

Losartan Effects on Emphysema Progression (LEEP)

Manual of Procedures (MOP) Version 1.4



LEEP Coordinating Center
Johns Hopkins Center for Clinical
Trials and Evidence Synthesis
415 N Washington St, 2nd Floor
Baltimore, MD 21231
Tel: 443-287-3170
Fax: 775-871-4030

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Revision History

Version 1.0 (01 March 2017)

Based on protocol v. 2 (15 Sep 2016)

Version 1.1 (20 June 2017)

(No protocol version change)

Section #	Section title Change/addition
4.2	Screening visit (V1) Overview section: HRCT scan (scheduled after lab results obtained) replaces HRCT scan (may be scheduled on a different day)
4.3	Randomization visit (V2) - Added instructions to be given to participant on how study drug is to be taken Instruct participant: - Study drug should be taken at about the same time each day (so morning or evening) - Missed doses are not “made up” (do not double the next dose)
5.1.1	Treatment titration visit (V3) – week 2 - Added: Instruct participant - To take full dose at one time, about the same time every day - That missed doses are not “made up” (do not double the next dose)
5.1.5	Final visit (V7) – week 48 - Additions: - To Equipment and materials list for V7 - Specimen collection, processing and storage supplies (if consented to provide specimens for future use) - During V7 - Draw blood and collect urine sample for specimen biorepository - Process samples and store for shipment - Record specimens on Biospecimen Collection (BC) form
6.1.1	Study drug description - Added - Dosing instructions for participant should include: - Take prescribed dose at the same time every day - Do not make up a missed dose; do not double up dosing - Can be taken with or without food - Before V3 - If participant takes dose in morning, the morning dose must be held - If participant takes dose in the evening, the evening dose on the day before V3 must be held

Section #	Section title Change/addition
6.1.4	Serious adverse reactions and drug interactions for losartan - Clarified that “Daily use of low-dose aspirin (defined as 325mg/day or less) is allowed”
6.1.5.1	Receipt and storage - Image of actual LEEP study drug/placebo bottle and capsules replaced generic image - Drug accountability section clarifies that: • List of bottles shipped will be with shipment • Reconciliation of drug received is in the data system • Packing list is to be signed and stored in Regulatory binder after reconciled • Contact LEEP DCC if drug is missing or bottle IDs do not match
7.1.3	HRCT visits - Time frame for HRCT visits was changed to reflect time needed for HRCT scan to be read - Window was changed from 0-4 weeks to 1-4 weeks
7.2	Spirometry - Added: “ Note: If pre-bronchodilator FEV₁ and/or FEV₁/FVC exceed the eligibility criteria, with a FEV₁ > 70% of predicted and/or a FEV₁/FVC > 0.70, then post-bronchodilator efforts should not be performed”
7.5.3.2	Blood draw for DNA, serum and plasma - Added: “<i>If the participant has NOT consented to DNA collection:</i> • Discard EDTA Vacutainer and remaining cell pellet. Do NOT retain DNA for a participant who has not provided explicit written consent.”
7.5.4	Specimen labeling - Clarified that each sheet of labels corresponds to <i>one visit for one participant ID – visit 2, 5 or 7.</i> - In description of label added, “with participant ID, space for alpha ID code, visit ID, type of specimen and aliquot number, and barcode”
7.5.4.1	Labels: the basics - Removed “p-cells” and replaced with “DNA”

Section #	Section title Change/addition
7.7.2.1	Example of a clinic label sheet - Removed from description of participant ID labels, “Satellite clinics will receive labels starting with L, followed by their assigned main site letters and 3 numbers starting at 200, 300, 400 and onward depending on the satellite” because each satellite will have a unique two letter code for the LEEP trial. - Changed that Clinics who misplace or lose their labels sheets should contact the NEMO (removed DCC) for a replacement sheet
10.2	Communication prototypes - Clarified that “For appropriate letters to be sent” it is “when participant is determined to be eligible”

V1.2 (28 September 2017)
Protocol V2.1 (11 September 2017)

Section #	Section title Change/addition
1.4.1	Communications – NEMO Added Ops Memos
1.4.2	Communications – DCC Removed PPMs and added emails
4	Screening, baseline and randomization In participant stage nomenclature figure added “and Screening (SC) form” to description of Enrollment
4.2	Screening visit (V1) • Clarification added with “Note: if pre-bronchodilator efforts exceed eligibility criteria, bronchodilation and post-bronchodilator spirometry results are not expected.” • Clarified how HRCT eligibility results are obtained: To see results click CT Eligibility Tracking System link on LEEPTrial.org website and select List All Entries • Clearly stated forms expected to be keyed: All V1 forms are to be data entered for participants that are eligible and willing to enroll based on responses on the Screening (SC) form. HRCT related forms (RT, RR) are required if a HRCT scan was done.
4.3	Randomization visit (V2) Corrected statement on V2 window to state that it is up to 8 weeks if needed for delays for “recycling or scheduling” (deleted for rescreening) and added “maximum time allowed between HRCT scan and randomization is 8 weeks”
5.1	Treatment phase study visits/contacts – Overview Updated images to reflect what is seen in the LEEP data system
7.1.6.1	HRCT Scan documentation – Forms For CT Technologist Instruction (ICT) form added: • ICT form should be presented to the CT tech at every LEEP HRCT scan
All	In addition, minor edits were made to correct formatting

V1.3 (9 March 2018)
(No protocol version change)

Section #	Section title Change/addition
6.2.2	Emergency unmasking DCC contact change
8.1.1.	Clinic certification instructions Nemo contact change
7.1.2	Order of procedures Changed number of puffs: "For same day procedures, participants will take 2 <i>puffs</i> of albuterol for the spirometry procedure before scan"
7.7.1	ID codes University of Pittsburgh added

V 1.4 (17 May 2018)
Protocol V 2.2 (17 May 2018)

Section #	Section title Change/addition
1.2	Inclusion criteria - The FEV1 values in the definition of mild to severe COPD were expanded from the original range of 30% to 70% to the revised range of 20% to 80%. Exclusion criteria - The chronic oxygen use criterion was replaced with "Resting SpO2 <89% on 2L nasal cannula continuous flow; unless at altitude > 4,000 feet, then resting SpO2 <89% on 4L NC continuous flow"
4.2	Added the below instructions on which forms to complete on ineligible. - If the person is ineligible based on Screening (SC) Form, key SC form only - If the person is ineligible due to lab value(s), key SC, Laboratory Data (LD) form and Early Exit (EE) forms - If the person is ineligible after HRCT, key SC, HRCT related (RT, RR) and EE forms
5.1.8.1	Added the instruction to enter new forms into the database using "Re-enter (replace) form" option"
5.1.8.2	Added the instruction to enter V2 forms into the database using "Re-enter (replace) form" option"

Section #	Section title Change/addition
12.4	Added statement: "For participants who consented but are later found to be ineligible, clinics should report serious adverse events that they learn of 7 days after the screening visit (V1). However, clinics do not have to actively follow up with ineligible individuals to collect for these events."
9.2	Added \$250 payment for screen fails
All	In addition, minor edits were made to correct formatting

V 1.4 (13 Feb 2020)
(no protocol version change)

Section #	Section title Change/addition
7.5.3.2	Added clarification on when blood draws are to occur When • V2, V5, and V7 (serum and plasma) • V2 only (DNA)
7.7.2	Added PTC Site IDs and Codes for the following new sites: • Northern New England Consortium – Western Connecticut • St. Louis University • University of Kansas • Louisiana State University

1. Overview

The Losartan Effects on Emphysema Progression (LEEP) trial is a parallel, placebo-controlled, randomized clinical trial designed to test the hypothesis that administration of losartan will decrease the progression of emphysema as measured by quantitative High Resolution Computed Tomography (HRCT) compared to placebo. 220 participants with mild to severe COPD and HRCT evidence of emphysema will be enrolled at multiple clinical sites across the United States. Study participants will be randomized to receive 100 mg losartan daily or placebo daily for 48 weeks. The primary outcome will be changes in quantitative measures of emphysema as determined by HRCT; secondary outcomes include measures of lung function (including spirometry and HRCT-measured lung volumes), assessment of respiratory symptoms and quality of life, and reports on the safety and tolerability of losartan in persons with emphysema.

1.1. Design summary

Title

Losartan Effects on Emphysema Progression (LEEP)

Objective

To test the primary hypothesis that administration of losartan 100 mg/day for 48 weeks will decrease the rate of progression of emphysema as measured by quantitative HRCT compared to placebo.

Specific study aims

- To measure the effect of losartan on HRCT-measured emphysema progression at 48 weeks
- To measure the effect of losartan on lung function (spirometry and HRCT-measured lung volumes)
- To explore sub-groups of interest for heterogeneity of treatment effects
- To determine the safety and tolerability of losartan in emphysema patients

Type of study

- Randomized, blinded, two arm parallel placebo-controlled trial
- Multicenter, ~ 17 clinical centers
- Fixed sample size; 220
- Allocation ratio 1:1

Study treatment

- Losartan 100 mg/day OR
- Placebo

Drug dosing

- V2 – V3
 - Losartan 50 mg (one capsule) OR placebo (one capsule) per day
- V3 – Dose titration
 - Trial dose of losartan 100mg (two capsules of 50 mg each) OR placebo (two capsules per day)
- V3 – V7
 - Losartan 100 mg per day (two capsules) OR placebo (two capsules) once a day
 - Losartan 50 mg (one capsule) OR placebo (one capsule) per day, if dose escalation not successful at V3

Primary outcome measure

- Change in percent emphysema measured by quantitative HRCT

Secondary outcome measures

- Spirometry. Changes in FEV₁ and FVC
- Other HRCT measures. Other measures include TLC, mean lung density, 15th percentile density, and airway lumen and wall thickness measured for small, medium, and large airways.
- Respiratory questionnaires. The St. George's Respiratory Questionnaire for COPD patients (SGRQ-C), the Modified Medical Research Council Dyspnea Scale (mMRC), and the COPD Assessment Test (CAT)
- Patient reported outcomes. The Patient Reported Outcomes Measurement Information System Questionnaire: Physical Function – Short Form 20a (PROMIS-20a)
- Adherence measured by capsule counts from returned containers.

Other data

- General health history
- Respiratory questionnaire: The ATS-DLD questionnaire, a general respiratory symptom questionnaire.
- Laboratory testing. Complete Blood Count (CBC) with differential (diff) and Comprehensive Metabolic Panel (CMP) will be obtained and analyzed at local labs to detect hematologic, electrolyte, renal, or hepatic abnormalities that indicate exclusion from treatment or adverse events.
- Blood and urine for biorepository
- Adverse effects to assess safety and tolerability
- Interval health history. Records of hospitalizations and deaths are obtained for verification of diagnoses and assessment of safety.
- An exit interview

1.2. Eligibility criteria

The goal is to randomize 220 participants. Participants will be asked to sign informed consent before any screening procedures are performed.

Inclusion criteria

- Males and females, age 40 years or older at V1
- Mild to severe COPD as defined by post-bronchodilation forced expiratory volume in one second (FEV₁) / forced vital capacity (FVC) ratio less than or equal to 0.70 and FEV₁ 20-80% of the predicted normal value at V1
- Current or former smoker with at least a 10 pack-year history at V1
- HRCT Scan with 5-35% of voxels with density less than -950 Hounsfield Units (HU) at V1
- Ability to understand and willingness to sign consent documents

Exclusion criteria

- Current therapy with angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB)
- Known intolerance to ACE inhibitor or ARB
- History of angioedema
- Conventional indication for ACE inhibitor or ARB (including history of myocardial infarction, known cardiomyopathy)
- Renal insufficiency (GFR <30 mL/min by Cockcroft-Gault calculation)
- Current regular use of NSAIDs defined as daily use 5 or more days of the week for more than one month
- Current treatment with a potassium sparing diuretic
- Potassium supplementation or serum potassium level of ≥ 5.0 mEq/L at V1
- COPD exacerbation requiring treatment within 6 weeks at V1
- Chronic systemic corticosteroid use > 10mg/day of prednisone
- Resting SpO₂ <89% on 2L nasal cannula continuous flow; unless at altitude > 4,000 feet, then resting SpO₂ <89% on 4L NC continuous flow
- Untreated arterial hypertension (systolic blood pressure >140 mm Hg, diastolic blood pressure > 90 mm Hg)
- Blood pressure less than 90 mm Hg systolic or 60 mm Hg diastolic while standing or sitting
- Known unilateral or bilateral renal artery stenosis >70%
- Previous lung resection surgery
- Evidence of interstitial, occupational or chronic infectious lung disease
- Changes to chest that preclude adequate HRCT imaging (e.g. Metallic objects in the chest such as shrapnel or pacemaker leads)
- For women of child bearing potential, positive pregnancy test or unwillingness to use two methods of birth control or abstinence for the duration of the study
- Major chronic illnesses which in the judgment of the study physician would interfere with participation in the study e.g. including but not limited to: cardiac, renal, hepatic (LFTs>2.5x normal upper limit), neurological, psychiatric, endocrine or neoplastic diseases, uncontrolled diabetes, uncontrolled HIV infection or other immune system disorder, hyperthyroidism, seizure disorders, non-skin cancer, rheumatic diseases
- Failure to keep screening appointments or other indicators of non-adherence
- Inability to be contacted by telephone
- Intention to leave area within 12 months

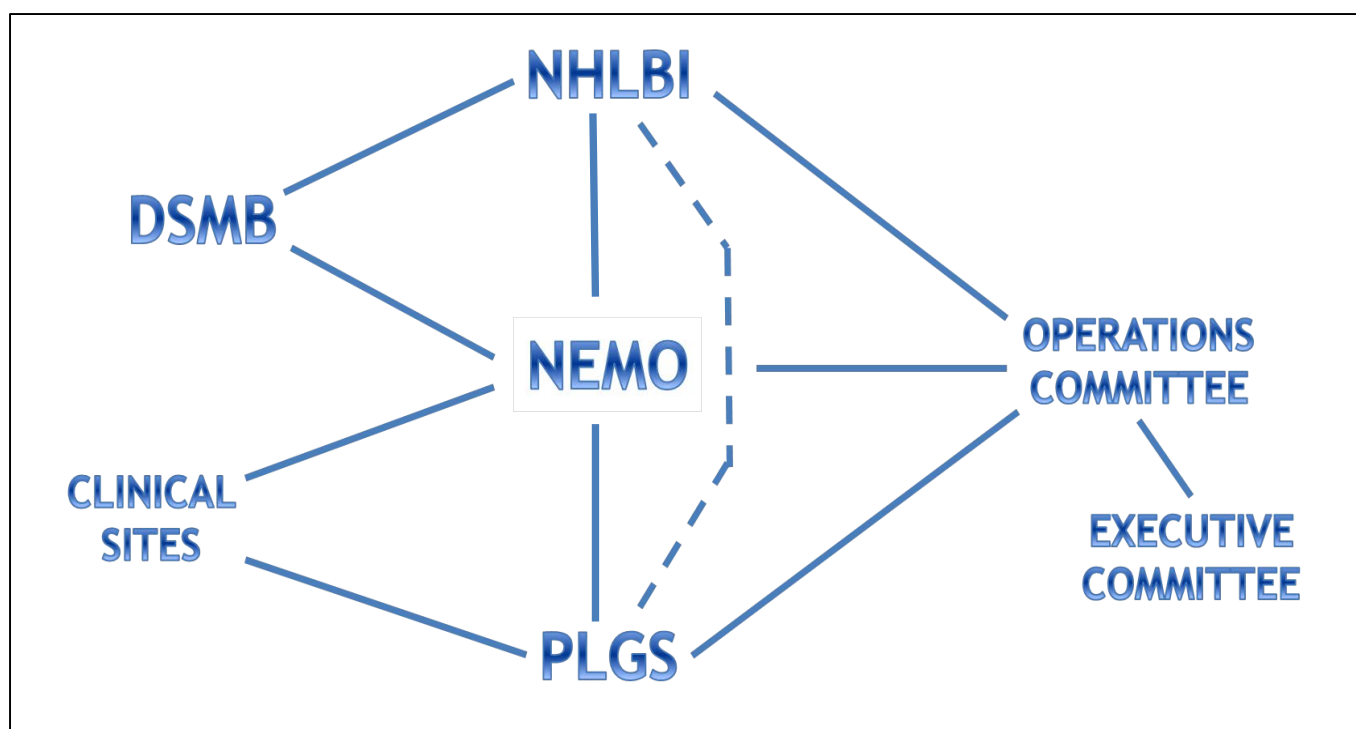
1.3. Organization

Overview of Pulmonary Trials Cooperative

The Pulmonary Trials Cooperative (PTC) is an initiative of the National Heart, Lung, and Blood Institute (NHLBI) to meet a need for pragmatic, “real world” studies in a variety of chronic pulmonary conditions, including, but not limited to, interstitial lung disease (ILD), pulmonary hypertension (PH), chronic obstructive pulmonary disease (COPD), sarcoidosis, and obstructive sleep apnea (asthma and acute lung injury and critical care are specifically excluded). The goals of the Cooperative are to carry out multiple clinical trials simultaneously, develop new treatments, test existing clinical management strategies, involve a wide range of institutions as clinical sites, increase the efficiency of participant recruitment, and explore opportunities for studying intermediate and comorbid conditions.

The PTC brings together several Protocol Leadership Groups (PLGs), a Network Management Core (NEMO), and 40-80 clinical sites.

Organization



1.3.1. *Components of the PTC*

As reflected in the chart above, the Pulmonary Trials Cooperative has a number of interlocking elements. Each is described below.

1.3.1.1. *PLGs: Protocol Leadership Groups*

The Johns Hopkins Data Coordinating Center is the PLG for the LEEP trial. PLGs enter the Cooperative when they have an approved study. Details of the current PLGs and studies can be found on the PTC website (www.pulmonarytrials.org)

The role of the PLGs is to design, implement, and conduct a pragmatic research study consistent with the goals of the PTC.

1.3.1.2. *NEMO: Network Management Core*

The NEMO's primary role is to facilitate the research conducted by the PTC. A key element of that role is selecting, activating, training, reimbursing, and monitoring the clinical sites that carry out the PTC protocols.

The NEMO also coordinates efforts to harmonize procedures, reports, data, and manuals as much as possible among the PTC studies. In addition, it provides administrative support, a communications structure, central facilities, and content area experts.

Content area co-investigators

Housed within the NEMO is a team of Content Leaders who have unique skillsets on a variety of topics related to the mission of the PTC (clinical trials, multiple facets of lung disease, bio banking, bid data, microbiome, and relationships with potential industry collaborators). These co-investigators are available to serve as a resource for PLGs and the NEMO throughout protocol development, clinical site selection, addressing study specific needs, and acting as medical monitors.

Additional available support

In order to aid PLGs, the NEMO has multiple resources available for their use. These resources include:

- Access to foundation registries and NIH and PCORI-funded cohorts and registries to aid in participant recruitment.
- Informatics resources to assist in use of Electronic Medical Records for recruitment
- A regulatory tracking system

- Central evaluation of clinical site performance
- Centralized reading centers, laboratories, repositories, and drug distribution
- Data coordination, management, harmonization, and analysis
- A core set of training materials for clinical site personnel
- A web based Publications and Presentations Monitoring System

PTC standards overview

The NEMO develops standards to be applied to data and specimen collection in general, and offers resources to aid sites and PLGs as they work to meet those standards. These standards are intended to ease site burden and further the purposes of the PTC.

1.3.1.3. Clinical sites

Clinical sites are identified by the NEMO and the PLGs. A clinical site can be involved in more than one study at a time and different PIs might be involved if that best meets study and institutional needs.

These clinical sites recruit and enroll research participants, deliver the study intervention, complete clinic visits and phone calls, collect and enter data, and carry out procedures as defined by each study's protocol.

1.3.2. Governing structure of the PTC

A number of Committees and Working Groups manage and coordinate efforts within the Cooperative.

1.3.2.1. Operations Committee

The Operations Committee of the Pulmonary Trials Cooperative (PTC) has primary responsibility for the implementation, oversight, and continuing evaluation of PTC trials and studies. The Operations Committee is responsible for monitoring the progress of the PTC and the individual trials, including enrollment, quality assurance, and changes to study design. The Operations Committee is also responsible for developing policies and procedures for the PTC, and oversees working groups and subcommittees.

Membership consists of a Study Chair appointed by the NHLBI, a representative from the NHLBI, the Principal Investigator(s) from each PLG, the Principal Investigators from the NEMO and NEMO Project Coordinator. If a PLG utilizes the multiple PI approach and both PIs from a PLG are unavailable for a call or meeting, a substitute may sit in.

The Operations Committee holds conference calls on a regular basis and has at least one in-person meeting annually. There is no quorum required to hold a call, but a majority of the Committee members must be present for a vote. Votes are allocated as follows: 1 for the Study Chair, 1 for the NHLBI, 1 for each PLG, and 1 for the NEMO.

1.3.2.2. *Executive Committee*

The Executive Committee of the Pulmonary Trials Cooperative (PTC) provides leadership and oversight to the PTC at large, specifically by ensuring that the Operations Committee is meeting its charge. The Executive Committee reviews Operation Committee agendas, guides the overall discussions within the Operations Committee's meetings, and addresses the needs of the PTC that do not require input from all PLGs.

Committee membership consists of the Study Chair appointed by the NHLBI, a representative from the NHLBI, the Principal Investigators from the NEMO, and the NEMO Project Coordinator. Executive Committee meetings are held in advance of the Operations Committee's meetings to review previous and upcoming agendas and address recently identified issues.

In place of formal votes, this committee reaches a consensus from which to guide the Operations Committee in fulfilling its mission.

1.3.2.3. *Working Groups*

Working Groups are formed and disbanded based on the current needs of the PTC as directed by the Operations Committee. They perform much of the detailed work of standardization and harmonization among the PTC studies. The PLGs, NEMO, and NHLBI are all represented on the Working Groups.

1.4. Communications

1.4.1. NEMO

Website

The NEMO maintains a PTC website consisting of a Public section, available to anyone, and a password-protected Researcher section available only to those granted access. There is also a Help Desk for use by all PTC members.

The website is located at www.pulmonarytrials.org.

- Public section of the website
 - Each current PTC study has a section within the Public website with a similar look-and-feel and content. These sections are where potential participants can find details about the research, basic eligibility criteria, a map of the clinical sites, and contact information for each clinical site.
- Researcher section of the website
 - Access to the Researcher website is granted after the NEMO approves a request, at which time the user is assigned a username and password. To request a password, click on the “Researcher Login” at the top right of the screen. Then choose “Register for Portal Access”.
- Help center
 - The help center is the primary tool for non-urgent questions. Help center questions are routed to the appropriate individual(s), as identified by the PLG and the NEMO.

Exceptions may be made in emergency situations (e.g., unmasking of treatment). In these instances, a direct call is appropriate and will be noted in the PLG MOP.

Internal and external communication

- Internal communication
 - Monthly reports will run by the PLG DCC and be distributed to the sites, the NEMO, and the NHLBI to identify issues and decide upon a course of action. Quarterly cross-study monitoring reports and regulatory tracking will be completed by the NEMO and distributed to the sites, the PLG, and the NHLBI. These reports will be reviewed on the following monthly joint call.
- External communication: media
 - If entities within the PTC want to invite media coverage to their work, approval must be sought by three entities—the institutions involved in the research, NHLBI, and the Operations Committee of the PTC. No PTC member should provide study information to an external person or entity without prior agreement by the communications officer at their institution, the PTC Operations Committee and the NHLBI.
- Joint communication
 - Every month there will be study-specific conference calls with the site clinical coordinators run jointly by the NEMO and the PLG.

- Operations Memos (Ops Memo)
 - These are emailed mainly to the center PIs and Lead Coordinators in regards to any communication about amendments to study protocols, consents, data collection forms, DSMB recommendations, or any other study procedures or announcements.
 - Ops Memos are uploaded on the PTC website (<https://my.pulmonarytrials.pitt.edu>).
 - Copies of PPMs should be filed electronically or placed in a PPM notebook at each clinic.

1.4.2. DCC

The DCC communicates with clinics primarily through:

- *Newsletters*
The DCC will issue updates to centers to communicate the status of the LEEP study usually on a weekly basis. This update may include certification/IRB status of clinics, enrollment/randomization numbers, tips of the week, upcoming events/calls, and other announcements as appropriate.
- *Coordinator calls*
There will typically be a monthly call with the DCC that the Lead Coordinator is expected to join. Other coordinators are welcome to call in as well. The purpose of this call is for the DCC to follow up with clinics on study status, present any announcements, troubleshoot issues coordinators are facing in the study, and answer any questions from coordinators. The call is also a time for coordinators to share ideas related to recruitment, and solutions to other challenges with each other.
- *Email from JHSPH.ala-acrc@jhu.edu*
Information that the DCC would like to share with coordinators and/or investigators may be emailed if an Ops Memo from the NEMO is not required.
- *Contacting the center's Lead Coordinator/PI*
The DCC will contact the center's Lead Coordinator or PI directly for center specific issues.

 **Note:** The Lead Coordinator at each center is responsible for distributing DCC communications to the rest of the LEEP staff at the clinic as appropriate.

A directory for the DCC contacts can be found on the LEEP section of the PTC website at <https://my.pulmonarytrials.pitt.edu/> and on the LEEP website <http://www.LeePTrial.org>

For payments or other financial support, contact the NEMO.

For drug issues, contact the DCC. Do NOT contact Almac directly.

2. Start-up requirements

Clinical sites must meet the following requirements prior to enrolling participants in the LEEP study:

1. IRB approval for the LEEP protocol and informed consent.
2. Provide sufficient documentation that the main clinical site has the required facilities, equipment, and personnel necessary to conduct LEEP. For more information, please see MOP section 8 on Training and Certification
3. HRCT scanner approved for use in LEEP. Process involves scanning a LEEP phantom and completing the required documentation. For more information, see MOP section 7.1.4 and Appendix A – Scanning Procedure for the LEEP Lung Phantom for phantom scanning procedures and certification requirements.
4. Complete personnel certification and training requirements for the LEEP study as necessary.
5. Receive a formal notification letter from the NEMO that the clinical site is certified and is allowed to enroll participants in the LEEP study.

3. Study visit time windows and data collection schedule

Visit	V1	V2	V3	V4	V5	V6	V7
Target (weeks)	-4	0	2	12	24	36	48
Visit window (weeks)	-4 to 0	0	2-4	10-14	22-26	34-38	46-50
Informed consent, eligibility evaluation	•						
Baseline medical history	•						
Adverse events/Interval health history		•	•	•	•	•	•
Pregnancy testing as indicated	•	•	•	•	•	•	•
Spirometry (pre and post BD)	•				•		•
Anthropometrics (height & weight)	•	•	•	•	•	•	•
ATS-DLD	•						
SGRQ-C, CAT	•	•		•	•	•	•
mMRC	• [†]	•		•	•	•	•
PROMIS-20a	•	•		•	•	•	•
Vital signs, Orthostatic blood pressure check, SPO ₂	•	•	•	•	•	•	•
Physical examination	•				•		•
CBC with diff, CMP	•			•			•
Blood and urine for biorepository		•			•		•
HRCT	•						• [*]
Treatment assignment		•					
Drug distribution		•	•	•	•	•	
Drug titration			•				
Drug return/capsule count				•	•	•	•
Exit interview							•

(V#) Visit Number
 (ATS-DLD) modified American Thoracic Society
 Division of Lung Disease questionnaire
 (BD) Bronchodilator
 (CAT) COPD Assessment Test
 (CBC) Complete blood count
 (CMP) Comprehensive metabolic panel
 (HRCT) High resolution computed tomography

(mMRC) modified Medical Research Council Dyspnea Scale
 (PROMIS-20a) Patient Reported Outcomes Measurement
 Information System: Physical Function – Short Form 20a
 (SGRQ-C) St. George's Respiratory Questionnaire for COPD
 (SPO₂) peripheral capillary oxygen saturation

* Window for V7 HRCT is 46-52 weeks

[†]Dyspnea scale for V1 included in ATS-DLD

4. Screening, baseline, and randomization procedures

Stages of enrollment

In the PTC, there are a few events that form key milestones as candidates are considered for participation in a study: **initial contact**, **informed consent**, and **randomization**. Within the parameters of these milestones, the following status categories may be defined.

Pre-screening stage

Pre-screening in the PTC is defined as any screening activity that occurs prior to actual contact with the potential participant. Chart reviews, registry scans, and physician referrals are all considered to be pre-screening.

Screening

Screening begins at the time of initial response from a potential candidate, either verbal or written, that provides basic information regarding inclusion and exclusion criteria. Information from screened participants should be entered into the Participant Screening Log (PS). During screening, a candidate may voluntarily withdraw from consideration, or may be found to be ineligible for the study. In these cases, re-screening may occur. The MOP specifies procedures on rescreening and recycling in MOP section 5.1.8.

Enrollment

Enrollment is defined in the PTC as the act of signing informed consent. Although in some studies the term “enrolled” is used only for randomized participants, many IRB and also the PTC’s DSMB reporting requirements consider any candidate who has signed informed consent to be enrolled. Thus, enrolled participants may be found to be ineligible, they may withdraw during screening, or they may go on to randomization.

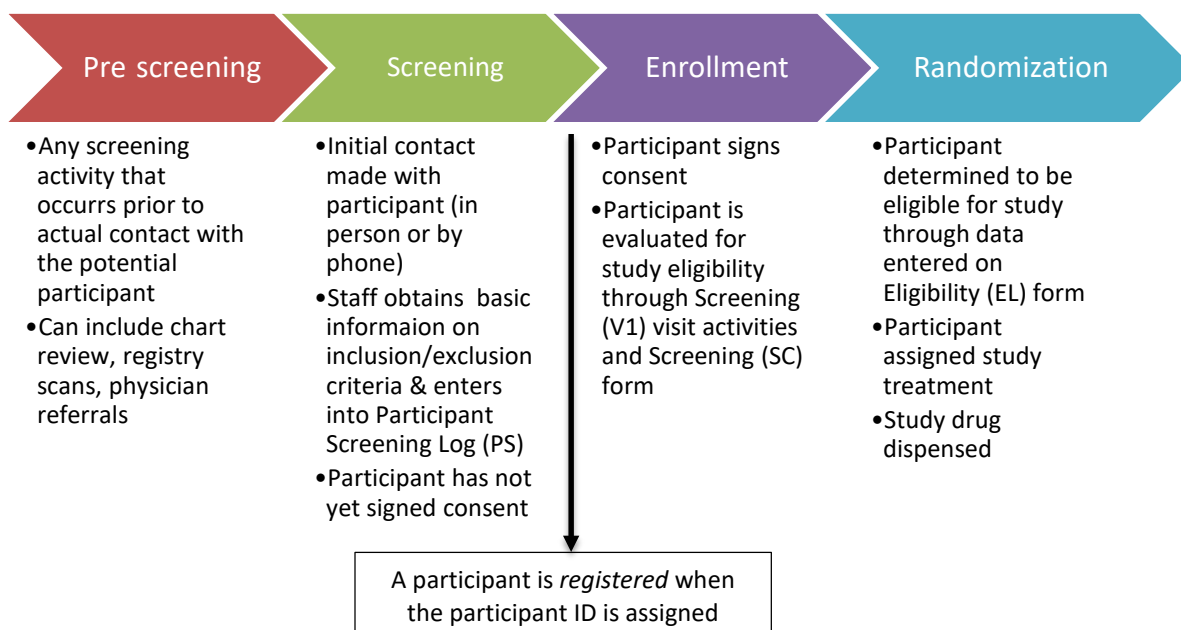
A participant is considered to have enrolled when they consent to be evaluated for LEEP via signing the informed study consent. After signing the consent form a participant must be registered in LEEP; that is, they must be assigned a participant ID in the study data system. If a participant completes Visit 1 activities successfully but then exits LEEP prior to randomization, the coordinator must complete an Early Study Exit (EE) form. This includes participants who are excluded from the study due to results from lab tests or HRCT scanning.

