Genetic Epidemiology of COPD
Clinical Center Manual of Procedures

Phase 2 Study Visits

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Administrative Core
National Jewish Health

Biorepository
Brigham and Women’s Hospital, Channing Lab

Data Coordinating Center
National Jewish Health

Genotyping and Analysis Core
University of Colorado Denver Anschutz Medical Campus
Brigham and Women’s Hospital/Harvard School of Public Health
Johns Hopkins School of Medicine

Imaging Core
National Jewish Health
University of Iowa
Brigham and Women’s Hospital

Pulmonary Function Core
LDS Hospital

Clinical Centers
Ann Arbor Veterans Administration Medical Center
Brigham and Women’s Hospital
Baylor College of Medicine
Columbia University Medical Center
Duke University Medical Center
HealthPartners Research Foundation
Johns Hopkins School of Medicine and Bloomberg School of Public Health
Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center
Michael E. DeBakey Veterans Administration Medical Center
Minneapolis Veterans Administration Medical Center
Morehouse School of Medicine
National Jewish Health
Reliant Medical Group
Temple University
University of Alabama, Birmingham
University of California, San Diego
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University of Michigan
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University of Pittsburgh
University of Texas Health Science Center at San Antonio

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1. COPDGene® Study Overview

1a. Rationale

COPD is the third leading cause of death in the United States. Of the top ten causes of death, COPD is the only one that has been steadily increasing over the past decade and is one of the most devastating disease epidemics in the United States. The determinants of the development of COPD and the factors that influence its progression remain poorly understood. Although the most common cause of COPD is cigarette smoking, a minority of people who smoke develop COPD. There are individuals who are prone to develop lung disease from cigarette smoking and other individuals who are protected from the effects of cigarette smoke. This study investigates the genetic determinants associated with the development of COPD.

COPD is a heterogeneous disease; for example, some people with COPD have emphysema and others do not have emphysema. A strength of COPDGene® is the ability to identify individuals with different subtypes of COPD and to assess the genetic determinants in these more homogeneous subtypes.

The Genetic Epidemiology of COPD Study (COPDGene®), funded by the National Heart, Lung, and Blood Institute (Grants: R01 HL089897 and R01 HL089856), has created a large cohort of subjects

1) with COPD (GOLD Stages 1 - 4) (see 2013 guidelines, www.goldcopd.org),
2) without COPD but have smoked cigarettes (smoking controls),
3) without COPD or airway limitation by FEV1/FVC ratio ≥ 0.70 but present with low FEV1 (<80% predicted) (Unclassified group), and
4) without COPD and do not smoke with no airflow limitation (nonsmoking controls).

This cohort has been phenotyped physiologically (spirometry, 6-minute walk), clinically (health status, dyspnea, BODE score), and radiographically (chest CT scan) at the initial study visit. Genome-wide association analysis has been performed, and the results are being analyzed. The cohort is one-third non-Hispanic African American, and two-thirds non-Hispanic White. The size of the cohort was chosen to provide sufficient statistical power to identify genetic risk factors in both White and African-American subjects.

COPDGene® Phase 2

The second phase of COPDGene® is designed to collect longitudinal data to define change in lung function and CT characteristics in smokers with and without COPD. Questionnaires and studies performed during the first visit will be repeated. Additional data will be collected including environmental and occupational exposures, socioeconomic status, depression and anxiety, diffusing capacity, cause of death, biomarkers, exome chip genotyping and whole genome and targeted DNA sequencing.

Please note: The name COPDGene® has been registered. When using this name in printed material, the registered symbol (®) should be included as a superscript following the name.
1b. Subjects

The total number of subjects in COPDGene® at the end of Phase 1 is 10,371.

All of these subjects are candidates for a return study visit during Phase 2.

