintain resting $SpO_2 \geq 89\%$, recheck the patient in 30 more days and if the patient still does not meet criteria for stopping supplemental oxygen, the patient will continue on oxygen until the patient's next annual LOTT follow-up visit when retesting would next occur.

6.1. No supplemental oxygen group

If the patient has moderate resting hypoxemia and severe exercise desaturation

- Inform the patient that he/she now meets criteria for starting oxygen during exercise.
- Prescribe oxygen as needed (setting of 2 or greater) to maintain saturation above 90% for 2 minutes while walking.
- Recheck the patient in 30 days.
- If the patient 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, then stop the oxygen.
- If the patient continues to have exercise desaturation and moderate resting hypoxemia, the oxygen prescription for walking will be continued for 30 more days and the patient will then be retested.
- If the patient continues to have isolated severe oxygen desaturation during ambulation (2^{nd} recheck), the patient will be continued on oxygen for walking for the duration of the trial.

Patients who become normoxic at rest

- If the patient becomes normoxic at rest during follow-up ($\geq$ 94% saturation), inform the patient of the event.
- Continue the patient on no supplemental oxygen.

Changes to prescription or prescription of oxygen by a non LOTT physician

- All patients should be instructed to call the Clinical Coordinator if changes are made to their oxygen prescription, or if prescribed oxygen by their primary care physician.
- Use of oxygen and prescription of oxygen is queried every 4 months, at the twice yearly telephone visits and the annual in person visit.

6.2 Supplemental oxygen group

Equipment overview

- Patients assigned to supplemental oxygen must be provided with both a stationary oxygen system and a portable oxygen system; see Oxygen equipment characteristics section for details.

Prescription and dosing overview

- Whole number doses only are used in LOTT.
- The LOTT oxygen prescription is tailored to the patient's needs at baseline
  - Patients who have resting moderate resting hypoxemia (89%-93%) at baseline will be prescribed 24-hour oxygen
  - Patients who have resting saturation at least 94% at baseline and at least 10 seconds of desaturation below 90% on 6 minute walk at baseline will be prescribed oxygen on physical activity and during sleep
  - The LOTT oxygen prescription does not change after randomization unless the patient becomes severely hypoxemic at rest (saturation 88% or less) or becomes severely hypoxemic on exercise (saturation 80% or less for at least one minute on 6 minute walk)
- The LOTT oxygen dose during sleep is 2 L/min
- The LOTT oxygen dose during rest (awake but not physically active) is 2 L/min
- The LOTT oxygen dose during physical activity is the dose that maintains saturation at 90% or higher for 2 consecutive minutes while the patient is walking at a normal pace; see Ambulatory dosing determination section.

Plane travel

- Patients assigned to supplemental oxygen may suspend oxygen during plane travel.

Management of nosebleed (epistaxis)

- Nosebleeds are an uncommon complication of nasal oxygen at the low flow rates used in LOTT, but could be significant in a person on anticoagulants or with a tendency to have nosebleeds prior to the oxygen.
- If the patient is moderately hypoxemic:
  - If life threatening epistaxis occurs, then discontinue oxygen permanently (definition of life-threatening is at the discretion of the LOTT Study Physician)
  - If significant epistaxis (defined as nosebleed that does not resolve with compression, requires medical attention, or results in anemia) occurs, then:
    - Discontinue oxygen until free of epistaxis for 1 week
    - Resume oxygen at usual dose
    - If epistaxis recurs, discontinue oxygen for 6 weeks
    - Then resume oxygen with the following strategies: Use nasal saline spray or gel 4-12 times per day to avoid nasal dryness and crusting; take frequent oxygen holidays (e.g. sleep with oxygen cannula in mouth as tolerated)
- If the patient is severely hypoxemic:
  - Management is be left to the treating physician who may consider changing the oxygen flow rate, delivery device, use of nasal saline or creams, oxygen holidays, etc.

If a patient in the supplemental oxygen group is prescribed oxygen outside of LOTT, the goals will be:

- Return the patient to their LOTT prescribed dose as quickly as it is safe to do so
- If the patient has become severely hypoxemic at rest (i.e., $SpO_2 \leq 88\%$ while on room air), inform the patient 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) while the patient is using oxygen (ie, you will check resting oximetry while using oxygen); the standard LOTT dose for ambulation will be sufficient to relieve this hypoxemia
- If the patient remains moderately hypoxemic at rest but has developed severe isolated hypoxemia during exercise (i.e., $SpO_2 < 80\%$ for at least 1 minute during room air 6 minute walk), inform the patient of that event; the LOTT ambulatory dose will relieve this hypoxemia
- If prescribing a dose that deviates from the LOTT standard dose, check the patient after 30 days to see if the dose can be returned to the LOTT standard dose

Checks for development of severe hypoxemia at rest or isolated severe hypoxemia during exercise

- All patients will undergo room air resting oximetry annually
- All patients will undergo room air 6 minute walk annually
- Patients who become severely hypoxemic at rest will undergo resting oxygen dose determination and walking dose determination to be sure that the prescribed doses alleviate the hypoxemia
- Patients who develop severe isolated hypoxemia during exercise will undergo oximetery while walking and using oxygen as a check on the adequacy of their walking dose to relieve the hypoxemia

If the patient develops severe hypoxemia at rest

- Inform the patient that he/she now meets conventional Medicare criteria for starting 24-hour oxygen
- Check the adequacy of 2 L/min oxygen to produce resting saturation $\geq 89\%$; the Study Physician may use his/her discretion regarding the protocol for determining dose greater than 2 L/min and determining adequacy of the dose; the suggested protocol is:
  - Have the patient breathe oxygen at 2 L/min for 15 minutes and then assess resting saturation
  - If resting oxygen saturation is 89% or greater while using 2 L/min, the patient will continue on 2 L/min
  - If the resting oxygen saturation is below 89%, increase the dose by 1 L/min (to 3 L/min) and assess after 1 minute
  - If saturation remains below 89%, repeat the process increasing dose by 1 L/min and assessing each minute until an oxygen dose is reached that achieves a resting saturation of at least 89% for at least 2 minutes.
- Check the room air resting oxygenation after 30 days
  - If the patient has $SpO_2 \geq 89\%$ while breathing room air, the patient should resume 2 L/min at rest and during sleep
  - If the patient continues to require the increased dose to maintain resting SpO2 $\geq 89\%$, recheck the patient in 30 more days and if the patient still does not meet criteria for resuming 2 L/min, the patient will continue on the higher dose until the patient's next annual LOTT follow-up visit when retesting would next occur.

If the patient has moderate resting hypoxemia and severe exercise desaturation

- Inform the patient that he/she now meets criteria for starting oxygen during exercise
- Remind the patient that their LOTT prescribed ambulatory dose will protect the patient against desaturation during exercise

Patients who become normoxic at rest after being hypoxemic at rest at baseline

- If the patient becomes normoxic at rest ($\geq 94\%$) during follow-up, inform the patient of the event

- Continue the patient on their LOTT prescribed oxygen dose

Patients who become normoxic during exercise after desaturating during exercise at baseline

- If the patient becomes normoxic during exercise (less than 10 seconds below 90% during the 6 minute walk) during follow-up, inform the patient of the event
- Continue the patient on their LOTT prescribed oxygen dose

Changes to prescription or prescription of oxygen by a non LOTT physician

- All patients should be instructed to call the study coordinator if changes are made to their LOTT oxygen prescription.
- Use of oxygen and prescription of oxygen is queried every 4 months, at the twice yearly telephone visits and the annual in person visit.

6.3 Oxygen equipment characteristics

Core requirements

- Each patient assigned to supplemental oxygen must be prescribed a stationary system and an ambulatory/portable/wearable system.
  - Patients with resting hypoxemia use the stationary system during sleep and at rest and the portable system during physical activity
  - Patients with normal resting saturation and desaturation on exercise use the stationary system during sleep and the portable system during physical activity
- If a device uses electricity, an estimate of the power consumption must be provided to the patient.
- Each patient must be offered an ambulatory/portable/wearable system (with regulator) weighing 6 pounds or less; patients may choose a heavier system if that is preferred by the patient.
- The ambulatory/portable/wearable system must be able to be configured to provide at least a setting of 3 for at least 3 hours before needing to be refilled or recharged.
- E cylinders may not be used as the primary ambulatory system but may be provided to patients as backup systems for use during power failures.

Required characteristics for specific types of equipment

- **Stationary concentrator**
  - Must be capable of providing at least 4 L/min continuous flow.
  - Must have easily readable, accurate meter that measures hours the oxygen supply is turned on.
  - Modern unit: small, quiet, low electrical consumption.
  - Supplier must provide the clinic with:
    - Manufacturer and model of the concentrator.
    - Meter reading upon delivery and date read.

- **Compressed gas tanks**
  - Provide a *single* tank size to a given participant for daily use (patients may have another tank size for emergency backup).
    - Tank must have consistent filling pressure.
  - Conserver valve is preferred.
    - Model should have demonstrated effectiveness in maintaining oxygenation in COPD.
    - Supplier must be willing to "trade out" conserver valve model in an individual patient if the model is shown to be incapable of maintaining saturation in LOTT ambulatory dose determination.
    - Continuous flow option is acceptable.
  - Supplier must provide the clinic with:
    - Manufacturer and model of tank.
    - Cylinder filling pressure of tank.
    - Type of regulator valve provided (continuous or pulse/conserver) and if pulse/conserver, must provide the clinic with manufacturer and model of the regulator.

6.3. Oxygen equipment characteristics

- **Liquid oxygen stationary unit**
  - Continuous flow preferred for home/sleep use of stationary unit
    - Conserver flow acceptable.
      - Model should have demonstrated effectiveness in maintaining oxygenation in COPD
  - Supplier's delivery staff must weigh stationary unit before and after each liquid oxygen delivery, and record before and after weights and date of delivery on patient-maintained log.
  - Supplier must provide the clinic with:
    - Manufacturer and model of stationary unit.
    - Type of regulator value provided (continuous or pulse/conserver) for use with stationary unit (if unit is to be used for home/sleep) and if pulse/conserver, must provide the clinic with manufacturer and model of the regulator.

- **Liquid oxygen portable unit**
  - Provide *single* size to a given participant
  - Conserver valve preferred
    - Model should have demonstrated effectiveness in maintaining oxygenation in COPD
    - Supplier must be willing to "trade out" conserver valve model in an individual patient if the model is shown to be incapable of maintaining saturation in LOTT ambulatory dose determination.
    - Continuous flow option acceptable
  - Supplier must provide the clinic with
    - Manufacturer and model of liquid oxygen portable tank
    - Capacity of tank provided (pounds of oxygen)
    - Type of regulator value provided for tank (continuous or pulse/conserver) and if pulse/conserver, must provide the manufacturer and model of the regulator)

- **Portable concentrator**
  - In most cases, prefer this to be provided in conjunction with a stationary concentrator (one exception might be if patient selects Eclipse unit)
  - Request collaboration to establish methods to determine adherence with portable concentrator models
  - Supplier must provide the clinic with:
    - Manufacturer and model of portable concentrator
    - Meter reading upon delivery and date read

6.4 Ambulatory dose determination

Data collection level
- All supplemental oxygen patients (Core) and control patients who are severely hypoxemic at rest or have isolated severe hypoxemia during exercise

When
- Visit rx (after randomization and patient has received his/her ambulatory system)
- Visits f12, f24, f36, f48, f60, and f72
- May be done before or after six minute walk on room air
- If severely hypoxemic at rest, resting oxygen dose must be determined before ambulatory dose is determined
- Patient must have been using oxygen at current resting dose (2 L/min if patient does not use oxygen at rest) for at least 15 minutes before the ambulatory dose determination begins

Who
- Oximetry Technician
- Study Physician

Form
- Ambulatory Oxygen Dose (MP) form

Patient preparation
- May be done pre or post bronchodilator
- No requirement for patient to have eaten a meal within 2 hours
- No requirement that patient rest for 10 minutes before doing the walk
- Patient should wear loose clothing and comfortable shoes but lack of either would not stop the assessment
- Patient should use his/her ambulatory system
- Patient must have been using oxygen at current resting dose (2 L/min if patient does not use oxygen at rest) for at least 15 minutes before the ambulatory dose determination begins