Eligibility

Eligibility is established only when all eligibility criteria are met, no ineligibility criteria have been met, and the participant has confirmed willingness to be randomized for the study. Candidates may voluntarily withdraw at any time during the screening process, but these are not considered to be ineligible. In DSMB reporting, these candidates are classified as “declined to participate.”

Randomization

Randomization is defined as assigning an intervention to an eligible patient. Randomized participants should be followed to V7 regardless of whether they stop treatment, in accordance with our intention to treat model.

Participant stage nomenclature

4.1. Order of procedures

Overall study visits

There is no specified order for study visit procedures except as noted below. However, it is recommended that the quality of life and COPD control questionnaires be completed at the beginning of the visit so that the responses are not influenced by study visit procedures.

Pregnancy testing

Pregnancy testing for women of childbearing potential should be performed at the beginning of **each** study visit, including HRCT visits, **before** any study assessments begin.

Women of childbearing potential includes all female participants except those who are surgically sterile (both ovaries and/or uterus removed), postmenopausal (no menstrual period for longer than 24 consecutive months), or incapable of pregnancy.

Screening visit and HRCT

HRCT scanning should not be performed until after all other enrollment criteria have been assessed, including spirometry and the results of the CBC and CMP. In practice, this may mean that the baseline HRCT scan will have to be scheduled on a different day than the initial screening visit.

Randomization visit

The online randomization should be completed after all other V2 procedures and tests are performed (including questionnaires, blood pressure assessment, and pregnancy testing, if applicable). Randomization includes treatment assignment.

Escalation visit

At V3, dose escalation must not occur until the first set of seated and orthostatic blood pressures have been assessed.

4.2. Screening visit (V1)

Overview

Screening includes the consenting process, initial evaluation for eligibility, acquiring baseline data, physical examination, orthostatic blood pressure check, blood draw, administration of questionnaires, pregnancy testing (for women of child bearing potential), pre-and post-BD spirometry and an HRCT scan (scheduled after lab results obtained)

Time frame

- Target: 4 weeks prior to Randomization (V2)
- Window: 0 to 4 weeks prior to Randomization (V2)
- Estimated duration: 4 hours (2.5 hours without HRCT)

Equipment and materials

- Consent form
- V1 forms and V1 checklist (VC1)
- Spirometer and albuterol
- Pulse oximeter
- Phlebotomy supplies for CBC with differential and CMP
- Blood pressure monitoring device
- Pregnancy test (for female participants of childbearing potential)

Tasks

During V1

- Consent process
 - Explain study to participant.
 - Review consent with participant.
 - Sign and date consent; provide copy to participant.
- Have participant complete a release statement, as applicable (see sample release statement in MOP section 10.2.2).
- Register participant (assign a LEEP participant ID)
 - Remove the next sequentially numbered label from Clinic Label Sheet (see example in MOP section 7.7.2.1) and place it on the SC form.
 - Register the participant ID in the LEEP data system.
- Pregnancy test (for female participants of childbearing potential)
 - If test is positive STOP, participant is not eligible
 - Complete Participant Information (PI) form.
 - Complete forms
 - Screening (SC) form
 - Baseline History (BH) form
 - Complete logs
 - Pulmonary Medications Log (CP)
 - Non-Pulmonary Medications Log (CM)
 - Coordinator to administer
 - ATS-DLD (AT)
- Participant to complete
 - COPD Assessment Test (CA)
 - PROMIS - 20a (PQ)
 - SGRQ-C (SG)

- Administer physical examination
 - Record exam results on Physical Examination (PE) form
- Check vital signs
 - Measure height and weight
 - Measure SPO₂
 - Measure seated and orthostatic BP

See MOP section 7.3 for detailed instructions on measuring and recording blood pressure measurements

- Record results on Physical Measurements (PM) form
- Study physician to complete brief physical examination
 - Record results on Physical Examination (PE) form
- Perform pre-and post-bronchodilator spirometry (see MOP section 7.2)
 - Record results on Pulmonary Function (PF) form
 - **Note:** if pre-bronchodilator efforts exceed eligibility criteria, bronchodilation and post-bronchodilator spirometry results are not expected.
- Draw blood for CBC with differential and CMP, and send to lab for analysis
- If participant is eligible, schedule HRCT scan
 - Scan may be conducted on a separate day than the V1 procedures/questionnaires. Participants will continue to V2 if they meet all eligibility criteria (including HRCT results).
 - See MOP section 7.1 and Appendix B – HRCT Scanning Procedure for detailed instructions on HRCT scan
- Schedule V2 (pending lab and HRCT results)

After the visit

- Data enter Screening form (SC).
 - If there is a  , skip to end. **The SC form must be data entered for ineligible individuals.**
 - The Screening (SC) form should be data entered immediately after completing a V1 and must be entered before a participant can be randomized at V2.
 - Forms for screen failures or incomplete screenings should be kept with study records.
- After obtaining lab results, complete Laboratory Data (LD) form, and determine if data affects eligibility status
 - Early Study Exit form to be completed and keyed if ineligible due to lab results
- HRCT
 - Upload HRCT scan to NEMO (see MOP section 7.1.7)
 - Data enter HRCT Acquisition (RT) form within 2 days

 **Note:** *RT form must be data entered before eligibility can be determined*

- Review radiologist's report; complete Radiologist Review (RR) form
- HRCT results
 - IF % voxels less than -950 HU is between 5-35% and all other criteria were met, then confirm V2 appointment
 - IF % voxels less than -950 HU is less than 5% or greater than 35%, participant is not eligible
 - Complete Early Study Exit (EE) form
 - Contact participant and cancel V2 appointment

Important: V1 HRCT scan is not to be repeated. Period.

- HRCT eligibility will be available in the LEEP data system within 5 business days of scan upload and RT form data entry. To see results, click [CT Eligibility Tracking System](#) link on LEEPTrial.org website and select [List All Entries](#).

For eligible participants

- Key other forms and questionnaires into LEEP data system within 10 working days
- All V1 forms** are to be data entered for participants that are eligible and willing to enroll based on responses on the Screening (SC) form. HRCT related forms (RT, RR) are required if a HRCT scan was done.

For ineligible participants

- If the person is ineligible based on Screening (SC) Form, key SC form only
- If the person is ineligible due to lab value(s), key SC, Laboratory Data (LD) form and Early Exit (EE) forms
- If the person is ineligible after HRCT, key SC, HRCT related (RT, RR) and EE forms

Questionnaires

- ATS-DLD (AT)
- COPD Assessment Test (CA)
- PROMIS-20a (PQ)
- SGRQ-C (SG)

Forms (abbreviation)

- Baseline History (BH)
- HRCT Acquisition (RT)
- Laboratory Data (LD)
- Missed data (MD)*
- Participant information (PI)
- Physical exam (PE)
- Physical measurements (PM)
- Pulmonary Function (PF)
- Radiologist review (RR)
- Screening (SC)
- Unanticipated Problem (UP)*
- Serious Adverse Event (SR)*
- Early Exit (EE)*

Logs and Administrative forms (abbreviation)

- Participant Screening Log (PS)
- Pulmonary Medications Log (CP) †
- Non-Pulmonary Medications Log (CM) †
- LEEP V1 task checklist (VC1) ‡

† Entered into database after final study visit

‡ Not entered into database

* *If applicable*

4.3. Randomization visit (V2)

Overview

Primary purpose of visit is randomization and treatment assignment. Visit includes confirmation of eligibility, interval medical history and assessment of adverse events, administration of questionnaires, collection of vital signs and orthostatic blood pressure checks, and pregnancy test, if applicable. For randomized participants the visit includes study drug administration (50mg losartan or placebo), observation and monitoring of orthostatic blood pressure and distribution of study drug.

Time frame

- Target: 4 weeks after Screening visit (V1)
- Window: 1 to 4 weeks after V1 (up to 8 weeks after HRCT if needed for delays for recycling or scheduling; maximum time allowed between HRCT scan and randomization is 8 weeks)
- Estimated duration: 3 hours

Equipment and materials

- V2 forms and V2 checklist (VC2)
- Pulse oximeter
- Specimen collection, processing and storage supplies (if consented to have specimens stored for future use)
- Blood pressure monitoring device
- Pregnancy test (for female participants of childbearing potential)
- Study drug (50mg losartan or placebo)

Tasks

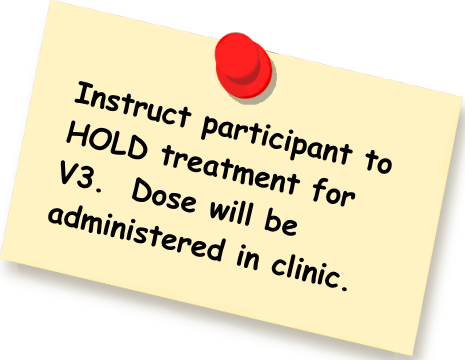
During V2

- Pregnancy test (for female participants of childbearing potential)
 - If test is positive STOP, participant cannot be randomized
 - Complete an Unanticipated Problem (UP) form and an Early Study Exit (EE) form and data enter within 10 working days
- Complete forms
 - Clinic Visit (CV) form
- Complete concomitant medication logs
 - Pulmonary Medications Log (CP)
 - Non-Pulmonary Medications Log (CM)
- Participant to complete
 - COPD Assessment Test (CA)
 - mMRC Dyspnea Scale (DS)
 - PROMIS-20a (PQ)
 - SGRQ-C (SG)
- Check vital signs prior to administering any study drug
 - Measure height and weight
 - Measure SPO₂
 - Measure seated and orthostatic BP
 - See MOP section 7.3 for detailed instructions on measuring and recording blood pressure

- Draw blood and collect urine sample for specimen biorepository only if participant consented for storage of biospecimens for future studies:
 - Process samples and store for shipment to specimen biorepository
 - ✎ **Note: DNA (Packed cells) is only stored for participants that consented specifically for genetic studies**
- **Verify all eligibility criteria with Eligibility (EL) form.** If participant meets all eligibility criteria, then he/she may be randomized to a study treatment:
 - If eligible, data enter SC and EL forms
 - If participant is not eligible to be randomized
 - Complete Early Study Exit (EE) form and data enter within 10 working days.
 - A participant that is not eligible at V2 to be randomized may be eligible to be recycled (see MOP section 5.1.8.2). Eligibility must occur within 8 weeks of V1 HRCT scan.
- Perform treatment assignment by completing the 'LEEP Treatment Assignment (Randomization)' on the main data system page. This step must be completed before giving any drug to the participant.
- Complete Drug Assignment and Dispensing (DA) form:
 - Affix the tear-off label from drug package onto the DA form **at the time drug is assigned to the participant**
 - **Key DA form into data system while participant is at the clinic** to avoid errors in drug distribution.
- To ensure treatment tolerance:
 - Instruct participant to take his/her first dose (one capsule)
 - Observe participant for two hours after he/she takes his/her first dose
 - Measure orthostatic BP

If BP is low (systolic less than 90 mm Hg/diastolic less than 60 mm Hg), notify study physician. Participant to continue in study even if off treatment.

 - If participant experiences unanticipated serious adverse reaction, complete a Serious Adverse Event (SR) form or Unanticipated Problem (UP) form as required (see MOP section 12.4.2.2 for expedited event reporting procedures).
 - ✎ **Note: Some drop in blood pressure after taking study drug is expected.**
- If study drug is tolerated (after two hours, the BP measurements are within acceptable range and no adverse events occur)
 - Distribute schedule of visits (SOV) with visit windows based on date of randomization
 - Distribute LEEP wallet card
 - Dispense study drug bottle to participant, with instruction to take 1 capsule per day, after filling in label on bottle with:
 - Dose (capsules per day)
 - Date dispensed
 - Participant's name
 - Study physician name
 - Emergency number for study staff
 - Instruct participant:
 - Study drug should be taken at about the same time each day (so morning or evening)



**Instruct participant to
HOLD treatment for
V3. Dose will be
administered in clinic.**

- Missed doses are not “made up” (do **not** double the next dose)

After the visit

- Key remaining forms and questionnaires into LEEP data system within 10 working days.

Questionnaires (abbreviation)

- COPD Assessment Test (CA)
- mMRC Dyspnea Scale (DS)
- PROMIS-20a (PQ)
- SGRQ-C (SG)

Forms (abbreviation)

- Clinic Visit (CV)
- Eligibility (EL)
- Drug Assignment and Dispensing (DA)
- Physical Measurements (PM)
- Biospecimen Collection (BC)
- Missed Data (MD)*
- Unanticipated Problem (UP)*
- Serious Adverse Event (SR)*
- Early Study Exit (EE)[§]

Information Sheets (if not handed out at V1)

- LEEP wallet card
- LEEP appointment card for next visit
- Schedule of visits (SOV) [‡]
- Primary physician introduction letter[‡]

Logs and Administrative forms (abbreviation)

- Pulmonary Medications Log (CP) [†]
- Non-Pulmonary Medications Log (CM) [†]
- LEEP V2 task checklist (VC2) [‡]

[†] Entered into database after final study visit

[‡] Not entered into database

* If applicable

[§] *Only if participant is not randomized*

5. Treatment phase study visits/contacts

5.1. Overview

The follow up schedule for the LEEP study should proceed according to the study visit windows listed below.

Visit	V2	V3	V4	V5	V6	V7
Target (weeks)	0	2	12	24	36	48
Visit window (weeks)	0	2-4	10-14	22-26	34-38	46-50

The follow up schedule for LEEP is based on the date of the randomization visit (V2) occurs. Subsequent visit targets and windows must be based on their time from V2, NOT on time from any other visit (screening, the most recent visit, etc.).

The LEEP data system has a tool that can be used to calculate visit target dates and visit windows for study participants. This tool can be found on the LEEP website, at <http://www.LEEP.Trial.org>. Below is an example of the visit window tool.

Clinic	ID	RZ Date	Target Contact Dates and Contact Windows				
			V3 (Visit 3)	V4 (Visit 4)	V5 (Visit 5)	V6 (Visit 6)	V7 (Visit 7)
		07/26/2017	08/09/2017 08/09/17-08/23/17	10/18/2017 10/04/17-11/01/17	01/10/2018 12/27/17-01/24/18	04/04/2018 03/21/18-04/18/18	06/27/2018 06/13/18-07/11/18
		08/11/2017	08/25/2017 08/25/17-09/08/17	11/03/2017 10/20/17-11/17/17	01/26/2018 01/12/18-02/09/18	04/20/2018 04/06/18-05/04/18	07/13/2018 06/29/18-07/27/18
		07/14/2017	07/28/2017 07/28/17-08/11/17	10/06/2017 09/22/17-10/20/17	12/29/2017 12/15/17-01/12/18	03/23/2018 03/09/18-04/06/18	06/15/2018 06/01/18-06/29/18
		08/15/2017	08/29/2017 08/29/17-09/12/17	11/07/2017 10/24/17-11/21/17	01/30/2018 01/16/18-02/13/18	04/24/2018 04/10/18-05/08/18	07/17/2018 07/03/18-07/31/18
		09/20/2017	10/04/2017 10/04/17-10/18/17	12/13/2017 11/29/17-12/27/17	03/07/2018 02/21/18-03/21/18	05/30/2018 05/16/18-06/13/18	08/22/2018 08/08/18-09/05/18
		08/30/2017	09/13/2017 09/13/17-09/27/17	11/22/2017 11/08/17-12/06/17	02/14/2018 01/31/18-02/28/18	05/09/2018 04/25/18-05/23/18	08/01/2018 07/18/18-08/15/18
		09/28/2017	10/12/2017 10/12/17-10/26/17	12/21/2017 12/07/17-01/04/18	03/15/2018 03/01/18-03/29/18	06/07/2018 05/24/18-06/21/18	08/30/2018 08/16/18-09/13/18
		06/08/2017	06/22/2017 06/22/17-07/06/17	08/31/2017 08/17/17-09/14/17	11/23/2017 11/09/17-12/07/17	02/15/2018 02/01/18-03/01/18	05/10/2018 04/26/18-05/24/18
		09/07/2017	09/21/2017 09/21/17-10/05/17	11/30/2017 11/16/17-12/14/17	02/22/2018 02/08/18-03/08/18	05/17/2018 05/03/18-05/31/18	08/09/2018 07/26/18-08/23/18
		07/31/2017	08/14/2017 08/14/17-08/28/17	10/23/2017 10/09/17-11/06/17	01/15/2018 01/01/18-01/29/18	04/09/2018 03/26/18-04/23/18	07/02/2018 06/18/18-07/16/18
		08/03/2017	08/17/2017 08/17/17-08/31/17	10/26/2017 10/12/17-11/09/17	01/18/2018 01/04/18-02/01/18	04/12/2018 03/29/18-04/26/18	07/05/2018 06/21/18-07/19/18
		07/18/2017	08/01/2017 08/01/17-08/15/17	10/10/2017 09/26/17-10/24/17	01/02/2018 12/19/17-01/16/18	03/27/2018 03/13/18-04/10/18	06/19/2018 06/05/18-07/03/18
		07/19/2017	08/02/2017 08/02/17-08/16/17	10/11/2017 09/27/17-10/25/17	01/03/2018 12/20/17-01/17/18	03/28/2018 03/14/18-04/11/18	06/20/2018 06/06/18-07/04/18
		08/02/2017	08/16/2017 08/16/17-08/30/17	10/25/2017 10/11/17-11/08/17	01/17/2018 01/03/18-01/31/18	04/11/2018 03/28/18-04/25/18	07/04/2018 06/20/18-07/18/18
		08/10/2017	08/24/2017 08/24/17-09/07/17	11/02/2017 10/19/17-11/16/17	01/25/2018 01/11/18-02/08/18	04/19/2018 04/05/18-05/03/18	07/12/2018 06/28/18-07/26/18

(click participant ID for detail view)

Key				
Contact Completed	Contact Missed	Window Open	Future Window	
Target Date	07/30/2017	07/30/2017	09/28/2017	11/27/2017
Ideal Window	06/18/17-09/17/17	06/18/17-09/17/17	08/17/17-11/16/17	10/16/17-01/15/18

A detailed view of each study participant's target visit dates and visit windows can be seen by clicking on that participant's ID.

Target Contact Schedule for Participant [REDACTED]

Visit		Target Date Window	Actual Visit Date
RZ	Visit 2	07/26/2017	
V3	Visit 3	08/09/2017 08/09/17-08/23/17	
V4	Visit 4	10/18/2017 10/04/17-11/01/17	
V5	Visit 5	01/10/2018 12/27/17-01/24/18	
V6	Visit 6	04/04/2018 03/21/18-04/18/18	
V7	Visit 7	06/27/2018 06/13/18-07/11/18	

Key

	Contact Completed	Contact Missed	Window Open	Future Window
Target Date	07/30/2017	07/30/2017	09/28/2017	11/27/2017
Ideal Window	06/18/17-09/17/17	06/18/17-09/17/17	08/17/17-11/16/17	10/16/17-01/15/18

5.1.1. Treatment titration visit (V3) - week 2

Overview

The primary purpose of this visit is dose escalation. During this visit, the participant is titrated to the full study drug dosage (2 capsules; 100mg losartan or placebo) and the participant is monitored to ensure that he/she can tolerate the increased dose. The visit includes an interval medical history, assessment of adverse events, check of vital signs including pulse oximetry and orthostatic blood pressure checks, and pregnancy test, if applicable, and an observation period to see if the higher dose is well tolerated.

Time frame

- Target: 2 weeks after Randomization (V2)
- Window: 2 to 4 weeks after V2
- Estimated duration: 1.5 hours

Equipment and materials

- V3 forms and V3 checklist (VC3)
- Pulse oximeter
- Blood pressure monitoring device
- Pregnancy test (for female participants of childbearing potential)
- Study drug (losartan or placebo; participant is to bring study drug bottle dispensed at V2 to this visit)

Visit to be rescheduled if participant has taken dose of study drug on day of V3 or does not bring study drug bottle.

Tasks

Before V3

- Remind participant that
 - NO study drug is to be taken of the day of V3; participant will take dose in clinic, under supervision
 - Participant must bring study drug bottle to visit with them

During V3

- Pregnancy test (for female participants of childbearing potential)
 - If test is positive, complete and data enter
 - Unanticipated Problem (UP) form and
 - Treatment Termination (TT) forms

 **Note:** Randomized participants should continue in LEEP to the end (V7), even if treatment has been terminated. Do NOT complete Early Study Exit form (EE).

- Check vital signs prior to administering any study drug
 - Measure height and weight
 - Measure SPO₂
 - Measure seated and orthostatic BP

See MOP section 7.3 for detailed instructions on measuring and recording blood pressure.

- Complete forms
 - Clinic Visit (CV) form
 - Physical Measurements (PM) form; record initial set of BP measurements

- Complete logs
 - Pulmonary Medications Log (CP)
 - Non-Pulmonary Medications Log (CM)
 - Dose escalation
 - Verify that participant has not taken study drug on the day of the visit
 - Verify participant has the drug bottle with him/her on the day of the visit
 - If participant has tolerated the one capsule a day dosing of the study drug prior to this visit, and blood pressure is 90/60 or higher, then administer full dose (two capsules) of study drug (masked losartan or placebo) from participant's assigned treatment bottle
 - **Observe participant for one hour** after he/she takes 2 capsules of study drug/placebo from his/her bottle assigned at V2
 - Measure orthostatic BP **after one hour**
 - If BP measurements are within acceptable range, and no adverse events occur, instruct participant to take 2 capsules of study drug per day starting the next day
 - Write new dose on the drug bottle label.
 - Complete Drug Dose (DD) form; indicate new dose.
 - If systolic blood pressure is less than 90 mm Hg or diastolic blood pressure is less than 60 mm Hg OR the participant complains of being light headed or dizzy, the study physician is to be contacted. Study physician to determine if participant should take 1 capsule per day or stop treatment.
 - If study drug/placebo is stopped temporarily
 - Complete Drug Dose (DD) form
 - Complete Drug Return/Adherence/Capsule Count (DR) form if applicable (e.g., participant to remain off treatment until next scheduled clinic visit)
-  **Note:** If treatment is permanently stopped, complete Treatment Termination (TT) form
- Instruct participant
 - To take full dose at one time, about the same time every day
 - That missed doses are **not** “made up” (do **not** double the next dose)

After the visit

- Key forms into LEEP data system within 10 working days.

Forms (abbreviation)

- Clinic visit (CV)
- Missed data (MD)*
- Drug Dose (DD)*
- Physical Measurements (PM)
- Treatment Termination (TT)*
- Unanticipated Problem (UP)*
- Serious Adverse Event (SR)*

Logs and Administrative forms (abbreviation)

- Pulmonary Medications Log (CP)[†]
- Non-Pulmonary Medications Log (CM)[†]
- LEEP V3 task checklist (VC3)[‡]

[†] Entered into database following final study visit

[‡] Not entered into database

* If applicable

5.1.2. Follow-up visit (V4) - week 12

Overview

During this visit, data are collected on interval health history, adverse events, vital signs including pulse oximetry and orthostatic blood pressure check. Blood is collected for safety labs and a pregnancy test for all female participants of childbearing potential is done. Questionnaires are administered. Participants return study drug bottle, capsules are counted to evaluate adherence, and a new bottle of study drug is assigned and dispensed.

Time frame

- Target: 12 weeks after Randomization (V2)
- Window: 10 to 14 weeks after V2
- Estimated duration: 2 hours

Equipment and materials

- V4 forms and V4 checklist (VC4)
- Pulse oximeter
- Blood pressure monitoring device
- Phlebotomy supplies for CBC with diff. and CMP
- Pregnancy test (for female participants of childbearing potential)
- Study drug (losartan or placebo; participant is to bring study drug bottle dispensed at V3 to this visit)

Tasks

Before V4

- Remind participant that
 - Participant must bring study drug bottle to visit with them

During V4

- Draw blood for CBC with diff and CMP and send to lab for analysis
 - Pregnancy test (for female participants of childbearing potential)
 - If test is positive, complete
 - Unanticipated Problem (UP) form and
 - Treatment Termination (TT) forms
-  **Note: Participant is to continue in LEEP to the end (V7), even if treatment has been terminated**
- Complete forms
 - Clinic Visit (CV) form
 - Complete logs
 - Pulmonary Medications Log (CP)
 - Non-Pulmonary Medications Log (CM)

- Participant to complete
 - COPD Assessment Test (CA)
 - mMRC Dyspnea Scale (DS)
 - PROMIS- 20a (PQ)
 - SGRQ-C (SG)
- Check vital signs prior to administering any study drug/placebo
 - Measure SPO₂
 - Measure seated and orthostatic BP
 - Record results on Physical Measurements (PM) form
- Medication adherence/Capsule count
 - Participant to return used/partially used bottle.
 - Complete Drug Return/Adherence/Capsule Count (DR) form
 - Record Bottle ID# on DR form
 - Count capsules and record on form. Capsules should be counted at least twice, or until result can be repeated.
 - Determine expected number of remaining capsules and compare to actual number returned.
 - Counsel participant on medication adherence, if there is discrepancy between expected and returned counts.
- Assign and dispense new drug bottle to participant
 - In LEEP data system, complete request for “Follow up treatment assignment”
 - Print out treatment assignment and store in participant’s record
 - Complete Drug Assignment and Dispensing (DA) form
 - Affix the tear-off label from drug package onto the DA form while participant is in the clinic
 - Enter DA form at the time of the visit (verifies correct treatment dispensed)

 **Note:** To verify that correct drug is dispensed, the DA form must be data entered IMMEDIATELY after drug is dispensed to the participant.

- Fill in bottle label (See MOP section 6.1.6) and then dispense to participant

After the visit

- Record results of CBC and CMP; notify study physician of any out of range values
- Key forms and questionnaires into LEEP data system within 10 working days.

Questionnaires (abbreviation)

- COPD Assessment Test (CA)
- mMRC Dyspnea Scale (DS)
- PROMIS-20a (PQ)
- SGRQ-C (SG)

Forms (abbreviation)

- Clinic visit (CV)
- Drug Assignment and Dispensing (DA)
- Drug Return/Adherence/Capsule Count (DR)
- Drug Dose (DD)*
- Lab data (LD)
- Physical Measurements (PM)
- Missed Data (MD)*
- Treatment Termination (TT)*
- Unanticipated Problem (UP)*
- Serious Adverse Event (SR)*

Log/Administrative forms (abbreviation)

- Pulmonary Medications Log (CP) [†]
- Non-Pulmonary Medications Log (CM) [†]
- LEEP V4 task checklist (VC4) [‡]

[†] Entered into database after final study visit

[‡] Not entered into database

* If applicable

5.1.3. Follow-up visit (V5) - week 24

Overview

During this visit, data are collected on interval health history, adverse events, vital signs and pulse oximetry, anthropometric data (height and weight), orthostatic blood pressure check, pre- and post-bronchodilator spirometry, and a pregnancy test, if applicable. Questionnaires are administered. Participants return study drug bottle, capsules are counted to evaluate adherence, and a new bottle of study drug should be assigned and dispensed.

Time frame

- Target: 24 weeks after Randomization (V2)
- Window: 22 to 26 weeks after V2
- Estimated duration: 3 hours

Equipment and materials

- V5 forms and V5 checklist (VC5)
- Spirometer and albuterol
- Pulse oximeter
- Specimen collection, processing and storage supplies (if consented to provide specimens for future use)
- Blood pressure monitoring device
- Pregnancy test (for female participants of childbearing potential)
- Study drug (losartan or placebo; participant is to bring study drug bottle dispensed at V4 to this visit)

Tasks

Before V5

- Remind participant that
 - Participant must bring study drug bottle to visit with them

During V5

- Pregnancy test (for female participants of childbearing potential)
 - If test is positive, complete
 - Unanticipated Problem (UP) form and
 - Treatment Termination (TT) forms and data enter within 10 working days

 **Note:** Randomized participants should continue in LEEP to the end (V7), regardless if treatment has been terminated. Do NOT complete Early Study Exit form (EE).

- Complete forms
 - Clinic Visit (CV) form
- Complete logs
 - Pulmonary Medications Log (CP)
 - Non-Pulmonary Medications Log (CM)
- Participant to complete
 - COPD Assessment Test (CA)
 - mMRC Dyspnea Scale (DS)
 - PROMIS- 20a (PQ)

- SGRQ-C (SG)
- Check vital signs
 - Measure height and weight
 - Measure SPO₂
 - Measure seated and orthostatic BP
 - Record results on Physical Measurements (PM) form
- Study physician to complete brief physical examination
 - Record results on Physical Examination (PE) form
- Draw blood and collect urine sample for specimen biorepository
 - Process samples and store for shipment
 - Record specimens on Biospecimen Collection (BC) form
- Perform pre-and post-bronchodilator spirometry (see MOP section 7.2 and Appendix F – MOP Spirometry)
 - Record results on Pulmonary Function (PF) form
- Medication adherence/Capsule count
 - Participant to return used/partially used bottle.
 - Complete Drug Return/Adherence/Capsule Count (DR) form
 - Record Bottle ID# on DR form
 - Count capsules and record on form. Capsules should be counted at least twice, or until result can be repeated
 - Determine expected number of remaining capsules and compare to actual number returned
 - Counsel participant on medication adherence if there is discrepancy between expected and returned counts
- Assign/dispense new drug bottle to participant
 - In LEEP data system, complete request for “Follow up treatment assignment”
 - Print out treatment assignment and store in participant’s record
 - Complete Drug Assignment and Dispensing (DA) form
 - Affix the tear-off label from drug package onto the DA form while participant is in the clinic
 - Enter DA form at the time of the visit (verifies correct treatment dispensed)
 - Fill in bottle label (See MOP section 6.1.6) and then dispense to participant

After the visit

- Key other forms and questionnaires into LEEP data system within 10 working days.