1c. Specific Aims

The initial data collected in the first visit and the Phase 2 longitudinal phenotypic, pathophysiological and genetic data will be used to accomplish the following Specific Aims for Phase 2:

1) Assess the Epidemiology of COPD Progression and Determine Which COPD Risk Factors and Subtypes are Associated with Disease Progression

We will perform repeat evaluation with spirometry, CT scans and questionnaires in all available COPDGene® subjects five years after their initial study visit, and we will continue biannual longitudinal follow-up (LFU) web-based or phone assessments for five years beyond the first visit (i.e., a total of 7-10 years of follow-up). We will evaluate relationships between baseline CT-defined phenotypes, lung function, co-morbid illnesses, environmental exposures, exacerbation frequency, and respiratory symptoms with COPD progression and mortality.

2) Identify Rare and Common Genetic Determinants of COPD:

We will perform whole exome sequencing and test for rare and common variant associations with baseline and longitudinal COPD-related phenotypes. We will perform whole genome sequencing and targeted DNA re-sequencing of subjects with distinct imaging characteristics to identify rare and common genetic variants influencing COPD susceptibility, emphysema, and airway disease.

3) Integrate Imaging, Clinical, and Genetic Data to Create a New Classification of COPD:

We will integrate common and rare genetic variant associations with clinical, physiological, biomarker, and CT-based phenotypes to develop and validate a new classification system for COPD based on pathophysiological subtypes of disease. This new COPD classification system will undergo clinical validation with longitudinal data from collaborating studies.

In addition to identifying COPD genetic determinants, we will characterize the natural history of COPD and identify well-characterized COPD subtypes. Improved understanding of COPD subtypes and genes controlling susceptibility to COPD could lead to novel pathophysiological insights, refined diagnostic criteria, and new treatment approaches. Moreover, the availability of comprehensive genetic data and longitudinal data on a large biracial group of smokers will be an invaluable national resource for other investigators.

1d. Study Structures and Websites

The COPDGene® Study has six Core Units (Administrative, Data Coordinating Center, Genotyping and Genetic Analysis, Biorepository, Imaging, and Pulmonary Function. In addition there are twenty-one Clinical Centers (See page 1).
COPDGene® Websites
There is a COPDGene® study website:

https://dccweb.njhealth.org/sec/COPDGene/MainPage.cfm

that provides study investigators, radiologists and coordinators with study documents, electronic versions of this manual of procedures, informed consent template, study protocol and directory of all study personnel. The study website is maintained by the Data Coordinating Center; see below for additional information.

There is also a COPDGene® public website:

http://www.copdgene.org/

that provides general information about the study and COPD. It provides links to related sites for subjects and interested non-participants. This website also provides a link to the LFU survey site and for study subjects to update contact information for their clinical center.
2. **Human Subject Protection**

Each site is required to submit an application to their local governing Institutional Review Board for Human Subjects (IRB). The most current version of the study protocol and template informed consent are available on the COPDGene® website [https://dccweb.njhealth.org/sec/COPDGene/MainPage.cfm](https://dccweb.njhealth.org/sec/COPDGene/MainPage.cfm).

The COPDGene® Administrative Core must approve any changes to the template informed consent form or study protocol prior to submission to the IRB. Such modifications should be sent to the COPDGene® Administrative Core in a tracked changes format as well as in final clean form. Send to Elizabeth Regan, MD, PhD, regane@njhealth.org. If required by local IRB regulations, a copy of the original application to the National Heart, Lung, and Blood Institute may be submitted along with the IRB application.

Written local IRB approval of the application is necessary before any subjects can be enrolled in Phase 2 of the study. A copy of the IRB approval letter and the approved informed consent with the local IRB stamp of approval must be transmitted to the COPDGene® Administrative Core prior to initiating Phase 2. A brief summary of any IRB-required changes should be noted in an email or accompanying letter. Clinical Centers are not permitted to enroll subjects until receipt of this information is confirmed by the COPDGene® Administrative Core.

Each site is also required to transmit updated renewal, stamped informed consent forms and IRB approval letters to the Administrative Core yearly and whenever the protocol is modified.

All study personnel are required to meet the certification requirements set forth by their local Institutional Review Board for Human Subjects.