Equipment
- Oximeter (Masimo Radical 7 handheld may be used but is not required)
- Patient uses his/her ambulatory system
- Patient should walk along a corridor/office area at a normal pace (this is not a treadmill walk)

Adjustment of dose
- Patient is started at current resting dose (setting of 2 if patient does not use oxygen at rest) regardless of current ambulatory oxygen dose
- Patient is told to walk at his/her own normal pace and at a comfortable pace
- Saturation is assessed after 1 minute and each minute thereafter
- Flow rate is increased in whole number increments as needed to keep saturation at 90% or higher for at least 2 consecutive minutes

Duration of walk
- Walk should last at least 2 minutes
- Walk may last as long as 10 minutes

6.5 Oxygen provider requirements

Requirements for being a LOTT oxygen provider

- Provider must be approved by Medicare
- Provider must agree to assist in providing equipment information as needed, such as:
  - Initial meter reading on concentrator
  - Pounds of liquid oxygen delivered and date delivered
  - Manufacturer and model of equipment items

Recommendations for oxygen providers for LOTT

- Provider agrees to waive copays for LOTT services

6.6 Conventional Medicare criteria for home oxygen

- **Resting oxygen saturation of 88% or less:** Medicare will cover 24-hour oxygen
- **Oxygen saturation of 88% or less during sleep in a patient whose saturation if 89% or greater while awake:** Medicare will cover nocturnal oxygen
- **Oxygen saturation of 88% or less during activity in a patient whose saturation is 89% or greater during the day while at rest:** Medicare will cover oxygen during exercise

6.7 Management of "non protocol" treatment situations

Oxygen patient has severe resting hypoxemia (resting saturation below 89%)

- If not detected as part of a LOTT annual followup visit, confirm with n visit MO form if patient is willing and it makes sense to do so
- Check adequacy of 2 L/min to relieve the resting hypoxemia and increase flow if needed (complete an n visit MQ form)
- Check adequacy of current ambulatory dose (complete an n visit MP form)
- Check in 30 days (complete another n visit MO form)
- If severe resting hypoxemia not found at 30-day check, patient will resume using 2 L/min at rest
- If found, continue any increase dose for 30 days and retest
- If severe resting hypoxemia not found at 30-day recheck (60 days) , patient will resume using 2 L/min at rest
- If found, continue any increase dose until the next annual LOTT followup visit and then retest

Oxygen patient has severe isolated exercise desaturation (desat below 80% for at least one minute)

- If not detected as part of a LOTT annual followup visit, confirm with n visit MM form if patient is willing and it makes sense to do so
- Check adequacy of current ambulatory dose (complete an n visit MP form)
- Check for change in resting saturation (complete an n visit MO); if detected, follow instructions for detection of severe resting hypoxemia in an oxygen group patient

Oxygen patient refuses to continue with home oxygen treatment or some issue occurs such that the home oxygen prescription is canceled

- Complete the TC form to document cancellation of the home oxygen prescription
- Continue to complete AH forms as required by the usual visit schedule; in this case, you will answer No to item 8 on the AH form (No, you did not speak to the patient in the window for the contact) and explain why (e.g., patient no longer using oxygen at home)
- Depending on your assessment of the patient's attitude toward LOTT and oxygen, the coordinator should decide whether to call for these contacts and whether it is appropriate to bring up restarting oxygen or explore reasons why the patient is not using oxygen. The coordinator will be best able to judge what is acceptable to the patient; LOTT does not want to annoy or scare off the patient; in some cases, resumption of oxygen after a hiatus may work

Oxygen patient has home oxygen prescription reinstated after a prior cancellation

- Complete the TC form to document resumption of the home oxygen treatment
- Complete a new OE form to document the newly issued equipment

Control patient has event that warrants checking for severe resting or exercise hypoxemia between annual LOTT visits

- Bring the patient in for an unscheduled visit and complete room air resting saturation (n visit MO) and room air 6MW (n visit MM)
- Depending on outcome of MO and MM, prescribe or don't prescribe home oxygen – see below

Control patient has severe resting hypoxemia (resting saturation below 89%)

- If not detected as part of a LOTT annual followup visit, confirm with n visit MO form if patient is willing and it makes sense to do so
- Prescribe 24-hour oxygen; complete the TC form
- Complete the MQ form to check adequacy of 2 L/min to relieve the resting hypoxemia and increase flow if needed
- Prescribe ambulatory dose (complete the MP form)

- Patient will not complete oxygen usage diaries and the OE form is not completed
- Check in 30 days (another n visit MO; 30 days is minimum interval, no maximum interval)
- If severe resting hypoxemia not found at 30-day visit, cancel home oxygen prescription (complete the TC form)
- If found, continue home oxygen prescription for 30 more days and then retest
- If severe resting hypoxemia not found at 30-day recheck (60 days), cancel home oxygen prescription (complete the TC form)
- If found, continue home oxygen prescription until next annual LOTT visit and then retest
- The oxygen is considered a LOTT protocol service; if prescribed by the LOTT study physician, the copays for the oxygen may be waived; however, the control patient is not eligible for the LOTT $350 subsidy for electricity that is paid to the oxygen group patients

Control patient has severe isolated exercise desaturation (desaturation below 80% for at least one minute)

- If not detected as part of a LOTT annual followup visit, confirm with n visit MM form if patient is willing and it makes sense to do so
- Prescribe home oxygen during physical activity (complete an n visit MP form); complete the TC form
- Check for change in resting saturation (complete an n visit MO); if severe resting hypoxemia is detected, complete n visit MQ form to check adequacy of 2 L/min to relieve the hypoxemia and increase flow if needed
- Check in 30 days (another n visit MM; 30 days is minimum interval, no maximum interval)
- If severe exercise desaturation not found at 30-day visit, cancel home oxygen prescription (complete the TC form)
- If found, continue home oxygen prescription and recheck in 30 days (60 days)
- If severe exercise desaturation not found at 30-recheck, cancel home oxygen prescription (complete the TC form)
- If found, continue home oxygen prescription until next annual LOTT visit and then re-test
- The oxygen is considered a LOTT protocol service; if prescribed by the LOTT study physician, the copays for the oxygen may be waived; however, the control patient is not eligible for the LOTT $350 subsidy for electricity that is paid to the oxygen group patients

Control patient started on home oxygen for COPD and initiation of oxygen was not part of a LOTT work up or visit, but LOTT will manage the oxygen treatment going forward

- Clinic is in the position of trying to get the treatment back onto the LOTT track
- Complete a TC form to document the initiation of home oxygen
- Check the patient for possibly stopping home oxygen as soon after 30 days of use as possible
- Complete n visit MO and n visit MM when the patient comes in for the 30-day check; continue or cancel prescription per MO and MM outcomes; if prescription is canceled, complete a TC form to document cancellation of the prescription

Control patient started on home oxygen for COPD and LOTT will manage the oxygen treatment going forward, but the patient and/or physician want the home oxygen prescription continued although the resting saturation is 89% or greater (eg, patient meets conventional criteria for oxygen during exercise or sleep)

- Complete a TC form to document the initiation of home oxygen if not already done
- Complete a TC form to document the cessation of home oxygen if and when it happens
- Patient continues to complete annual LOTT visits
- Clinic will not try to impose LOTT protocol of 30-day checks and rechecks

Control patient started on home oxygen by non LOTT physician for COPD and non LOTT physician

is managing the oxygen treatment

- Complete a TC form to document the initiation of home oxygen
- Complete a TC form to document the cessation of oxygen if and when it happens
- Patient continues to complete annual LOTT visits
- Clinic will not try to impose LOTT protocol of 30-day checks and rechecks

Control patient started on home oxygen for non COPD reason

- Complete the TC form to document the initiation of home oxygen
- Continue regular LOTT followup schedule
- If oxygen can (eventually) be stopped, complete a TC form to document the cessation of home oxygen

6.8 Oxygen safety considerations

The safe use of oxygen equipment by LOTT patients is of paramount importance. Safe use should be stressed with the patient at each visit and should be reviewed at each visit. This should include review of the safety educational materials provided by the patient's oxygen supplier regarding the specific equipment used by the patient. This review must cover, but is not limited to, the topics below:

Oxygen helps fires spread quickly

Patients and family members should understand that oxygen increases the speed at which things burn once a fire starts. Home oxygen therapy increases the amount of oxygen in the environment. It will saturate clothing, fabric, hair, beards, and anything in the area. Even flame-retardant clothing can burn when the oxygen content increases.

- Never smoke or light a match while using oxygen.
- Stay at least 5 feet away from open flames, including gas stoves and lighted wood burning stoves, candles, and fireplaces.
- Do not operate any appliance that sparks.
- Keep all flames and heat sources away from oxygen containers and systems. Store oxygen cylinders and equipment away from heaters, heat producing and electrical appliances. Store tanks and liquid base units upright in a well-ventilated area (not in closets, behind curtains, or other confined space) – the small amount of oxygen that vents from these vessels can accumulate in a small space and become a fire hazard.
- Do not place oxygen tubing under rugs or furniture.
- Do not allow smoking inside of a home where oxygen is used. Post a No Smoking sign in the home. Even if it is not being used at a particular moment, the home is still an oxygen enriched environment, and fire can get out of hand quickly.

Personal precautions

- Use water-based lubricants on your lips and hands. Don't use an oil-based product like petroleum jelly or petroleum based creams or lotions. Vaseline, Blistex, and Chapstick are oil-based products.
- Avoid nylon or woolen clothing because it is more likely to cause static electricity.

Precautions in the home

- **The patient should have a fire escape plan**: Staff should talk with patients about the patient's fire escape plan.
  - Plan for two escape routes from each room and make sure the escape routes are free of obstacles.
  - Arrange for special care or assistance if the patient has mobility issues.
  - Practice the escape plan at least twice a year.
- **Smoke detectors should be present in the home:**
  - Have the detectors tested at least once a month.
  - Change the batteries at least once a year.
  - Specialized smoke detectors are available for the hearing impaired.
- **A fire extinguisher should be present in the home**
- **Suggestions:**
  - Keep a phone by the bed or any place the patient usually occupies.
  - Consider if a medic alert alarm would be useful.

Cigarettes and home oxygen systems can be a fatal combination

- Googling "home oxygen fire news" brings up examples, some of which may be local to a LOTT site; staff can consider whether discussion of these with patients would be useful.

6.8. Oxygen safety considerations

Selected links to oxygen safety materials provided by fire departments or oxygen companies (there are many available on the internet, this is just a selection)

- http://ci.santa-rosa.ca.us/doclib/Documents/IB%20048.pdf
- http://www.nfpa.org/assets/files//PDF/oxygensummary.pdf

7 Adherence promotion

Purpose
- To promote adherence to LOTT assigned treatment

Overview
- Because adherence to supplemental oxygen requires lifestyle changes by the patient and learning about, developing confidence in, and operating oxygen equipment, the LOTT adherence promotion program is more extensive for the supplemental oxygen patient than the control patient
- Adherence promotion contacts are a mix of both in person and telephone contacts
- The contact schedule is most intense at the start of followup
- Instructional materials provided by patient's oxygen supply company will be used

Who
- All patients (Core data collection), but schedule differs by treatment assignment
- Adherence Educator

When
- Control group
  - Visit rz (in person)
  - Visit w01 (telephone)
- Supplemental oxygen patient
  - Visit rz (in person)
  - Visit rx (in person)
  - Visits w01, w02, w03, w04, a02, a03, a04, a05, a06, a08, a10 (telephone)
  - Visits f12, f24, f36, f48, f60, and f72 (in person)
  - As needed after f12 if patient needs contacts and appears receptive to contacts

Forms
- Documentation of randomization and randomization day adherence promotion contact (XZ) form (all patients)
- Control Group Adherence Promotion Contact - Visit W01 (AC) form
- Oxygen Group Adherence Promotion Contact - Initial Walking Dose Determination (AE) form
- Oxygen Group Adherence Promotion Contact - Telephone or Annual Visit (AH) form

Procedures
- See Adherence Educator Training Manual

8 Adherence monitoring

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8.1 Overview of adherence monitoring

Monitoring of adherence to assigned treatment will proceed in 3 formats:

- **Self-report by interview (both groups):** All patients will be queried about their use of supplemental oxygen since the prior interview. Patients assigned to supplemental oxygen will be asked to estimate their daily hourly use in the past 7 days for their stationary and ambulatory systems separately. Patients assigned to control (no supplemental oxygen) will be asked if they have used supplemental oxygen since the prior visit and if yes, details will be recorded (calendar period of use; dose during rest, exercise, and sleep; estimated total daily hours of use).