Questionnaires (abbreviations)

- COPD Assessment Test (CA)
- mMRC Dyspnea Scale (DS)
- PROMIS-20a (PQ)
- SGRQ-C (SG)

Forms (abbreviation)

- Clinic Visit (CV)
- Drug Assignment and Dispensing (DA)
- Drug Return/Adherence/Capsule Count (DR)
- Drug Dose (DD)*
- Physical Exam (PE)
- Physical Measurements (PM)
- Pulmonary Function (PF)
- Biospecimen Collection (BC)
- Missed Data (MD)*
- Treatment Termination (TT)*
- Unanticipated Problem (UP)*
- Serious Adverse Event (SR)*

Log/Administrative forms (abbreviation)

- Pulmonary Medications Log (CP) †
- Non-Pulmonary Medications Log (CM) †
- LEEP V5 task checklist (VC5) ‡

† Entered into database after final study visit

‡ Not entered into database

* If applicable

5.1.4. Follow up-visit (V6) - week 36

Overview

During this visit, data are collected on interval health history, adverse events, vital signs, and pulse oximetry. Questionnaires are administered, and a pregnancy test is performed, where applicable. Participants return study drug bottle, capsules are counted to evaluate adherence, and a new bottle of study drug is assigned and dispensed.

Time frame

- Target: 36 weeks after Randomization (V2)
- Window: 34 to 38 weeks after V2
- Estimated duration: 2 hours

Equipment and materials

- V6 forms and V6 checklist (VC6)
- Pulse oximeter
- Pregnancy test (for female participants of childbearing potential)
- Blood pressure monitoring device
- Study drug

Tasks

Before V6

- Remind participant that
 - Participant must bring study drug bottle to visit with them

During V6

- Pregnancy test (for female participants of childbearing potential)
 - If test is positive, complete
 - Unanticipated Problem (UP) and
 - Treatment Termination (TT) forms and data enter within 10 working days
- Participant to complete
 - COPD Assessment Test (CA)
 - mMRC Dyspnea Scale (DS)
 - PROMIS- 20a (PQ)
 - SGRQ-C (SG)
- Check vital signs
 - Measure height and weight
 - Measure SPO₂
 - Measure seated and orthostatic BP
 - Record results on Physical Measurements (PM) form
- Complete forms
 - Clinic Visit (CV) form
- Complete logs
 - Pulmonary Medications Log (CP)
 - Non-Pulmonary Medications Log (CM)
- Medication adherence/Capsule count
 - Participant to return used/partially used bottle.

- Complete Drug Return/Adherence/Capsule Count (DR) form
- Record Bottle ID# on DR form
- Count capsules and record on form. Capsules should be counted at least twice, or until result can be repeated
- Determine expected number of remaining capsules and compare to actual number returned
- Counsel participant on medication adherence if there is discrepancy between expected and returned counts
- Assign/dispense drug to participant
 - In LEEP data system, complete request for “Follow up treatment assignment”
 - Request new bottle ID
 - Print out treatment assignment and store in participant’s record
 - Complete Drug Assignment and Dispensing (DA) form
 - Affix the tear-off label from drug package onto the DA form while participant is in the clinic
 - Data enter DA form while participant is in clinic (verifies correct treatment dispensed)
 - Fill in bottle label (See MOP section 6.1.6) and then dispense to participant

After the visit

- Key other forms and questionnaires into LEEP data system within 10 working days.

Questionnaires (abbreviation)

- COPD Assessment Test (CA)
- mMRC Dyspnea Scale (DS)
- PROMIS-20a (PQ)
- SGRQ-C (SG)

Forms (abbreviation)

- Clinic visit (CV)
- Drug Assignment and Dispensing (DA)
- Drug Return/Adherence/Capsule Count (DR)
- Drug Dose (DD)*
- Physical Measurements (PM)
- Missed Data (MD)*
- Treatment Termination (TT)*
- Unanticipated Problem (UP)*
- Serious Adverse Event (SR)*

Logs and Administrative forms (abbreviation)

- Pulmonary Medications Log (CP) [†]
- Non-Pulmonary Medications Log (CM) [†]
- LEEP V6 task checklist (VC6) [‡]

[†] Entered into database after final study visit

[‡] Not entered into database

* If applicable

5.1.5. Final visit (V7) - week 48

Overview

During this visit, data are collected on interval health history, adverse events, vital signs, pulse oximetry, anthropometric data (height and weight), orthostatic blood pressure check, and pre- and post-bronchodilator spirometry. Blood is collected for safety labs and a pregnancy test is performed, if applicable. Questionnaires and Study Evaluation are administered. Participants return study drug bottle and capsules are counted to evaluate adherence.

Time frame

- Target: 48 weeks after Randomization (V2)
- Window: 46 to 50 weeks after V2
- Duration: 4 hours (2.5 hours not including HRCT scan)

Equipment and materials

- V7 forms and V7 checklist (VC7)
- Spirometer and albuterol
- Pulse oximeter
- Blood pressure monitoring device
- Phlebotomy supplies for CBC with diff and CMP
- Specimen collection, processing and storage supplies (if consented to provide specimens for future use)
- Pregnancy test (for female participants of childbearing potential)
- Exit envelope (includes participant exit letter and sealed treatment unmasking envelope)

Tasks

Before V7

- Remind participant that
 - Participant must bring study drug bottle(s) to visit with them; this includes any bottles not returned at previous visits

During V7

- Draw blood for CBC with diff and CMP
 - Send CBC with diff and CMP to lab for analysis
 - Process blood and urine for biorepository and store for shipment
- Pregnancy test (for female participants of childbearing potential)
 - If test is positive, complete
 - Unanticipated Problem (UP) form and data enter within 10 working days
- Complete forms
 - Clinic Visit (CV) form
- Complete logs
 - Pulmonary Medications Log (CP)
 - Non-Pulmonary Medications Log (CM)
- Participant to complete
 - COPD Assessment Test (CA)
 - mMRC Dyspnea Scale (DS)
 - PROMIS- 20a (PQ)
 - SGRQ-C (SG)

- Check vital signs
 - Measure height and weight
 - Measure SPO₂
 - Measure seated and orthostatic BP
 - Record results on Physical Measurements (PM) form
- Study physician to complete brief physical examination
 - Record results on Physical Examination (PE) form
- Perform pre- and post-bronchodilator spirometry (see MOP section 7.2 and Appendix F – MOP Spirometry)
 - Record results on Pulmonary Function (PF) form
- Medication adherence/Capsule count –
 - Participant to return used/partially used bottle.
 - Complete Drug Return/Adherence/Capsule Count (DR) form
 - Record Bottle ID# on DA form
 - Count capsules and record on form. Capsules should be counted at least twice, or until result can be repeated.
 - Determine expected number of remaining capsules and compare to actual number returned.
- Draw blood and collect urine sample for specimen biorepository
 - Process samples and store for shipment
 - Record specimens on Biospecimen Collection (BC) form
- Schedule HRCT scan (for same day, or on a different day)
 - Scan may be conducted on a separate day than the V7 procedures/questionnaires
 - See MOP section 7.1 and Appendix B – HRCT Scanning Procedure for detailed instructions on HRCT scan
- Conduct exit interview with participant
 - Complete Study Evaluation (SV) and Study Closeout (SL) forms
- Complete Treatment Termination form (TT), if not done previously
- Complete Unmasking form (UM), if not done previously
- Give participant:
 - Exit envelope which includes
 - Participant exit letter (see prototype in MOP section 10.2.5)
 - Sealed treatment unmasking envelope
 - Copy of final spirometry results

After the visit

- After obtaining lab results, complete Laboratory Data (LD) form
- Submit HRCT data
 - Upload scan to NEMO (see MOP section 7.1.7)
 - Data enter HRCT Acquisition (RT) form
 - Review radiologist's report; complete Radiologist Review (RR) form
- Key forms and questionnaires into LEEP data system within 10 working days.
- Send physician exit letter (see prototype in MOP section 10.2.3) to participant's primary COPD physician

Questionnaires (abbreviations)

- COPD Assessment Test (CA)
- mMRC Dyspnea Scale (DS)
- PROMIS-20a (PQ)
- SGRQ-C (SG)

Forms (abbreviation)

- Clinic visit (CV)
- Drug Return/Adherence/Capsule Count (DR)
- Study evaluation (SV)
- Study closeout (SL)
- Spirometry (PF)
- Treatment termination (TT)
- HRCT Acquisition (RT)
- Laboratory Data (LD)
- Participant information (PI)
- Physical exam (PE)
- Physical measurements (PM)
- Pulmonary Function (PF)
- Radiologist review (RR)
- Specimen collection (BC)
- Missed data (MD)*
- Unanticipated Problem (UP)*
- Serious Adverse Event (SR)*

Log/Administrative forms (abbreviation)

- Pulmonary Medications Log (CP)
- Non-Pulmonary Medications Log (CM)
- LEEP V7 task checklist (VC7) [†]

[†] Not entered into database

* *If applicable*

5.1.6. Exit tasks

Purpose

To notify participant of their assigned study treatment via sealed treatment envelope and to provide participant with exit materials (exit letter, spirometry results) after participant completes V7

Timeframe

- Conducted at V7
- If participant does not return to clinic for V7, conduct study evaluation interview over the phone and mail written materials

Materials

- Participant exit letter (may need to be reviewed and approved by local IRB before it is used)
- Sealed treatment assignment envelope

Tasks

- Conduct interview and record on Study Evaluation (SV) form
- Complete Study Closeout (SL) form
- Complete Treatment Termination (TT) form if appropriate
- Give the participant
 - Participant exit letter signed by Study Physician (see prototype in MOP section 10.2.5.)
 - Sealed treatment assignment envelope
 - Copy of final spirometry results
- Complete Unmasking form (UM)
- Review contents of the exit letter with participant
- Send physician exit letter
- Key forms into LEEP data system within 10 working days (including completed Pulmonary Medications Log and Non-Pulmonary Medications Log)

Forms (abbreviation)

- Study Evaluation (SV)
- Study Closeout (SL)
- Treatment Termination (TT)
- Unmasking Form (UM)
- Pulmonary Medications Log (CP)
- Non-Pulmonary Medications Log (CM)

5.1.7. Missed procedures/missed visits

Time frame (for enrolled participants)

- After time window has closed for a specified study visit or any of the following were missed:
 - All requirements for a visit (missed visit).
 - One or more of the procedures or forms required for a visit (missed data at a visit).

Tasks

- Attempt to schedule next visit at a more convenient time, preferably early in the time window.
- If you are unable to contact participant,
 - Attempt to contact at all telephone numbers listed (home, work, cell and other contacts) on Participant Information (PI) form.
 - Make calls at different times of the day.
 - Attempt to e-mail participant.
 - Send a letter to participant.
- Record specific procedures missed or reason visit was missed on Missed Data (MD) form.

Out of window visits

- A visit can be done out of window and that is preferable to missing a visit completely.
- NOTE: Randomization Visit (V2) cannot be done outside of window.
 - If V2 cannot be scheduled within 8 weeks of screening **and HRCT has NOT been done**, participant may be re-screened, i.e. V1 should be conducted again. **If HRCT has been done, participant cannot be rescreened**
- V4 should not be missed, and should be conducted even if V5 window has opened. This visit includes laboratory blood tests for safety, CBC with differential and CMP. All V4 procedures should be completed. At least four weeks must separate V4 and V5.
- Other than V4, only do a visit out of window if the following visit can be done in-window.
- There must be a minimum of four weeks between visits.

Forms (abbreviation)

- Missed Data (MD)
- Participant Information (PI)*

*Not entered into database

5.1.8. Rescreening and recycling**5.1.8.1. Rescreening****Definition**

To perform the screening process again by re-evaluating a participant who previously did not meet eligibility criteria during screening at V1.

Reasons to rescreen

- Elevated blood pressure (>140/90)
 - Refer to PCP. If participant wants to be in the study, provide PCP with information on LEEP trial and indicate that participant could be eligible if blood pressure is well controlled on a calcium channel blocker, if PCP deems it appropriate
 - Rescreen after participant's blood pressure is well controlled on new medication
- Participant currently on ACE inhibitor or ARB for blood pressure control.
 - If participant wants to be in the study, provide PCP with information on LEEP trial and indicate that participant could be eligible if blood pressure is well controlled on a calcium channel blocker, if PCP deems it appropriate
 - Rescreen after participant's blood pressure is well controlled on new medication
- Participant has recent history of chest infection and/or COPD exacerbation
 - Participant must be fully recovered before being rescreened.
 - If participant has had recent pneumonia, then wait at least 8 weeks since pneumonia resolved.
 - Note: HRCT will be compromised if participant has not returned to usual state of health.
- Current use of NSAIDs or corticosteroids
 - If use of an NSAID or a systemic corticosteroid is for an acute condition, such as recent injury, poison ivy or recent COPD exacerbation, participant can be rescreened after such condition has resolved and use of the drug has stopped.
 - If use of NSAIDs or systemic corticosteroids is for a chronic condition, and use of these is on a consistent or frequent basis, the participant should not be rescreened. Examples of regular or chronic could be for the treatment of rheumatoid arthritis, lupus, or osteoarthritis.

Tasks

For participants who were not able to meet entry criteria at screening (V1), but who may be eligible in the future:

- Mark paperwork as “screen failure” and keep in file
- After a 4 week waiting period, you may try to re-screen a participant

Important: *HRCT scans are **NEVER** to be repeated. The need to rescreen a participant must be determined **BEFORE** HRCT scan has been performed*

For participants with orthostatic (sitting or standing) BP outside of the acceptable range at V1:

- If BP is >140 systolic and/or >90 diastolic, retake BP after having participant sit and rest for 30 minutes. If BP is still >140 systolic and/or >90 diastolic, refer to PCP, and have participant return for rescreening when BP is controlled
- Refer to blood pressure flowchart (Appendix D – Blood Pressure Flowcharts) for more information

When screening a participant again:

- Redo all V1 procedures
- Use the participant ID number and name code that were originally assigned
- Complete a new set of V1 forms
- Continue to save paperwork from previous V1
- Enter new forms into the database using “Re-enter (replace) form” option
- DO NOT delete original forms from the database

 **Note:** There is not a limit on the number of times a participant can be re-screened for initial eligibility, but clinics should use their discretion as to what is reasonable.

Log/Administrative form (abbreviation)

- Screening (SC)

5.1.8.2. Recycling

Definition

Recycling is an additional attempt to randomize a participant into the trial who met eligibility criteria at V1 (including HRCT scan results), but not at randomization (V2).

Comment

Recycling will be used in LEEP only for unusual circumstances, on a case by case basis

- Contact the DCC for permission and specific instructions
- A participant may be recycled **one time**.
- The second attempt at randomization **must be within 8 weeks of the HRCT scan** done during V1.
 - If BP is not within acceptable range at second V2, then the participant can have his/her BP checked again, as long as it is within 8 weeks of the HRCT scan.

A participant can have multiple BP checks within the 8-week period.

When a participant is recycled because of high blood pressure

- If at **second V2** the participant's blood pressure (sitting or standing) is outside of the acceptable range:
 - Retake BP after having participant sit and rest for 30 minutes.
 - If systolic BP is between 90 and 140 systolic and diastolic BP between 60 and 90, the participant is eligible for randomization if all other inclusion criteria are met
 - If BP remains out of the acceptable range, refer to PCP.
 - Complete Early Exit form. Participant is not eligible for LEEP
- Refer to blood pressure flowchart (Appendix D – Blood Pressure Flowcharts) for more information

Tasks

- Contact the DCC for permission and specific instructions if you believe your participant should be recycled
- If given permission from the DCC, in addition to any other instructions you receive, do the following:
 - Complete new V2 forms
 - Data enter all new V2 forms using “Re-enter (replace) form” option
 - Complete an Unanticipated Problem (UP) form, if necessary
 - DO NOT delete original V2 forms from database
 - Follow tasks for V2

Forms for recycling (abbreviation)

- Forms for V2 (Randomization)
- Unanticipated Problem (UP) form, if applicable

6. Treatment administration

6.1. Study drug

6.1.1. Study drug description

This study is a comparison of losartan and placebo. Losartan is an FDA approved angiotensin receptor blocker (ARB) most often prescribed for hypertension, heart failure, and for renal protective effects in diabetics. Study drug will be prescribed as follows:

- After randomization, at V2
 - Masked study drug, one capsule per day of losartan 50 mg OR placebo
- At V3, continuing to V7
 - Masked study drug, two capsules per day of losartan 100mg OR two capsules placebo
 - Dose is only increased if participant has tolerated dose escalation (e.g., no complaints of lightheadedness or dizziness) and blood pressure (for both seated and orthostatic measures) is at least 90/60
 - If participant's blood pressure is **less than 90/60 mm Hg** after higher dose, then participant to continue in trial on one capsule (masked 50mg losartan or placebo) per day
- Dosing instructions for participant should include:
 - Take prescribed dose at the same time every day
 - Do not make up a missed dose; do not double up dosing
 - Can be taken with or without food
 - Before V3
 - If participant takes dose in morning, the morning dose must be held
 - If participant takes dose in the evening, the evening dose on the day before V3 must be held

6.1.2. Side effects of losartan

The doses being used in this study (50 and 100 mg per day) are well tolerated by non-hypertensive patients without significant effect on blood pressure.

The most common side effects are fatigue and dizziness. Serious adverse reactions that are rare include angioedema, hypotension, renal dysfunction, blood dyscrasias, hepatitis or rhabdomyolysis. **Table 1** shows common side effects and rates of occurrence compared to placebo.

Table 1

	Losartan and Conventional Antihypertensive Therapy Incidence % (n=751)	Placebo and Conventional Antihypertensive Therapy Incidence % (n=762)
<i>Body as a Whole</i>		
Asthenia/Fatigue	14	10
Chest Pain	12	8
Fever	4	3
Infection	5	4
Influenza-like disease	10	9
Trauma	4	3
<i>Cardiovascular</i>		
Hypotension	7	3
Orthostatic hypotension	4	1
<i>Digestive</i>		
Diarrhea	15	10
Dyspepsia	4	3
Gastritis	5	4
<i>Endocrine</i>		
Diabetic neuropathy	4	3
Diabetic vascular disease	10	9
<i>Eyes, Ears, Nose and Throat</i>		
Cataract	7	5
Sinusitis	6	5
<i>Hemic</i>		
Anemia	14	11
<i>Metabolic and Nutrition</i>		
Hyperkalemia	7	3
Hypoglycemia	14	10
Weight gain	4	3
<i>Musculoskeletal</i>		
Back pain	12	10
Leg pain	5	4
Knee pain	5	4
Muscular weakness	7	4
<i>Nervous System</i>		
Hypesthesia	5	4
<i>Respiratory</i>		
Bronchitis	10	9
Cough	11	10
<i>Skin</i>		
Cellulitis	7	6
<i>Urogenital</i>		
Urinary tract infection	16	13

6.1.3. *Contraindicated medications and supplements*

The following medications are contraindicated for use in LEEP, and therefore use of them at the time of enrollment is an exclusion and any participant should not use them while in LEEP (on either losartan or placebo):

- **Angiotensin Receptor Blockers (other than study treatment)**
- **ACE inhibitors**
- **Potassium supplements and potassium sparing diuretics.**
- **Nonsteroidal anti-inflammatory drugs (NSAIDs)**

To prevent or limit complications from contraindicated treatments:

1. Review the LEEP wallet card with the participant. It explicitly states that these medications are not to be taken. Replace wallet card if it is lost.
2. Send the letter to the participant's PCP which states the purpose of the trial and that participants should not take the following drugs while enrolled in this trial:
 - Other angiotensin receptor blocking (ARB) drugs
 - Angiotensin converting enzyme (ACE) inhibitors
 - Potassium supplements
 - Potassium-sparing diuretics
 - NSAIDs, when used daily (5 or more days of the week) for more than one month
3. Complete the entire CV form while participant is in clinic. It requires documentation that the participant has not started taking an ACE, ARB, or potassium sparing diuretic.
4. Complete the concomitant medication logs at each study visit. Alert physician if any contraindicated drugs or supplements are noted.
5. Refer to the list of ACE inhibitors, ARBs or potassium sparing diuretics that is provided to help identify these categories of drugs (lists are by brand name and by generic name).

6.1.4. *Serious adverse reactions and drug interactions for losartan*

While losartan is safe and well tolerated, the following are significant risks:

- **Pregnancy** – Losartan is an FDA pregnancy category D drug, a potential human teratogen, particularly in the second trimester of pregnancy. In addition, losartan can cause low blood pressure, severe kidney failure or even death in the newborn. There may be other risks associated with the use of losartan in pregnancy that are not yet known. To minimize this risk:
 - All women of childbearing potential must have a pregnancy test at each clinic visit
 - All pregnant women must discontinue study drug/placebo as soon as pregnancy is discovered
 - Any pregnancy must be reported to the DCC and must be followed until completion of pregnancy
 - Any woman who is breastfeeding is ineligible to enroll in LEEP because it is not known whether losartan passes into breast milk or if it could harm a nursing baby.
- **Increased serum potassium (K⁺) levels** – Individuals with type 2 diabetes are at increased risk of developing elevated serum K⁺ levels. Symptoms of elevated serum K⁺ include slow heart rate, weak pulse, muscle weakness, and tingly feeling. To minimize this risk:
 - Participants taking potassium supplements are not eligible to enroll.
 - Participants with hyperkalemia (V1) or significant renal dysfunction are not eligible to enroll because of this risk
 - Serum K⁺ will be checked at V1, V4, and V7. If K⁺ levels are elevated:
 - Lab test will be repeated for confirmation
 - If level is > 5mEq/L, study physician can opt to decrease study dose from 2 capsules to one capsule per day, or can opt to stop study treatment.
- **Interaction with NSAIDs or aspirin** – concurrent use of these drugs with losartan can decrease kidney function and possible cause kidney failure. To minimize this risk:
 - Use of NSAIDs while enrolled in LEEP is to be discouraged.
 - Participant's PCP should be told that participant is taking losartan or placebo
 - Daily use of low-dose aspirin (defined as 325mg/day or less) is allowed
- **Interaction with other blood pressure medications** – combining blood pressure medications increases the risk of hypotension; combining an ARB with an ACE or aliskiren (Tekturna) reduces kidney function. Participants with diabetes or renal impairment are at the highest risk of adverse effects from combining these drugs. To minimize this risk:
 - Review and document all current medications at V1. Participants on contraindicated medications are not eligible.
 - Review all medications at each study visit to identify potential drug interaction
 - Kidney function is to be assessed at V1, V4, and V7

- **Interaction with lithium** – increased blood levels of lithium and lithium toxicity have occurred when an ARB and lithium are combined. To minimize this risk:
 - Individuals taking Lithium at V1 should not be enrolled
 - For individuals prescribed lithium after randomization
 - The study physician should decide, using best medical judgement, if the participant should continue on losartan or placebo
 - Doctor prescribing lithium should be informed of the following:
 - Participant is in a clinical trial and has been on losartan or placebo
 - The study physician's decision regarding termination of treatment.
- **Rhabdomyolysis** - in rare instances, losartan can cause this condition that results in the breakdown of skeletal muscle tissue, which can lead to kidney failure. Symptoms include: unexplained muscle pain, tenderness or weakness; dark colored urine; unusual tiredness and fever.
 - Participants must be encouraged to report new, unusual, and severe symptoms.
 - If Rhabdomyolysis is suspected, participant must seek medical care immediately
- **Liver function** – in rare instances, ALT (alanine transaminase) is increased; and post-marketing reports have included Hepatitis, increased liver enzymes, increased bilirubin, pancreatitis, and liver function abnormalities. To minimize risk:
 - Blood drawn at V1, V4, and V7 will include liver function tests
 - Study physician to be made aware of any abnormal lab values
 - Study physician's best medical judgment should determine changes in study drug dosing

6.1.5. Receipt and distribution

6.1.5.1. Receipt and storage

All drugs will be packaged and distributed by Almac. The LEEP DCC is responsible for coordinating the distribution of specific drug bottles to clinics, as well as ordering additional drugs for clinics, as needed.

The Lead Coordinator at each clinical site is responsible for maintaining records related to the receipt, issuance, and destruction of study drug.

Receipt of new drug from Almac

Upon receipt of study drug from Almac, the Lead Coordinator is responsible for reconciling the shipment log with the study drug bottles received.

- If there is a discrepancy, contact the DCC.

Clinics will receive a batch of bottles, each containing either study drug or placebo; each bottle will have a unique bottle ID. The drug label will be perforated; one section of the label will be torn off when the drug is dispensed. Please see Drug Assignment section below.



Storage

All study drugs are to be stored:

- In a secure, locked location with limited public access and in accordance with your institution's policies (e.g., study drug may be kept in your local pharmacy if required).
- At room temperature, (59-86°F).
- With Bottle ID labels intact until assigned and dispensed to a participant

Drug accountability

The shipment will include a packing list, and list each individual bottle. The coordinator is to reconcile the listing with actual bottles (those not yet dispensed) using the LEEP Drug Distribution System link, and the [Mark Kit\(s\) As Received](#) link. Once reconciled the packing list should be signed by the coordinator and stored in the Regulatory binder.

Any discrepancies are to be addressed at the time the list is being reconciled. If drug is missing or bottles do not match the packing list contact the LEEP Data Coordinating Center (JHSPH.ala-acrc@jhu.edu).

Missing drug (lost at site, not lost by participant) will be reported as protocol deviation on an Unanticipated Problem (UP) form.

Drug that is returned from participants is to be destroyed in accordance with your institution's guidelines. It is extremely important that return capsule counts are verified before remaining drug is destroyed.

Study drug will not be returned to Almac, University of Pittsburgh or the DCC for destruction.

Expired drug, that was not dispensed, is to be destroyed after replacement drug has arrived.

6.1.6. Drug assignment and dispensing

All randomized participants will receive a new bottle (200 capsule count) at V2, V4, V5, and V6.

 **Note:** No two bottles will have the same Bottle ID#.

V2 – Randomization to treatment

To obtain a bottle assignment at randomization:

1. Enter the following forms into the LEEP data system:
 - Screening (SC) form
 - Eligibility (EL) form
 2. Complete treatment assignment:
 - In Data System menu, select [LEEP Treatment Assignment \(Randomization\)](#) link
 - Enter participant information
 - Print out treatment assignment generated by the LEEP data system; store in participant's research record
 3. Document treatment assignment
 - Attach tear off label to Drug Assignment and Dispensing (DA) form
 - Data enter the DA form at the time of the visit
- Important:** Data entry of the drug assignment verifies that the correct treatment was dispensed to the participant.
4. Drug label (attached to the bottle), fill in
 - Dose (capsules per day)
 - Date dispensed
 - Participant's name
 - Study physician name
 - Emergency number for study staff

V4, V5, and V6 or at an “unscheduled visit” – resupply study drug/placebo

To assign and dispense follow-up study drug/placebo (“resupply”):

1. In the LEEP data system, click on [Drug Distribution System](#)
2. Click on [Assign Follow-up Bottle](#)
3. Enter the following: Clinic, Participant ID and Alpha ID Code and the Randomization Bottle ID
4. Print out Treatment Assignment; this to be stored in participant's study record
5. Affix tear off label to DA form at the time the bottle is dispensed.
6. Complete DA form and data enter it at the time of the visit

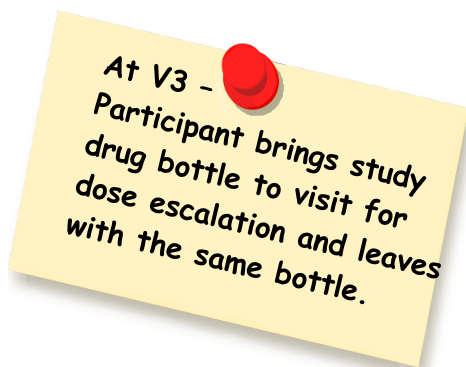
7. On drug label, fill in
 - Dose (capsules per day)
 - Date dispensed
 - Participant's name
 - Study physician name
 - Emergency number for study staff

6.1.6.1. Adherence

Participants are to bring previously dispensed study drug bottle to his/her next clinic visit.

Return of **empty or partially used** bottle of study drug (at V4, V5, or V6):

- Document on Drug Return/Adherence/Capsule Count (DR) form
- Compare actual capsules returned to number of capsules expected (Adherence Calculation worksheet available):
 - If number of capsules returned are not as expected, discuss importance of adherence with participant
- Store empty/partially empty study drug/placebo bottles at the clinic until instructed to destroy them by the DCC



Adherence

- Prevent missed study drug/placebo doses
 - Each bottle contains 200 capsules; enough for the 12 weeks between visits, plus a buffer of 2 ½ weeks
 - Avoid follow up visits late in the visit window;
 - Instruct participants to call if they lose or damage study drug/placebo capsules so study drug can be resupplied as soon as possible.
- Remember when calculating expected capsules (in returned bottle)
 - One capsule per day dosing from V2 to V3
 - Use dose participant expected to be taking
 - Date of last dose of study drug/placebo should be used if participant has terminated treatment (e.g. participant instructed by study physician to stop treatment due to side effects)
- All changes in dosing must be documented on the Drug Dose (DD) form.
 - Dose prescribed should be written on the bottle when dispensed and corrected if dose is adjusted

6.2. Unmasking of treatment assignment

Overview

Masked treatment is critical to the study design. Participants and clinic staff are to remain masked, except for extenuating circumstances. If unmasking is necessary during a participant's time in LEEP, it is important to limit the number of individuals who are unmasked. Ideally, site staff are not unmasked.

In LEEP, unmasking envelopes will be used to reveal treatment assignment:

- The LEEP DCC will send a template of an unmasking letter to the clinic to submit to their local IRB for review and approval
- The LEEP DCC will send each clinic a number of sealed treatment unmasking envelopes
- Each unmasking envelope will have a unique envelope ID and verification code on the front of the envelope
- Upon receipt of the unmasking envelopes, the clinic is to store them in a secure location, with access limited to LEEP study team members, until study closeout. **These envelopes are to remain sealed.**

6.2.1. Routine unmasking of treatment assignment at V7 or after

When

- At V7, after all study data are collected for the participant, including V7 HRCT scan,
- After V7 HRCT scan is done, if scan was done after V7 clinic visit, or
- After the V7 window is closed for the participant who missed V7

Procedure for unmasking at V7 or after

- If unmasking occurs during the clinic visit, all data should be collected prior to unmasking
- Study coordinator will go to the LEEP data system website to obtain the unmasking envelope ID. The data system will assign an unmasking envelope ID based on the participant's treatment assignment and envelopes assigned to the clinic.
- The study coordinator will retrieve the unmasking envelope that matches the assigned unmasking envelope ID.
 - If the site cannot locate the envelope with the specified ID, the coordinator should contact the DCC by phone.
- On the Unmasking (UM) form **both** the Unmasking envelope ID and the Verification code must be recorded
- The **sealed** unmasking envelope is given to the participant if V7 clinic visit and V7 HRCT scan are complete
 - If V7 HRCT scan has not been completed, the envelope assignment (LEEP data system) can take place at V7, but the unmasking envelope is only given to the participant **after the HRCT scan** has been completed.
 - At the time the Unmasking envelope is retrieved the Participant's ID should be written on the envelope
 - The Unmasking (UM) form should be dated to reflect the actual date the envelope is mailed to or handed to the participant.