2a. **Informed Consent Form**

The most current model informed consent form is available on the COPDGene® website [https://dccweb.njhealth.org/sec/COPDGene/MainPage.cfm](https://dccweb.njhealth.org/sec/COPDGene/MainPage.cfm). The informed consent form for each site may be modified as needed to meet local IRB regulations. Every attempt should be made not to delete any key concepts and information from the model consent, but rather information may be added as needed. Questions about IRB issues should be directed to Barry Make, MD, Clinical Center Director (makeb@njhealth.org; 303-398-1720), at the Administrative Core.

2b. **Informed Consent Process**

No procedures can be performed on any subject prior to the subject providing informed consent.

Informed consent is a *dynamic interactive process* requiring that the subject first fully understand the protocol and all COPDGene® study procedures. The subject should be provided ample opportunity to ask questions about the project and understand the nature of the procedures involved. When possible, a local site investigator should meet with subjects to answer any questions and review subject understanding of the project. Only after subject’s complete understanding of all procedures, may the subject then sign the informed consent. The local site
investigator may then co-sign the consent statement acknowledging subject understanding and consent to participate.

Although the informed consent process may be delegated to a research coordinator, the local site Principal Investigator has ultimate responsibility for informed consent.

2c. General Comments on Subject Enrollment

It is extremely important to make people who volunteer for this research project feel good about their experience in order to assure the long term success of COPDGene®. We want all subjects who help us by volunteering to have a sense that their efforts to complete the testing and expend their valuable time are appreciated by all the study personnel involved in the project.

Study coordinators have the greatest impact on the subjects since they will be contacting the subjects and spending time with them. There are a number of ways that coordinators and investigators can maximize the positive aspects of subjects’ encounters with COPDGene®. Many of these ideas will include your usual behaviors to comply with human subjects protection rules.

The importance of establishing rapport with each subject is of paramount importance to maintain long-term contact with subjects. This investigation includes additional longitudinal follow-up (LFU) by web-based or telephonic communication and additional longitudinal follow-up will be the subject of future grant applications.

Following are some techniques that should be used to ensure that subjects have a positive experience with COPDGene®.

Establish a rapport:

• Understand some of the subject’s reasons for participating and address subject’s issues if appropriate.
• Listen empathically to subject’s concerns about symptoms and limitations imposed by their COPD, other medical conditions and age.
• Get some idea of family supports and relationships as you gather information about contacts. This will also assist in obtaining information about secondary contacts.

Treat subjects with respect:

• Ask how subjects would like to be addressed. Start with formal salutation until told otherwise.
  o Keep a record of their preference in your personal notes.
• Carry on discussions of health issues in private spaces.
• Allow time for questions and explanations.
• Recognize or ask about preferences for taking rest breaks, refreshments, and scheduling.
• Be aware of cultural preferences and barriers.
Be honest without setting negative expectations including:
• Time involved for study participation.
• Discomforts and potential side effects.
• Necessity to complete all of the parts of the study visit (while recognizing that a study subject can withdraw at any time).

Be attuned to the unique needs of an older population and the impact of COPD and chronic illness. This requires the coordinator to have an understanding of COPD and other issues faced by older subjects enrolled in COPDGene. The local site investigators are appropriate providers of such education:
• Transportation problems.
• Hearing impairments.
• Fatigue.
• Anxiety.
• Shortness of breath.
• Effects of age and low oxygen on thinking and processing information.
• Mobility limitations.

Shape the visit with an eye to the future:
• Make it pleasant.
• Convey your interest in subjects as individual, unique people and your personal appreciation of their efforts.
• Keep commitments (e.g., to call back or update them about schedule changes).

Subject Continuity:
• Encourage long-term participation in COPDGene®.
• Explain what the study goals are and the importance of their current and future participation.
• Remind subjects about periodic future contacts by LFU program.
• Ask about issues/problems with periodic contacts and try to maintain reduced contact schedule rather than discontinue all contacts.
• Emphasize the importance of updating contact information including email addresses. Consider moves to more supportive levels of care such as assisted living and nursing homes over time.
• Inquire about their planning for other care needs and whether we can continue contacting subjects after hospitalization or moving to assisted living.