- **Self-report of oxygen equipment, use and settings by mail every 2 months (supplemental oxygen group):** Patients 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 usual settings with their stationary and ambulatory systems.

- **Automated monitor report (planned):** 200 patients in the supplemental oxygen group will participate in substudy that will monitor adherence via recording monitors attached to their stationary and ambulatory oxygen systems. 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 patients in the self-report by mail.

8.2 Adherence monitoring by mail

Who

- Supplemental oxygen patients
- Clinical Coordinator
- Not the Adherence Educator (to try to keep adherence promotion activities separate from monitoring activities)

When

- Every 2 months from randomization through the end of the trial

How/what

- **Mailing to patient; Clinical Coordinator does the following:**
  - Generates and prints patient's personal equipment listing (OF form printout) from O2 Adherence data system
  - Prints blank oxygen equipment usage log appropriate to the patient's oxygen equipment
    - AS form, stationary concentrator and compressed gas tanks (print double-sided)
    - AQ form, liquid oxygen system (print double-sided)
    - AP, portable oxygen concentrator
  - Fills in items 1-6 (Section A) on the log form
  - Prepares stamped return envelope addressed to Clinical Coordinator
  - Prepares cover instructional memo to patient
  - Mails all items to patient
- **Upon receipt by patient, patient does the following:**
  - Checks OF listing for corrections (writes in corrections or writes "no changes")
  - Finalizes the oxygen equipment usage log (AS, AQ, or AP) form that the patient has been keeping for the past 2 months
    - Totals up liquid oxygen delivered
    - Counts up tanks used and records ending date for log
    - Reads meter on concentrator and records reading and date of reading
  - Returns completed log and marked up OF listing to clinic in envelope provided
  - Starts completing the blank log just received by entering the start date for the log
- **Upon receipt by clinic, Clinical Coordinator does the following:**
  - Checks OF form printout for updates, completes the Administrative Information section, and keys any needed updates to the O2 Adherence data system, and files in patient chart
  - Checks AS, AQ or AP form for completion and checks totals recorded by patient (calculates totals if patient omits these); completes Administrative Information section, keys form to O2 Adherence data system, and files in patient chart
- **Followup on unreturned reports:**
  - Clinical Coordinator should call patient if report is overdue by 1 week or more

Reports

- Reports of oxygen used per day (total hours per day and hours of stationary use and hours of ambulatory use) will be available from the O2 Adherence data system if oxygen usage forms are keyed for the patient

9 Adverse events and unanticipated problems

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9.1 Overview

The LOTT adverse event and unanticipated problem reporting protocol is based on NHLBI and OHRP guidelines

- NHLBI guidelines for reporting adverse events http://www.nhlbi.nih.gov/funding/policies/adverse.htm
- OHRP guidelines for reporting unanticipated problems http://www.hhs.gov/ohrp/policy/AdvEvntGuid.htm.

Definitions

- **Adverse event:** 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.
- **Unanticipated problem:** 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 patients 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
  - (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.

LOTT forms that may be used in reporting adverse events or unanticipated problems

- Unexpected Related Serious Adverse Event or Unanticipated Problem (AN) form
- Adverse Event/Unanticipated Problem Worksheet (EW) form
- COPD Exacerbation (EX) form
- Death Report (DR) form
- Followup Report for Event Previously Reported on AN, EX, or IE Form (FR) form
- Interim Event Report (IE) form
- History forms (HI, HT), procedure forms (SP, BV) or others relevant to the associated LOTT data collection

Classifying events

- 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.
- The Adverse Event/Unanticipated Problem Worksheet (EW) form can be used to classify an event and determine the appropriate reporting form and process

Local IRB requirements regarding adverse events

- Sites must always follow and comply with their own local institution's adverse event reporting requirements which may differ from those adopted by LOTT. Depending on the local requirements, a site may report events locally and not report those events to LOTT.

9.2 Reporting process

Unexpected serious adverse events possibly, probably or definitely related to LOTT participation and all unanticipated problems

- Report on the Unexpected Related Serious Adverse Event or Unanticipated Problem (AN) form
  - Fatal or life threatening events must 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 must be reported within 14 days of when the clinic learned of the event
- Each such event is reported on its own form
- Key the form and also send it to the DCC (see time frame requirements above)
- Each AN form received by the DCC will be forwarded to the DSMB, OHRP, NHLBI, CMS, study chair, and Steering Committee in real time
- Clinics will be instructed to forward the report to their IRB
- Unanticipated problems: The site where the event happened is responsible for reporting the event to OHRP; generally, the site's IRB does the resporting to OHRP

Unexpected related adverse events of lesser severity, unexpected unrelated events of any severity, or expected adverse events of any severity

- Report to LOTT on the Interim Event Report (IE) form or a regular interview form (HI or HT form); if the event is a COPD exacerbation, report to LOTT on the EX form
- If you want to bring the event to the immediate attention of the DCC, fax the IE, HT, or HI form to the DCC; otherwise, key the form and the form will be reported in aggregate form to the DSMB at the time of regular data reports
- All forms faxed to the DCC will be forwarded to the DCC Safety Officer for review and discussion by the Steering Committee and for consideration of immediate reporting to the DSMB.
- Similarly, the DCC has the option of bringing any event noted by its staff to the attention of the Steering Committee

9.3 Adverse events expected in LOTT

- 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.

9.4 COPD exacerbation reporting process

Definition

- Event characterized by a worsening in the patient's baseline dyspnea, cough, and/or sputum that is beyond normal day-to-day variation, is acute in onset, and may warrant a change in regular medications
- Note: It is hard to disentangle pneumonia from a COPD exacerbation; report any pneumonia as a COPD exacerbation unless there is a compelling reason not to do so; the EX form includes a check off to indicate that pneumonia is also present

Forms

- COPD Exacerbation (EX) form
- One exacerbation per EX form
- Followup Report for Event Previously Reported on AN, EX, or IE Form (FR) form

When to report

- In general, events should be reported on study forms and keyed to the database as soon as they are reported to clinical center staff; however, reporting of COPD exacerbations on the EX form may be delayed for a reasonable amount of time (eg, up to a month) until the exacerbation has resolved or stabilized; this will be a judgement call by clinic staff; we want the event evolved enough to characterize it and its treatment
- If you report the exacerbation before it has resolved, you can use the FR form for a followup report

Who

- Clinical Coordinator
- Study Physician

9.5 Example adverse event scenarios

Note: The sample scenarios provided below are given as examples to help staff think about the events that occur to their patients. The site needs to evaluate the event and their patient and determine their course of action. Completing the Adverse Event/Unanticipated Problem Worksheet (EW) form can help determine whether to report an event to LOTT and if reporting to LOTT, what form to report it on.

- **Massive nosebleed**: A patient assigned to the oxygen group develops massive epistaxis requiring posterior nasal packing, a three day hospitalization, and three units blood transfusion.
  - **Serious?** Yes. The patient was hospitalized and the event might be considered life-threatening.
  - **Unexpected?** No. Nosebleeds are a complication of oxygen therapy that are noted on the consent form. Some judgment is required whether the severity of the nosebleed is in keeping with that associated with oxygen treatment. If it is judged to be more severe than anticipated, then this would be answered No.
  - **Related?** Yes.

- **Spontaneous pneumothorax**: A patient in LOTT assigned to oxygen is hospitalized with acute shortness of breath and is found to have a pneumothorax requiring a chest thoracostomy tube.
  - **Serious?** Yes. The patient was hospitalized.
  - **Unexpected?** No. Pneumothorax is a known complication of COPD, even though it is not noted in the consent form.
  - **Related?** No. There is no known association of oxygen treatment with development of a pneumothorax.

- **Pneumothorax after study visit:** A patient in LOTT in the non-oxygen group has a study visit with performance of spirometry and a six-minute walk test. The evening after the visit, the patient develops some vague chest pain and the next morning is brought to the emergency room with increasing dyspnea. A chest x-ray shows a pneumothorax, which is treated with simple needle aspiration and the patient is observed for 12 hours without recurrence. He is sent home for a follow-up visit with his physician the next day.
  - **Serious?** No. The patient was not hospitalized. Some physicians might consider this life-threatening, but the fact that he was sent home suggests that it was a small pneumothorax.
  - **Unxpected**: No. Spontaneous pneumothorax is a known complication of COPD. However, pneumothorax is not specifically mentioned in the consent form as a complication of spirometry or six-minute walk, so this might be answered yes if the respondent thinks that it was related to these tests.
  - **Related?** Possibly. The deep inspirations associated with the lung function testing or exertion during the six-minute walk might have been associated with the pneumothorax. If the chest pain and dyspnea occurred more than two days after the testing procedures, then it would reasonably not likely be associated with the testing.

- **Fatal COPD exacerbation:** A patient has a COPD exacerbation requiring admission to the ICU, and after a period of respiratory failure dies with ventilator-associated pneumonia.
  - **Serious?** Yes. The event was both life-threatening, and fatal, and required hospitalization.
  - **Unexpected?** No. Patients with COPD are susceptible to respiratory failure.
  - **Related?** No.

- **Sudden death:** A patient with COPD in the non-oxygen group is found dead in bed in the morning. He was apparently in his usual state of health the night before. No autopsy is performed. Review of records indicated that the patient had periodic nocturnal desaturations but not to an extent that excluded him from LOTT.
  - **Serious?** Yes. The event was fatal.
  - **Unexpected?** No. Patients with COPD are known to be susceptible to sudden death, although it is not listed on the consent form as a complication of treatment.
  - **Related?** Possibly. It is a reasonable assertion that COPD patients with nocturnal desaturations are more susceptible to sudden death at night, but this is not well-established by evidence. Moreover, there is no evidence that indicates that such patients treated with oxygen benefit in terms of mortality.

- **House fire:** A home of one of the LOTT patients on oxygen burns down and the patient's wife receives life-threatening burns. The LOTT patient has a minor exacerbation from the smoke and is not hospitalized, but is given a course of prednisone to take as an outpatient. Investigation of the fire indicates that it started in the kitchen and that the oxygen tank in the kitchen was an accelerant.
  - **Serious?** No. Even though the wife had a serious adverse event, she is not, strictly speaking a LOTT participant. The participant was not hospitalized and the records indicate that his smoke exposure was not life-threatening.
  - **Unexpected?** No. Fires are listed as a complication of oxygen treatment.
  - **Related?** Yes. The investigation indicated that the oxygen supplied by LOTT was, in part, responsible for the fire.

- **Subdural hematoma:** A patient is undergoing spirometry for a LOTT visit. He becomes light-headed and passes out, hitting his head on a radiator. He does not lose consciousness. Three days later he notes weakness of his left hand and he is brought to the emergency room where a head CT demonstrates a subdural hematoma. The hematoma is evacuated and after a three-day hospitalization he is sent home without residual effects.
  - **Serious?** Yes. The patient required hospitalization and the event was potentially life-threatening.
  - **Unexpected?** Yes. Subdural hematoma is not a well-described complication of pulmonary function testing, and is not described in the consent form.
  - **Related?** Yes. The head injury occurred during the testing procedure.