- It is important that the clinic staff remain masked:
 - The participant is to open the envelope **AFTER** leaving the visit
 - The study staff do **NOT** discuss the treatment assignment with the participant
 - The participant should share the treatment assignment with his/her PCP or pulmonologist
- If the V7 window has closed and no additional data will be collected, the envelope will be mailed to the participant. The participant's ID should be written on the sealed envelope when it is retrieved. The UM form should reflect the date the unmasking envelope is mailed.

Form

- Unmasking (UM) form

6.2.2. *Emergency unmasking (before V7)*

Unmasking of treatment assignment prior to V7 should be limited to emergency situations, such as accidental ingestion by a child. Unmasking before V7 should not be for medical management of the participant's COPD or blood pressure. If a participant experiences an adverse event that the study physician believes the study treatment should be stopped, the study treatment should be terminated without unmasking, and the participant then treated according to best medical judgment.

Procedure for unmasking before V7

- During business hours (general, M-F 8:30-5:00 p, Eastern Time) call the LEEP DCC for emergency unmasking:
 - Anne Casper at 443-827-2363
 - Alexis Rea at 443-287-8496
 - Bob Wise at 410-905-5688
 - Main number 443-287-3170
- During non-business hours or if a DCC staff member is not available, use the data system link "Emergency Unmasking" to perform an emergency unmasking
 - This will require that the participant ID be data entered
- Reporting requirements:
 - Depending on the reason for unmasking the clinic should complete and submit an Unmasking (UM) form, **and**, if applicable, an Unanticipated Problem (UP) form or Serious Adverse Event (SR) form
 - If the reason for unmasking involves an unanticipated problem or SAE, the details should include:
 - The reason for emergency unmasking
 - Who requested the unmasking (name and title)
 - All emergency unmasking will be reviewed by the LEEP DCC and the DSMB; improper use of the emergency unmasking system will be considered misconduct.

7. Clinical procedures

7.1. High Resolution Computed Tomography (HRCT)

Purpose

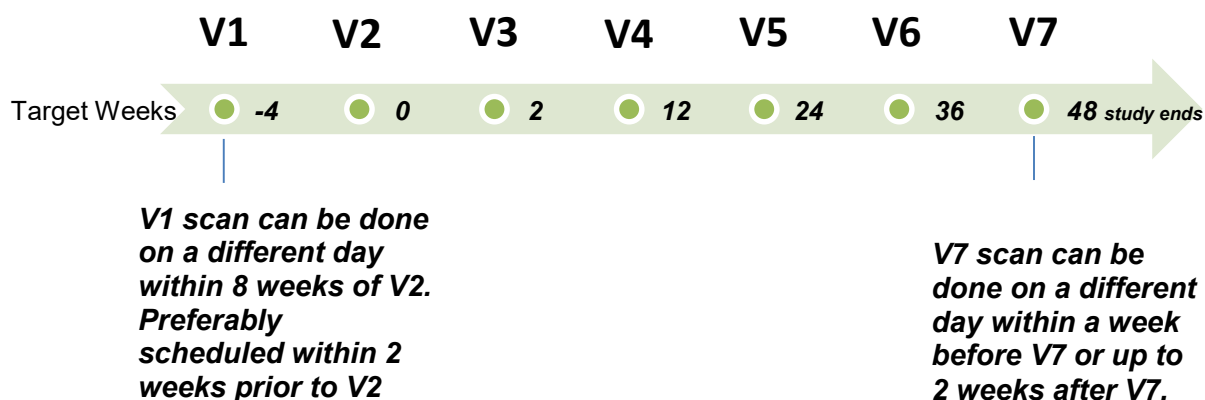
Determine percent of lung voxels with density less than – 950 Hounsfield Units (HU):

- Eligible participants must have 5-35% of voxels with density less than -950 HU at V1
- Measure change in emphysema (% of voxels with density less than -950 HU) at V7

When

- V1 and V7

7.1.1. Timeline for HRCT scans



- HRCT scans refer to a standard (AP) scout at TLC and an Inspiratory HRCT scan; these will be performed at both V1 and at V7

7.1.2. Order of procedures

Required order of procedures

- Pregnancy test - must be done if a participant is a woman of childbearing potential.
 - Must be done prior to HRCT scan
 - Must be done on day of HRCT scan regardless of most recent pregnancy test
- **Medication:** The participant is to take all COPD medications on day of HRCT scan. Participant must take 2 puffs of albuterol within 6 hours of the scan.
 - For same day procedures, participants will take 2 puffs of albuterol for the spirometry procedure before scan.
 - For participants being seen for just HRCT scan:
 - If participant has taken at least 2 puffs of albuterol **within 6 hours** of HRCT scan (e.g., took a few hours prior to visit), no additional albuterol is required.
 - If participant has not taken albuterol prior to HRCT visit, then participant should take 2 puffs at least **30 minutes prior to HRCT scan**

- Any long-acting medication(s) used for COPD must have been used within the past 12 hours for twice a day dosing, or within 24 hours if once a day dosing. The most recent scheduled dose is to have been taken.
- HRCT scans **MUST NOT** be repeated for any reason.

 **Note:** The scout (AP) scan, which involves a low radiation exposure, may be repeated, if necessary. It is critically important that the scout scan image includes the bases of the lungs.

7.1.3. HRCT visits

Overview

V1 HRCT – Eligibility and baseline

Must occur after **all** other eligibility requirements are met. Randomization must occur within 8 weeks of scan.

Time frame

- Target: Within 2 weeks of V1 Screening
- Window: 1 - 4 weeks before randomization
- Duration: 1 hour

Final visit (V7) - primary outcome measure

Time frame

- Target: At V7
- Window: 46 - 52 weeks after randomization
- Duration: 1 hour

Equipment and materials

- Visit forms
- LEEP - HRCT scanning procedure guide (Appendix B)
- Blank DVD for HRCT and phantom image data
- Pregnancy test for women of childbearing potential

HRCT Visit Tasks

Prior to scan:

- Coordinator
 - Confirm eligibility
 - Pregnancy testing, if applicable
 - At V1, only continue if participant has fulfilled all other eligibility criteria including results of blood work
 - Assess that participant is in “usual state of health” before scan. Participant should not have an URI, or recent history of a COPD exacerbation (minimum of two weeks since exacerbation) or pneumonia at the time of a scan; these conditions would compromise the quality of the scan.
 - Determine and document BMI on HRCT Scan Acquisition (RT) form
-  **Note:** BMI calculated at V1 is used for both V1 and V7 scans
- Participant prep
 - Medicate with albuterol, if necessary
 - Offer participant opportunity to use the bathroom before the scan

- Coach the participant using the script on the CT Technologist Instruction (ICT) form
- Provide CT technologist with:
 - CT Technologist Instruction (ICT) form for the LEEP approved scanner
 - Printout of LEEP HRCT scanning procedure (Appendix B of this MOP)
- ✎ **Note:** The same scanner and settings **MUST** be used for V7 HRCT scan that were used for the participant's scan at V1
- Verify scanner settings
- CT technologist
 - Review LEEP scan procedures
 - Sign LEEP Signature and Delegation of Authority Log (SD)

Important: CT Technologist must ensure that the subject is well coached and able to follow the commands appropriately **PRIOR** to imaging procedures

During scan:

- CT technologist is to:
 - Complete section E of HRCT Scan Acquisition form (RT)
 - Conduct scans according to LEEP protocol (refer to Appendix B - HRCT Scanning Procedure)
 - Review and archive scan
 - Send the scan to radiologist to over-read; over-reading should be completed within 24 hours of scan acquisition
 - Confirm scan is saved in radiology archive
 - Appropriately label blank DVD with soft-tipped permanent pen prior to burning
- Burn CT scan on the DVD disk
- Coordinator is to
 - Complete HRCT Scan Acquisition (RT) form
 - Coordinator is expected to observe scans

After scan:

- Coordinator is to:
 - Transfer HRCT data to NEMO
 - Protected Health Information (PHI) is removed before data transfer
 - Refer to MOP section 7.1.7 for data transfer instructions
 - Obtain radiologist report
 - Assure that study physician reviews radiologist report and that physician signs Radiologist Review (RR) form;
 - Complete RR form
 - Follow up as necessary on any incidental findings – see MOP section 7.1.8
 - Store HRCT disk with participant's study records
 - Key RR and RT forms into the LEEP data system

Forms (abbreviation)

- HRCT Scan Acquisition (RT)
- Radiologist Review (RR)

Information Sheets (abbreviation)

- CT Technologist Instruction (ICT)*
- Appendix B – HRCT Scanning Procedure

*Not entered into database

7.1.4. HRCT Scan Procedures

Detailed procedures are in the Appendices:

- Appendix A – Scanning Procedure for the LEEP Lung Phantom
- Appendix B – HRCT Scanning Procedure
- Appendix C – Data Transfer of HRCT Scans to NEMO

7.1.5. Missed HRCT procedures/missed visits

If a participant completes their HRCT scan at V1, but does not perform HRCT scan at V7, complete a Missed Data (MD) form to indicate that for V7 no Scan Acquisition Form (RT) form was completed.

7.1.6. HRCT Scan documentation

7.1.6.1. Forms

Phantom Acquisition (PT) form

- Used to document the scan of the phantom by a specific scanner
- Used to document scan of phantom on approved scanners for quality control
- CT technologist is to complete section B
- Key form into data system within 5 working days

 **Note:** Separate PT forms must be completed for each scanner being used in LEEP

HRCT Scan Acquisition (RT) form

- To be completed for each HRCT scan visit (V1 and V7)
- Used to record information of HRCT scans collected
- The technologist should complete Section E on the form
- Data enter the form into the data system within 10 working days

Radiologist Review (RR) form

- The radiologist should review the scans within 24 hours of scan acquisition for incidental clinical findings. Radiologist's report and comments to be stored with the RR form
- One Radiologist Review (RR) form should be completed for each visit per participant
- Each form should be stored with the report from the radiologist for that visit

 **Note:** The RR form must be completed for each HRCT scan completed

CT Technologist Instruction (ICT) form

- This form assists the CT technologists to use the approved scanner settings and breathing instructions to complete the scans within the guidelines of the study.
 - Each form will contain the required breathing instructions and scan parameters for clinical center scanners.
 - The form should be handed to the technologist prior to each scan that is performed
 - Breathing instructions are to be followed verbatim.

- There is a specific ICT determined by the make and model of the scan; scanner settings are machine specific ICT
- ICT forms are posted on the PTC LEEP website
- ICT form should be presented to the CT tech at every LEEP HRCT scan

7.1.6.2. *DVD labeling*

Participant ID and Alpha ID, along with visit ID should be written with a soft-tipped permanent marker on the DVD. The DVD is to be protected from scratching and will be stored with participant's study records as source documentation.

7.1.7. *Transfer of HRCT data*

Refer to Appendix C – Data Transfer of HRCT Scans to NEMO for procedures

If there are errors in the process of transferring the data, contact the NEMO. Potential errors include:

- Wrong participant identifier(s) used
- Incorrect visit ID
- PHI not removed

7.1.8. *Incidental findings*

Incidental findings on HRCT scans will be identified locally by the clinical center's radiologist.

Review of radiologist's report

The radiologist's report of the scan should be available within 24 – 48 hours.

The Clinic Coordinator's responsibilities are to:

- Obtain the report
- Document on the HRCT Radiologist Review (RR) form that the report has been:
 - Reviewed by a local LEEP study physician and
 - Any clinically significant Incidental findings have been indicated
- Key the RR form into the data system within 10 working days of the HRCT scan
- File the radiologist's report with RR form in participant's study record
- Assure follow up on any **clinically significant** incidental findings
 - Complete an Unanticipated Problem (UP) form, if the finding is new or shows a change from a previous scan, **and** requires action or follow up
 - Complete a Serious Adverse Event (SR) form, if the finding meets the criteria for a serious adverse event (e.g., requires hospitalization or is life threatening, is unexpected and possibly related)

Sharing incidental findings with participant

The clinical center PI and study physician are to be made aware of any incidental findings.

The study physician or his designee will:

- Give information regarding the finding to the participant
- Share the information regarding the incidental finding with the participant's usual caregiver for appropriate medical care or follow-up with participant's permission

7.2. Spirometry

Purpose

- Measure FEV_1 (the amount of air expired in the first second during a forced expiratory maneuver) and FVC (forced vital capacity) before and after bronchodilator

When

- V1, V5, and V7

Supplies

NEMO will provide

- EasyOn spirometer
- Spirometry training
- Spirometry certification

Procedure

Refer to Appendix F – MOP Spirometry for spirometry protocol and procedures.

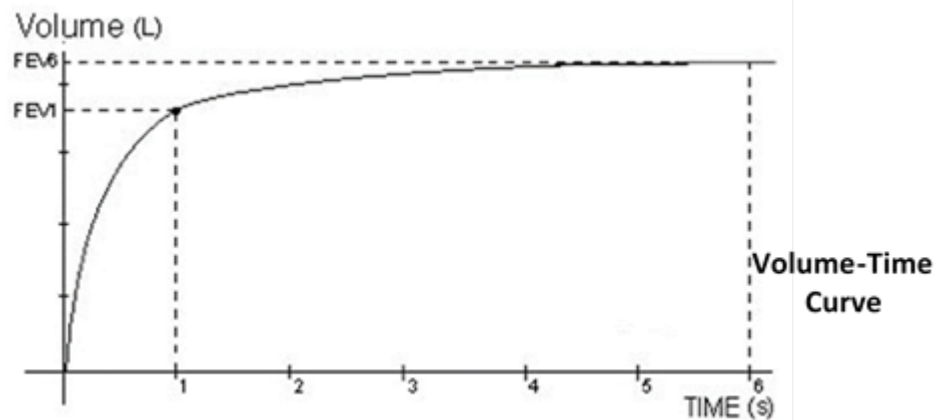
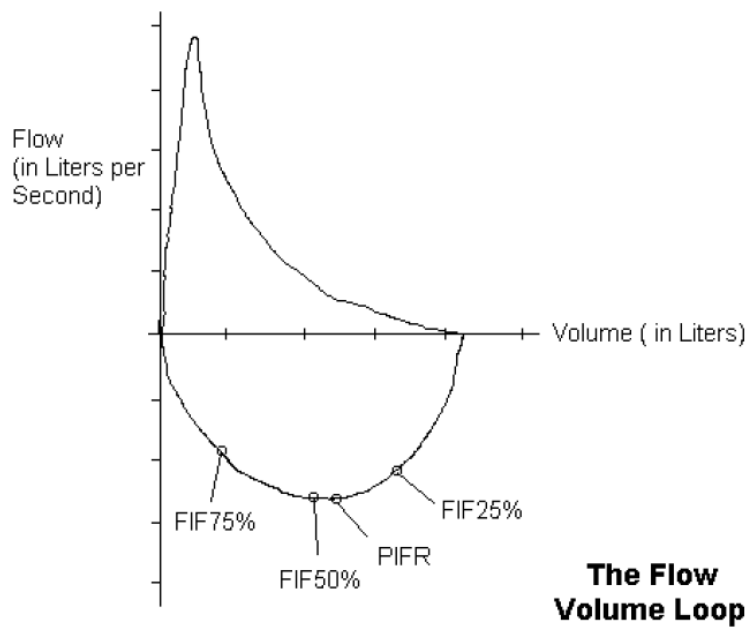
 **Note:** If pre-bronchodilator FEV_1 and/or FEV_1/FVC exceed the eligibility criteria, with a $FEV_1 > 70\%$ of predicted and/or a $FEV_1/FVC > 0.70$, then post-bronchodilator efforts should not be performed

Forms (abbreviation)

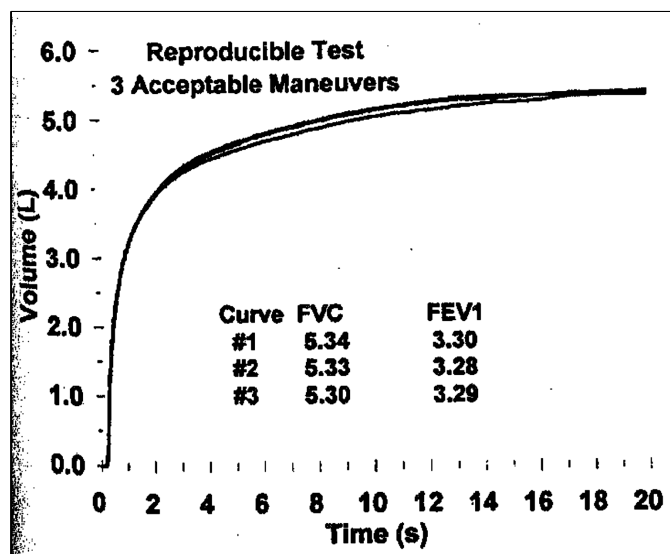
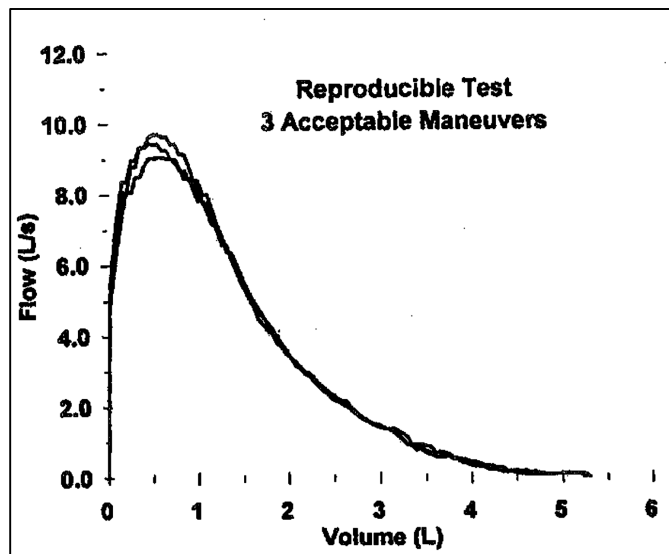
- Pulmonary Function Test (PF)

Spirometry examples

Ideal curves

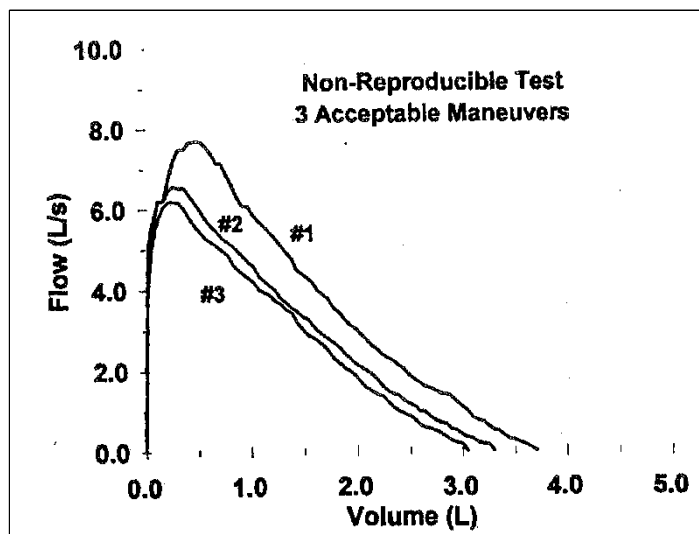
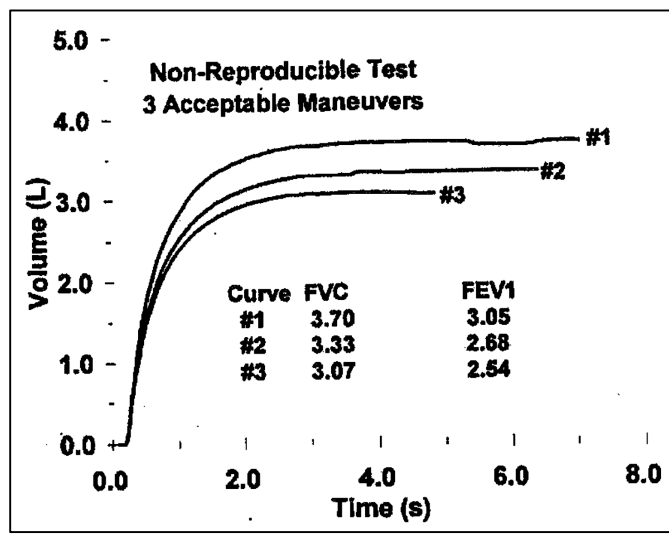


Acceptable and reproducible maneuvers

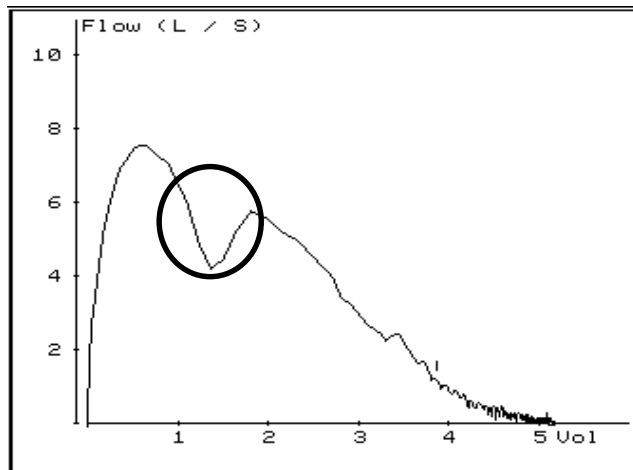


Reproducible test with three acceptable flow-volume curves

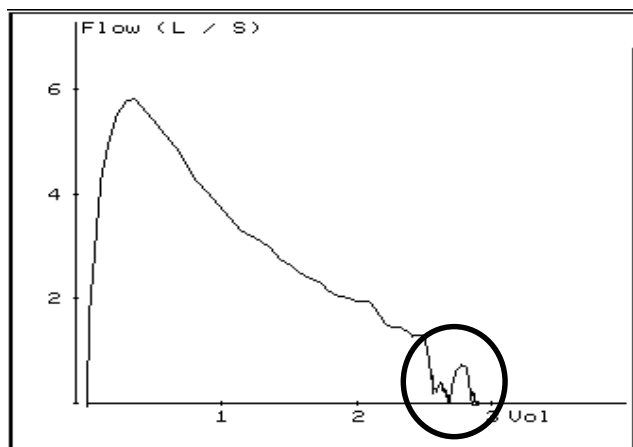
Acceptable non-reproducible maneuvers



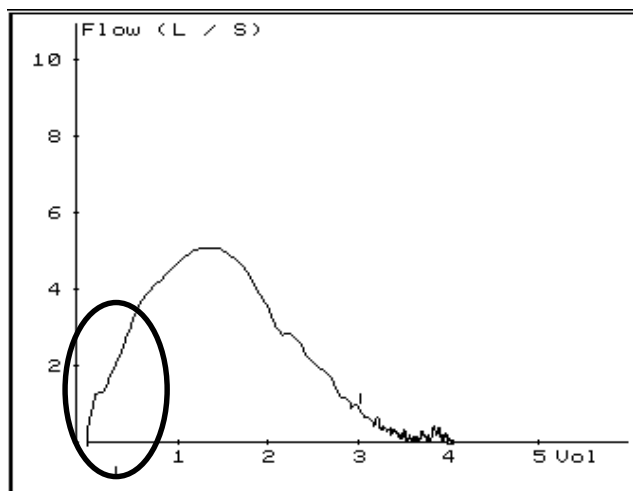
Non-reproducible test with three acceptable flow-volume curves

Maneuvers that are NOT acceptable

Cough
Flow-volume tracing



Abrupt termination
Flow-volume curve



Slow start
Flow-volume curve

7.3. Blood pressure measurement

Use of an automatic blood pressure cuff is preferred. If, due to medical reasons, the participant cannot be measured for blood pressure on either arm, a femoral blood pressure reading with an appropriate sized cuff may be taken by experienced staff. Consult the clinical physician for systolic pressure > 140 mmHg or diastolic pressure > 90 mmHg.

Equipment

- Vital signs monitor or automatic blood pressure cuff
- Manual cuff, sphygmomanometer and stethoscope, only if automatic cuff is not available or if femoral BP is necessary

Participants should not have engaged in vigorous exercise, ingested food or caffeine, or smoked within a half hour before the measurement. Ask the participant if there are any other reasons that the blood pressure cannot be done on either arm (sides). Remove all clothing that covers the location of the cuff placement; do not roll up the sleeve to expose the upper arm.

Blood pressure should be measured using the same equipment at screening and follow up visits for consistency. Automatic cuffs and manual blood pressure equipment should be inspected regularly, using manufacturer guidelines. Follow the manufacturer instructions for the specific cuff used at your site

- Participants should sit quietly for ten minutes before the first measurement.
- Neither the observer nor the participant should talk during the measurement procedure
- Cuff size should be determined by measuring the participant's upper arm circumference and choosing the appropriate size that corresponds.
- Do not roll up the sleeve to expose the upper arm.
- Seat the participant with the arm supported at heart level, palm facing upwards, legs uncrossed, and the back supported.
- If the measurement cannot be taken from either arm, then a thigh, calf, or ankle may be used.
- Record measurement in mmHg. Measurements may be first recorded on the PM form and then entered into the database.
- For subsequent study visits, BP should be recorded using the same arm as initially recorded at screening.

7.3.1. Orthostatic blood pressure measurement

Purpose

- Measure orthostatic blood pressure to assess participants' eligibility for study enrollment, eligibility to begin study drug and escalate study drug dosing, and as an ongoing safety measure.

Timeframe

Conducted at all study visits

Materials

- Blood pressure monitoring device
- Exam table
- Blood pressure flow chart (Appendix D)

Tasks

Blood pressure assessment should be performed in a quiet area of the clinic. The staff member performing the assessment should stay alert to the participant's status throughout the test and urge them to sit or lie down should they become lightheaded.

1. Measure and record seated blood pressure.
2. Have the participant stand quietly for three minutes. A staff member should remain with the participant while standing should the participant become lightheaded.
3. Measure and record standing blood pressure.

If at any point during the testing the participant complains of dizziness or lightheadedness, the procedure should be stopped and the research physician contacted.

Blood pressure measurements are used to make treatment decisions at varying points throughout the LEEP trial. Below is an outline of how this data should be used.

V1

If any recorded blood pressure is less than 90 systolic or less than 60 diastolic:

- Inform the study physician. The participant should be informed of the finding and may be referred to their PCP for additional follow-up if the study physician deems appropriate.
- The participant is ineligible for the study, but may be rescreened if there is reason to believe the low reading was temporary (medication change, dehydration, other transient factor).

If ALL recorded blood pressures are between 90 and 140 systolic, and 60 and 90 diastolic, the participant is eligible to continue with the study visit.

If any recorded blood pressure is greater than 140 systolic or greater than 90 diastolic:

- Have the participant sit for 30 minutes, then retake their blood pressure.
 - Record 2nd measurement on PM form
 - If high measurements persist, the participant should be referred to their PCP with information regarding the trial. The PCP should be advised that if treatment for elevated BP is necessary, they should prescribe either a calcium channel blocker or diuretic.
- The participant may return for rescreening when their blood pressure is controlled.

V2**Start of visit:**

If any recorded blood pressure is less than 90 systolic or less than 60 diastolic:

- Inform the study physician. The participant should be informed of the finding and may be referred to their PCP for additional follow-up if the study physician deems appropriate.
- The participant is ineligible to continue with randomization.

If ALL recorded blood pressures are between 90 and 140 systolic and 60 and 90 diastolic, the participant is eligible to continue with randomization.

If pre-randomization blood pressure is greater than 140 systolic or greater than 90 diastolic:

- Have the participant sit for 30 minutes, then retake their blood pressure.
 - Record repeat measure on PM form
 - If high measurements persist, the participant should be referred to their PCP with information regarding the trial. The PCP should be advised that if treatment for elevated BP is necessary, they should prescribe either a calcium channel blocker or diuretic.
- The participant may return for recycling when their blood pressure is controlled.

Treatment Tolerance (one capsule):

Measure orthostatic BP two hours after participant takes his/her first dose of study drug/placebo.

If any recorded blood pressure is less than 90 systolic or less than 60 diastolic

- Inform the study physician.
- Participant to continue in study even if off treatment.

V3**Start of visit:**

If any recorded blood pressure is less than 90 systolic or less than 60 diastolic:

- The participant is ineligible to proceed with dose escalation.
- Inform the study physician. Study physician to determine if participant should continue on 1 capsule per day or stop treatment.

If ALL recorded blood pressures are at least 90/60 the participant is eligible to continue with dose escalation.

If any recorded blood pressure is greater than 140 systolic or greater than 90 diastolic:

- The participant should continue with dose escalation.
- The participant should also be referred to their PCP with information regarding the trial. The PCP should be advised that if treatment for elevated BP is necessary, they should prescribe either a calcium channel blocker or diuretic (other than potassium sparing diuretic).

Dose Escalation:

Measure orthostatic BP one hour after participant takes 2 capsules of study drug/placebo.

If blood pressure is lower than 90/60 OR the participant complains of being light headed or dizzy:

- Inform the study physician.
- Study physician to determine if participant should continue on 1 capsule per day or stop treatment

Forms (abbreviation)

- Physical Measurements Form (PM)

7.4. Oxygen saturation measurement

Purpose

- Measure oxygen saturation to assess participants' state of health and as an ongoing safety measure.

Timeframe

Conducted at all study visits

Materials

- Pulse oximeter (provided by clinic)

Tasks

Refer to Appendix E – Clinical Procedures for oxygen saturation measurement procedures.

7.5. Specimen collection

Purpose

- Safety labs will be collected for assessment of baseline kidney/liver function as well as monitoring while in the study.
- Urine and/or serum samples will be collected for pregnancy testing for women of childbearing potential.
- Biospecimens (blood and urine) will be collected for future storage (optional).

When

- *Required:* blood draw will be done at V1, V4, and V7 to assess hepatic, renal, electrolyte, and hematological measures.
- *Required:* pregnancy testing will be done at all study visits and before each HRCT scan for women of childbearing potential.
- *Optional:* blood and urine will be collected at V2, V5, and V7 for storage for future ancillary studies. DNA will be collected at V2.