Acknowledge end of life issues that may be raised in response to the request to obtain information about cause of death.

Express appreciation to the subjects for their participation.
3. Data Coordinating Center (DCC)

The Data Coordinating Center is located at National Jewish Health within the Division of Biostatistics and Bioinformatics, which is headed by Douglas Everett, PhD. The DCC develops, maintains and updates the study forms for data collection, maintains the study website, receives data from the Clinical Centers and all study Cores, performs quality control of the data, and provides reports to facilitate the conduct of the study.

Contact information for other Data Coordinating Center personnel are on the study website. Questions about the protocol and manual of operations should be addressed to Elizabeth Regan MD, PhD, Associate Director, regane@njhealth.org, 303-398-1531; or Barry Make, MD, Clinical Center Director, makeb@njhealth.org, 303-398-1720.

Study Website
Essential and supplementary information about COPDGene® is located on the study website. The home page of the COPDGene® website is:

https://dccweb.njhealth.org/sec/COPDGene/MainPage.cfm

The COPDGene® study website is used to collect all information, data and tests in the study and to track transmission of spirometry and diffusing capacity results, shipment of CT scans, and shipment of blood samples. Contact information for all study personnel is on the website including Administrative Core, the Data Coordinating Center, Biorepository Core, Imaging Core, and Pulmonary Function Core. Contact information for all Clinical Center personnel is also located on the website. All changes in study personnel including additions and deletions should be reported promptly to the Administrative Core (email to: steppl@njhealth.org) at National Jewish Health. Other study information including the current study protocol, model informed consent, and manual of operations are on the website and updated as necessary.

Each COPDGene® investigator and coordinator is required to have a unique login identity and password to use the website. **Passwords and logons should not be shared with other individuals at any time during the study.** Doing study data entry under a false login is a serious breach of research ethics and may result in termination of the individual from the study. Clinical coordinators and investigators should be registered through the COPDGene® Administrative Core before they request a logon. In order to obtain your logon identity and password, please contact Ruthie Knowles (knowlesr@njhealth.org, 303-398-1878) at the Data Coordinating Center.

Quality Control
Data entry for the study is critical for good quality. Good quality data will allow accurate conclusions to be drawn from the project. Data entry must always be done based on truthful and correct responses. At no time should a coordinator, investigator or other researcher provide or upload information to COPDGene® that he or she knows or suspects is incorrect. The DCC will perform quality checks on all data and query clinical centers about inconsistent or out of range data entry.

**Responses to DCC queries should be provided promptly and always within 5 working days.**
4. Phase 2 Nonsmoker Controls

4a. Recruitment of New Nonsmoker (NS) Controls

The purpose of recruiting additional “healthy” nonsmoker controls is to assess the processes involved in normal lung aging, looking at pulmonary function, lung imaging, mortality data and comorbid disease progression over time. Nonsmoking control subjects are critical for defining genetic and pathological findings within smoking and diseased subject groups by acting as a baseline for normal pulmonary physiology within a genetically mixed and aging population.

During the recruitment process of new nonsmoker subjects, it is important to select subjects from the general population to create a “healthy” but representative subset of the general population. Therefore, it is critical to avoid recruiting subjects:

1) From urgent care facilities, hospitals, specialty clinics, and nursing homes that are likely to have excessively ill subjects
2) From homeless shelters, transitional housing areas
3) Who are spouses of current participants, due to exposure to second-hand smoke
4) Who have chronic exposure to dust, toxic chemicals, and fumes

Recruitment Ideas

- Primary Care Offices – people coming in for wellness checks and routine care visits
- Place ads, handouts, and brochures in local grocery stores, community centers, churches, fitness centers, shopping malls, dentist offices, etc.
- Friends of participants in Phase 1 who do not live with the subject and are not exposed regularly to second-hand smoke
- Radio ads, clinical center website
- Avoid using the word research in handouts, instead replace with study or project

Recruitment Goals

COPDGene® is currently approved to recruit 300 new nonsmoker control subjects for Phase 2. The overall goal, once funding is available, is to recruit up to a total of 1500 NS controls.