- **Rapid atrial fibrillation:** A patient develops light-headedness and chest pressure during a six minute walk test. The heart rate is 149 at the termination of the test. The symptoms persist and the heart rate does not slow after 5 minutes of resting in a chair. The patients vital signs are otherwise normal. An EKG shows atrial fibrillation. The patient is sent to the ER, where an acute MI is ruled out in the short-stay unit (less than 24 hours). The atrial fibrillation spontaneously converts to normal sinus rhythm after treatment and the patient is sent home.
  - **Serious?** No. The event was not life-threatening, and the patient did not stay overnight in the hospital.
  - **Unexpected?** Yes (?). The consent form did not mention atrial fibrillation as a complication of six-minute walk testing. However, it is known that patients with COPD are prone to develop atrial fibrillation.
  - **Related?** Probably. Exercise may induce atrial fibrillation.

- **Hip fracture after tripping over oxygen tubing, inability to recover and ultimately death:** A patient trips over their oxygen tubing, breaks a hip, and never walks again and dies in a nursing home 3 months later.
  - **Serious?** Yes.
  - **Unexpected?** No. Tripping over tubing is mentioned in the consent form.
  - **Related?** Yes.

- **Excessively high heart rate:** Patient who is screening for LOTT starts resting oximetry which shows a pulse rate greater than 150. Coordinator obtains EKG on patient, calls patient's physician, and patient is admitted to the hospital. Patient had not performed spirometry or 6 minute walk for LOTT – just the consent, interview, and then resting oximetry was started.
  - **Serious?** Yes.
  - **Unexpected?** Yes.
  - **Related?** No.

LOTT MOP

10 Cause of death adjudication

Determining cause of death for LOTT decedents will be the responsibility of the individual site director.

1. General considerations

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 information that is relevant to the interpretation of the treatment effects of the trial may be captured.

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 site directors adjudicate the cause of death using a common conceptual framework. Reliability of this method will be determined by having a sample of deaths adjudicated by a second independent reviewer.

2. Acquisition of medical records

Ascertainment of cause of death will require acquisition of medical records and information on the events surrounding death for each decedent. This process can be arduous, but is facilitated by the following:

- Having each patient sign a medical release of information at each annual visit, because some jurisdictions will not recognize medical releases more than 12 months old.
- Maintaining timely contact information for each patient's next of kin who are required to sign for release of death certificates containing diagnosis in certain jurisdictions.
- Direct involvement of study physicians in contact with medical facilities, treating sources, and family witnesses to obtain information.

Medical facilities will sometimes refuse to transmit medical information for the purpose of research, citing HIPAA restrictions. Research physicians, however, are considered treating physicians for patients enrolled in clinical research studies under their supervision. Thus, they are not excluded from acquiring medical records of research patients under HIPAA for the purpose of medical treatment and quality assurance. Such records are essential for reporting of serious adverse events to IRBs or other levels of review, and for ascertainment whether treatments or trial participation are potentially harmful to patients.

Medical records that should be obtained on each decedent are:

- Records of final hospitalization including discharge summary, reports of radiographs, pathology reports, operative reports, autopsy reports.
- Witness accounts for out of hospital deaths.
- Pathology report confirmation of all cancer diagnoses.

3. Witness interviews

For patients who die out of hospital, witness accounts are important for determining cause of death. Usually, this involves contacting next of kin, which can be an uncomfortable situation shortly after a study patient has died. Experience, however, has shown that next of kin are less likely to be cooperative in providing information the longer the duration after death.

The witness interview should start with an introduction by the site director that the deceased was a patient in a research trial conducted by the site director and to express condolences and appreciation that the

decedent participated in the research. It should be explained that, as a part of the research it is important to know the circumstances of the patient's death and ask if they would be willing to answer a few questions in a brief interview. If necessary, it is also important to ask the next of kin if they would sign a release to obtain any medical information, including death certification. This should be mailed immediately with a stamped return envelope to the next of kin if they agree. If family members indicate that they do not wish to speak about the death, they should be asked whether they would agree to speak at a later time or if there is another family member who might be willing to be interviewed.

The witness interview should include the following points:

- When was the decedent last seen alive prior to death?
- Was the decedent in their usual state of health?
- Were there any symptoms that preceded the death? Specifically, was there increasing shortness of breath, a respiratory infection, or chest pains?
- When had the decedent last seen a physician? Who was the physician and what is their contact information?
- What were the circumstances of the death?
- Was an autopsy performed?
- Are there any other family members or witnesses who should be interviewed?

4. Assignment of cause of death

The following principles, which were developed and used by the TORCH clinical endpoint committee, should be used in determination of cause of death.

The site director will designate cause of death by probable cause. Causes of death will be grouped by general categories, e.g. Respiratory, Cardiovascular, Cancer, or Other. If a cause of death cannot be ascertained, the cause of death will be classified as Unknown. The general principles and methods used in this classification are:

4.1 All diagnoses of cancer should be corroborated by the primary medical record. This should include imaging studies, histologic diagnoses, operative or procedure notes, and records of treatment. If the primary medical record cannot be obtained to confirm the diagnosis, this should be affirmatively stated in the documentation, and the committee will determine a diagnosis based on their best judgment.

Patients who die with an uncured cancer will be designated as dying from the cancer. For example, a patient with documented gastric cancer who dies of gastrointestinal hemorrhage will be classified to have died from gastric cancer. A patient who dies from neutropenic sepsis while undergoing chemotherapy for lymphoma will be classified as dying from lymphoma.

Relatively low-grade cancer that is not metastatic, e.g. localized skin cancer or prostatic cancer, will not be generally be designated as cause of death, unless the death was a complication of treatment for such cancers.

4.2 Death certificates should be sought in all cases. If they cannot be obtained, it should be affirmatively stated in the documentation.

4.3 If medical records are inadequate and cannot be obtained as affirmatively stated in the documentation, a cause of death will be adjudicated based on the best available evidence of record. If a probable cause of death cannot be adjudicated, it will be classified as unknown.

4.4 The primary cause of death should be attributed to the disorder that causes the patient to

present for medical treatment. This should be distinguished from terminal events that are the immediate cause of death.

- For example, if a patient is admitted to the hospital with a COPD exacerbation, from which they do not fully recover, and the patient subsequently develops complications such as pneumonia, respiratory failure, renal failure, sepsis, or myocardial infarction, the primary cause of death will be attributed to COPD.
- For example, if a patient undergoes surgery for cancer and dies from complications of the surgery or during the immediate post operative period, the primary cause of death will be attributed to cancer, even if the cancer was potentially curable by the surgery.
- For example, if a patient is admitted to the hospital with pneumonia and develops complications such as respiratory failure, gastrointestinal bleeding, etc. the cause of death will be attributed to pneumonia.
- If it is unclear if a patient is admitted with a COPD exacerbation or pneumonia, the cause of death will be based on the hospital admission chest radiograph. If pneumonia is present on the admitting chest radiograph, the cause of death will be designated pneumonia. If pneumonia is present only on subsequent chest radiographs, the cause of death will be designated as COPD.

4.5 Sudden death is defined as death that occurs within 24 hours of being observed alive and without evidence of a deteriorating medical condition. If the interval between death and last being observed alive is greater than 24 hours, and there is no other known cause of death, the cause of death will be classified as unknown.

- The diagnosis of myocardial infarction will require pathologic evidence, or evidence of medical records, including electrocardiographic tracings, blood enzyme measurements, and compatible clinical findings.

4.6 In cases of out of hospital death, the Clinical Coordinator or Study Physician should interview family or witnesses to ascertain the following information:

- When was the decedent last known to be alive?
- When was the decedent found to be deceased?
- What were the events surrounding the death?
- Did the decedent have any symptoms or change in health status that preceded the death? Special reference should be made to dyspnea, febrile illnesses, chest pain, abdominal pain, syncope, seizures, paralysis and change in mental status.
- Were there recent medical visits or recent changes in medication?
- Was an autopsy performed?
- Permission to obtain medical records should be requested from next-of-kin.

5. <u>Determination of COPD relatedness.</u>

All cases will have a secondary classification to determine whether the death is related to COPD. The possible choices are YES, NO, UNKNOWN, POSSIBLE, PROBABLE.

5.1 All cases where primary cause of death is COPD will be classified as YES

5.2 In cases where primary cause of death is NOT COPD, the classification of COPD relatedness will be based on the sequence of terminal events:

- If the terminal event is documented to be hypercapnic respiratory failure or failure to wean from a ventilator the case will be classified YES

- For example, patient dies in hospital on ventilator but succumbs to fatal pneumonia, arrhythmia, or care is withdrawn.

• If the patient would have been judged to have survived the terminal illness had COPD not been present, the case will be classified YES
  - For example, patient dies from Stage I lung cancer because they have insufficient lung function to undergo surgery.
• For example, patient has pneumonia or influenza that is fatal, but a patient without COPD would have, more likely than not survived.
• If the death occurs at home, where the patient is receiving palliative care for advanced COPD, the case will be classified YES
  - For example, a patient receiving continuous oxygen, confined to bed and chair, with cor pulmonale, or with advanced malnutrition.
• If the terminal event is NOT respiratory, and would be likely fatal for patients without COPD, the case will be classified NO.
  - For example, death from metastatic cancer, cerebral hemorrhage, meningitis, severe cardiomyopathy, or cardiogenic shock.
• If there is another clear explanation for terminal respiratory failure that would likely have occurred in patients without COPD, then the case will be classified NO
  - For example respiratory failure secondary to CVA, drug overdose, or asphyxia.

5.3 If the data are inadequate to make a clear YES or NO classification, it will be designated as UNKNOWN, POSSIBLE, or PROBABLE based on the best evidence available.

6. Data quality/reliability

[To be determined]

11 Certification and clinical center operations

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11.1 Overview

What is certification?

- It is an internal (i.e., related to the study) procedure designed to identify the staff responsible for specific data items or data collection procedures or decisions about eligibility.
- It is a managerial and quality assurance tool for the trial.

Who and what does it apply to?

- It applies to:
  - LOTT staff at RCCs and satellites
  - Each RCC and satellite
- Certification for LOTT is required before any patient visits or data collection may occur; patients may not begin any screening examinations, sign any consent statements, or complete any study forms until the clinical site has been certified for the trial.
- More than one staff member may be certified for a function and it is recommended that more than one staff member be certified for a function.

Why do we require it?

- Primary purpose is to help assure consistent conduct of the trial over time, within and across clinical sites. The conduct of procedures should be similar across patients and in serial testing of the same patient over the duration of followup.
- Study procedures may vary from the usual practice of a participating clinical site, but it is important that methods be carried out in the same manner within and across clinical sites.
- It identifies the staff and sites that carry out study procedures and identifies to staff that they and their site are a part of the LOTT trial.
- It provides a mechanism for tracking who collected key data items or made key decisions.
- The certification process may help a clinical site prepare for LOTT activities by presenting the training, facility, and equipment needs in an organized fashion and requiring acquisition or completion of these items before LOTT specific activities may begin.