Tasks

Safety labs performed for the LEEP study must assess, at minimum, the following elements:

For complete blood count with differential (CBC with diff):

- Red blood cell count
- Mean corpuscular volume
- Red blood cell distribution width
- Hemoglobin
- Hematocrit
- Platelets
- White blood cells
- Neutrophils
- Lymphocytes
- Monocytes
- Eosinophils
- Basophils

For comprehensive metabolic panel (CMP):

- Sodium
- Potassium
- Chloride
- Bicarbonate
- Blood urea nitrogen (BUN)
- Creatinine
- Glucose
- Calcium
- Total protein
- Albumin
- Total bilirubin
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Alkaline phosphatase

Safety lab results must be reviewed prior to randomizing a participant. If a participant's Visit 1 labs return any of the following results, he or she may not be randomized in the LEEP study.

- Potassium level of ≥ 5.0 mEq/L
- Total protein, albumin, total bilirubin, AST, ALT, or alkaline phosphatase > 2.5 times the normal upper limit
- Glomerular filtration rate < 30 mL/min according to the Cockcroft-Gault calculation (determine using LEEP data system online calculator)

7.5.1. Overview of specimen collection

Safety labs (Required)

Specimen	CBC with differential	CMP
Collection Tube	EDTA tube, size per local lab requirements	Serum separator tube, size per local lab requirements
Label	Local site patient identification label	Local site patient identification label
Processing	▪ Gently invert tube 10 times to allow mixing ▪ Send to local lab for analysis	▪ Gently invert tube 10 times to allow mixing ▪ Send to local lab for analysis
Results	Record results on LD Form	Record results on LD Form

Pregnancy testing (Required)

Pregnancy testing will be done locally at each clinic visit and before each HRCT scan.



WARNING: Participant is **NOT** eligible if pregnancy test is positive at V1 or V2.
 Participant must **NOT** perform HRCT scan if pregnancy test is positive.
 Participant must immediately **STOP** taking study drug if pregnancy test is positive

Research specimens (Optional)

Specimen	Plasma/Packed Cells	Serum	Urine
Collection Tube	10 mL lavender top Vacutainer (EDTA)	10 mL clot activator Vacutainer tube (tiger top)	100 mL urine collection cup
Label	Designated Barcode labels from Label Sheet	Designated Barcode labels from Label Sheet	Designated Barcode labels from Label Sheet
Processing	- Draw at least 8 mL of blood into participant labeled Vacutainer - Gently invert 5 times - Centrifuge for 7 mins at 4°C at 2000g - Immediately aliquot plasma from Vacutainer tube - Place 1-1.8 mL of plasma into each 2 mL cryovial - Sample to be divided between 4 2 mL cryovials - Store in -20 to -80°C freezer <u>If participant consents to DNA collection, retain packed cells:</u> - Firmly replace HemoGuard closure on the Vacutainer. - Label Vacutainer with barcode. - Store in -20 to -80°C freezer	- Draw at least 8 mL of blood into participant labeled Vacutainer - Allow sample to clot for about 30 minutes at room temp. - Centrifuge at 1300g (2500 rpm) for 15 minutes - Place a minimum of 0.5mL of serum into each 2 mL cryovial - Sample to be divided between 4 2 mL cryovials - Store in -20 to -80°C freezer	- Ask participant to collect at least 20 mL of urine using urine collection cup - Using transfer pipette or pouring, place a minimum of 20 mL urine from urine collection cup into 10 2 mL barcode labeled cryovials - Store in -20 to -80°C freezer
Shipping	- Batch ship plasma on dry ice (frozen) priority overnight to: Pharmacogenetics Center c/o Ed Mougey Research, 9th floor Nemours Children's Clinic 807 Children's Way Jacksonville, FL 32207 - Upon shipment, send email to emougey@nemours.org - If participant consented to DNA collection, batch ship packed cells on dry ice (frozen) priority overnight to above address	- Batch ship serum on dry ice (frozen) priority overnight to: Pharmacogenetics Center c/o Ed Mougey Research, 9th floor Nemours Children's Clinic 807 Children's Way Jacksonville, FL 32207 - Upon shipment, send email to emougey@nemours.org	- Batch ship urine on dry ice (frozen) priority overnight to: Pharmacogenetics Center c/o Ed Mougey Research, 9th floor Nemours Children's Clinic 807 Children's Way Jacksonville, FL 32207 - Upon shipment, send email to emougey@nemours.org

7.5.2. Supplies for collection and processing

Supplied by DCC (only for biospecimens collected for future use)

- 10 mL EDTA vacutainer tube (lavender top) for collection of plasma and packed cells
- 10 mL clot activator (tiger top) vacutainer tube for collection of serum
- 2 mL cryovials (orange top) for storage of plasma, serum, and urine aliquots
- Urine collection cup, 60 mL
- Transfer pipettes
- Barcode Label Sheets for each LEEP study participant
- Cryovial boxes and dividers for specimen storage (8"x 8')

Supplied by clinic

- Local participant labels for sample collection (for vacutainers and urine collection cup)
- Vacutainers for CBC with diff and CMP
- Needle (appropriate gauge for age of participant)
- Needle holder
- Gloves
- Swabs for cleaning blood draw site
- Band-Aids
- Scotch tape
- Emergency supplies readily available

7.5.3. Collecting samples

7.5.3.1. General requirements

- Gloves must be worn at all times when handling specimens. This includes during removal of the rubber stopper from the blood tubes, centrifugation, pipetting, disposal of contaminated tubes, and clean-up of any spills.
- Tubes, needles, and pipettes must be properly disposed of in biohazard containers, in accordance with institutional requirements.
- Universal precautions and OSHA (Occupational Safety and Health Administration) and institutional requirements (<http://www.osha.gov/SLTC/biologicalagents/index.html>) should be followed, including gloves, eye protection or working in a biosafety cabinet for blood processing
- Use the appropriate barcode labels from the Label Sheet for each participant sample once processed.

7.5.3.2. Blood draw for DNA, serum and plasma

Purpose

- To collect blood specimens for future studies related to COPD.
 **Note:** Do not save DNA specimen (packed cells) without participant consent.

When

- V2, V5, and V7 (serum and plasma)
- V2 only (DNA)

Draw blood:

- Prepare labels for all specimens collected.
 - Use labels from participant specific sheet of barcoded labels for aliquots. If spare labels are used, fill in with fine point, permanent marking pen. Print legibly. Refer to MOP section 7.5.4 for detailed instructions for Specimen labeling.
- Affix local participant labels to Vacutainers.
- Affix the appropriate barcoded specimen labels **lengthwise** to
 - 4 cryovials (2 mL) of plasma and
 - 4 cryovials (2 mL) of serum.
- If participant has consented to DNA collection, affix barcoded packed cells/DNA specimen label **lengthwise** to 10 mL EDTA (lavender top) vacutainer.
- Collect at least 8mL into 10 mL EDTA (lavender top) vacutainer and at least 8 mL into 10 mL clot activator tube (tiger top).

EDTA processing:

- Gently invert EDTA tube 10 times after collecting
- Sample to be processed promptly, may store at 4° C for up to 30 minutes
- Centrifuge at 2000g for 7 minutes at 4°C.
- Using fresh pipette remove plasma 1- 1.8 mL at a time and aliquot into labeled 2 mL tubes.
- Cap the plasma cryovials.
- Store cryovials in freezer between -20 to -80°C.

If the participant has consented to DNA collection:

- Replace Vacutainer top (lavender HemoGuard closure) and retain packed cell pellet.
- Store labeled Vacutainer in freezer between -20 to -80°C.
 **Note:** Lay Vacutainer tube horizontal in freezer for 20 minutes prior to storing upright, otherwise expansion of ice crystals may crack the tube.
- If DNA cannot be drawn at V2, draw blood at a following clinic visit and use spare labels to label form and specimens. Record as a protocol deviation.

If the participant has NOT consented to DNA collection:

- Discard EDTA Vacutainer and remaining cell pellet. **Do NOT retain DNA for a participant who has not provided explicit written consent.**

Serum (tiger top) processing:

- Allow sample to clot for about 30 minutes at room temperature.
- Centrifuge at 1300 g (2500 rpm) for 15 minutes.
- Transfer serum (upper layer) into 4 labeled 2mL orange top cryovials. Do not fill beyond 1.8mL line.
- Store cryovials in freezer between -20 to -80°C.

7.5.3.3. Urine collection**Purpose**

- To collect urine specimens for future studies related to COPD.

When

- V2, V5, and V7

Draw blood:

- Prepare labels for all specimens collected.
 - Collection cup should be labeled with participant's name/local collection labels.
 - Use labels from participant specific sheet of barcoded labels for aliquots. If spare labels are used, fill in with fine point, permanent marking pen. Print legibly. Refer to MOP section 7.5.4 for detailed instructions for Specimen labeling.
- Affix local participant labels to collection cup. Affix barcoded specimen labels **lengthwise** to 10 2 mL cryovials.
- Provide participant with labeled urine collection cup.
- Instruct participant to collect about 30 mL of urine. It may be helpful for the coordinator to mark the 30 mL line on the collection cup with a marker. Urine may be collected either by having participant urinate directly into specimen cup or into a specimen collection hat.
- Using transfer pipette or alternatively simply pouring, transfer urine into 10 labeled 2 mL cryovials and place on ice immediately. Each cryovial should contain 1.8mL of urine.
- Store in freezer between -20 to -80°C.

7.5.4. Specimen labeling

Purpose

- To label cryovials and Vacutainers for specimen shipping and tracking

When

- V2, V5, and V7

Overview

- Each sheet of labels corresponds to one visit for one participant ID – visit 2, 5 or 7.
- Specimen labels are printed in identical pairs: one for the specimen (e.g., cryovial) and a matching one for the Specimen Collection (BC) form.
- Labels are arranged in separate columns; each column corresponds to a specimen type. Each column has the two identical labels
- Part of a label sheet for participant LXX100:

LXX100	LXX100
V2	V2
Serum A4	Plasma A1
	
2011000214	2011000211

LXX100	LXX100
V2	V2
Serum A4	Plasma A1
	
2011000214	2011000211

← One of the labels for the matched pair for a specific specimen, with participant ID, space for alpha ID code, visit ID, type of specimen and aliquot number, and barcode

← The 2nd label for the matched pair

It is extremely important when you enroll new participants that you make sure to use a participant ID for which you have a corresponding sheet of barcode labels. If labels are not available, notify the DCC immediately to acquire labels before enrollment.

7.5.4.1. Labels: the basics

- Label diagram (one of a pair):

LXX100

V2
Serum A1

2011000211

← Participant ID

----- for hand entry of Alpha ID code

← Visit ID

← Specimen type (Plasma, Serum, DNA or Urine) and aliquot number (A1 - A10)

← Barcode

Barcode number

- Using the pre-printed barcode labels:
 - Fill in Alpha ID Code on both labels
 - Attach 1st of the pair to the specimen container
Wrap label around as shown for label to scan successfully
 - Cover label with clear scotch tape
 - Attach 2nd of the pair to the BC form in specimen-specific location

9. Serum

a. Was serum stored:

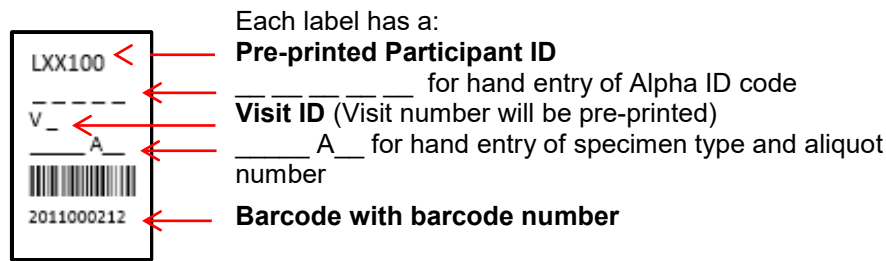
Yes (✓ 1) No (2)

10

b. Aliquot 1 stored:

7.5.4.2. Spare labels

- Spare label diagram



It is extremely important to note that spare labels are to be used for the specific participant whose ID is pre-printed on it

- Using the spare labels:
 - **Always use spare labels as a pair**
 - Use spare labels:
 - if the pre-printed labels are damaged or unusable
 - if pre-labeled were previously used (e.g. a failed collection at a prior)
 - if samples collected at a visit other than V2, V5, or V7 (complete UP form and indicate collection on BC form for that visit)
 - Fill in name code, visit ID, specimen type, and aliquot number
 - Attach 1 of the pair to specimen container and wrap clear tape around the label
 - Attach 2nd of pair to the Specimen Collection form in appropriate box

7.5.5. Specimen storage

Purpose

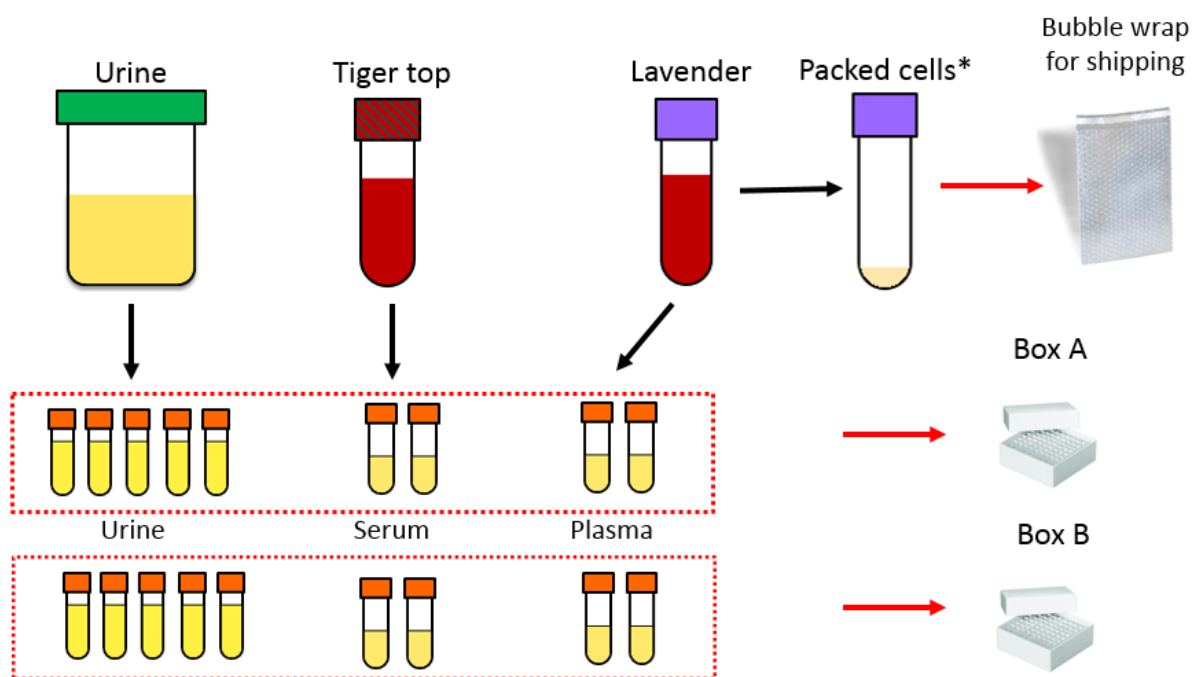
- To store cryovials in preparation for shipment

When

- V2, V5, and V7

Overview

- Specimen boxes should be filled on a continuous basis as participants proceed through the LEEP study. Specimens from each collection should be divided evenly between two cryovial boxes, A and B (i.e. if 4 plasma aliquots are collected at a participant's V2, 2 aliquots should go into box 1A, and 2 into box 1B). Both primary and secondary boxes may be shipped every six months, or when full. However, an A and B box set should NEVER be shipped on the same day. Proceeding in this manner should reduce the possibility of losing all the specimens from any one participant. See image below for details.



*if participant consents to DNA

7.5.6. Specimen shipping

When

- When two specimen boxes are full, or every 6 months

General overview

- When a number of specimens are ready for shipping, the process is to log them in the LEEP data system to generate a shipping log.
- After entering clinical identification information, you will be prompted to enter the barcodes from each specimen into a web application.
- Scan each specimen vial with your provided barcode reader and make sure the number entered on the screen matches the number printed beneath the barcode on the label.
- If your barcode scanner is malfunctioning or you are having difficulty scanning the barcodes, please make sure that:
 - There is no condensation over the label,
 - Your barcode scanner is plugged in and recognized by your computer. Individual labels that are difficult to scan may be entered by hand.
 - If you believe your scanner is malfunctioning, contact the NEMO to request a replacement.
- Once you have finished entering all the barcodes for one shipment container, the system will generate a shipping log identifying all the specimens in your shipment box. Please look over the log to make sure all specimens match those that are being shipped.
- Print a copy of the log to place in the shipment container, and retain another copy at the clinic.

Shipping supplies include

- Supplied by DCC
 - Styrofoam box with outer cardboard box (shipper)
 - Plastic biohazard specimen bag (8"x8")
 - Absorbent sheet
 - Dry ice label (UN1845)
 - UN3373 label
 - FedEx air bill
- Supplied by clinic
 - FedEx air bill
 - Packing material (bubble wrap, "peanuts", or crumpled newspaper)
 - Dry ice

Planning your shipment

1. Be certain the lab will be available to receive specimens
 - Only ship Monday through Wednesday
 - Do not ship within 3 days of a holiday (labs may close for different holidays)
 - Assess that weather should not be a factor (no pending hurricane or snow storm) at your site, the receiving site or transfer (check FedEx for any warnings they may have posted)
2. Set aside sufficient time to complete the process; specimens are sensitive to changes in temperature; the process of scanning/packaging/shipping should not be interrupted
3. Have the following ready
 - ALL specimens to be shipped

- Shipping box/container with dry ice
- Computer access to LEEP site, printer and barcode scanner
- 4. Shipments are to be done by LEEP coordinator who is:
 - Familiar with the LEEP specimen shipment protocol
 - IATA certified.

Note: If specimens are to be packed and/or shipped by a non-LEEP staff member, it is the responsibility of the Lead Coordinator to train and verify the shipment is performed per LEEP requirements.

5. Remember the limit is one shipment per day. This one shipment should contain 2 cryovial boxes.

General packaging and shipping tasks

Specimen boxes should be shipped every six months or when full. Primary and secondary specimen boxes should NEVER be shipped on the same day, to avoid the possibility of loss.

How to scan study specimens and prepare the Specimen Shipment Record

1. Go to the appropriate study website and select specimen shipping. Accessing the shipping page will require you to log in.

ACRC Login

Clinic:	<no selection> ▼
PIN:	
Password:	
Login Reset	

Note: Currently the data entry page is viewable only in Internet Explorer version 9 and below. If you are using Internet Explorer 10 or higher, please enable Compatibility View and add “jhcct.org” to the list of websites to be displayed in that mode.

2. Click on “Specimen Shipping and Receipt”
3. On the following screen, click on “Ship Specimens.” The screen for Specimen processing and tracking includes:
 - a. Simple instructions (at top of page)
 - b. Display of barcode(s) scanned for shipment as entered
 - c. A brief description of any specimen with issues, such as “specimen not found”

Note: The system will know to expect a sample barcode only if the BC form is entered into the data system.
4. With the cursor placed in the box next to “Scan specimen here”, scan the barcode on the sample to be shipped.
 - a. Verify that sample has been added to list of specimens for shipment
 - b. Confirm that the participant ID and visit ID correspond to the label on the specimen
 - c. Systematically scan all specimens for shipment
 - i. Keep the specimens at the appropriate temperature before and immediately after scanning specimens
 - ii. If there are errors or issues with scanning a specimen, please refer to **Table 2.**

Tips and other important information

- Only scan one vial at a time. The laser used to scan the barcode is quite long, so attempting to scan vials in close proximity to each other may result in recording an incorrect barcode.
- If a barcode is unable to be scanned, it can also be typed in.

For other issues refer to Troubleshooting below or contact the DCC.

5. Verify the total number of specimens scanned equals the number being shipped.
6. Click the “Done scanning, Continue” button
7. Click “OK” when prompted to “Save data and prepare shipment log”
8. Print out the Specimen Shipping Log that is displayed on the following page
 - a. Click “Print” button

 **Note: If you are unable to print to a printer at the moment, you can print to PDF (providing you have Adobe Acrobat installed on your computer).**

- b. Print two copies of the Specimen Shipping Log
 - i. One copy to be included as the shipping record
 - ii. Additional copy to store for your records

General packaging and shipping procedures

Batch ship frozen samples (plasma, packed cells and urine) on a regular basis

1. Contact FedEx to schedule/confirm pick-up service.
2. Prepare shipper box:
 - a. Fill Styrofoam shipper halfway with dry ice
 - i. Styrofoam shipper box is to be filled with **at least 10 pounds** of dry ice
 - b. Affix proper labels on outside of cardboard shipper box
 - i. UN3373 label (Biological Specimens)
 - ii. UN1845 (Dry ice label)
3. Place each cryovial box into a separate clear Biohazard bag and seal. Please send 2 cryovial boxes per shipment where possible (i.e. boxes 1A and 2A).
4. Place the overwrapped cryovial box(es) in the Styrofoam shipper
5. Cover box(es) with the remaining dry ice
 - a. There should be little room for air in the container, extra moisture resistant packing material can be used to fill the container or eliminate more air space
 - b. Dry ice should be above and below the samples
6. Place Styrofoam cover on the container
7. Place signed shipping record (print out of scanned specimens) in a sealed bag on top (outside) of the Styrofoam lid
8. Seal cardboard shipper with packing tape
9. Prepare FedEx Airbill:
 - a. LEEP FedEx account to charge is: **830192646**
 - b. Item 4a: Express Package Service check FedEx Priority Overnight
 - c. Item 5: Packaging – select other
 - d. Item 6: Special Handling
 - i. Indicate “Yes. Shipper’s Declaration not required.”
 - ii. Check “Dry Ice” and fill in weight of dry ice in kilograms (10 lbs. = 4.4 kg)
 - e. Verify same day pick-up
 - f. Verify that Biological Specimen and Dry Ice labels are attached to shipper
 - g. Item 3: Recipient to ship to :

Pharmacogenetics Center
c/o Ed Mougey
Research, 9th floor
Nemours Children's Clinic
807 Children's Way
Jacksonville, FL 32207
(904) 697-3781

- h. Affix FedEx label to shipper
- i. Verify shipment is for same day pick up
- 10. Immediately upon shipment, notify lab by sending email to emougey@nemours.org.
Include FedEx tracking number in email
- 11. Shipment is not considered complete until you have verified that it arrived at the lab by:
 - a. email from lab or
 - b. FedEx confirmation (with tracking number)

Tracking specimen shipments with FedEx

To track a shipment on FedEx.com, click the following link:

https://www.fedex.com/fedextrack/?cntry_code=us&tab=1&tracknums=&clienttype=wtrk

Troubleshooting for specimen shipments

The table below includes suggestions for solving and preventing problems with specimen shipment. If you have an issue that is not addressed below, you can submit a data feedback form or call the DCC. Since the system will not save information if it times out, you may find it preferable not to ship a “problem” specimen with a later shipment.

 **Note:** At this time, specimens without barcodes and specimens with barcodes that cannot be read (e.g. rubbed off in part or in full) cannot be shipped, but should be kept in appropriate storage conditions until system can accommodate them.

Table 2

Issue	Solution (s)	Prevention
Scans (can see the light, hear the beep) but number does not show up on screen	1. Be certain cursor is in the box for the value to go in. 2. Be sure that scanner is securely attached to the computer. 3. Barcode number can be typed in if scanner not working.	
Specimen has a spare label on it	Scan the same as for other barcode labels. Spare label is participant and specimen specific.	Before using labels always verify: Right participant Right specimen Right visit
The label is for the correct participant , but the wrong specimen type	1. Complete a spare label for the correct participant and specimen type 2. Dry off tube. 3. Apply new label and apply clear tape over label 4. Attach 2nd spare label to the BC form 5. Amend data entry of BC form with new barcode; include notation regarding event 6. Notify DCC	Always verify: Right participant Right specimen Right visit Right place (one on specimen one on BC form)
The label is for the wrong participant, but with 100% certainty the correct participant ID is known	Re-label with extreme care: 1. Complete the correct label (if available) or complete spare labels 2. Dry outside of tube or cryovial 3. Apply new label and apply clear tape over label 4. Attach matched 2nd label to the BC form 5. Amend data entry of BC form with new barcode 6. Complete a UP form and notify the DCC	Always verify: Right participant Right specimen Right visit Right place (one on specimen one on BC form)

Issue	Solution (s)	Prevention
System gives message that specimen has not been collected. If it is because: 1. BC form not data entered 2. BC barcode entry does not match barcode on specimen tube 3. Barcode not in system because specimen labels applied incorrectly (applied duplicate labels to specimens and BC resulting in specimens having one set of matched labels and the BC having the other matched set).	Message indicates only that barcode data from BC is not in the system. Solutions: 1. Verify whether the BC form has not been entered. Manually verify that barcode labels match and ship. 2. Compare specimen label to BC form label. Remember the specimen ID must be identical before specimen can be shipped. Correct BC entry if necessary. Note: This is more likely to happen if barcode information is typed in. 3. Requires re-labeling: - Carefully complete spare label sets - Dry outside of tube or cryovial - Apply new label(s) and apply clear tape over the label on specimen(s) - Attach matched 2nd label(s) to the BC form - Amend data entry of BC form with new barcode information - Complete a UP form	- Enter BC data within 10 days of visit and - Use barcode scanner to enter barcode in data system - Always verify labels are applied one to specimen and one to BC form
How do I know what specimens I need to ship?	Access the Specimen Status page to see status of all specimens	
Will the data system save a partially entered shipment?	If the page times out, the data entered will be lost. <i>Note: Page times out after about 15 minutes.</i>	Set aside enough time to scan, package and ship specimens as one continuous process.
What if I can't print the shipping log/manifest?	If the page cannot be printed to paper, the following are suggested: 1. Print to PDF and save to your computer 2. Use print screen function and save as a file Remember this log is for your records and is to be included in the shipping container. Do not ship specimens without it.	Always have printer access when entering shipment.

7.6. Questionnaires

7.6.1. General guidelines

7.6.1.1. Establishing rapport

Establishing rapport with a participant is important to elicit cooperation with study procedures. The interaction between the coordinator and participant could affect the participant's performance and responses. Establishing rapport with the participant is essential so that they are at ease and are able to give their best performance during testing. A participant who is anxious or uncomfortable will be too distracted to perform adequately.

Tips on establishing rapport

- Try to establish rapport and put the participant at ease before beginning. Engage in a bit of casual conversation before testing.
- Always be pleasant and patient.
- Check to make sure the participant is comfortable before testing (e.g., warm enough, need to use restroom, etc.).
- Be sure to give the participant a good idea of exactly what will happen during the visit before beginning.
- Do not rush any of the aspects of your interaction with the participant.
- Allow participant sufficient time to respond and to ask questions.
- Keep in mind that each participant's personality will be different and some will respond better to you than others. Adjust your interaction with them accordingly. For example, keep a slower pace for those who require it, and move more quickly for those who prefer that kind of interaction.
- Always thank the participant at the end of the session. Say something like, "I want to thank you for your participation today. I really appreciate your effort, attention, time (whatever is appropriate). It was a pleasure working with you."
-

7.6.1.2. Questionnaire administration

General administration guidelines

- Administer all tests according to the directions on the forms; make note of the time period for each questionnaire.
- Do not rephrase items.
- Under ordinary circumstances, you should not tell the participant whether a specific response is correct or incorrect. If s/he asks, say something like "You're doing fine. Let's try this one." If s/he insists, simply reply, "I'm really not allowed to say."
- Use good judgment and common sense.
- Be prepared to make accommodations for auditory or other deficits. In case of hearing impairments, be sure to look at the participant when speaking, speak in lower tones, and do not speak too quickly.
- Be flexible, but try to adhere to standardized test administration without being rude. For example, if a participant begins to tell an involved story, say something like, "I don't want to

interrupt, but we really need to move along with the testing – do you mind finishing that story when we're all through?"

- On participant-completed questionnaires, it is very important to check the questionnaire to make sure a response has been given to every question. If they have missed an item, return the questionnaire to the participant for completion before they leave.
- Document any assistance provided to the subject in completing questionnaires (e.g., coordinator read questions and responses to participant, etc.); coordinator should be sure to initial and date this note.
- Allow for sufficient time to complete questionnaires. When possible, plan to administer questionnaires at a time when participant will not be rushed to get to another test, perhaps at the end of a visit.

7.6.2. Administering the SGRQ-C

The questionnaire should be completed in a quiet area, free from distraction and the patient should ideally be sitting at a desk or table. Explain to the patient why they are completing it, and how important it is for clinicians and researchers to understand how their illness affects them and their daily life. Ask him or her to complete the questionnaire as honestly as they can and stress that there are no right or wrong answers, simply the answer that they feel best applies to them. Explain that they must answer every question and that someone will be close at hand to answer any queries about how to complete the questionnaire.

It is designed for supervised self-administration. This means that the patients should complete the questionnaire themselves, but someone should be available to give advice, if required. It is designed to elicit the patient's opinion of his/her health, not someone else's opinion of it, so family, friends, or members of staff should not influence the patient's responses. If the spouse or partner has accompanied the patient, they should be asked to wait in a separate area. Similarly, do not allow patients to take the SGRQ-C home to be completed since you cannot be sure that it will be completed without the help of family or friends. A recent study of the use of surrogates to complete the questionnaire has shown small but significant differences in scores obtained from the patients themselves (Santiveri et al *Respiratory Medicine* (2007) 101, 439–445)

Once the patient has finished, it is very important that you check the questionnaire to make sure a response has been given to every question. If they have missed an item, return it to the patient for completion before they leave.

Responding to a patient's queries regarding completion of the questionnaire

If a patient asks for help with a question, do not provide an answer for them. The questionnaire is designed to get an understanding of how the patient views his or her illness. It is appropriate to clarify a question but not to provide an answer. Questions may be read aloud if patients have difficulty with reading, but the responses must be theirs alone. If a patient gives an answer you disagree with, it is not appropriate to challenge their response or to query it. It is their view of their condition we are interested in – no matter how strange the response! However, participants must give a single response when required (e.g., if they circle two responses they must be asked to choose one of the two)

The following are notes that may help you explain to patients what is required.

1. In Part 1 of the questionnaire (questions 1 through 7), emphasize to patients that you are interested in how much chest trouble they have had recently. The exact period is not important. We are looking for an impression or perception of health.
2. An attack of chest trouble (Part 1, Question 5) is any episode of worse symptoms that constitutes an attack in the patient's own judgment. Not just severe attacks as judged by medical staff.
3. For Part 1 Question 6, emphasize that you are interested in the number of good days that they have had.
4. COPD can vary day-to-day. Part 2 (questions 8-40) is concerned with the patient's current state (i.e. on average over 'these days'), not necessarily just today.
5. In Part 2, Questions 8 and 40 require a single response, but Questions 9 to 39 require a response to every question. It may be worth emphasizing this to the patient.
6. Many patients do not engage in physical activity. It is important to determine whether this is because they do not wish to (in which case the answer would be 'False') or cannot engage in these activities because of their chest trouble (in which case the answer would be 'True').
7. Responses to Questions 27 through 39 concern limitations due to breathing difficulties and not any other problems. If the patient does not engage in an activity for another reason, they should tick 'False'.