Subjects will be stratified by race, age, and gender to create an even distribution within the study population. We will recruit 1/3 African Americans, 2/3 Non-Hispanic Whites, between the ages of 45 to 85, with a 50:50 ratio of females to males.

<table>
<thead>
<tr>
<th>Age</th>
<th>NHW</th>
<th>AA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>F</td>
</tr>
<tr>
<td>45-54</td>
<td>0</td>
<td>0</td>
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<tr>
<td>55-64</td>
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<td>0</td>
</tr>
<tr>
<td>75-85</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Red = FULL

Figure 4-1. This table, located on the Nonsmoker Eligibility Form of the COPDGene website, dynamically displays the total number of participants recruited, organized into categories based on race, age and gender. Once a category has reached its targeted enrollment, a center will be unable to enroll a new subject with those characteristics.
4b. **Subject Inclusion/Exclusion Criteria for Non-smoker Controls**

**Inclusion Criteria**
- Age 45-85 years (for non-smokers)
- Non-Hispanic Whites and African Americans
- No smoking history as defined by less than 100 cigarettes smoked in a lifetime, less than 52 cigars smoked in a lifetime, and less than 12 oz. of pipe tobacco smoked in a lifetime
- No airflow limitation defined as pre-bronchodilator FEV1/FVC ≥ 0.70, FEV1 > 80% predicted

**Exclusion Criteria**
- Respiratory disorders (including, but not limited to, COPD, asthma, diffuse bronchiectasis, cystic fibrosis, or interstitial lung disease)
- Any lung surgery
- Lung cancer
- History of Pneumothorax
- Pleural procedure (including, but not limited to, chest tube placement, pleural surgery)
- History of any pulmonary procedures: diagnostic bronchoscopy, lung biopsy, except research bronchoscopy
- Uncontrolled cancer, as defined as ongoing radiation therapy, ongoing chemotherapy, narcotics for pain control, or known metastatic disease
- History of radiation therapy to the chest (other than radiation for breast cancer)
- Subjects receiving treatment for active TB
- Severe cirrhosis
- Renal disease requiring dialysis
- Pulmonary Hypertension
- Congestive heart failure
- Inability to use albuterol
- First or second-degree relative (parent, brother, sister, daughter, son, aunt, uncle, nephew, niece, half-sibling, grandparent, grandchild) of a subject enrolled in COPDGene®
- Subjects who indicate they are in more than one racial category
- Subjects who do not authorize the storage of personal identifiers (social security number, name, address, phone number) in the COPDGene® Data Coordinating Center
- Metal objects that may interfere with chest CT quantification including presence of a cardiac pacemaker, defibrillator, metal prosthetic heart valve, metal projectile or metal weapon fragment (bullet, shrapnel, shotgun shot) or metal shoulder prosthesis
- Inability to provide personal telephone contact number(s) and complete information for two additional contacts (next of kin, relative or close friend, not living with subject)
4c. Subject Identification Number

As the required first step, a Subject Identification Number (SID) should be obtained for new nonsmoker controls. This MUST be done before a subject is seen for an in-person Study Visit and prior to completing a preliminary Eligibility Form with a subject.

Assignment of a SID does not necessarily indicate that the subject has signed an informed consent or that the subject has been enrolled in COPDGene®. By requiring a Subject Identification Number in all potential subjects that are screened, we will be able to assess the number of control subjects excluded from enrolling in the study and the reason for this exclusion.

Each subject who participates in screening either in person or over the phone should be given a unique SID. The following process should be followed to obtain a SID.

1) Log on to the study website using a computer with a secure Internet connection. The location to obtain a study ID number is:

   https://dccweb.njhealth.org/sec/COPDGene/sm/register.cfm

   [Alternately, you may log in to the study site home page and then choose “Forms” and under the New Nonsmokers column, select “New Subject ID.” Use the login name and password provided to you by the Data Coordinating Center (DCC).]
The subject ID consists of a 5-digit number followed by a character. The character is a check-digit that catches transposition of numbers in the numeric portion of the ID. In order to facilitate identification of the Center at which a subject is enrolled, a 3-character Clinical Center prefix is attached automatically to the ID: for example, NJC_99999Z. The subject ID number is generated by the Data Coordinating Center.