11.2 Personnel certification

Staff functions requiring certification

- Study Physician
- Principal Clinical Coordinator
- Clinical Coordinator
- Principal Adherence Educator
- Adherence Educator
- Oximetry Technician
- Six Minute Walk Tester
- Spirometry Technician
- Data Entry Technician
- Physical Exam Assessor (if staff member is neither a Study Physician nor Clinical Coordinator; Study Physician and Clinical Coordinator certification includes certification for completion of physical exams for LOTT)

Requirements

- Everyone
  - Read the LOTT Protocol
  - Read the LOTT consent statement
  - Complete the Knowledge Assessment (KA) form; this is a written general knowledge assessment about the LOTT (open book)
  - Complete the Personnel Certification (CP) form; this form identifies the functions applied for and provides an assurance of data confidentiality and integrity
- Additional requirements for Study Physician
  - Be an MD or DO
  - Site director (RCC Principal Investigator or Satellite Center Director) must sign a statement that staff member is approved to act as Study Physician for the site
- Additional requirements for Principal Clinical Coordinator
  - Each RCC can have only one Principal Clinical Coordinator
  - Must complete the additional requirements for Clinical Coordinator
- Additional requirements for Clinical Coordinator
  - Read Manual of Operations, Part 1: Patient Procedures and Clinical Center Operations
  - Read Manual of Operations, Part 2: Web-based Data Management System
  - Complete the requirements for Data Entry Technician certification
  - Site director (RCC Principal Investigator or Satellite Center Director) must sign a statement that staff member is approved to act as Clinical Coordinator for the site
- Additional requirements for Principal Adherence Educator
  - Each RCC can have only one Principal Adherence Educator
  - Must complete the additional requirements for Adherence Educator
- Additional requirements for Adherence Educator
  - Also see Adherence Educator Training Manual
  - Site director (RCC Principal Investigator or Satellite Center Director) must sign a statement that staff member is approved to act as Adherence Educator for the site
  - Satisfactory completion of the Knowledge Assessment for Adherence Educator (KE) form
  - Satisfactory completion of an interview with Kathleen Harrington of the University of Alabama
- Additional requirements for Oximetry Technician
  - Read Manual of Operations sections on resting oximetry, 6 minute walk with oximetry, and 24-hour oximetry, and ambulatory oxygen dosing

  - Work with a practice patient to complete 3 practice resting oximetry sessions including completion of MO form and submit the forms to the DCC; use xx000 for the patient ID (xx=your site ID, eg, aa for the BWH RCC, fb for the Loma Linda VA satellite of LABRI RCC) and any 4 character text string for the patient code
- Additional requirements for Six Minute Walk Tester
  - Must be certified in cardiopulmonary resuscitation with a minimum of Basic Life Support by an American Health Association-approved cardiopulmonary resuscitation course
  - Read Manual of Operations sections on 6 minute walk with oximetry
  - Work with a practice patient to complete 3 practice 6 minute walks including completion of MM form and submit the forms to the DCC; use xx000 for the patient ID (xx=your site ID, eg, aa for the BWH RCC, fb for the Loma Linda VA satellite of LABRI RCC) and any 4 character text string for the patient code
  - Site director (RCC Principal Investigator or Satellite Center Director) must sign a statement that staff member is approved to do six minute walk testing and associated oximetry for the site
- Additional requirements for Spirometry Technician
  - Site director (RCC Principal Investigator or Satellite Center Director) must sign a statement that staff member has completed at least 50 spirometry sessions that meet ATS standards and is approved to do spirometry for the site
- Additional requirements for Data Entry Technician
  - Complete the Data Entry Certification/Decertification Request (CD) form
  - Read Manual of Operations, Part 2: Web-based Data Management System
  - Complete the data system tutorial
  - RCC Principal Investigator, Satellite Center Director, or RCC Principal Clinical Coordinator must sign a statement that staff member is approved to do data entry for the site
- Additional requirements for Physical Exam Assessor
  - RCC Principal Investigator must sign a statement that staff member is approved to complete physical examinations for LOTT for the site

Process

- Send required materials to the DCC
- The DCC will send written notice of approval for certification or pending certification
- Each staff member will be issued a Personnel Identification Number (PIN)

Staff PINs

- Each staff member certified for at least one function will be issued a PIN which will consist of 4 characters – the 1st character will identify the RCC, the 2nd character will identify the satellite site, and the next two characters will be a sequential number assigned by the DCC
- The PIN is used when completing forms
- The Data Entry Technician uses his/her PIN when signing on to the LOTT data system
- Staff may be certified for more than one function but will have only one PIN

11.3 RCC and satellite certification

General comments

- Each clinical site (RCC or satellite) participating in LOTT must be certified for that participation
- Each RCC must complete the Regional Clinical Center Certification (CR) form
- Each satellite must complete the Satellite Certification (CS) form
- IRB approval for the LOTT protocol and consents is required
- The DCC certifies RCCs and the DCC certifies satellites that an RCC proposes and submits forms for

Purpose of clinical site certification

- Provide information regarding how the clinical site will conduct different aspects of the protocol
- Guide a clinical site through the steps of getting ready for the LOTT – provide a checklist of what needs to be in place before patient activities begin

Requirements for certification of a clinical site

- Complete the appropriate clinical site certification form (CR or CS form)
- Certify at least one person for each function that the site will conduct that requires certification (a person may be certified for more than one function)
- Obtain IRB approval of the LOTT protocol and consent documents
- Satellite sites: the satellites's RCC must be certified
- Receive written notice of approval (email) from the DCC that the site is certified

11.4 Data management at satellite sites

General

- Each RCC and satellite pair may decide how data entry of forms for patients seen at the satellite will be handled; options are:
  - Satellite does data entry for its patients
  - Satellite sends forms to the RCC for data entry at the RCC
- The LOTT data management system is structured so that satellite sites may complete data entry on site at the satellite through certification of a Data Entry Technician located at the satellite and by accessing the data management website through their RCC's portal
- If a RCC and satellite pair decide that the satellite's patient forms will be sent to the RCC for keying, then there are some issues to be considered

Forms management considerations if the satellite sends forms to the RCC for entry

- **How will the forms get to the RCC from the satellite and where will the originals be stored:** Will the satellite messenger or mail original forms from the satellite to the RCC for keying and then keep the originals at the RCC or send them back to the satellite, or will the satellite fax forms to the RCC? The original forms, wherever they reside, are the official LOTT records. The original forms and the electronic database must match at all times.
- **How will edits to forms be managed:** If a satellite faxes forms to the RCC for data entry, the RCC and satellite will need to consider the following issues. Faxing creates a third set of forms -- the paper originals at the satellite are one set, the paper faxes at RCC are a second set, and the electronic database is a third set and all 3 sets must match at all times. The DCC advice is that sites consider faxed forms to be transient. If the Data Entry Technician at the RCC is able to key the form as completed, he/she should dispose of the faxed form immediately after keying. If a correction is needed, the Data Entry Technician at the RCC should key the form as completed to the extent possible and key the questionable items with question marks (items keyed with question marks will be listed in batch edits from the DCC and hence will eventually have to be reviewed). If the data system will not accept question marks, the Data Entry Technician should cancel the transaction. The Data Entry Technician SHOULD NOT key the form the way it should have been completed. A postit note should be affixed to the form with the problems to remind RCC staff that an edit is pending and the satellite should be informed of the problem. The Data Entry Technician at the RCC should insist that corrections be made to the original form and the corrected, original page be refaxed to the RCC. When the corrected page is received, the correction should be keyed and the faxed form and the faxed corrected page should be disposed of. The purpose of the postit note is to remind RCC staff that edits are pending and where the corrections need to be made. If RCC staff are firm in insisting that corrections be made to the original form and that the corrected page be refaxed before the correction is keyed to the database, and if forms from the satellite are complete, correct, and legible when faxed for data entry, this process should go reasonably well. Satellite sites do have an extra burden on them to make their forms as correct as possible before the forms are sent for data entry, since the process of correcting errors is complicated by the original form not being available to the Data Entry Technician and since faxing and photocopying reduces legibility.
- **How will the satellite keep track of which satellite forms have been keyed and which need to be keyed:** As forms are keyed, the keyed box at the top of each form should be checked, dated, and initialed by the Data Entry Technician. In the case of forms faxed from a satellite, the original form is not available for such annotation. Satellite staff should note on each form the date when it was faxed to RCC. The RCC could send the satellite an inventory of forms keyed for the patient (the LOTT data management system has the capability of printing an inventory of all forms keyed for a patient). The RCC could print such an inventory whenever forms are keyed for a patient or at pertinent points in screening or followup. The satellite could then annotate the original form with a check indicating that the form has been keyed. Another alternative is for the RCC to print the

keying confirmation screen after the form has been keyed and to provide that printout to the satellite. The satellite could attach that printout to the form.

11.5 Communications between sites and website access

- All staff may communicate with the DCC, but satellite staff should copy their RCC Principal Clinical Coordinator on all communications to the DCC and similarly, the DCC will include the RCC Principal Clinical Coordinator on all communications with satellite staff
- All satellite and RCC staff will have access to the study website, www.lottsite.org
- Satellite staff will access the study data system website through their RCC's portal, but each Data Entry Technician, both those at RCCs and at satellites, will use their own PIN and their own password

11.6 Site use of the LOTT laptop

LOTT rules for use of the LOTT laptop include:

- Prohibition from installing software applications or files on the laptop or flash drive except as instructed by the Data Coordinating Center;
- Prohibition from changing any security settings, including passwords and account names; and
- Prohibition from attempting to store any PHI on the laptop.

11.7 Transfer patients

Some sites have patients who are moving to a new location that is near another LOTT site and who want to continue participating in LOTT. The steps, issues, and procedures related to transfer of patients from one LOTT site (the enrolling site) to another LOTT site (the adopting site) are:

- **Discuss the prospective transfer with the proposed adopting site:** The first step should be for the enrolling principal investigator/coordinator to talk with the proposed adopting principal investigator/coordinator about transfer. LOTT supports and encourages transfers but recognizes that individual sites have to be able to work out the details within their institutional constraints.

- **ID number and code:** The patient will continue to use the ID number and code under which the patient was randomized regardless of where the patient completes visits.

- **Consent:** At the first visit to the adopting site, the patient should sign the LOTT consent, HIPAA statement, and medical records release form in use at the adopting site. The adopting site should check with their IRB for any additional local requirements for transfer patients.

- **Timing of transfer:** The initial visit at the adopting site should be an in person visit; this will allow the patient to sign the LOTT consent and HIPAA statement in use at the adopting site before that site attempts to collect any data from the patient. Until an in person visit has been completed at the adopting site, the enrolling site should continue to complete telephone and mail followup visits and telephone adherence contacts.

- **Transfer Notification (TN) form:** The Transfer Notification (TN) form is the mechanism by which the DCC is notified of the transfer so that credit for completed visits can be assigned correctly and it is also the mechanism by which the LOTT data system is modified so that the adopting site may key the patient's data. It is needed for both transfers within an RCC network and transfers across RCC networks. The enrolling site initiates the TN form – the enrolling site completes Parts A-C of the TN form and then sends it to the adopting site; the adopting site completes Parts D-E and then sends the form to the DCC. The DCC will key the form to the LOTT data system and will notify the adopting site when data entry may begin. The completed TN form should be sent to the DCC before the patient completes the first visit at the adopting site.

- **Data entry in the LOTT data system:**
  - Transfer within a RCC network of sites: There are no data entry issues for transfer within an RCC network of sites; the adopting site will be able to key forms for the patient without the DCC modifying the data system.
  - Transfers from one RCC network into another RCC network: The adopting site will be able to key forms for the patient once the DCC has processed and keyed the Transfer Notification (TN) form to the data system. If the patient is transferring between RCCs, the DCC will notify the adopting site when data entry may begin. After the TN form is keyed by the DCC, the data system tasks such as Missing forms, Visits due, etc will list the transfer patient as one of the adopting site's patients.

- **Oximetry:** When the adopting site completes oximetry for the transfer patient, the RCC entered into the LOTTOx software must be the enrolling RCC, not the adopting RCC; the adopting site will be able to key in the transfer patient's ID number on the LOTT laptop if the RCC is specified as the enrolling RCC (the LOTTOx software will allow you to choose any of the RCCs in the drop down menu but recognizes which ID numbers are associated with each RCC). Note – oximetry files for visits completed at the enrolling site cannot be transferred to the adopting site.

- **Patient materials to send to adopting site:** Items that the enrolling site should provide to the adopting site before the patient attends the first visit at the adopting site are:
  - The patient's visit window listing
  - The patient's follow-up visit labels
  - The most recently completed Interim History (HI) and Interim History at 4 months Telephone Visit (HT) forms
  - If the patient is assigned to the oxygen group, then the most recently completed Adherence Contact (AH) and Ambulatory Oxygen Dose (MP) forms should be sent, as well as the most recent OF form (oxygen equipment listing)
  - The adopting site may request additional records from the enrolling site if desired.