7.6.3. Administering the ATS-DLD

The preamble printed on the questionnaire should be read to the subject.

Use the exact wording of each question. If the respondent expresses doubt as to the meaning of the question, repeat it exactly. Emphasizing individual words or phrases often makes the meaning clear. Further explanation may be needed, but do not cross-examine the respondent. When after brief explanation doubt remains as to whether the answer should be yes or no, the answer should be recorded as no.

Some questions may need additional clarification as follows:

Section B, Cough and Section C, Phlegm definitions:

3 months (question 5 under cough and 11 under phlegm) means 3 consecutive months. "On getting up" (question 3 under cough and 9 under phlegm) may be at night for night workers.

Section C, Phlegm:

Emphasis should be placed upon phlegm as coming up from the chest and postnasal discharge is discounted. This may be determined by: "Do you raise it up from your lungs, or do you merely clear it from your throat?" Some subjects admit to bringing up phlegm without admitting to cough. This claim should be accepted without changing the replies to "cough." Phlegm coughed up from the chest but swallowed counts as positive. Include, if volunteered, phlegm with first smoke or "on first going out of doors."

Section D, Episodes of Cough and Phlegm:

This section is to identify persons with exacerbations of their symptoms. They may or may not have lost time from work or been confined to their homes (see question 24). For question 14, record actual number of years.

Section E, Wheezing:

This section is intended to identify subjects who have occasional and/or frequent wheezing. Those questions pertaining to asthma are asked in questions 17 and 33, but these questions may check that diagnosis. Subjects may confuse wheezing with snoring or bubbling sounds in the chest; a demonstration "wheeze" will help if further clarification is requested. The interviewer can ask, "Does your husband (or wife) regularly complain of your wheezing (not snoring) at night?"

Section F, Breathlessness:

If a subject volunteers that he or she is disabled from walking by any condition other than heart or lung disease, or obviously is confined to a wheelchair or uses crutches continuously, then question 21a should be answered "yes", a brief description of the condition(s) should be provided below, and question 22 is not to be asked. If asked, the questions refer to the average condition during the preceding winters. No attempt is to be made to separate out cardiac breathlessness.

Section G, Chest colds and chest illnesses:

Question 23 refers only to colds in the head followed by or occurring simultaneously with (increased) cough and sputum. Disregard "occasionally" and regard "usually" as more than half of the colds. This question may be modified on inquiry by the respondent: "That is, do colds usually settle in your chest before they leave you?" Force the respondent to decide whether more than half go to his or her chest. If he or she is in doubt, the answer should be coded no. A chest illness is defined as one with cough or phlegm (or increased cough or phlegm in the case of those respondents who regularly have cough or phlegm). The 3-year time period (in questions 24, 25, and 26) refers to any illness within 3 years prior to the day of interview.

Section H, Past illnesses:

Bronchitis (question 28): This diagnosis may be confused with pneumonia or bronchial asthma. The prominent feature is rapid onset of cough and phlegm that completely changes in character for those who have cough and phlegm always and then returns to its former state or comes and goes over a relatively short period of time.

Asthma (question 33) is to be considered "still present" if the respondent has visited a physician for it during the preceding 12 months or is on medication or has had an "attack" within the past 12 months.

Other chest illnesses or operations (question 34) are inquired about to identify restrictive lung disease that might impair pulmonary function test response. Pleurisy, fibrosis, and surgery on the lung are recorded here; fractured ribs may be ignored if healed.

Questions 35-38: Treatment for heart disease or hypertension discontinued more than 10 years before the date of present interview is to be recoded as no. Treated hypertension with pregnancy during the past 10 years is to be recorded as yes.

Section I, Occupational history:

The purpose of these questions is to obtain a coarse estimate of exposure to dust, chemical irritants, or other occupational exposures associated with lung diseases. If participant worked more than one job, determine total years worked at all jobs and on average if exposure was mild, moderate, or severe. For some individuals, question 48 may repeat answers contained in questions 41, 42, 45, and 46.

Section K, Family history:

The participant may raise some question about why family history is included. It is fair to say that some respiratory diseases "run in families" and it is important in any consideration of the kind of data being collected that a brief family history be obtained. The reason for knowing mother's and father's age and whether alive is to estimate risks of disease (for example, risk of getting emphysema).

7.6.4. ATS-DLD Alterations

The ATS-DLD questionnaire used in LEEP has been altered from the original to better reflect the goals of the study. The alterations are as follows:

- Section F, "Breathlessness", question 22: Question wording and grading have been slightly altered to reflect the Spiromics version of the Modified Medical Research Council (mMRC) dyspnea scale.
- Section J, "Tobacco smoking": question 55, "How many years in total did you regularly smoke cigarettes?" has been added to help calculate pack-year history.
- Questions 69 through 73, about e-Cigarettes, have been added.

7.7. Data collection and forms completion

7.7.1. List of forms, questionnaires, logs

Forms/Log name	Abbreviation	Data entered
Forms		
Baseline History Form	BH	✓
Clinic Visit Form	CV	✓
Drug Assignment and Dispensing	DA	✓
Drug Dose	DD	✓
Drug Return/Adherence/Capsule Count Form	DR	✓
Early Study Exit Form	EE	✓
Eligibility Form	EL	✓
HRCT Radiologist Review	RR	✓
HRCT Scan Acquisition	RT	✓
Laboratory Data Form	LD	✓
Missed Data	MD	✓
Participant Information	PI	No
Physical Exam	PE	✓
Physical Measurements	PM	✓
Pulmonary Function Testing	PF	✓
Screening Form	SC	✓
Study Closeout	SL	✓
Study Evaluation	SV	✓
Serious Adverse Event Report	SR	✓
Biospecimen Collection	BC	✓
Treatment Termination	TT	✓
Unanticipated Problem	UP	✓
Unmasking	UM	✓
Questionnaires		
ATS-DLD Respiratory Questionnaire	AT	✓
COPD Assessment Test (CAT)	CA	✓
mMRC Dyspnea Scale	DS	✓
PROMIS - 20a	PQ	✓
SGRQ - C	SG	✓
Logs/Administrative Forms		
Participant Screening Log	PS	✓
Pulmonary Medications Log	CP	✓
Non-Pulmonary Medications Log	CM	✓
Participant Information Sheets		
LEEP Appointment Card		
LEEP Wallet Card		
Signature and Delegation of Authority Log	SD	No
Clinical Center Certification		
Certificate of Confidentiality	CoC	No
LEEP Personnel Assurance Statement	PA	No
Phantom Acquisition Form	PT	✓
Consent Statement		No

7.7.2. ID codes

Codes

- Reference #
- Site ID
- Participant ID
- Alpha ID code
- Visit ID
- Clinical Center ID
- Personnel Identification Number (PIN)
- Phantom ID

Reference

- Assigned by data system after successful form submission
- Unique to every form entered into the data system
- Recorded onto form by data entry personnel upon form submission confirmation

Site ID

- Assigned by the NEMO when a site begins the regulatory and contractual process to join the PTC. The site ID remains constant across all PTC studies.
- Most often represents an institution, but if two or more sites with distinct PIs are located within the same institution, they will be assigned distinct site IDs. Note that if a PI leaves and is replaced by a new PI, the site ID does not change, and if a PI moves to a different institution and opens a new site there, a new site ID will be assigned.
- Formatted as NNNX, where NNN represents a three-digit number and X represents a letter to indicate whether the site is a primary site (A) or a satellite site (B-Z).
- A current list of site IDs is posted on the PTC website <or should be soon>.

Clinic ID

- Two letter ID assigned to each individual clinic

Participant ID

- Center-specific 6-character alphanumeric code taken sequentially from the sheet of Clinic Labels
- Distributed to the LEEP Clinical Center by the NEMO
- Unique identifier assigned to each participant who signs consent (V1)
- All participant forms will be identified by participant ID
- Clinical site's 2 letter code is embedded in participant ID

A participant's ID will start with "L" (for LEEP), followed by assigned site letters and 3 numbers and continuing sequentially.

Alpha ID code

- 4-character code, unique for every participant enrolled at a site
- Assigned by coordinator at participant registration
- Site to determine an assignment scheme
 - e.g. can use a 4-letter word
- It is strongly suggested that the unique participant ID or participant's initials NOT be included in this name code

Visit ID

- May be pre-printed on the form or label by the DCC or hand recorded
- Screening visit (first clinic visit) = V1; Randomization visit (second clinic visit) = V2, etc.
- N = not associated with a study visit; e.g., Serious Adverse Event Report

Personal Identification Number (PIN)

- Unique 5-character alphanumeric identification code for each clinic staff member completing data forms
- First 2 letters identify clinical site (see table below for assigned site letters)
- Staff members must be “registered” by being entered in the online directory (by Lead Coordinator) for a PIN to be generated
- PIN is LEEP specific

Phantom ID

- 6-character identifier entered on the Phantom Acquisition (PT) form
- First digit is L (for LEEP)
- Next two are the Clinic ID (two letter code)
- Last 3 digits are 9 9 9

Site letters for Participant IDs and PINs

- 2 letter code identifying LEEP Clinical Center site

Site	PTC Site ID	Code
New York Consortium – Columbia University	101A	CL
New York Consortium – New York University	101B	NY
New York Consortium – Cornell University	101C	CR
University of California – San Diego	102A	SD
University of California – San Francisco	103A	SF
Baylor College of Medicine	104A	BA
Duke University Medical Center	105A	DU
The Illinois Consortium – Northwestern University	106A	NW
The Illinois Consortium – University of Chicago	106B	CH
The Illinois Consortium – University of Illinois at Chicago	106C	IL
The Illinois Consortium – Rush Presbyterian	106D	RP
National Jewish Consortium – National Jewish Health	107A	NJ
National Jewish Consortium – Mount Sinai School of Medicine	107B	MS
Nemours Children’s Consortium – Nemours Children’s Center	108A	NC
Nemours Children’s Consortium – University of Florida, Jacksonville	108B	FJ
Northern New England Consortium – University of Vermont	109A	VT
Northern New England Consortium – Western Connecticut	109B	WC
Pacific Northwest Airways	110A	PN
Washington University in St. Louis	111A	SL
St. Louis University	111B	SU
University of Kansas	111C	KS
St. Vincent Hospital and Health Care Center, Inc.	112A	SV
Temple Lung Center	113A	TL
University of Pittsburgh	113B	PT
The UAB Lung Health Center – University of Alabama Birmingham	114A	AB

Louisiana State University	114B	LS
University of Arizona	115A	AZ
University of Michigan	116A	MI
University of South Florida	117A	FT

7.7.2.1. *Example of a clinic label sheet*

Clinics will receive a sheet of participant ID labels at the start of the trial. A participant's ID will start with "L" (for LEEP), followed by your assigned site letters and 3 numbers starting at 100 and continuing sequentially.

To assign a participant ID, attach the next sequential label to item #2 on the participant's Screening (SC) form.

Clinics who lose or misplace their label sheets should immediately contact the NEMO for a replacement sheet.

Clinic label sheet (example)

LXX100	LXX101	LXX102
LXX103	LXX104	LXX105
LXX106	LXX107	LXX108
LXX109	LXX110	LXX111
LXX112	LXX113	LXX114
LXX115	LXX116	LXX117
LXX118	LXX119	LXX120
LXX121	LXX122	LXX123

7.7.3. *Completing forms*

General guidelines

- Use dark blue or black ink
- Written responses should be legible to other people
- Limit use of abbreviations
- All completed forms should be reviewed by clinic coordinator to ensure that:
 - All items are answered
 - Written responses are legible
 - Data are consistent
- Never change the wording of questions, decimal places, or the unit for a response that is pre-coded on a form
- A response space should have only one letter or digit per space
- Numeric responses are to be right justified with all spaces completed. Use lead zeros as necessary. Example: 0 0 3 2
- Alpha or alphanumeric responses are to be left justified. If blank spaces remain, leave them blank. Example: P 1 2 _; D C C
- Data on forms should always match database
- All forms must be signed off by a Study Physician or clinic coordinator who is certified for the study

Error correction

- Do not obliterate erroneous responses
- Never use correction fluid or tape to erase a response
- Draw a single line through the incorrect response and indicate correct response clearly, above or next to the erroneous response
- Use a different color ink; e.g., green or red, to make edits
- Staff member making changes to a form should initial and date each change in the margin and provide a brief explanation for the change; e.g., “error”, “participant changed mind”
- Be sure that the database is updated with the revised information
- Staff should do the utmost to ensure all study forms are completed. However, if data is missing from a form, staff should leave the item blank and make a note in the margin

Rounding rules

- Responses should have only one letter or digit per space
- The number of spaces or location of a decimal point on a form must never be added or changed
- If a response has a greater number of digits to the right of a decimal point than spaces allow, the response should be rounded as follows:
 - If the first digit following the last data space is less than 5, round down; e.g., if the form has spaces for a 2-digit response with one decimal between the digits (_ . _), then 4.71 would be rounded to 4.7 and 4.14 would be rounded to 4.1
 - If the first digit following the last data space is 5 or more, then round up; e.g., if the response field is for 2 digits with a decimal between the digits (_ . _), then 4.78 and 4.75 would be rounded to 4.8 and 4.15 would be rounded to 4.2

More examples:

- For a response field of three digits (__ __ __), 79.485 would be recorded as 079 and 79.584 would be recorded as 080
- For a response field of (__ . __ __), 4.2745 would be recorded as 4.27 and 4.2754 would be recorded as 4.28

 **Note:** Do not round responses unless the number of digits in a response field requires it. Otherwise, record data as collected.

If there are more whole integer digits than the response field allows, contact the Data Coordinating Center.

7.7.4. Description of study forms

7.7.4.1. Data forms and logs

Purpose

- Record study data on standardized data collection instruments
- Guide data collection and visit procedures

Procedures

- **Baseline History Form (BH)** to document general health status
- **Specimen Collection Form (BC)** to document information about specimen collection of packed cells, plasma, serum, and urine
- **Clinic Visit Form (CV)** used to record interval medical history (e.g. COPD exacerbations, changes in medications, symptoms)
- **Pulmonary Medications Log (CP)** to record all COPD-specific medications used by participant during LEEP.
- **Non-Pulmonary Medications Log (CM)** to record all non-COPD specific medications used by participant during LEEP.
- **Drug Return/Adherence/Capsule Count Form (DR)** to document adherence with study drug and return of study drug bottle
- **Drug Assignment and Dispensing Form (DA)** to document treatment assignment and distribution of study drug and provide time sensitive tracking of study drug supply
- **Drug Dose Form (DD)** to document any change in dose (number of capsules) participant is instructed to take daily
- **Early Study Exit Form (EE)** used to document reason for participant's exit from study after V1 and prior to V7 from study
- **Eligibility Form (EL)** to document eligibility for randomization
- **HRCT Radiologist Review (RR)** to document review of the HRCT image by center radiologist and indicate if clinically significant incidental findings were noted
- **HRCT Scan Acquisition Form (RT)** to document eligibility for HRCT scan and record collection of scan; required at V1 for the LEEP eligibility and at V7 for primary outcome
- **Laboratory Data Form (LD)** to document laboratory test results
- **Missed Data Form (MD)** to record information about missed study data
- **Participant Information (PI)** to record participant and contact information
- **Phantom Acquisition Form (PT)** to record information on CT scanner to be used in LEEP; for initial approval and every 6 months for quality control
- **Physical Exam (PE)** to record information about a participant's health
- **Protocol Deviation (PD)** to document a protocol deviation
- **Pulmonary Function Testing (PF)** to record the results of spirometry
- **Screening Form (SC)** to document screening.
- **Study Closeout (SL)** to evaluate study staff's experience in LEEP and record distribution of exit materials.
- **Study Evaluation (SV)** to evaluate a participant's experience in LEEP
- **Serious Adverse Event Report (SR)** to report a serious adverse event (SAE)
- **Treatment Termination (TT)** to record permanent termination of study drug
- **Unanticipated Problem (UP)** completed to report unanticipated problems.
- **Unmasking (UM)** to record unmasking of study treatment

7.7.4.2. Questionnaires

Purpose

- To collect information directly from the participant concerning aspects of their physical health

Information collected

- **ATS-DLD Respiratory Questionnaire (AT)** to assess participant's respiratory symptoms, respiratory health history, and family history.
- **COPD Assessment Test (CA)** to collect data to determine CAT score.
- **Modified Medical Research Council dyspnea scale (DS)** to document information about COPD symptoms.
- **PROMIS-20a (PQ)** to assess physical functioning.
- **St. George's Respiratory Questionnaire – COPD (SG)** to assess respiratory symptoms and quality of life.

Please refer to MOP section 7.6 and to individual questionnaires for specific guidelines on administration, completion, and scoring.

7.7.4.3. Logs/Administrative forms

Purpose

Obtain additional specimen collection supplies and provide records of participants screened for the trial.

Procedures/Timeframe

- **LEEP Specimen Supply Order Form (SO)** is used to order additional specimen collection supplies from the DCC.
- **Participant Screening Log (PS)** is used to keep a record of demographic information and disposition of all participants evaluated for eligibility for the trial. During screening, participant information is entered into the PS though the participant may not sign consent. All participants that are registered in LEEP are to be listed on the PS.
- **Signature and Delegation of Authority Log (SD)** is used to record the names, roles, delegated duties, signature, initials and dates of study involvement for **all** clinic center staff that work on LEEP. This includes PI, coordinators, data system operators, CT technologists/technicians, physicians, etc.

7.7.4.4. *Participant information sheet*

Purpose

Provide instructions about study procedures for participants

Procedures/Time frame

- **LEEP Appointment Card:** is a wallet size card listing the participant's next scheduled appointment and contact information for the clinic.
- **LEEP Wallet Card:** is a wallet size card with contact information for study.

7.7.4.5. *Certification forms and consent*

Purpose

- To assure that all necessary personnel and approvals are in place before LEEP is open to participants

Task/Timeframe

- **LEEP Personnel Assurance Statement (PA)** is to be signed by all personnel requesting certification and a PIN to conduct LEEP. Signed statement sent to NEMO and a copy is kept by the clinic.
- **Phantom Acquisition Form (PT)** is used to record the collection of inspiratory and expiratory phantom scanning information. It is to be completed when phantoms are scanned. Completed form sent to NEMO and a copy is kept by clinic.

Informed Consent Form

- **Research Subject Information and Consent Form (ICF)** is read and signed by the participant. Co-signed by person obtaining consent and PI (if someone different from person obtaining consent).

7.7.5. *Distributed data entry*

Purpose

- To collect all trial data
- To track participant activity
- To monitor LEEP Clinical Center performance

Background/Procedures/Timeframe

- Refer to the Data System Manual for information

8. Training and certification

8.1. Clinical center responsibilities

- The following are the required roles for each LEEP clinical center:
 - Principal Investigator
 - Study Physician
 - Lead Coordinator
 - HRCT Coordinator
 - Data System Operator
 - Spirometry Tester
-  **Note:** Staff may carry out the duties for more than one role, but additional staff members are recommended for sufficient coverage
- Study drug will be distributed by Almac to the clinical center directly. The LEEP clinical center is to designate one staff member at one address for receipt of LEEP study drug. The LEEP clinical center must record receipt and distribution of all study drug/placebo
- The Lead Coordinator is responsible for keeping the PTC web-based directory current for their clinical center
- The Lead Coordinator is responsible for the distribution of correspondence and study materials to all other LEEP staff members at the main clinical center as appropriate
- The Principal Investigator is responsible for the distribution of correspondence and study materials to other study investigators as appropriate

8.2. Clinic certification

Purpose

- Provide confirmation and documentation that the main Clinical Center has obtained the required approvals, facilities, equipment, personnel, and training necessary to conduct LEEP.
- Ensure consistent conduct of study procedures over time within and across clinics so that findings from all clinics are comparable.

When

- Before a Clinical Center may recruit participants and conduct study procedures for the Losartan Effects on Emphysema Progression (LEEP) trial.

8.2.1. Consent statement and consent checklist

NEMO will provide an Informed Consent template for clinics to use when creating the Informed Consent Documents for LEEP. The template contains all information, which must be present on all clinical center consent documents. Clinical centers are not required to use this template, however, it is provided as a tool to make the development of clinics' Informed Consent document easier.

- All consents must be reviewed and approved by the NEMO after all changes have been made by the site and its IRB.
- When clinical centers send their Informed Consent statements to the NEMO, they should use the Informed Consent Checklist, which is provided by the NEMO and is located on the PTC website's LEEP documents area (www.pulmonarytrials.org)
- The items listed on the checklist are mandatory items, which are required to be present somewhere in the consent. The clinical center should review the checklist and note on which page each item can be found.
- In addition, the clinical center should e-mail a copy of their consent in Microsoft Word, with the item number from the checklist added to the document as a comment. Example is shown below:

Why is this research being done?

This research is being done to look at how a medicine called **Losartan** helps people with Chronic Obstructive Pulmonary Disease (**COPD**) with emphysema – a disease of the lungs.

Commented [JS6]: 3

If any further changes are made after initial NEMO approval, the clinical center should contact the NEMO to approve any additions or subtractions from the document. If a NEMO re-review is required, the clinical center should again include the consent checklist with any applicable changes made.

8.2.2. Clinic certification instructions

The Lead Coordinator should submit the following documentation to the NEMO for site approval.

Documentation

- IRB approval
 - Copy of IRB notice of protocol approval
 - Letter or stamp of IRB approval on the LEEP informed consent form
 - Original checklist if no changes were made to consent, or an updated checklist if changes were made to consent after NEMO pre-approval
 - Proof of IRB approval for other materials given to participants, including:
 - Certificate of Confidentiality
 - Recruitment brochure
 - COPD educational materials
 - “The ‘Whats’ of COPD” from the COPD Foundation
 - “Now That You Know It’s COPD” from NIH
 - “My COPD Action Plan” from the ALA
 - Study questionnaires (forms AT, CA, DS, PQ, and SG)

- Physician and participant letters (see MOP section 10.2 for prototypes)
- Wallet card
- Appointment card
- Product insert for losartan
- Regulatory paperwork
 - Protocol signature page signed by site PI9s0
 - Proof of GCP and Human Subjects training for study staff
 - Current CV(s) for Principal Investigator(s)
 - Signature and Delegation of Authority (SD) log (available on the PTC LEEP website for downloading)

Please use one of the following methods to submit these documents to the NEMO

- Email to PulmonaryTrials@edc.pitt.edu
- Fax to 412-624-3775
- Mail to:
PTC c/o Amanda Baucom
Epidemiology Data Center, University of Pittsburgh
4420 Bayard Street, Suite 600
Pittsburgh, PA 15260

8.2.3. Required facilities and equipment

Facilities required for certification

- Secure area for study drug storage
- Private area to conduct participant interviews and study visits
- Secure storage area for storage of study supplies, documents, and forms
- Place to draw blood for safety labs and biospecimens

Equipment and materials

- EasyOn spirometer to measure FEV₁ and FVC (provided by the NEMO)
- EasyOn spirometer software (provided by the NEMO)
- Equipment to measure height and weight
- Equipment to measure blood pressure and blood oxygen saturation
- AART certified HRCT scanner with a minimum of 64 slices/detectors
- Computer for data entry with the following specifications
 - Microsoft Windows
 - Microsoft Internet Explorer (version 6.0 or above)
 - Adobe Acrobat Reader (5.0 or above—available free from www.adobe.com)
 - Printer

8.2.4. HRCT equipment requirements

8.2.4.1. Scanner requirements

- Scanners must be certified by ARRT
- Scanners **MUST** have a minimum of 64 slices/detectors

8.2.4.2. Scanner approval

Any scanner to be used in LEEP is to be approved **before** any participant has a scan for LEEP. Ideally, one scanner is used for all LEEP scans. No more than two scanners at a site are to be approved for use in LEEP. It is essential that participants have their V1 and V7 scans done on the same scanner.

 **Note:** If a site will be adding a new scanner after the site is certified, the phantom must be scanned for the new scanner before it is used for the study.

8.2.4.3. Scanner approval process

Equipment and supplies

NEMO will distribute:

- LEEP Lung Phantom (CTP674 Lung Phantom™-The Phantom Laboratory, Salem, New York) – to be shipped back to the NEMO after scan
-  **Note:** Clinics with a SPIROMICS, COPDGene or other CTP674 phantom may use that phantom for LEEP certification
- DVDs for burning phantom scans
- Appendix A – Scanning Procedure for the LEEP Lung Phantom

Clinical centers will provide

- Phantom Acquisition (PA) form (download from LEEP website)

Documentation for certification of scanner

Phantom Acquisition (PT) form is used to document that the phantom has been scanned. The form:

- Must be completed for each scanner that has been identified for use in LEEP
 - PT form includes documenting specifics of the scanner (make, model, and serial number)
- The CT technologist is to complete Section B on the form
- Form must be keyed into the data system within 2 days

Scan is to be burned to DVD

- Data from phantom scan is uploaded using DataStream software for review and approval. Refer to Appendix A – Scanning Procedure for the LEEP Lung Phantom for complete instructions.

Procedures

Scanning the phantom, refer to Appendix A – Scanning procedure for the LEEP Lung Phantom
Transfer of phantom scan data, refer to Appendix C – Data Transfer of HRCT Scans to NEMO

Scanner approval

- NEMO will provide feedback that a scanner is approved for use in LEEP
- The LEEP Reading Center will contact the coordinator if there are issues with the scan

No HRCT scans are to be performed on participants until the scanner and staff are certified; that is, the HRCT Reading Center has signed off that the phantom scan is acceptable and the staff certification completion is documented

8.3. Personnel certification

Any personnel at a clinic center who will perform functions for LEEP must be certified for that function by the NEMO prior to conducting any procedures. In order to obtain clinical center certification, each site must have personnel certified for each of the following roles:

- Center Director/PI
- Co-PI/Study Physician
- Lead Coordinator
- Clinic Coordinator
- Spirometry Tester
- Data System Operator
- HRCT Coordinator (study staff member)

Please note that a single person can be certified in multiple roles.

All study staff are to have completed training in Human Subjects Research and Good Clinical Practice.

8.3.1. Center Director/PI

The Center Director/Principal Investigator is responsible for the leadership and oversight of the main LEEP clinic. This person is the primary point of contact for the ALA and the DCC; and is responsible for disseminating information to satellite centers (if applicable).

To be certified, the center director/PI must:

- Complete online General Knowledge Assessment (GEN) through PTC/LEEP website. A score of 80% is required to pass.
- Complete and sign the Signature and Delegation of Authority Log.
- Complete and sign a LEEP Personnel Assurance statement.

8.3.2. Co-PI/Study Physician

The Co-Principal Investigator/Study Physician is responsible for performing physical exams and providing physician support during study procedures.

To be certified, the Co-PI/Study Physician must:

- Complete online General Knowledge Assessment (GEN) through PTC/LEEP website. A score of 80% is required to pass.
- Complete and sign the Signature and Delegation of Authority Log.
- Complete and sign a LEEP Personnel Assurance statement.

The study physician may designate another physician or another **licensed** healthcare provider to perform this role, such as a Nurse Practitioner (NP) or Physician's Assistant (PA), but the duties must fall within the scope of practice for the designee and appropriate oversight must be in place.

8.3.3. Lead Coordinator

The Lead Coordinator is a specialized Clinic Coordinator who, in addition to completing study tasks, takes on the responsibilities below.

Lead Coordinators:

- Serve as the primary contact for the LEEP DCC
- Enter all staff into the LEEP directory (<http://www.LEEPTrial.org>) in order to obtain a PIN and password, necessary to complete certification procedures.
- Keep the web-based directory current for their clinical center.
- Distribute correspondence and study materials to all other staff members at the clinical center and satellite centers (if applicable).
- Participate in LEEP training and complete certification as Data System Operator

Lead Coordinators should complete, at minimum, the Clinic Coordinator training listed below.

8.3.4. Clinic Coordinator certification

The clinic coordinator completes the LEEP study forms, administers the LEEP assessments, and dispenses study drug.

Clinic Coordinator requirements:

- Complete online General Knowledge Assessment (GEN) through PTC LEEP website. A score of 80% is required to pass.
- Complete and sign the Signature and Delegation of Authority Log.
- Complete and sign a LEEP Personnel Assurance statement.
- Complete online MOP Knowledge Assessment through PTC LEEP website. A score of 80% is required to pass.

8.3.5. Spirometry Tester certification

Certification will be done by the NEMO. For more information, consult Appendix F – MOP Spirometry.

8.3.6. Data System Operator certification

The Data System Operator enters study data into the LEEP data system.

Data System Operator requirements

- Complete online General Knowledge Assessment (GEN) through PTC/LEEP website. A score of 80% is required to pass.
- Complete and sign the Signature and Delegation of Authority Log.
- Complete and sign a LEEP Personnel Assurance statement.
- Complete Data System training module
- Complete online Data System Knowledge Assessment through LEEP website. A score of 80% is required to pass.

8.3.7. HRCT Coordinator certification

Each clinical center must have at least one coordinator complete the HRCT coordinator certification process. The HRCT coordinator works with the CT Technologist to ensure high quality HRCT scans are obtained for LEEP study participants.

To ensure that all LEEP scans are performed consistently and accurately, it is essential that the LEEP protocol for HRCT scans be followed exactly. Only a coordinator that has completed the HRCT module and test is permitted to:

- Accompany the participant to the HRCT suite
- Verify that the HRCT scanner has been approved (Phantom scan and approval)
- Verify that the scanner settings are those required by the LEEP protocol
- Provide CT technologist with protocol
- Obtain the disk (copy) of the de-identified HRCT scan
- Complete and sign off on the HRCT Acquisition (RT) form

HRCT Coordinator certification requirements:

- Complete online General Knowledge Assessment (GEN) through PTC/LEEP website. A score of 90% is required to pass.
- Complete and sign the Signature and Delegation of Authority Log.
- Complete and sign a LEEP Personnel Assurance statement.
- Complete HRCT training module
- Complete online HRCT Knowledge Assessment through PTC/LEEP website. A score of 90% is required to pass.

8.3.8. CT Technologist requirements

The CT technologist is responsible for performing HRCT scans on LEEP study participants and for scanning the phantom. The CT technologist does not have to complete the knowledge assessments and is not assigned a PIN.

However, the CT technologist must be familiar with the LEEP scanning procedure, the required settings, and the specific breathing instructions/coaching. The quality and consistency of the HRCT scans are critical to the success of the LEEP trial. The HRCT Coordinator is responsible for assuring that the CT technician completes all requirements listed below.