2) Fill in the information requested in order to receive a Subject Identification Number.

3) When an ID number is assigned, print the page with the ID number and keep this information with the source documents at your site for future reference.

4d. Preliminary Study Visit Procedures

First, obtain a Subject Identification Number. A Preliminary Eligibility Assessment may be completed prior to the Study Visit, if approved by your Clinical Center IRB. This may be done at the first contact with a potential subject by phone or in person. Use of this form will reduce the number of ineligible subjects unnecessarily scheduled for a Study Visit. Check on the “Preliminary” button on the Form only when entering information for screening prior to an in-person Study Visit. This information may be saved for later review and should also be printed as a source document.

To save the preliminary information, check the box to confirm you have reviewed all responses, and then click on “Save Preliminary.” If preliminary data is entered, this information can be retrieved at a later time for that subject, as long as it has been saved. To retrieve the Preliminary Eligibility Assessment, re-enter the subject ID, select “Preliminary screening,” and click on “Edit Preliminary.” The data entered previously for this subject will be shown on the screen.

Use of a preliminary eligibility form will ensure that new non-smoker subjects are reserved enrollment in the applicable age, race, and gender group. In the event that enrollment for a certain group becomes full, having a preliminary eligibility in the system will ensure the subject can proceed with the visit, as long as they meet all other eligibility requirements.

4e. Final Eligibility Assessment

A Final Eligibility Assessment must be performed to ensure the subject is still eligible and that information has not changed since the time of the Preliminary Eligibility Assessment.

When completing a Final Eligibility Assessment on the website, the study coordinator should perform this assessment one-on-one with the participant during the Study Visit. The coordinator will have to obtain the subject’s actual height and weight for entering on the final eligibility assessment form. This step is required before any questionnaires are administered, before spirometry, and prior to any testing. This form incorporates the inclusion and exclusion criteria for the study and certifies that subjects are eligible for the study prior to any evaluations. Subjects who do not pass the Final Eligibility Assessment are considered to have failed screening.

Even if a Preliminary Eligibility Assessment was completed prior to the in-person Study Visit, a Final Eligibility Assessment MUST be completed with the patient after the informed consent is
obtained to assure it is accurate and correct. Actual height and weight measured at the clinical center must be entered onto the final eligibility. **Do NOT click the FINAL button until you are ready to reenter all of the eligibility information. Clicking on FINAL will clear all data.**

Follow this process for the Final Eligibility Assessment during the in-person Study Visit.

a. From the study site home page, choose “NS Eligibility” on the left hand side of the page
b. Enter the subject ID and click on “Final.”
c. Complete all fields.
d. At the bottom of the form, there is a checkbox to confirm the data has been reviewed (to reduce input errors). Confirm you have entered the information correctly and click on the “Confirm” button.
e. This will then bring up the Print and Submit buttons.
f. “Print” the form for your on-site records
g. “Submit” the form to the DCC.

4f. **Assignment of Nonsmoker Controls to Study Group**

Subjects must first read and sign the Informed Consent form, and complete the Safety Assessment and Demographics and Physical Characteristics forms prior to conducting the spirometry test.

Once subjects have passed the Final eligibility assessment, they must also receive normal results on spirometry, indicating no airflow limitation, to be included in the study. Unlike Phase 1, the new non-smoker controls will not be assigned to separate study groups based on spirometry results. If a non-smoker control is found to have airflow limitation, the subject is excluded from the COPDGene® study. A Discontinuation form must be completed.

Follow this process for the Assignment of nonsmoker controls:

a. From the study site home page, choose “Forms” on the left hand side of the page. Select “Assign Nonsmokers” under the heading, New Nonsmokers
b. Complete all fields using the pre-bronchodilator test results. If the subject has a pre-bronchodilator FEV1/FVC ≥ 0.70, FEV1 > 80% predicted, they meet the inclusion criteria.
c. Once you have entered all values into the form, “Submit” the form to the DCC.
d. Once the form is submitted to the DCC, participants who are found to have no airflow limitation determined by FEV1/FVC ≥ 0.70, FEV1 > 80% predicted, will be included as a non-smoker control for Phase 2.
e. If a participant is found to have values that indicate airflow limitation, these subjects will be automatically excluded from the study.