- **Oxygen services:** If the patient was randomized to oxygen, the adopting site should work with the patient and the new oxygen company to get the OF listing updated with the new equipment; send the marked up OF form to the DCC and the DCC will generate an updated OF form.

- **Shared transfers:** If a patient wants to attend visits at more than one LOTT site, the DCC is OK with this, but data entry of the patient's forms needs to be done at the enrolling site. The adopting site would complete the forms and then fax or email them to the enrolling site for data entry. Modifying the data system to allow a patient's data to be keyed at multiple RCCs simultaneously is not possible.

- **Transfer from a VA site to a non VA site:** There may be difficulties if the patient is a veteran without Medicare coverage and the adopting site is not a VA site. Prior to initiation of the transfer, the enrolling site should explore the issues with the proposed adopting site and the local (non LOTT) VA and determine if there is any mechanism by which the adopting site can be reimbursed for LOTT clinical services (visit procedures) and if there is any way to continue the LOTT oxygen treatment previously paid by the enrolling VA. For instance, it may be possible to continue oxygen treatment with the local (non LOTT) VA paying for the oxygen if the patient has exercise desaturation, since the VA will pay for oxygen under those conditions. If reimbursement for clinic visit procedures cannot be worked out, then the plan to transfer should be abandoned and the enrolling site should continue to follow the patient by mail and phone (i.e., the enrolling site will continue to do the 4 month telephone visits and will complete the annual visit interim history by phone and the questionnaires by mail) provided the patient is willing. In person procedures will be missed. If reimbursement for clinical procedures but not oxygen treatment is possible at the adopting site, then you should proceed with the transfer, but oxygen treatment will stop. Document the cessation of oxygen treatment with a Post Randomization Initiation or Cancellation of Home Oxygen Treatment (TC) form. Followup visits can continue, even if oxygen treatment has stopped.

- **Transfer from non VA site to a locale with only a LOTT VA site available:** This type of transfer will not work in LOTT – LOTT VA sites will not be able to provide clinical services and oxygen supervision for participants who are not veterans. Therefore, the enrolling site should continue to follow the patient by mail and telephone to the extent possible, and oxygen therapy, if applicable, should be maintained as long as possible. The enrolling site should contact the patient to complete interim history interviews and questionnaires by phone and mail respectively, if the patient is willing. Interviews should continue even if oxygen treatment has to be stopped. If oxygen treatment is stopped, document the change in treatment with a Post Randomization Initiation or Cancellation of Home Oxygen Treatment (TC) form.

- **Capitation payments:** Once the TN form has been processed by the DCC, the monthly capitation report will list newly completed visits for the patient under the heading of the site completing the visit.

- **Accounting in performance tables:** Once the TN form has been processed by the DCC, the DCC will attempt to apportion credit and debit for visits made by transfer patients between the adopting and enrolling sites appropriately.

12 Forms management

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12.1 RCC and satellite identifiers

General

- RCCs are identified by
  - 2-5 character alphabetic RCC ID
  - Single character letter code
  - Site ID constructed from the single character letter code identifying the RCC and the satellite letter code identifying the site (see below)
- Alphabetic RCC IDs are based on the name of the institution with which the RCC is affiliated
- The single character letter code assigned to an RCC is the first character in the ID numbers assigned to that RCC (and its satellites) and is also the first character in the staff PINs assigned to that RCC (and its satellites)
- Each satellite will be assigned a single character letter code unique within each RCC; this code is the second character in the ID numbers assigned by that RCC
- This strategy identifies the RCC and satellite which enrolled each patient and identifies the staff member at each RCC and satellite

Assigned RCC IDs

Institution	Alpha ID	Letter code	Prefixes for Patient IDs
Brigham and Women's	BWH	a	aa (RCC), ab (1st satell), ac (2nd satell) ...
Cleveland Clinic	CLCF	b	ba (RCC), bb (1st satell), bc (2nd satell) ...
Denver Health and Hospital	DHHA	c	ca (RCC), cb (1st satell), cc (2nd satell)...
Duke Medical Center	DUKE	d	da (RCC), db (1st satell), dc (2nd satell) ...
Kaiser Hospital Foundation	KFH	e	ea (RCC), eb (1st satell), ec (2nd satell) ...
Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center	LABRI	f	fa (RCC), fb (1st satell), fc (2nd satell) ...
Ohio State University	OSU	g	ga (RCC), gb (1st satell), gc (2nd satell) ...
Temple University	TU	h	ha (RCC), hb (1st satell), hc (2nd satell) ...
University of Alabama	UAB	j	ja (RCC), jb (1st satell), jc (2nd satell) ...
University of Michigan	UMI	k	ka (RCC), kb (1st satell), kc (2nd satell) ...
University of Pittsburgh	UPIT	m	ma (RCC), mb (1st satell), mc (2nd satell) ...
University of Utah	UUT	n	na (RCC), nb (1st satell), nc (2nd satell) ...
University of Washington	UW	p	pa (RCC), pb (1st satell), pc (2nd satell) ...
Washington University	WU	r	ra (RCC), rb (1st satell), rc (2nd satell) ...

Satellite codes

- The code "a", as a satellite ID, is reserved for the RCC; b, c, d, e, f, g, h, j, k, m, n, p, r, s, t, u, v, w, x, y will be assigned in sequence to satellites certified by the RCC; the letters i, l, o, and q are not used due to their potential confusion to numbers
- Satellite letter codes will be assigned by the DCC during certification; satellites are jointly certified by the RCC and the DCC
- There is no minimum number of satellites nor a cap on satellites

Examples

- The Brigham and Women's Hospial RCC has at least 3 identifiers:
  - Their RCC ID is BWH
  - Their single character letter code is "a"
  - Their Site ID is "aa"
- The Boston VA satellite of the BWH RCC has satellite letter "c" and Site ID "ac"
- The Boston Medical Center satellite of the BWH RCC has satellite letter "d" and Site ID "ad"

12.2 Patient identifiers

What

- Patient ID number
- Patient code

Patient ID number

- Patient ID numbers have the format zxnnn (2 alpha characters, 3 numeric characters) where z identifies the RCC, x identifies the satellite, nnn is a sequential number
- ID numbers beginning za belong to the RCC assigned the letter code z (i.e., satellite code a is reserved for the RCC)
- Preprinted ID number labels (used with the Registration (RG) form) will be distributed to sites by the DCC; if more labels are needed, contact the DCC
- Letter codes i, l, o, and q are not used for RCCs nor for satellites because of their potential confusion with numbers

Ranges of patient IDs assigned to RCCs and their satellites

Brigham and Women's	BWH	aa001-aa999, ab001-ab999, ac001-ac999, etc
Cleveland Clinic	CLCF	ba001-ba999, bb001-bb999, bc001-bc999, etc
Denver Health and Hospital	DHHA	ca001-ca999, cb001-cb999, cc001-cc999, etc
Duke University	DUKE	da001-da999, db001-db999, dc001-dc999, etc
Kaiser Foundation Hospitals	KFH	ea001-ea999, eb001-eb999, ec001-ec999, etc
Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center	LABRI	fa001-fa999, fb001-fb999, fc001-fc999, etc
Ohio State University	OSU	ga001-ga999, gb001-gb999, gc001-gc999, etc
Temple University	TU	ha001-ha999, hb001-hb999, hc001-hc999, etc
University of Alabama	UAB	ja001-ja999 , jb001-jb999, jc001-jc999, etc
University of Michigan	UMI	ka00a-ka999, kb001-kb999, kc001-kc999, etc
University of Pittsburgh	UPIT	ma001-ma999, mb001-mb999, mc001-mc999, etc
University of Utah	UUT	na001-na999, nb001-nb999, nc001-nc999, etc
University of Washington	UW	pa001-pa999, pb001-pb999, pc001-pc999, etc
Washington University	WU	ra001-ra999, rb001-rb999, rc001-rc999, etc

Patient code

- 4 character alpha code generated randomly by the DCC and printed on the ID number label
- Each patient code is unique across the LOTT

12.3 Visit ID code

- 1 to 3 character alpha-numeric code
- Generally of the format txx where t designates the time units or visit type and xx designates the ideal number of units from randomization that the visit should occur; for example, the w01 visit ideally takes place 1 week after randomization and the f04 telephone followup visit ideally takes place 4 months after randomization and the a04 adherence promotion contact ideally takes place 4 months after randomization
- Every visit has a window surrounding the ideal date for the visit; the visit may take place at any time during the window and the data collected will be valid data for that visit
- Visit ID codes

sb	Screening and baseline
rz	Randomization (both groups)
rx	Visit shortly after randomization for determination of ambulatory oxygen dose (supplemental oxygen group)
w01	1 week adherence promotion contact (both groups)
w02	2 weeks adherence promotion contact (supplemental oxygen group)
w03	3 weeks adherence promotion contact (supplemental oxygen group)
w04	4 weeks adherence promotion contact (supplemental oxygen group)
a02	2 months adherence promotion contact (supplemental oxygen group)
a03	3 months adherence promotion contact (supplemental oxygen group)
f04	4 months telephone visit (both groups)
a04	4 months adherence promotion contact (supplemental oxygen group)
a05	5 months adherence promotion contact (supplemental oxygen group)
a06	7 months adherence promotion contact (supplemental oxygen group)
f08	8 months telephone visit (both groups)
a08	8 months adherence promotion contact (supplemental oxygen group)
a10	10 months adherence promotion contact (supplemental oxygen group)
f12	12 months (1 year) clinic visit (both groups) and adherence promotion contact (supplemental oxygen group)
f16	16 months telephone visit (both groups)
f20	20 months telephone visit (both groups)
f24	24 months (2 years) clinic visit (both groups) and adherence promotion contact (supplemental oxygen group)
f28	28 months telephone visit (both groups)
f32	32 months telephone visit (both groups)
f36	36 months (3 years) clinic visit (both groups) and adherence promotion contact (supplemental oxygen group)
f40	40 months telephone visit (both groups)
f44	44 months telephone visit (both groups)
f48	48 months (4 years) clinic visit (both groups) and adherence promotion contact (supplemental oxygen group)
f52	52 months telephone visit (both groups)
f56	56 months telephone visit (both groups)

f60	60 months (5 years) clinic visit (both groups) and adherence promotion contact (supplemental oxygen group)
f64	64 months telephone visit (both groups)
f68	68 months telephone visit (both groups)
f72	72 months (6 years) clinic visit (both groups) and adherence promotion contact (supplemental oxygen group)
f76	76 months telephone visit (both groups)
f80	80 months telephone visit (both groups)
n	Code used for unscheduled visit or form not associated with a specific visit
n2, n3,...	Code used when more than one of the same type of form is completed for the same patient on the same date (eg, if a patient reports two COPD exacerbations since the last contact, use visit code n for the first EX form completed and use n2 for the 2nd EX form completed that day for the patient)

12.4 General guidelines for forms completion

Ink

- Forms should be completed in blue or black ink that is dark enough to photocopy legibly

Changing responses on forms

- If an error is made on the form, correct the response by marking through the response with one or two lines and writing the correct response next to or above the original response. The staff member making the correction should put their initials and the date in the margin by the correction. A brief explanation for the change should also be written in the margin; e.g., 'error', 'pt changed mind', 'wrong response checked'.
- Do not obliterate, erase, or white-out incorrect responses
- The idea is to preserve an audit trail of the original response and subsequent changes to it – to provide the staff with enough clues so that if the changes are questioned in the future, the staff can explain and justify the change (can report the who, when and why of the change)

Multipage forms

- The patient ID number should be written on the top right of every page of every form in the space provided -- protect yourself against ineffective staples and photocopying mishaps
- Labels will be provided for use on the standardized questionnaires that will be given to the patient to self-complete

Miscellaneous

- All written responses should be printed legibly so the responses can be keyed to the database
- Do not use abbreviations or short-hand that may not be easily understood or keyed in the written responses
- Numeric data should be recorded in the units prescribed on the form and to the level of precision (number of digits) indicated on the form
- All numbers should be right justified and leading and trailing zeroes should be recorded on the form where applicable (enter a digit for each write-in space provided on the form for a numeric item; e.g., the diastolic blood pressure item has a format of _ _ _ and a reading of 80 would be completed as "0 8 0" and keyed as 080)
- All letter codes should be left justified with the remaining spaces left blank (e.g., a visit ID for the sb visit code (format _ _ _) would be completed as "s b _ " and keyed as sb).
- The Clinical Coordinator should review all responses for completeness and accuracy before signing off on the form
- Wherever possible, forms should be completed in real time, not retroactively. Interviews and questionnaires should be completed on the actual data form.
- The data on some forms, such as the Blood Values (BV) form, will be transcribed from worksheets or lab reports after the testing is complete; the visit date on the form should correspond to the date the testing took place.
- Staple relevant lab reports and worksheets to the data form; if your lab reports are transmitted to you electronically, print a paper copy of the report and staple the copy to the LOTT form.