Requirements

- Review the LEEP HRCT scanning procedure (Appendix B)
- Review the CT Instruction form for the scanner to be used in LEEP
 - Ideally the CT technician will load and save the appropriate LEEP scanning protocol into the scanner
- Complete and sign the LEEP Signature and Delegation of Authority Log

9. Payment procedures

9.1. Contracting

The NEMO negotiates a single subaward with the ALA for capitation payments. The capitation payments, in turn, are supplemented and distributed by the ALA to the ACRC centers based on study enrollment and completion of study procedures. The ALA distributes payments to clinical sites as grant awards without additional contracting.

Affiliated sites will receive an award notice from ALA contingent on acceptance of the ALA-ACRC terms and conditions. Affiliated sites will need to provide institutional sign-off, Tax ID, and financial transfer information to the ALA.

9.2. Payment

Payment to clinical sites is based on completion of study visits according to the following schedule:

TASK	AMOUNT	CRITERIA
Screening (ineligible)	\$250	Screen fail Enter SC form
Randomization Visit	\$1,500	Successful randomization Enter CV Form Enter HRCT Form
Week 2 Titration Visit		Enter CV Form
Week 12 Follow-up Visit	\$400	Enter CV Form
Week 24 Follow-up Visit	\$400	Enter CV Form
Week 36 Follow-up Visit	\$400	Enter CV Form
Week 48 Follow-up Visit	\$1000	Enter CV Form
Week 48 HRCT	\$1,300	Enter HRCT Form
TOTAL	\$5,000	
The NEMO will provide a \$1,000 start-up payment to sites upon completion of certification requirements.		

Each quarter after enrollment begins, each clinical site PI receives a list of the patient IDs and tasks for which the site is due payment. This is generated based on data generated by the LEEP PLG.

The list must be reviewed, approved, and returned to NEMO by email. The patient list should be reviewed by someone familiar with the study (i.e., PI or coordinator). The purpose is to ensure that the NEMO's records and calculations are accurate and the clinical site is receiving the correct payment. Payment is based on data entry; data entered on or after the first day of

the new quarter appears on the next quarter's invoice. Inquiries concerning the content of the patient list should be directed to the NEMO Financial Administrator.

Once the NEMO receives the approved and participant/task list from the clinical sites, the NEMO sends a master list and an invoice to the ALA. The invoice must be printed, signed by an authorized ALA signee, and returned to the NEMO for payment. Once the NEMO receives the signed invoice, the NEMO Financial Administrator processes the paperwork for payment. All checks are mailed within six weeks with the invoice and/or patient listing enclosed. The ALA then issues payments to the clinical sites.

10. Study supplies and communication prototypes

10.1. Study supplies

NEMO will distribute the following:

- Participant supplies
 - Participant registration label sheets
 - LEEP appointment cards
 - LEEP wallet/study information cards
 - LEEP recruitment brochure
 - COPD educational brochures
 - Laminate cue cards for use with the Baseline History (BH) form
- Other study supplies
 - Blank DVDs for HRCT and phantom scans
 - Barcode scanner
 - Pill counter

Ordering additional supplies from NEMO

- Order supplies, as needed
- Requests should include number of items and date needed
- Fax, email, or mail to NEMO or select the “Supplies Ordering” category in the PTC website Help Center

Ordering specimen from the DCC

- Order supplies, as needed
- Complete LEEP Supply Order (SO) form
- Requests should include number of items and date needed
- Fax to DCC at (775) 871-4030, email to DCC at JHSPH.ala-acrc@jhu.edu, or mail to DCC at:
 - Johns Hopkins University
 - Center for Clinical Trials
 - 415 N Washington St, 2nd Floor
 - Baltimore, MD 21231

Clinical centers will provide

- Blood collection supplies (needles, tourniquet, etc.)
- Pregnancy testing supplies
- Study forms and questionnaires.
 - Download from PTC LEEP website: <https://my.pulmonarytrials.pitt.edu>

10.2. Communication prototypes

Purpose

- To communicate with participant and participant's COPD care provider regarding participation in LEEP

When

- Appropriate letter(s) to be sent when participant determined to be eligible and when participation in trial ends (regardless if participant was randomized)

Supplies

- Prototype communications are included. The letters you will use are to have your institution's requisite approvals.

10.2.1. Physician communication introduction letter

Dear Dr(s).

Your patient, _____, was recently enrolled in the clinical trial, Losartan Effects on Emphysema Progression (LEEP). This study is a randomized, double-masked, placebo-controlled study designed to test the hypothesis that administration of losartan 100 mg/day for 48 weeks will decrease the rate of progression of emphysema as measured by quantitative HRCT compared to placebo. Eligible participants are those with mild to severe COPD and emphysema with HRCT scans showing 5-35% of voxels with density less than -950 HU. As part of this study, your patient will have two HRCT scans to determine his/her percentage of emphysema – one at the beginning of the study, and one approximately 52 weeks later.

Your patient will be randomly assigned to receive either losartan or placebo. Your patient will start on one capsule a day (losartan 50mg or placebo). There will be a dose titration visit after 2 weeks, when the dose will be escalated to 2 capsules (losartan 100 mg or placebo). If your patient does not tolerate the escalated dose, he/she will remain on a dose of one capsule a day (50mg losartan or placebo). The trial will collect information including demographics, medical history, lung function, and questionnaires. Your patient will be followed for approximately 48 weeks.

Your patient should continue to use you as their primary care physician and/or primary COPD care physician.

The dose of losartan used in this study is well tolerated by non-hypertensive patients without significant effect on blood pressure. In order to reduce the risks of side effects, participants taking losartan should not take the following drugs while enrolled in this trial:

- Other angiotensin receptor blocking (ARB) drugs
- Angiotensin converting enzyme (ACE) inhibitors
- Potassium supplements
- Potassium-sparing diuretics
- NSAIDs, when used daily (5 or more days of the week) for more than one month

At the end of the study, your patient will learn which study treatment he/she received, and will be given a copy of the pulmonary function test and HRCT scan results from the final visit. HRCT scans will be reviewed by a radiologist. If there are clinically significant incidental findings, your patient will be notified. Your patient will be told that he/she may contact our clinic for emergencies, if necessary, during the interim period. Please feel free to contact our clinic (xxx-xxx-xxxx) or me personally if you have any questions.

Sincerely,
Principal Investigator
Institution

10.2.2. Participant release to share results letter**Prototype:** Participant release to send spirometry results to COPD care providers

**CONSENT TO RELEASE
RESEARCH SUBJECT BREATHING TEST AND HRCT RESULTS FORM**

Title: Losartan Effects on Emphysema Progression

Protocol No.: IRB Name Protocol # XXXXX

Funding Source: The National Heart, Lung, and Blood Institute (NHLBI) under the Pulmonary Trials Cooperative (PTC)

Investigator: <<Site Investigator>>

Site(s): <<Site name>>
<<Site address>>
<<Site city, state, zip>>

**STUDY-RELATED
PHONE NUMBER(S):** Research study questions
<<Site Investigator>>
<<Investigator Phone>>

Research-related injury
<<Site Investigator>>
<<Investigator Phone>>
<<Investigator Phone, 24 hours>>

SUBINVESTIGATOR(S): <<Site Investigator>>

Permission to Notify Physician(s):

I give permission for study personnel to fax/send my breathing test and HRCT test results to my primary care physician and/or my primary COPD care physician.

Printed Name of Subject

Signature of Subject

Date

CLINIC SIGNATURE(S)

Signature of Person Conducting Informed Consent
Discussion

Date

Signature of Investigator (if different from above)

Date

10.2.3. Physician exit letter (for use after participant has been randomized)

Dear Dr(s). _____ -
_____:

Your patient, _____, recently completed participation in the clinical trial, Losartan Effects on Emphysema Progression (LEEP). This study is a randomized, double-masked, placebo-controlled study designed to test the hypothesis that administration of losartan 100 mg/day for 48 weeks will decrease the rate of progression of emphysema as measured by quantitative HRCT compared to placebo. Eligible participants had mild to severe COPD and emphysema with HRCT scans showing 5-35% of voxels with density less than -950 HU. Participants that could not tolerate the full dose continued in the trial on just one capsule (50 mg losartan or placebo) daily.

Your patient had two HRCT scans of the lungs on _____ and _____ (dates). Your patient's most recent HRCT showed _____ percent of voxels density less than - 950 HU.

Your patient has now completed all study visits and has received an envelope indicating the assigned study treatment and the results from his/her last pulmonary function test. We have counseled your patient to show you the treatment assignment and the results of his/her final spirometry tests.

We hope participation in this clinical trial was beneficial to your patient. Please contact our clinic (xxx-xxx-xxxx) or me personally, with any questions.

Sincerely,
Principal Investigator
Institution Name

10.2.4. HRCT prep letter

Dear _____,

Thank you for your participation in the clinical trial Losartan Effects on Emphysema Progression (LEEP). We have made an appointment for you to return to our clinic on _____ at ____: ____ (AM / PM) to have a high-resolution computed tomography (HRCT) scan as part of the LEEP study. Please follow the directions below to prepare for your HRCT appointment.

Reasons to reschedule:

- If you have an exacerbation (bad episode) of COPD or a chest infection before the appointment and you need to take a new steroid or antibiotic to treat it, please call the clinic as soon as possible to reschedule your appointment.
- If you become pregnant prior to the appointment, please call the clinic as soon as possible.

Medication:

- Please take all your medications as prescribed before coming in for your HRCT appointment, including your COPD medications.
 - If you use short-acting bronchodilators for your COPD, take as needed. Short-acting bronchodilators include Proventil HFA, ProAir, Ventolin HFA, and Xopenex.
 - If you take long-acting COPD medications, take your normal dose at your normal time before coming into the clinic. Long-acting bronchodilators include Spiriva, Tudorza, Serevent, Arcapta, and Brovana

If you have any questions about this appointment or the study in general, please contact the clinic staff at (xxx-xxx-xxxx). We look forward to seeing you.

Sincerely,

Principal Investigator
Institution Name

10.2.5. Participant exit letter

Dear _____,

Thank you for participating in the clinical trial Losartan Effects on Emphysema Progression (LEEP). This study is looking to see if losartan 100 mg/day for 48 weeks will decrease the rate of progression of emphysema as measured by quantitative HRCT compared to placebo.

The treatment group you were assigned to is in the enclosed, sealed envelope. We have also provided the results of your final pulmonary function test (breathing test). We recommend that you show your COPD care provider the results of your final pulmonary function test.

There are other participants in the study, enrolled after you, who are still being treated and followed. It is important that you do not inform me, the other study personnel, or other study participants what treatment you were assigned because the study is still collecting information on these people. We make it a point not to know what treatment participants are assigned during the study so that knowledge of the treatment assignment does not influence the data we are collecting.

Again, thank you for your participation in LEEP.

Sincerely,

Principal Investigator
Institution Name

Enclosures:
Treatment assignment envelope
Results of final pulmonary function tests

11.HRCT data management

11.1. External data transfer

Overview

Refer to Appendix C - Data Transfer of HRCT Scans to NEMO for complete information on setting up the hardware and software necessary for the transfer of CT data to the NEMO. The system must be set up and tested before the first scanned phantom images can be transferred for certification.

The clinical site, the site's IT department, and NEMO will consult to address specific hardware and technical issues. The system requires:

- A windows based computer (i.e., DataStream computer) identified/allocated at the clinical center for the purpose of a local image data storage and transfer to the NEMO's central server.
- DataStream software provided by the NEMO be installed on the identified computer; DataStream Anonymizer prepares files for transfer to the central server. It removes values of unwanted DICOM tags in the image header, renames the files, and organizes them into the transfer folder.
- Routable IP address of the computer be provided to NEMO so that the appropriate firewall exception can be made to permit communication to NEMO's central server.

12. Reports

12.1. Study progress reports

LEEP study progress will be reviewed by the PTC Operations Committee and the DSMB. Data required for reporting on study progress includes:

- Study startup information on personnel roles and training requirements, and regulatory documentation including IRB approvals and modifications
- Monthly summary statistics on recruitment, accrual, randomization, and retention
- Quarterly data collection and quality information that reflects site performance
- Event data regarding safety and protocol compliance, such as reportable adverse events and unanticipated problems

Startup and regulatory documentation will be communicated from the clinical centers to the NEMO via its dedicated email address PulmonaryTrials@edc.pitt.edu, from where it will be fed into the NEMO's Regulatory Tracking System (RTS). The RTS will provide reports on outstanding regulatory issues, and alerts on upcoming renewals and recertification timelines.

DSMB and monthly summary reports are described below in MOP sections 12.2 and 12.3, while event handling and reporting requirements are presented as part of MOP section 12.4, Safety Monitoring. Quarterly site performance reporting is described in MOP section 13, Study and Site Monitoring, in MOP section 13.1.3.

12.2. Monthly and quarterly reports

Monthly reports will be run on site and study progress (by the NEMO) and patient accrual and retention, forms completion, and visit completion (by the LEEP PLG). These reports will be distributed and reviewed each month on a joint Operations Committee call between the LEEP PLG, the NEMO, and the NHLBI.

Quarterly cross-study monitoring reports and regulatory tracking will be completed by the NEMO. The NEMO will distribute reports to the sites, the LEEP PLG, and the NHLBI. The reports will be reviewed on the following monthly Operations Committee call (PLGs, the NEMO, and the NHLBI) to identify issues and decide a course of action. If a particular issue with a site applies to multiple studies, it will be addressed by the NEMO.

12.3. Semi-annual DSMB reports

The PTC Data Safety and Monitoring Board, under the direction the NHLBI, meets about every six months to review the study progress and safety of all PTC studies. To inform these meetings, the LEEP DCC will prepare summary reports. Among information included are recruitment and retention summaries, baseline characteristics of randomized patients, data completeness statistics, protocol deviations, and adverse event occurrences.

12.4. Safety monitoring

This section defines a minimum standard for reporting of the various adverse events and unanticipated problems that occur during the course of clinical trials. It also provides the reporting requirements and timelines relevant to each of these events. Categories of events include adverse events (serious and non-serious), unanticipated problems, protocol deviations and regulatory non-compliance. Many events carry classifications specifying their severity, expectedness, and relatedness to the research being performed.

Safety monitor should be conducted on all participants during the course of the study. For participants who consented but are later found to be ineligible, clinics should report serious adverse events that they learn of 7 days after the screening visit (V1). However, clinics do not have to actively follow up with ineligible individuals to collect for these events.

12.4.1. Definitions

Adverse event*: Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with a person's participation in the research, whether or not considered related to a person's participation in the research.

Serious adverse event (SAE)*: Any Adverse Event that meets any of the following criteria:

1. results in death;
2. is life-threatening (i.e. places a participant at immediate risk of death from the event as it occurred);
3. requires inpatient hospitalization or prolongation of existing hospitalization;
4. results in a persistent or significant disability/incapacity;
5. results in a congenital anomaly/birth defect; OR
6. any other adverse event that, based upon appropriate medical judgment, may jeopardize the participant's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (e.g. allergic bronchospasm requiring intensive treatment in the emergency room or at home).

Relatedness:†# Relatedness refers to the extent to which an adverse event is considered to be related to the intervention or study procedures. An adverse event is considered related if there is a reasonable possibility that the event may have been caused by the procedure. In the LEEP study, the relatedness of an event can only be determined by the primary investigator.

The following definitions apply to relatedness:

- Unrelated
 - Adverse event is clearly due to extraneous causes (e.g., underlying disease, environment)
- Unlikely (Adverse event **must meet 2** of the following):
 - Does not have temporal relationship to intervention
 - Could readily have been produced by the participant's clinical state
 - Could have been due to environmental or other interventions

- Does not follow known pattern of response to intervention
- Does not reappear or worsen with reintroduction of intervention
- Possible (Adverse event **must meet 2** of the following):
 - Has a reasonable temporal relationship to intervention
 - Could not readily have been produced by the participant's clinical state
 - Could not readily have been due to environmental or other interventions
 - Follows a known pattern of response to intervention
- Probable (Adverse event **must meet 3** of the following):
 - Has a reasonable temporal relationship to intervention
 - Could not readily have been produced by the participant's clinical state or have been due to environmental or other interventions
 - Follows a known pattern of response to intervention
 - Disappears or decreases with reduction in dose or cessation of intervention
- Definite (Adverse event **must meet 4** of the following):
 - Has a reasonable temporal relationship to intervention
 - Could not readily have been produced by the participant's clinical state or have been due to environmental or other interventions
 - Follows a known pattern of response to intervention
 - Disappears or decreases with reduction in dose or cessation of intervention and recurs with re-exposure

Expectedness: An unexpected event is one that has not been documented previously as an established adverse reaction to the study intervention and that is not recognized as part of the natural progression of the disease.

A particular event may also be considered unexpected if it has a higher severity grade than what has been documented or identified previously. Events that occur as a consequence of study procedures and are not noted in the informed consent document are also considered unexpected in nature.

Unanticipated problem (UP)*: Any incident, experience, or outcome that meets all of the following criteria:

1. Unexpected in terms of nature, severity, or frequency, taking protocol research procedures and participation population characteristics into consideration.
2. Related or possibly related to a persons' participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research).
3. Places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Examples of unanticipated problems may include:

1. Unusual medical events: medical events that are not considered “serious” but may be important for the study, such as a reaction to a study procedure such as spirometry, pregnancy, a suspected safety issue concerning any aspect of the trial
2. Atypical problems: examples of these include breach of confidentiality and inadvertent loss of study records.
3. Communications that need to be recorded but are not captured on other data forms.

Expected adverse events that are more frequent or severe than expected may become Unanticipated Problems

Protocol deviation*: Any change, divergence, or departure from the IRB-approved research protocol. The impact of a Protocol Deviation is characterized by designation as serious or not serious.

Examples of not serious Protocol Deviations include, but are not limited to:

1. Scheduling a protocol visit slightly outside of the timing in the protocol, but at a time that would not compromise the interpretation of the study data or impact the health of the participant.
2. Inability to obtain a sample that is needed for exploratory analysis that does not impact the health of the participant.
3. Protocol specifications for clinical testing are not followed.

Examples of serious Protocol Deviations

1. The deviation has harmed or posed a significant or substantive risk of harm to the research participant. Examples include, but are not limited to: a research participant received the wrong treatment or incorrect dose or a research participant received an excluded concomitant medication.
2. The deviation compromised the scientific integrity of the data collected for the study. Examples include, but are not limited to: a research participant was enrolled but does not meet the protocol’s eligibility criteria or changing the protocol without prior IRB approval
3. The deviation is a breach of human participant protection regulations or NIH policies or procedures. Examples include, but are not limited to: failure to obtain informed consent prior to initiation or study-related procedures, performing tests or procedures beyond those anticipated in the protocol or by those not approved to perform such actions by the IRB, or falsifying research or medical records.
4. The deviation involves a serious or continuing noncompliance with applicable federal, state, local or institutional human participant protection laws, regulations, or policies, or procedures. Examples include, but are not limited to: working under an expired professional license or certification, failure to follow federal and/or local regulations, and intermural research or NIH Clinical Center policies, or repeated protocol deviations (i.e., a study site repeatedly performing a study assessment incorrectly despite recognition of the problem).

5. The deviation is inconsistent with the NIH Human Research Protection Program's research, medical, and ethical principles. Examples include, but are not limited to: a breach of confidentiality and/or privacy, or inadequate or improper informed consent procedures.

Some serious protocol deviations may place the participant at a greater risk of physical or psychological harm. In such cases, the event should be reported on the Unanticipated Problem (UP) form.

Noncompliance:* The failure to comply with applicable NIH HRPP policies, IRB requirements, or regulatory requirements for the protection of human research participants. There are three types of non-compliance:

1. Serious non-compliance: Non-compliance that: increases risks, or causes harm to participants, decreases potential benefits to participants, compromises the integrity of the NIH HRPP, or invalidates the study data.
2. Continuing non-compliance: Non-compliance that is recurring. It could also include a failure to respond to IRB requests to resolve previous allegations of non-compliance.
3. Minor (non-serious) non-compliance: Non-compliance that is neither serious nor continuing.

*NIH HRPP SOP 16 v2 (10/1/13), Reporting Requirements for Unanticipated Problems, Adverse Events and Protocol Deviations

† National Institutes of Health, Office of Human Subjects Research, Adverse Event Reports, May 26, 2000, Appendix 2

‡ US Department of Health and Human Services, Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events, January 15, 2007

12.4.2. Event reporting

Adverse events may occur over the course of a study. Site personnel are responsible for documenting all adverse events and problems in the study database regardless of severity or other characteristics. To meet PTC reporting requirements, all adverse events regardless of severity must be classified by organ systems involved and reported as part of the DSMB reports.

Some adverse events and problems require expedited reporting to regulatory agencies. Site PIs are required to promptly report all serious adverse events (SAEs) and unanticipated problems to the study DCC, including an assessment of relatedness and expectedness.

Dr. Robert Wise is the Medical Monitor for the LEEP PLG, and he is responsible for the review of serious and unexpected adverse events across the study. The MM should remain masked to the treatment assignment while making his/her evaluation of the serious adverse event.

At a minimum, DCC's must send all unexpected SAEs to the study MM for final assessment of relatedness and expectedness. The MM may provide feedback on prognosis and treatment. In all cases, the MM's assessment determines the reporting requirements.

Figure 1 describes the process site PIs should follow in classifying adverse events and determining the action required. Events in this figure are labeled as those that require Systematic Reporting (SR) and those that also require Expedited Reporting (ER).

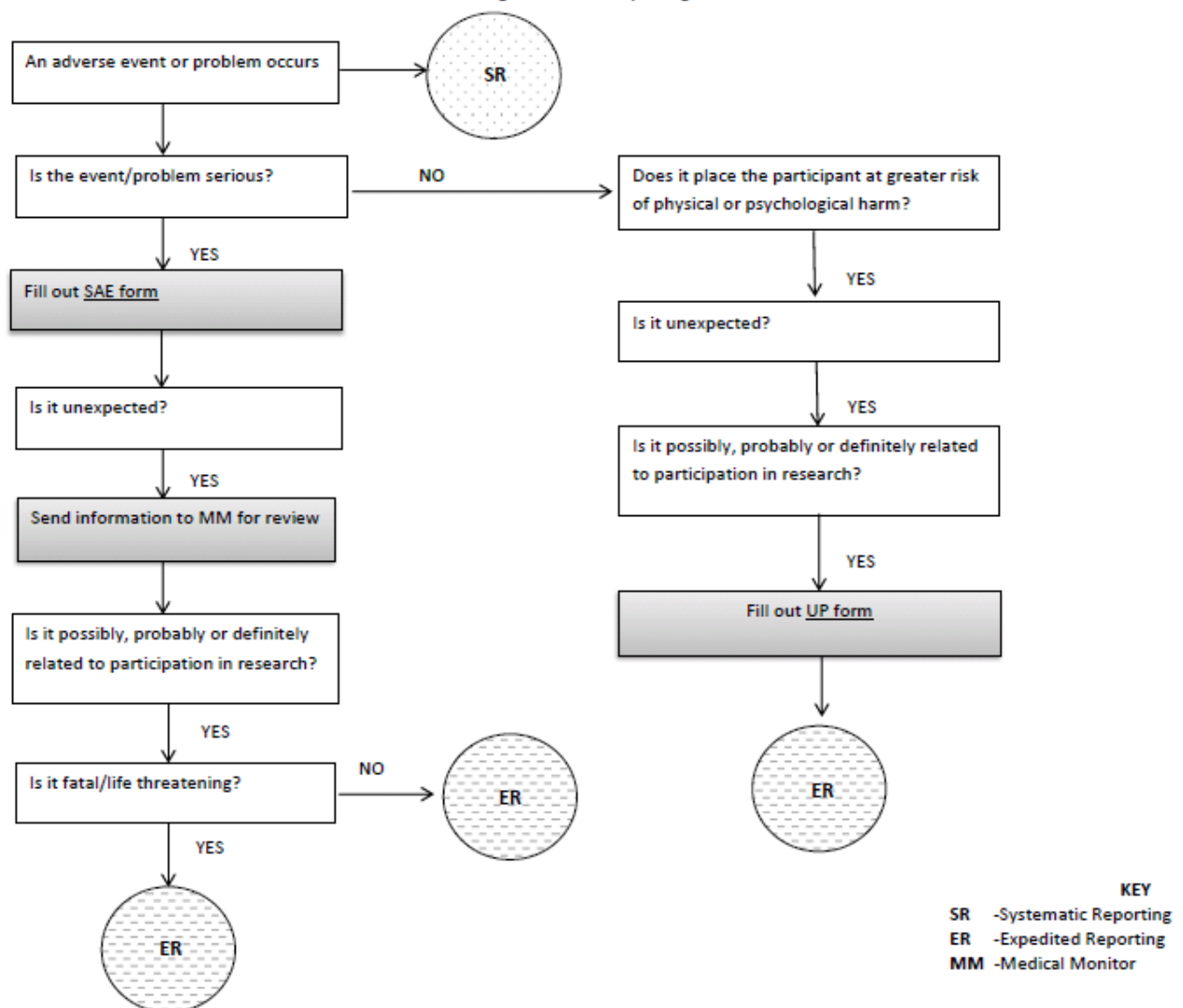
12.4.2.1. Systematic adverse event reporting

All adverse events (serious and non-serious) and unanticipated problems must be reported to the DSMB and NEMO on a regularly scheduled basis (such as the semi-annual DSMB meetings and as data for the NEMO quarterly reports). This includes events and problems previously reported to the DSMB through expedited reporting.

Protocol deviations that are not serious are reported on the Protocol Deviation (PD) form.

Protocol deviations that are serious (e.g., involve increased risk) are reported as unanticipated problems in an expedited manner (see below).

Figure 1: Event Reporting Flowchart



12.4.2.2. Expedited event reporting procedures

There are three classes of events that need to be reported in an expedited manner. These are also presented in Figure 1.

- (i) Fatal or life threatening unexpected SAE
- (ii) Non-fatal, non-life threatening unexpected SAE
- (iii) Unanticipated problem

The process for expedited reporting for SAEs is summarized in Figure 2. The assigned study staff member should fill out an SAE form whenever the event is deemed serious in nature. In cases where the event is not serious but places the participant at greater risk of physical or psychological harm, and is both unexpected and possibly related to the study, the assigned study staff member should fill out an Unanticipated Problem (UP) form. The process for expedited reporting for UPs is summarized in Figure 3.

The completed SAE and UP forms should be sent to the Study DCC within 24 hours. In the case of SAE forms, staff at the study DCC should then forward this form along with relevant patient history such as comorbidities, to the study's medical monitor for review.

Following the medical monitor's feedback on the expectedness and relatedness of the SAE, the study DCC should complete an SAE Report incorporating the event details and the medical monitor's feedback. This report should be sent to the NEMO who will forward it to the DSMB and NHLBI. The study DCC should ensure that the NEMO receives the SAE narrative at least 24 hours prior to when it is due to the regulatory authorities. All reporting should follow the timelines shown in Figures 2 and 3. For further details on reporting timelines, refer to <http://www.nhlbi.nih.gov/research/funding/human-subjects/adverse-event>

Upon receipt of the expedited report, the DSMB members will decide whether the event should be a) discussed at the next scheduled DSMB meeting or b) discussed as soon as possible at an ad hoc meeting.

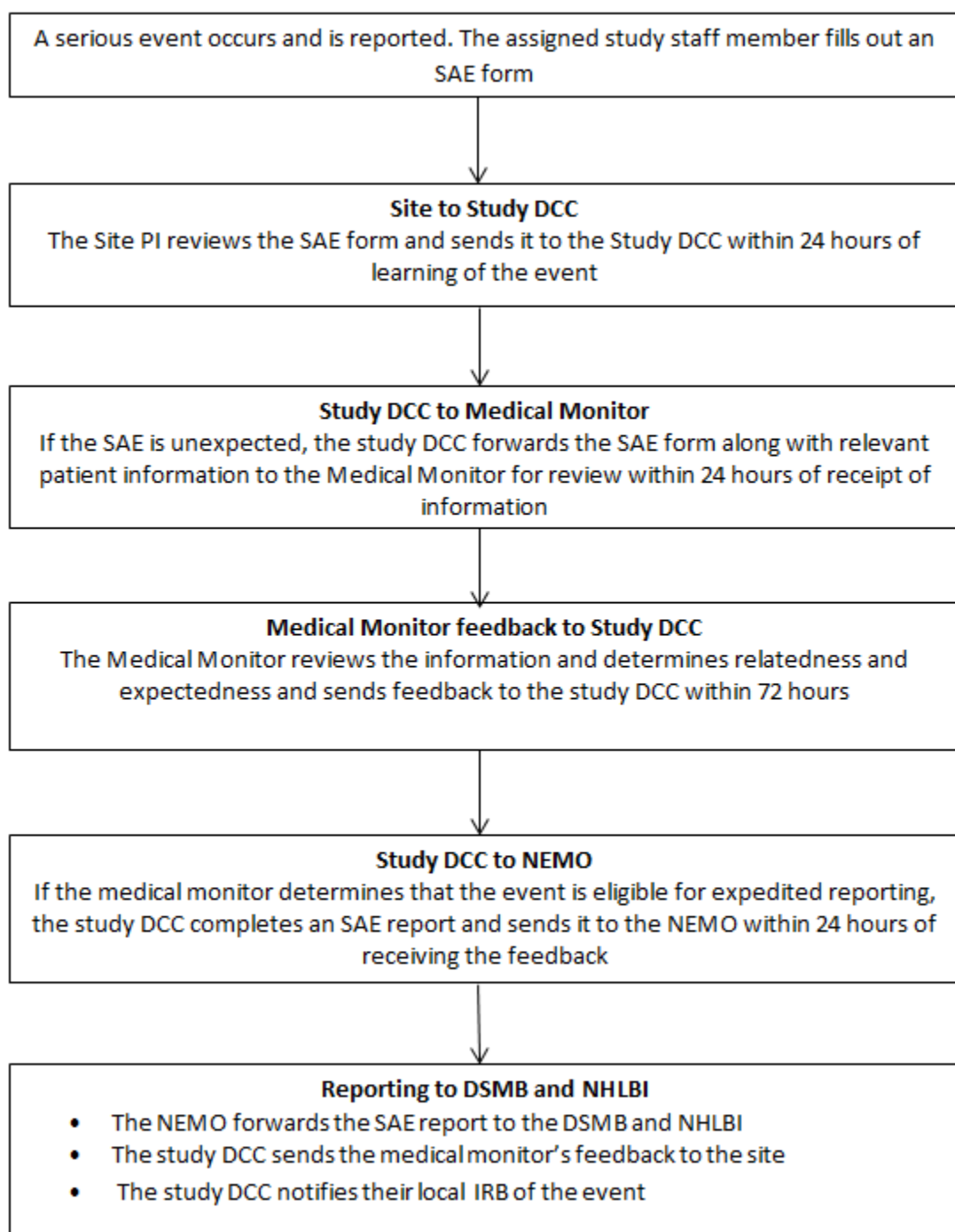
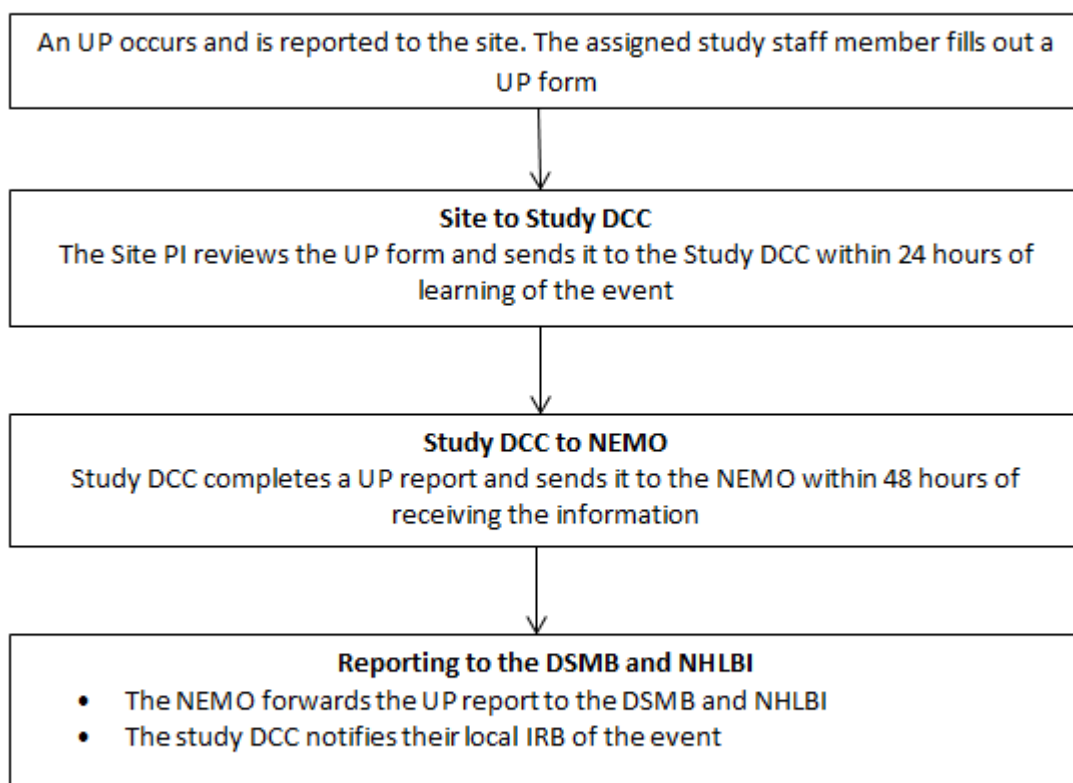
Figure 2: Steps in expedited reporting of SAEs

Figure 3: Steps in expedited reporting of UPs

12.4.2.3. Pregnancy reporting

Participants who become pregnant are to **STOP** study drug; staff must complete the Treatment Termination (TT) form. However, if the participant has been randomized, she should continue to complete all remaining study visits; pregnant participants will **not** have HRCT scans done.