Calculations

- All calculations should be performed using a calculator
- Values should be rounded according to the LOTT data rounding rule (see section on data rounding rule, later in this chapter)

12.5 Form anatomy

Headers and footers

- Each page of each form includes headers and footers which identify the form and the patient. The top right of the first page of each form has a space to check when the form is keyed [( )keyed]. The top right of subsequent pages is reserved for the patient ID number. The footers include the form abbreviation, form revision number and date, the form name, and the page number. For example:

LOTT Patient ID: __ __ __ __ __

Form RG
Revision 0 (31 Mar 08) RG - Registration Page 2 of 3

- The keyed box (on page 1 of every form requiring data entry) should be √ed when the form is keyed; the person keying the form should also date and initial the form next to the keyed box
- The patient ID number should be written on each page of the form or labels should be used as indicated on the form

Instruction box

- Each form includes an instruction box at the top of the first page. This instruction box specifies the purpose of the form, the data collection level (Core or Expanded) for the form, when it should be completed, who administers the form, the respondent, and the instructions for the form

Key fields

- The first 6 items of each form include the key fields which identify the RCC, patient, and visit

A. Center, patient and visit identification
   1. RCC ID: __ __ __ __ __
   2. Patient ID: __ __ __ __ __
   3. Patient code: __ __ __ __
   4. Date form completed: __ __ - __ __ __ - __ __
      day mon year
   5. Visit code: __ __ __
   6. Form & revision: __ __ __

- The form and revision number will be printed on the forms in item 6; if a form is only used for one specific visit, the visit code will also be printed on the form
- When a form revision affects the data that are collected, the form revision number and date will change; if this occurs, older revisions of that form may no longer be used for data collection
- If the form is revised without affecting the data collection, e.g., the wording of an item is revised, only the revision date of the form will be changed.

Administrative sign off

- Each form contains a section for administrative sign off
- These items include the Clinical Coordinator PIN and signature and the date the form was reviewed
- Depending on the form, they may also include the PIN and signature of other staff

12.6 Form skips, stops, ineligibility symbols

Skip pattern

- Skips are designated by an arrow from that response to a box with the number of the next item to be completed.

Caution sign

- Cautions are designated by a triangle enclosing a C

Stop sign

- Stops are indicated by an arrow from the response to a stop sign – instructions are given that must be fulfilled in order to continue with the form. For example, Form RG (Registration) asks if the patient has signed the consent form; if the response is "no", the form is stopped with the instructions that *'the consent form must be signed prior to continuing with screening'*.

Ineligibility sign

- Ineligible conditions are designated by an arrow from the response to the symbol:

Other

- Other special instructions are indicated on the form in *italics*. Some examples are:
  - *check only one*: only one of the listed responses should be checked
  - *check all that apply*: one or more of the listed responses may be checked
  - *specify*: a response should be printed on the line(s) provided

12.7 Missing data

- If a data item is missing and cannot be obtained when the form is completed or reviewed, write the appropriate code in the first left hand space of the empty data field:

  ? = data temporarily missing or inconsistent; to be collected or resolved in the near future; items keyed with a ? will need to be followed up on and resolved
  d = patient does not know the answer
  n = not applicable in this situation
  m = data missing
  r = patient refused

- When using any of the above codes, the entire data field does not need to be filled with the code (e.g., a missing height would be completed as m _ _ . _).

- If data are missing on the form, an explanation for the missing values should be written on the form and keyed to the database in the General Comments section of the keying.

12.8 Labels used with forms

Overview
- The DCC will provide preprinted labels used with forms and blood tubes at visit sb
- Subsequent to randomization, the DCC will provide preprinted labels used with forms at visits f04, f12, f16, f24, f36, f48, f60, and f72

Labels for visit sb
- One sheet of labels per ID number and code
  - Patient ID number and code for use with the Registration (RG) form
  - 36 labels for use with the EP, HA, PQ, QF, QG and QW forms
  - 8 labels for use with the BC form and blood and serum shipment tubes
- See figure below

Labels for visits f04 and f16
- One sheet of labels for each followup visit
- Each sheet includes labels for use with the QG and QW forms and a row of extra labels

Labels for visit f12, f24, f36, f48, f60, and f72
- One sheet of labels for each followup visit
- Each sheet includes 35 labels for use with the HA, PQ, QF, QG and QW forms and a row of extra labels

Dos and don'ts for labels
- Never make up an ID number label
- Never use the same ID number for 2 patients (don't recycle ID numbers assigned to patients who turn out to be ineligible)
- Contact the DCC for resupply

Sample sheets
- Images of the sheets for visit sb, f04 and for f12 follow; the sheet for f16 has format similar to the sheet for f04 and the sheets for f24, f36, f48, f60, and f72 are similar to the sheet for f12

LOTT

sb visit
Patient ID: **zz123**
Patient code: **lulu**

LOTT (RG form)

Patient ID: **zz123**
Patient code: **lulu**

LOTT
Patient ID: **zz123**
Patient code: **lulu**

Visit: sb

LOTT
Patient ID: **zz123**
Patient code: **lulu**

Visit: sb

LOTT
Patient ID: **zz123**
Patient code: **lulu**

Visit: sb

Blood for PAXGENE

Tube and form labels ===>

LOTT
PAXGENE tube

Patient ID: **zz123**
Patient code: lulu

LOTT
PAXGENE form

Patient ID: **zz123**
Patient code: **lulu**

Blood for EDTA tube

EDTA tube and form labels ==>

LOTT
EDTA tube

Patient ID: **zz123**
Patient code: **lulu**
Visit: sb

LOTT
EDTA form

Patient ID: **zz123**
Patient code: **lulu**
Visit: sb

Blood for Serum

(Red top tube, form and shipment tube and form labels) ===>

LOTT
Red top tube

Patient ID: **zz123**
Patient code: **lulu**
Visit: sb

LOTT
Red top form

Patient ID: **zz123**
Patient code: **lulu**
Visit: sb

LOTT
Serum shipment tube

Patient ID: **zz123**
Patient code: **lulu**
Visit: sb

LOTT
Serum shipment form

Patient ID: **zz123**
Patient code: **lulu**
Visit: sb


LOTT
f04 visit
Patient ID: da003
Patient code: altu
f04
LOTT
Patient ID: da003
Patient code: altu
Visit: f04
Extra labels

LOTT

f12 visit
Patient ID: da003
Patient code: altu

f12

LOTT
Patient ID: da003
Patient code: altu

Visit: f12

LOTT
Patient ID: da003
Patient code: altu

Visit: f12

Extra labels

LOTT
Patient ID: da003
Patient code: altu

Visit: f12

12.9 Data rounding rule

To round data, examine the digits following the last position required on the form:

- If the first digit following the last data position required for the response is less than 5, leave the digit in the last data position required for the response unchanged

  For example, if you need to round to _._, then 4.73 rounds to 4.7 and 1.44 rounds to 1.4

- If the first digit following the last data position required for the response is 5 or more, round up the digit in the last data position required for the response

  For example, if you need to round to _._, then 4.78 rounds to 4.8 and 4.75 rounds to 4.8

When completing a calculation for LOTT, apply the rounding rule only at the last step, when required to record a quantity on the LOTT form.

12.10 Data audits and edits

Data audits

- The Data Coordinating Center will conduct periodic data audits as a quality control measure
- Audits may be done by mail or on-site
- During an audit, the forms will be reviewed to see if they were completed and keyed correctly; the forms will also be checked against the source documents to be sure that values were transcribed correctly.

Source documents include but are not limited to:

- Printed oximetry reports
- Printed spiromery reports
- Laboratory test result reports
- There are no source documents for questionnaires (the questionnaires are the original documents for the data collection)

Data edits

- Computerized data edits will be sent to the RCCs periodically
- The data edits check for consistency and questionable values in the database.

Changes resulting from audits or edits

- Changes made to the forms as a result of an audit or an edit should be marked "per audit" or "per edit" and should be dated and initialed.

12.11 Handling forms

Form duplication

- The forms will be available on the LOTT website
- You can print master copies from the website and then photocopy as needed or print as needed from the website – if you print copies ahead of time, do not print huge quantities as forms may be revised, especially in the early days of a study
- If a master copy gets frayed or faded, print a new master — always use clear copies for reproduction masters.

Form storage

- Forms for patients registered but not enrolled in LOTT should be kept in a single folder in a locked room or locked filing cabinet.
- Each patient who is enrolled in LOTT will have a patient file – either a notebook or file folder which is kept in a locked room or locked filing cabinet. The patient file should contain all LOTT documents for the patient – consents, forms, appointment schedule, labels, randomization materials. The forms should be arranged in the notebook or folder chronologically by visit. Tabs may be used to separate the visits.

13 CMS

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13.1 CMS overview

Medicare is covering clinical services in the Long-term Oxygen Treatment Trial

In March 2006, the Centers for Medicare and Medicaid Services issued National Coverage Determination (NCD) 240.2.1 (CAG00296N) (http://www.cms.hhs.gov/mcd/viewncd.asp?ncd_id=240.2.1&ncd_version=1&basket=ncd%3A240%2E2%2E1%3A1%3AHome+Use+of+Oxygen+in+Approved+Clinical+Trials).
This NCD covers the home use of oxygen for Medicare beneficiaries with arterial oxygen partial pressure measurements from 56 to 65 mmHg or resting oxygen saturation above 88% who are enrolled in certain clinical trials sponsored by the National Heart, Lung, and Blood Institute (NHLBI). The LOTT is such a trial. Medicare will cover the costs of certain LOTT clinical services for Medicare beneficiaries enrolled in the trial; beneficiaries must have Part B coverage. This NCD provides the following advantages with respect to coverage for Medicare beneficiaries enrolled in the LOTT:

- Coverage is provided for the home oxygen prescribed in LOTT.
- Regional variation in interpretation of what constitutes "routine" costs associated with care provided per protocol is replaced by this NCD's definitions of coverage, providing one consistent interpretation for sites across the United States.
- "Non-routine" costs of care provided per protocol are covered under this NCD.
- The coding instructions for LOTT follow those of the Medicare Clinical Trial Policy. These are explained in more detail below.

What protocol procedures will Medicare cover for beneficiaries participating in the LOTT?

- Home oxygen
- Physician visits
- Spirometry
- Resting oximetry
- Six minute walk test with oximetry (EKG if needed to clear patient to complete six minute walk test)
- Hematocrit and hemoglobin blood draw and tests
- Serum cotinine blood draw and tests
- A1AT blood draw and test

All protocol required treatments and clinical procedures, including clinical procedures for eligibility, in concordance with the LOTT Protocol's specifications and calendar, are covered unless excluded as explained in the next section entitled "**What costs and LOTT protocol procedures are NOT covered by Medicare**".

What costs and LOTT protocol procedures are NOT covered by Medicare?