Pregnancies require documentation

- Document pregnancy on the Clinic Visit (CV) form in the appropriate section.
 - Pregnancies in LEEP should be reported using the Unanticipated Problem (UP) form. To update, edit the original Unanticipated Problem (UP) form.

Follow-up information is to be added when:

- the pregnancy has ended (via birth, miscarriage, or termination) or
- if there has been a significant* change in the patient's condition or
- if the physician's judgment regarding the event has changed.

 **Note:** The Study Physician should use his/her judgment in deciding what is significant.

- Any pregnancy outcome other than normal live birth must be reported as an SAE (SR)

NEVER perform an HRCT scan on a pregnant or nursing mother

Forms (abbreviation)

- Clinic Visit (CV) form
- Serious Adverse Event (SR) form
- Unanticipated Problem (UP)
- Treatment Termination (TT) form

12.5. Quality assurance

12.5.1. Data checks

Data for the study will be entered from data forms into an online data system. The data system works with Microsoft Internet Explorer on computers running Microsoft Windows (Newer versions of Internet Explorer may need to operate in “Compatibility View” in order to access the LEEP data system, refer to Data System Manual.). The user interface employs standard web controls and does not require any additional software to be installed. The user's browser must have JavaScript enabled.

Data validation consists of four distinct levels

1. Field-level validation upon entry of each data element
2. Double-data-entry requiring duplicate entry of form and resolution of any inconsistencies
3. Intra-form validation permitting logic-checking between fields on a single form
4. Inter-form validation with logic-checking across fields on different forms

All validation is completed before data is committed to the study database. The data system employs redundant data storage, in both a flat text format and Microsoft .MDB format, with complete date-stamped storage of all changes for full audit reports.

The data system also features a Data Quality Query (DQQ) Management function to allow for feedback to clinics regarding data entries that are incorrect or questionable. Samples of data forms will be audited to ensure consistency between the source documents and the data system; inconsistencies are added to the DQQ Management system for subsequent resolution by the clinics. DQQs are added on a regular basis and are expected to be resolved by the clinics in a timely manner.

12.5.2. Data audits and data quality queries

On-going data audits

- Periodically during and after the clinical phase of the trial, the DCC will audit clinic data
 - DCC will send an email to a clinic requesting copies of forms for particular participant(s)
 - Within 2 weeks, clinics should send copies of the requested forms via FedEx (FedEx Account number for LEEP use only is: 830192646)
 - The DCC will review the data on the paper form and compare it to entries in the data system
 - Clinics will be notified of discrepancies through the DQQ Management System or queried via email.

Data Quality Queries (DQQs)

- The DCC will generate a Data Quality Query (DQQ) for a discrepancy found during an audit. A separate DQQ is created for each discrepancy found on a form
- All DQQs will be posted on the DQQ Management System. To access the DQQ page, go to the LEEP website, <http://www.LEEPTrial.org>, and follow the link to the Data System page
- Clinics will see a message alerting them that new DQQs are posted
- Clinics should respond to the posted DQQs

- After reviewing the DQQs, investigate the problem (usually by inspecting the source document) and make any necessary changes to the data system, the paper form, or both
- Changes to the paper form must be made according to the error correction procedures outlined in MOP section 7.7.3
- Changes to the data system
 - After necessary changes to the data system and/or paper forms have been made, go to the DQQ page, click on “View/Edit DQQ” choose one of the available options to indicate how the DQQ has been resolved (i.e., data system edited, data form altered, etc.), and click “Submit” button. The DQQ will be removed from the clinic’s DQQ list
 - Contact the DCC if there are questions concerning the proper resolution of a DQQ
- Many coordinators find it easiest to go to the DQQ page, print out their list of pending DQQs, investigate and resolve each one, and mark on the paper list how each DQQ has been resolved. Then, they go back to the DQQ system and mark each as resolved by choosing and submitting the appropriate response

Drug Accountability Audits

- Periodically, the DCC will request materials from centers to audit drug distribution
- The DCC will email Lead Coordinators who are responsible for submitting materials to the DCC
- The DCC will request:
 - List of IDs for all un-assigned study drug bottles currently at the clinic

First randomization audits

- The full set of forms for V1, V2, and V3 will be audited for the first participant randomization completed by a coordinator at a site
- If problems are identified, forms from the second and possibly third randomization completed by that coordinator may be audited

13. Study and site monitoring

13.1. NEMO site monitoring

Given the NEMO/Site relationship, monitoring conducted by the NEMO focuses on human subject protection and compliance, and secondarily, on site performance. NEMO monitoring efforts employs a three-tiered approach — remote data monitoring, quarterly performance metric reporting, and on-site monitoring.

13.1.1. Remote data monitoring

Sites are required to provide copies of essential documents to the NEMO. These documents are tracked in the NEMO Regulatory Tracking System, a robust relational database that flags future actions and produces timely communication to NEMO and site staff to ensure sites maintain regulatory compliance.

Routine audits of the tracking system take place to ensure any oversights or errors are acknowledged or addressed.

In addition, the LEEP PLG will review monthly summary reports (MOP section 12.2) with the NHLBI and the NEMO to identify any problematic issues and decide upon a course of action. In general, the escalation plan will be as follows:

- Initial contact with the site is made by the LEEP PLG
- If the problem persists (or applies to multiple studies within the site), the NEMO will contact the site.

13.1.2. Performance metrics

On a quarterly basis, the LEEP DCC will submit a dataset of performance metrics to the NEMO for each active site. Metrics quantify site performance in areas of regulatory compliance, patient accrual, data completeness and timeliness, and appropriate handling of adverse and unexpected events.

Site metrics will document activity occurring in specific timeframes:

Quarter 1: January 1st through March 31st

Quarter 2: April 1st through June 30th

Quarter 3: July 1st through September 30th

Quarter 4: October 1st through December 31st

13.1.3. On-site monitoring

Monitoring visits occur on a rolling basis using a risk based monitoring approach. If concerns are raised about a site's performance through remote data monitoring or sub-par performance metrics, an on-site monitoring visit may be required.

Site Monitoring Visits (SMV) are conducted in accordance with applicable sections of Title 21 of the CFR as outlined below.

The objectives are to:

- Document and report on clinical study progress
- Document that the protocol and associated forms are current
- Update the site team of any changes in study conduct/documentation
- Ensure PTC requirements and investigator obligations are met
- Ensure continued acceptability of the Investigator, his/her team, and facility
- Ensure adequate IP inventory and storage, including ensuring that only trained personnel dispense and administer study drug.

Prior to an SMV the Site Monitor:

- Contacts the Site Investigator or Study Coordinator to schedule a date and time for the visit. A proposed schedule is provided including a list of documents to be reviewed, outstanding issues requiring resolution, and the study personnel required at the visit.
- After scheduling, a letter is sent to the Site PI and site personnel confirming date, time, and location of the visit, the purpose of the visit, the site personnel who are required to attend, and contact information for the Site Monitor. A copy of this letter is retained in the Trial Master File (TMF) and should be placed in the site regulatory binder.
- Review the regulatory tracking information maintained by the NEMO and list any outstanding essential documents.
- Review previous visit reports, correspondence, serious adverse event forms, and any other relevant material, and prepare a list of outstanding issues that require resolution.

The Site Monitor performs the following monitoring activities during the SMV:

- Review the Site Regulatory Binder
 - Sign and date the Monitoring Visit Log each day of the visit
 - Verify that all required study documents are present in their current and prior versions
 - Retrieve any new or revised essential regulatory documents
 - Provide the site with copies of any missing documents
- Safety Reporting
 - Confirm that all AE/SAE's have been reported to the IRB and sponsor, as required.
 - Verify submission of safety reports and DSMB reports to the IRB, as appropriate.
- Investigator and Site Personnel Responsibilities
 - Review the Staff Signature and Delegation of Authority Log and ensure that it is complete and up-to date. If revisions have been made, obtain a copy.
 - Review Site PI and site personnel responsibilities with the appropriate site personnel, as applicable

- Verify that the Site PI and site personnel are adhering to the protocol and conducting the study according to FDA regulations, ICH GCP, and any applicable regulatory requirements
 - Provide and document any needed Site PI and site personnel training
- Laboratory and Outcome Measure Supplies
 - Verify that laboratory certifications and reference ranges are current and present in the site regulatory binder.
- Investigational Product (IP)
 - Review IP records.
 - Verify that IP storage conditions are secure and acceptable.
- Facilities Review
 - Conduct ongoing review/assessment of the facilities, ensuring that the facility or facilities remain adequate for study participation
 - Ensure that the site has adequate clinical trial materials and that storage conditions are secure and adequate
 - Review temperature and shipping documentation of biosamples
- Visit Conclusion
 - Meet with Site PI and site personnel to ensure they are adequately informed about the trial.
 - Discuss any site deficiencies or outstanding items.

After each SMV the Site Monitor:

- Places any documents obtained during the SMV in the TMF and logs them into the NEMO Regulatory Tracking System
- Provides a SMV report to the NEMO PIs, LEEP PIs, TMF, Site PI, and site personnel listing any pending actions and any general concerns
- Works with the Site PI and site personnel to resolve any pending actions
- Provides guidance to the communication committee regarding frequent issues identified at SMVs. These may be placed in newsletters.

13.2. LEEP DCC site monitoring

The LEEP DCC will focus their monitoring efforts on review of trial data as outlined below:

- Informed Consent Review
 - Review ICFs for all subjects
 - Confirm the presence of an original IRB approved informed consent form presented in a language understandable to the signer and signed and dated by each subject or legally authorized representative (LAR), the site personnel obtaining consent, and the Site PI
 - Ensure that each consent form is signed and dated by the study subject prior to any study procedures being performed
 - Verify that the appropriate version of the ICF and any ICF Amendments have been signed and dated by each subject or LAR, the site Personnel obtaining consent, and the Site PI and that the consent process is documented appropriately in the subject source record

- Verify that the site personnel who signed the ICF are listed on the Staff Signature and Delegation of Authority Log and have been delegated to this responsibility by the Site PI
- Outcome Assessment Verification
 - Verify that only site personnel who have successfully completed the associated training are performing outcome assessments as required by the protocol
- Source Document and CRF/EDC Review
 - Review a specified minimum percent of source documentation and electronic case report forms of study visits
 - Confirm the current status of each subject
 - Verify that accurate, complete, and current source documentation for each subject, who has signed the ICF, is being maintained by the site
 - Verify that all subjects enrolled since the last monitoring visit meet the in/exclusion criteria as defined in the protocol
 - Verify that all missed visits, clinical procedures, and tests are recorded appropriately and reported to the IRB as protocol deviations, as applicable
 - Verify that all AEs, concomitant medication, and intercurrent illnesses are documented and reported according to the protocol
 - Verify that all withdrawals and dropouts of enrolled subjects are recorded in the source documentation and reported in the CRFs
 - Ensure that the Site PI reviews and signs completed CRFs after the last correction to the CRF is made
- Safety Reporting
 - Review the source documentation for any unreported AEs/SAEs
 - Follow-up on previously reported SAEs
 - Verify the data recorded in the source documentation against the data recorded on the SAE forms and the electronic case report forms
- Protocol Deviations
 - Verify that all protocol deviations discovered during the monitoring visit are documented and explained in the source document.
 - Determine whether waivers were granted prior to the occurrence of the protocol deviation
 - Ensure that appropriate documentation of the waiver is present at the site
 - Instruct the site to comply with its IRB requirements for reporting protocol compliance issues.
- On-Site Data Corrections
 - Verify that only authorize site personnel, as documented on the Staff Signature and Delegation of Authority Log, complete necessary changes to the source using proper correction techniques.
- Laboratory and Outcome Measure Supplies
 - Review laboratory reports or out-of-range values
 - Verify that all laboratory results have been reviewed in a timely manner, and are signed and dated by the Site PI.
 - Verify that the Site PI has included comments about the clinical significance of out of range values.

14. Publications procedures and policies

14.1. LEEP specific guidelines

Mainline publications will be authored by a writing committee composed of the Principal Investigator of the participating site and representation from the LEEP DCC and ALA.

Proposals for secondary manuscripts can be submitted to the LEEP PLG by using the Publication proposal (PR) form.

Please follow the guidelines below when working on publications:

- Site PIs, the Study Chair and the NEMO should be included as co-authors.
- The acknowledgements section is to include an acknowledgement of the members of the DSMB.
- The title of each publication or presentation should include the name of the PLG and the Pulmonary Trials Cooperative (Title of the article: LEEP PLG, Pulmonary Trials Cooperative).
- When using corporate authorship, please format as follows: "By the American Lung Association Airways Clinical Research Centers and the NIH-NHLBI Pulmonary Trials Cooperative.
- When using a list of authors, please format as follows: Name 1, Name 2, etc. for the LEEP PLG of the Pulmonary Trials Cooperative
- The primary outcome paper for LEEP will include a credit roster, which will include all investigators, lead coordinators, DSMB members and NEMO investigators and key staff. If over the course of the study, a given clinical site has had multiple PIs and/or coordinators, the names are listed alphabetically with each classification

Once approved by the LEEP DCC, all publications and presentations must be approved by the PTC Operations Committee. To ensure that timely feedback can be provided, any drafts of publications and presentations must be submitted to the PTC Operations Committee one month prior to any deadline.

14.2. Cross study

Members of the PTC, either the NEMO or from a PLG, may be interested in combining data across PLGs for a secondary data analysis. Such secondary data analyses may be requested at any time during the course of the PTC. All requests should be submitted to the NEMO at PulmonaryTrials@EDC.PITT.EDU. The NEMO is responsible for distributing the request to the PLGs for review. All reviews occur within one month. If questions exist, they are sent by the PLG directly to the individual requesting data, with a copy to the NEMO and the PIs of any other PLG involved in the data request. Upon approval by the PLGs, the request is reviewed by the PTC Operations Committee.

Once approved, those making the request are responsible for interacting with the PLGs to obtain the necessary data and relevant documentation.

Those requesting data are only to analyze, publish and present data with respect to the request that was made. Only one active request for a given individual may be open at any given time before another request has been made. An open request is defined as a formal request has

been submitted to the NEMO and the data have been submitted for publication in a peer-reviewed journal (note, submission of an abstract is not sufficient for a request to be considered closed). As appropriate, publication policies for each PLG should be applied to any publication.

14.3. Industry collaboration

There are two primary routes for private industry to collaborate with the PTC:

- Providing funding to conduct a study
- Providing materials for a study

If a potential industry partner is interested in collaborating with the PTC, the potential partner would need to go through the NEMO to coordinate.

A PLG may receive materials to aid in the conduct of the study and reduce the overall cost of the study. This may be through providing drug, technology, or service at no or a reduced cost. In this instance, it is the responsibility of the PLG to ensure that all interactions meet with NIH standards and that the procedures are in place to ensure that the academic integrity of the research study is maintained.

15. Ancillary studies

Proposals for ancillary studies should be submitted to the LEEP PLG for review and approval. Once funding for the ancillary study has been secured and before the ancillary study is to be implemented, the protocol must be review and approved by the PTC Data and Safety Monitoring Board.

The review of an ancillary study application is to include feedback from the NEMO on two aspects:

- The burden of the clinical sites to collect the new data
- The adequacy of the funds to be provided to the site for the collection of the additional information

Upon approval, all ancillary study applications must be approved by the PTC Operations Committee. To ensure that timeliness of feedback can be provided, any ancillary study application must be submitted to the PTC Operations Committee one month prior to any submission deadline.

All ancillary studies must acknowledge the LEEP PLG, the ALA, and the PTC in any publication or presentation related to the ancillary study.

Any approved ancillary study to LEEP has access to resources available through the NEMO (e.g., biospecimen repository). During the development of the ancillary study application, the ancillary study investigators should contact the NEMO to identify needs and associated costs.

16. References

- 1 US Burden of Disease Collaborators. The state of US health, 1990-2010: burden of diseases, injuries, and risk factors. *JAMA*. 2013 Aug 14;310(6):591-608.
- 2 Anthonisen NR, Connett JE, Murray RP. Smoking and lung function of Lung Health Study participants after 11 years. *Am J Respir Crit Care Med*. 2002;166(5):675-9.
- 3 Anthonisen NR, Skeans MA, Wise RA, Manfreda J, Kanner RE, Connett JE; Lung Health Study Research Group. The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial. *Ann Intern Med*. 2005;142(4):233-9
- 4 Mancini GB, Etminan M, Zhang B, Levesque LE, FitzGerald JM, Brophy JM. Reduction of morbidity and mortality by statins, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers in patients with chronic obstructive pulmonary disease. *J Am Coll Cardiol*. 2006 Jun 20;47(12):2554-60
- 5 Mancini GB. The 'double dip' hypothesis: simultaneous prevention of cardiovascular and pulmonary morbidity and mortality using angiotensin II type 1 receptor blockers. *Can J Cardiol*. 2005; 21(6):519-23
- 6 Andreas S, Herrmann-Lingen C, Raupach T, Lüthje L, Fabricius JA, Hruska N, Körber W, Büchner B, Crieé CP, Hasenfuss G, Calverley P. Angiotensin II blockers in obstructive pulmonary disease: a randomised controlled trial. *Eur Respir J*. 2006;27(5):972-9
- 7 Wang R, Alam G, Zagariya A, Gidea C, Pinillos H, Lalude O, Choudhary G, Oezatalay D, Uhal BD. Apoptosis of lung epithelial cells in response to TNF-alpha requires angiotensin II generation de novo. *J Cell Physiol*. 2000;185(2):253-9
- 8 Papp M, Li X, Zhuang J, Wang R, Uhal BD. Angiotensin receptor subtype AT(1) mediates alveolar epithelial cell apoptosis in response to ANG II. *Am J Physiol Lung Cell Mol Physiol*. 2002;282(4):L713-8
- 9 Yoshida T, Tuder RM. Pathobiology of cigarette smoke-induced chronic obstructive pulmonary disease. *Physiol Rev*. 2007 Jul;87(3):1047-82
- 10 Neptune ER, Frischmeyer PA, Arking DE, Myers L, Bunton TE, Gayraud B, Ramirez F, Sakai LY, Dietz HC. Dysregulation of TGF-beta activation contributes to pathogenesis in Marfan syndrome. *Nat Genet*. 2003; 33(3):407-11
- 11 Habashi JP, Judge DP, Holm TM, Cohn RD, Loeys BL, Cooper TK, Myers L, Klein EC, Liu G, Calvi C, Podowski M, Neptune ER, Halushka MK, Bedja D, Gabrielson K, Rifkin DB, Carta L, Ramirez F, Huso DL, Dietz HC. Losartan, an AT1 antagonist, prevents aortic aneurysm in a mouse model of Marfan syndrome. *Science*. 2006; 312(5770):117-21
- 12 Podowski M, Calvi C, Metzger S, Misono K, Poonyagariyagorn H, Lopez-Mercado A, Ku T, Lauer T, McGrath-Morrow S, Berger A, Cheadle C, Tuder R, Dietz HC, Mitzner W, Wise R, Neptune E. Angiotensin receptor blockade attenuates cigarettes smoke-induced lung injury and rescues lung architecture in mice. *J Clin Invest*. 2012;122:229-40
- 13 Schroeder JD, McKenzie AS, Zach JA, Wilson CG, Curran-Everett D, Stinson DS, Newell JD Jr, Lynch DA. Relationships between airflow obstruction and quantitative CT measurements of emphysema, air trapping, and airways in subjects with and without chronic obstructive pulmonary disease. *AJR Am J Roentgenol*. 2013;201:W460-70
- 14 Hansel NN, Washko GR, Foreman MG, Han MK, Hoffman EA, DeMeo DL, Barr RG, Van Beek EJ, Kazerooni EA, Wise RA, Brown RH, Black-Shinn J, Hokanson JE, Hanania NA, Make B, Silverman EK, Crapo JD, Dransfield MT; COPD Gene Investigators. Racial differences in CT phenotypes in COPD. *COPD*. 2013;10(1):20-7
- 15 Cerveri I, Corsico AG, Grosso A, Albicini F, Ronzoni V, Tripon B, Imberti F, Galasso T, Klersy C, Luisetti M, Pistolesi M. The rapid FEV(1) decline in chronic obstructive pulmonary disease is associated with predominant emphysema: a longitudinal study. *COPD*. 2013;10(1):55-61

- 16 Parr, D.G., Stoel, B.C., Stolk, J. and Stockley, R.A. Validation of computed tomographic lung densitometry for monitoring emphysema progression in alpha-1 antitrypsin deficiency. *Thorax* 2006; 61: 485-90.
- 17 Newell JD Jr, Hogg JC, Snider GL. Report of a workshop: quantitative computed tomography scanning in longitudinal studies of emphysema. *Eur Respir J.* 2004;23:769-75
- 18 Nishimura M, Makita H, Nagai K, Konno S, Nasuhara Y, Hasegawa M, Shimizu K, Betsuyaku T, Ito YM, Fuke S, Igarashi T, Akiyama Y, Ogura S; Hokkaido COPD Cohort Study Investigators. Annual change in pulmonary function and clinical phenotype in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2012 Jan1;185(1):44-52
- 19 McAllister DA, Ahmed FS, Austin JH, Henschke CI, Keller BM, Lemeshow A, Reeves AP, Mesia-Vela S, Pearson GD, Shiao MC, Schwartz JE, Yankelevitz DF, Barr RG. Emphysema predicts hospitalisation and incident airflow obstruction among older smokers: a prospective cohort study. *PLoS One.* 2014 Apr 3;9(4):e93221
- 20 Anthonisen NR, Connett JE, Kiley JP, Altose MD, Bailey WC, Buist AS, Conway WA Jr, Enright PL, Kanner RE, O'Hara P, et al. Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV₁. The Lung Health Study. *JAMA.* 1994 Nov 16;272:1497-505
- 21 Tashkin DP, Celli B, Senn S, Burkhart D, Kesten S, Menjoge S, Decramer M; UPLIFT Study Investigators. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med.* 2008;359:1543-54
- 22 Lung Health Study Research Group. Effect of inhaled triamcinolone on the decline in pulmonary function in chronic obstructive pulmonary disease. *N Engl J Med.* 2000 Dec 28;343(26):1902-9
- 23 Stolk J, Putter H, Bakker EM, Shaker SB, Parr DG, Piitulainen E, Russi EW, Grebski E, Dirksen A, Stockley RA, Reiber JH, Stoel BC. Progression parameters for emphysema: a clinical investigation. *Respir Med.* 2007;101(9):1924-30
- 24 Stockley RA, Parr DG, Piitulainen E, Stolk J, Stoel BC, Dirksen A. Therapeutic efficacy of α -1 antitrypsin augmentation therapy on the loss of lung tissue: an integrated analysis of 2 randomised clinical trials using computed tomography densitometry. *Respir Res.* 2010 Oct 5;11:136
- 25 Stolk J, Cooper BG, Stoel B, Rames A, Rutman O, Soliman S, Stockley R. Retinoid treatment of Emphysema in Patients on the Alpha-1 International Registry. The REPAIR study: study design, methodology and quality control of study assessments. *Ther Adv Respir Dis.* 2010;4:319-32
- 26 Roth MD, Connett JE, D'Armiento JM, Foronjy RF, Friedman PJ, Goldin JG, Louis TA, Mao JT, Muindi JR, O'Connor GT, Ramsdell JW, Ries AL, Scharf SM, Schluger NW, Sciurba FC, Skeans MA, Walter RE, Wendt CH, Wise RA; FORTE Study Investigators. Feasibility of retinoids for the treatment of emphysema study. *Chest.* 2006;130:1334-45
- 27 Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CP, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J; ATS/ERS Task Force. Standardisation of spirometry. *Eur Respir J.* 2005 Aug;26(2):319-38
- 28 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;159:179-87
- 29 Garfield JL, Marchetti N, Gaughan JP, Steiner RM, Criner GJ. Total lung capacity by plethysmography and high-resolution computed tomography in COPD. *Int J Chron Obstruct Pulmon Dis.* 2012;7:119-26
- 30 Martinez CH, Chen YH, Westgate PM, Liu LX, Murray S, Curtis JL, Make BJ, Kazerooni EA, Lynch DA, Marchetti N, Washko GR, Martinez FJ, Han MK; COPD Gene Investigators.

- Relationship between quantitative CT metrics and health status and BODE in chronic obstructive pulmonary disease. *Thorax*. 2012 May;67(5):399-406
- 31 Mahler DA, Waterman LA, Ward J, McCusker C, ZuWallack R, Baird JC. Validity and responsiveness of the self-administered computerized versions of the baseline and transition dyspnea indexes. *Chest*, 2007. 132(4): p. 1283-90
 - 32 Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the COPD assessment test. *Eur Respir J*. 2009 Sep;34(3):648-54
 - 33 Aletaha, D. (2010). From the item to the outcome: the promising prospects of PROMIS. *Arthritis Research & Therapy*, 12(1), 104
 - 34 COZAAR – Losartan potassium tablets [package insert]. Whitehouse Station. NJ: Merck & Co, Inc; 2014
 - 35 COZAAR – Losartan potassium tablets [package insert]. Whitehouse Station. NJ: Merck & Co, Inc; 2014
 - 36 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;159:179-87
 - 37 Andersen PK. "Analysis of Longitudinal Data. 2nd ed." af P.J. Diggle, P. Heagerty, K.Y. Liang, S.I. Zeger. *ISCB Newsletter*. 2004;(37):5
 - 38 Chi, Yueh-Yun, and Joseph G. Ibrahim. "Joint models for multivariate longitudinal and multivariate survival data." *Biometrics* 62.2 (2006): 432-445
 - 39 Rosner, B. *Fundamentals of Biostatistics*, Sixth Edition, page 335

17. Glossary

ACE	Angiotensin converting enzyme
ACR	American College of Radiology
ARB	Angiotensin receptor blocker
AT1	Angiotensin 1
ATS	American Thoracic Society
ATS-DLD	modified American Thoracic Society - Division of Lung Disease questionnaire
BD	Bronchodilator
BMI	Body Mass Index
BP	Blood pressure
CAT	COPD Assessment Test
CBC	Complete blood count
CMP	Comprehensive metabolic panel
COPD	Chronic Obstructive Pulmonary Disease
DCC	Data Coordinating Center
DSMB	Data and Safety Monitoring Board
ERS	European Respiratory Society
FDA	US Food and Drug Administration
FEV ₁	Forced Expiratory Volume in one second
FVC	Forced Vital Capacity
GFR	Glomerular Filtration Rate
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HRCT	High resolution computed tomography
HU	Houndsfield Units
IRB	Institutional Review Board
LEEP	Losartan Effects on Emphysema Progression
LFT	Liver Function Test
MDI	Metered dose inhaler
mEq/dL	Milliequivalent/ deciliter
MID	Minimal important difference
MM	Medical Monitor
mMRC	Modified Medical Research Council
mSv	millisievert
NEMO	Network Management Core of the Pulmonary Trials Cooperative
NHANES	National Health and Nutrition Examination Survey
NHLBI	National Heart, Lung, and Blood Institute
NSAID	Non-steroidal anti-inflammatory drug
OC	Operations Committee
PLG	Protocol Leadership Group
PFT	Pulmonary Function Test
PHI	Protected health information
PTC	Pulmonary Trials Cooperative
PROMIS-20a	Patient Reported Outcomes Measurement Information System: Physical Function – Short Form 20a
RENAAL	Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan study
SAE	Serious adverse event
SD	Standard deviation
SMV	Site monitoring visit

SPO ₂	Peripheral capillary oxygen saturation
TGFb	Transforming Growth Factor Beta
TMF	Trial Master File
SGRQ-C	St. George's Respiratory Questionnaire for COPD patients
TLC	Total Lung Capacity