- Costs covered by NHLBI for any patient enrolled in the study are not covered by Medicare. For example, administration of the quality of life questionnaires is covered by NHLBI for all patients in the LOTT.
- Coinsurance and deductibles are not covered by Medicare. If the patient has Medigap insurance that covers Part B copayments and/or deductibles, these costs may be billed to the Medigap insurer. Many, but not all, Medigap policies cover Part B copayments and several cover Part B deductibles. If the patient does not have Medigap insurance that covers Part B copayments and/or deductibles, the patient is responsible for these costs unless the provider has agreed to waive copayments and deductibles for LOTT services.
- Costs that do not fall into a Medicare benefit category are not covered by Medicare. For example, quality of life questionnaires do not fall into a benefit category and their administration is not covered by Medicare. However, doctor visits that include administration of such questionnaires may be billed to Medicare.

- Medicare does not cover data collection NOT used in the direct care or management of patients.

Are Medicare HMO patients able to participate in the LOTT?

Yes, Medicare HMO patients are able to participate in the LOTT. Medicare will cover LOTT services for beneficiaries with "ordinary", fee for service Medicare plans, as well as for beneficiaries with Medicare plans provided via Health Maintenance Organizations (HMOs), Preferred Provider Organizations (PPOs), Medicare Advantage, etc. The beneficiary must have Part B coverage. The HMO, PPO, and Medicare Advantage providers will bill Medicare as if the beneficiary was a fee for service beneficiary. All Medicare beneficiaries, regardless of type of plan (fee for service, HMO, PPM, Medicare Advantage, etc), will be responsible for co-insurance and deductibles for LOTT clinical services covered by Medicare unless the provider has agreed to waive copays and deductibles for LOTT clinical services or the beneficiary has Medigap insurance that covers copays and/or deductibles for Part B services.

What are the instructions for billing for a Medicare covered service in the LOTT?

- Use the ICD–9-CM diagnosis code of **V70.7** in the second diagnosis code position (on all types of claims) and condition code **30** (on inpatient and outpatient facility claims) to show that the claim involves a clinical trial.
- Use the "**Q1**" modifier with the applicable procedure code **for routine clinical costs** (those paid under usual care, if no study was involved; for example, spirometry, oximetry, 6 minute walk, hemoglobin, hematocrit, serum cotinine, A1AT, home oxygen if the patient has deteriorated and become severely hypoxemic at rest) on physician/provider claims.
- Use the "**Q0**" (zero) modifier with the applicable procedure code **for non routine clinical costs** (the home oxygen itself while the patient is moderately hypoxemic at rest) on physician/provider claims.
- The Certificate of Medical Necessity (CMN) is required for the initial claim for home oxygen submitted for each patient prescribed oxygen under the LOTT protocol. It is not required again for the duration of the patient's participation in LOTT.
- Use of the clinicaltrials.gov identifier for LOTT (NCT00692198) will facilitate claims processing and generation of the claims database for analytical purposes. Information on use of the clinicaltrials.gov identifier may be found at http://www.cms.hhs.gov/Transmittals/2008Trans/itemdetail.asp?filterType=dual,%20keyword&filterValue=clinical%20trial&filterByDID=0&sortByDID=2&sortOrder=descending&itemID=CMS1207575&intNumPerPage=10

What if a patient is not on Medicare, will other insurers provide this same coverage?

- This coverage decision applies **ONLY** to Medicare plans. This coverage decision applies to "ordinary" (fee for service) Medicare, as well as Medicare plans provided via Health Maintenance Organizations (HMOs), Preferred Provider Organizations (PPOs), Medicare Advantage, etc.
- If no law exists, some private insurers "follow the lead" of Medicare in their decisions about paying for clinical trials. Your billing office may wish to call or email their contact at the particular insurer, telling them that Medicare has made a special decision. Sending this Medicare coverage information will inform them of this CMS determination and may impact their decision on coverage.

Summary reimbursement table

This table outlines the specific study elements that are coved by Medicare (as well as those not covered by Medicare such as research questionnaires which are supported by study funds). It is available on the LOTT website (www.lottsite.org; click on Oxygen Providers and scroll down to Medicare billing instructions or click on Documents and scroll down to Medicare billing instructions).

13.1. CMS overview

For more information

- Billing offices may learn about Medicare's National Coverage Determination Clinical Trials Policy at: http://www.cms.hhs.gov/mcd/viewncd.asp?ncd_id=310.1&ncd_version=2&basket=ncd%3A310%2E1%3A2%3ARoutine+Costs+in+Clinical+Trials
- The procedures, including use of the Q0 and Q1 modifiers, are described in CMS Medlearn Matters Article No. MM5805 and Change Request 5805 dated 1/18/08, found in Transmittal 1418 of Medicare Pub. 100-04, Medicare Claims Processing: http://www.cms.hhs.gov/MLNMattersArticles/downloads/MM5805.pdf and http://www.cms.hhs.gov/Transmittals/downloads/R1418CP.pdf.
- The link below has additional links to postings related to billing under the Clinical Trial Policy: http://www.cms.hhs.gov/Transmittals/2008Trans/itemdetail.asp?filterType=dual,%20keyword&filterValue=clinical%20research&filterByDID=0&sortByDID=2&sortOrder=descending&itemID=CMS1207579&intNumPerPage=10

13.2 Terminology used by CMS

Carrier - pays Medicare Part B costs
Cost sharing - the amount you pay for health care and/or prescriptions; this amount can include copayments, co-insurance, and/or deductibles
DME - durable medical equipment
Intermediary (fiscal intermediary) - pays Medicare Part A costs
HIC - health insurance claim number; a patient's HIC is their Medicare number; usually 9 digits followed by one or more alphabetic characters
Medicare Part A - generally covers inpatient hospital expenses
Medicare Part B - generally covers outpatient health care expenses including doctor's fees and home oxygen (covered under durable medical equipment, DME)
Medigap insurance - supplemental insurance policies sold by private insurers that may cover costs that usual Medicare does not cover; most, but not all, Medigap policies cover Medicare deductible and co-insurance payments; BUT if Medicare covers a service and the Medigap policy covers deductibles and co-insurance payments, then the Medigap policy will cover the deductible and coinsurance for the service – in the context of LOTT, this means that a Medigap policy that covers Part B deductible and co-insurance has to cover LOTT associated deductibles and co-insurance even though home oxygen is generally not covered for patients with moderately severe resting hypoxemia

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Link to online Medicare glossary
http://www.medicare.gov/Glossary/search.asp?SelectAlphabet=F&Language=English

13.3 Coverage of costs of protocol elements

Note: When billing Medicare, please use the appropriate codes to identify the claim as associated with LOTT: use V70.7 in the 2nd diagnosis code position, use condition code 30 (on inpatient and outpatient facility claims), use the modifier indicated in the table below, and use the clinicaltrials.gov identifier for LOTT, NCT00692198. Medicare will cover the items and services considered routine as well as the investigational (non-routine items; the stationary and portable oxygen systems).

Coverage of Costs of LOTT Protocol Elements			
Protocol element	**Timing of protocol element**	**Coverage**	**Modifier**
Baseline and Randomization			
Physician visit including health history (includes MMRC dyspnea score) and limited physical exam (height/armspan; weight; vital signs; chest exam; edema assessment)	Pre randomization evaluation	Medicare	Q1
Room air resting oximetry	Pre randomization evaluation	Medicare	Q1
Room air 6 minute walk with oximetry (including EKG if needed to clear patient to complete 6 minute walk)	Pre randomization evaluation	Medicare	Q1
Spirometry, pre and post bronchodilator	Pre randomization evaluation	Medicare	Q1
Hemoglobin and hematocrit blood draw and test	Pre randomization evaluation	Medicare	Q1
Serum cotinine blood draw and test	Pre randomization evaluation	Medicare	Q1
A1AT blood draw and test (if not available by chart review)	Pre randomization evaluation	Medicare	Q1
Epworth Sleepiness Scale, Pittsburgh Sleep Quality Index, Hospital Anxiety and Depression Scale	Pre randomization evaluation	Study funds	n/a
Quality of Well-Being Scale, St George's Respiratory Questionnaire, SF-36v2 Questionnaire	Pre randomization evaluation	Study funds	n/a

13.3. Coverage of costs of protocol elements

Coverage of Costs of LOTT Protocol Elements			
Protocol element	**Timing of protocol element**	**Coverage**	**Modifier**
Blood draw for DNA collection	Any time; preferably during Pre randomization evaluation, but may occur during followup	Study funds	n/a
Blood draw for serum and plasma collection and processing blood sample to serum	Pre randomization evaluation	Study funds	n/a
Treatment			
Stationary home oxygen system while the patient is moderately hypoxemic at rest ($SpO_2 > 88\%$)	Randomization through end of trial	Medicare	Q0 (investigational item)
Portable home oxygen system while the patient is moderately hypoxemic at rest ($SpO_2 > 88\%$)	Randomization through end of trial	Medicare	Q0 (investigational item)
Stationary home oxygen system if the patient deteriorates and becomes severely hypoxemic at rest ($SpO_2 \leq 88\%$)	Through end of trial	Medicare	Q1 (routine item since patient is severely hypoxemic at rest)
Portable home oxygen system if the patient deteriorates and becomes severely hypoxemic at rest ($SpO_2 \leq 88\%$)	Through end of trial	Medicare	Q1 (routine item since patient is severely hypoxemic at rest)
Visit to determine ambulatory oxygen dose	Just after randomization and as needed	Medicare	Q1
Routine Followup Post Randomization			
Adherence monitoring telephone contacts	1, 2, 3, 4 weeks and 2, 3, 4, 5, 6, 8, 10 months	Study funds	n/a
Adherence monitoring in person contacts	1, 2, 3, 4, 5, 6 years	Study funds	n/a

13.3. Coverage of costs of protocol elements

Coverage of Costs of LOTT Protocol Elements			
Protocol element	**Timing of protocol element**	**Coverage**	**Modifier**
Adherence monitoring diaries (mailing and processing)	q2 months from randomization through end of trial	Study funds	n/a
Interim history telephone contacts	4, 8, 16, 20, 28, 32, 40, 44, 52, 56, 64, 68, 76, 80 months	Study funds	n/a
Physician visit including interim history (includes MMRC dyspnea score) and limited physical exam (weight, vital signs, chest exam, edema assessment) and ambulatory dose check (if assigned to oxygen)	1, 2, 3, 4, 5, 6 years	Medicare	Q1
Room air resting oximetry	1, 2, 3, 4, 5, 6 years and as needed to check need for oxygen prescription	Medicare	Q1
Room air 6 minute walk with oximetry (including EKG if needed to clear patient for 6 minute walk)	1, 2, 3, 4, 5, 6 years	Medicare	Q1
Spirometry, pre and post bronchodilator	1, 2, 3, 4, 5, 6 years	Medicare	Q1
Serum cotinine blood draw and test	1 year	Medicare	Q1
Pittsburgh Sleep Quality Index, Hospital Anxiety and Depression Scale	1, 2, 3, 4, 5, 6 years	Study funds	n/a
Quality of Well-Being Scale, St George's Respiratory Questionnaire, SF-36v2 questionnaire	1, 2, 3, 4, 5, 6 years	Study funds	n/a
Treatment Adjustment (visits/procedures designed for safety checks or for getting patient back on protocol treatment)			
Resting oximetry while on oxygen	As needed for those who develop severe resting hypoxemia	Medicare	Q1
Physician visits to assess need for oxygen or to assess safety of stopping oxygen	As needed	Medicare	Q1

14 Glossary

A1AT	-	alpha-1 antitrypsin
CMS	-	Centers for Medicare and Medicaid Services
COPD	-	Chronic Obstructive Pulmonary Disease
DCC	-	Data Coordinating Center
DME	-	Durable medical equipment
IRB	-	institutional review board
LOTT	-	Long-term Oxygen Treatment Trial
MMRC	-	Modified Medical Research Council questionnaire
NETT	-	National Emphysema Treatment Trial
NHLBI	-	National Heart, Lung, and Blood Institute
NOTT	-	Nocturnal Oxygen Treatment Trial
PIN	-	Personnel Identification Number
QWB	-	Quality of Well-Being Scale Questionnaire
RCC	-	Regional Clinical Center
SF-36	-	SF-36 quality of life questionnaire
SGRQ	-	St. George's Respiratory Questionnaire