4g. **Study Visit Procedures for NS Controls**

The nonsmoker control study visits will follow the same steps and procedures as the standard study visits.
Note: There are specific forms and questionnaires that are to be used for the nonsmokers. Please make sure to use the correct forms for NS controls and to download new forms before every study visit.

The nonsmoker specific forms include the Medical History, Respiratory, Residential and Occupational Health, and Socioeconomic questionnaires. These are located under the New Nonsmokers column of the “Forms” page. All other forms are applicable to both Phase 2 return subjects and new nonsmoker control subjects.

4h. Order of Procedures for NS Controls

Prior to the Visit
1. Obtain a Subject ID
2. Complete Preliminary Eligibility with Subject ID

At the Visit
1. Subject signing of Informed Consent and Informed Consent and Permissions Granted Form
2. Obtain actual height and weight on subject (will be recorded on Final Eligibility as well as Demographics and Physical Characteristics Form).
3. Final Eligibility, Stop if subject BMI >35 (exclusion criteria)
4. Pregnancy Test, if applicable
5. Demographics and Physical Characteristics Form
6. Safety Assessment Form
7. Pre-Bronchodilator Spirometry
8. GOLD Assignment
   a. STOP if subject ineligible due to airflow limitation (inclusion) or BMI >35, and complete a Discontinuation Form
   b. If subject qualifies after GOLD assignment proceed to rest of visit
9. Post-BD Spirometry
10. DLco
11. Remaining questionnaires, Six Minute Walk, Blood Sampling, CT.

4i. Longitudinal Follow-up for NS Controls

Nonsmoker controls will be enrolled into the Longitudinal Follow-up System and coordinators will follow the same procedures as they would for all other study participants. Once you have a new SID and have collected subject contact information, (subject first and last name, a primary and secondary phone number if available, an email address if available, an optional email password for accessing the Web Survey, and an option for manual contact only), you will need to update the Master Excel Spreadsheet for the LFU web system monthly uploads. The Clinical Coordinator will maintain the subject follow-up by adding any newly enrolled NS subjects to a Master Excel document that contains all subjects for that site. Clinical Coordinators will also be responsible for amending the Master Excel document when new information on the subject becomes available. The LFU System cannot amend the Master spreadsheet automatically. It will be important to remember to update this spreadsheet for each new nonsmoker subject enrolled.
Obtaining an email address on the COPDGene® subjects greatly enhances the process of maintaining longitudinal contacts and makes it easier to get these updates on the subjects’ health. Please explain to the subject the advantage of providing information for LFU by the website. We find that this is faster for subjects to complete than the automated phone calls if the subjects are comfortable with a computer. Although unwillingness to participate in the LFU is not a formal exclusion from the study, we do not want to enroll subjects who are unwilling to continue long-term participation in the COPDGene® study since it is a longitudinal study.

Please follow the LFU Coordinator Guide, Section 8 of the MOP, for greater details on the LFU system.

4j. **Blood Shipment**

Each center will receive pre-assigned New Subject IDs to use for the new nonsmoker subjects. Channing Laboratory will provide pre-printed labels and tube kits, identical to the kits for the return subjects, for the NS controls. Channing Lab will clearly mark these kits as New Subjects so they are distinguishable from the return subject kits.

If a subject is assigned an ID but is later found to be ineligible for the study, this ID number is no longer usable. Please do not discard. Save in an envelope and ship the used subject ID label back to the Biorepository (can include with a future blood shipment). The extra supplies can be discarded or saved for extras.

4k. **Study Visit Payments**

New nonsmoker controls will be reimbursed the same amount as the return study subjects ($75). They must complete all study visit procedures, including the CT scan, blood draw, completing all forms and questionnaires, and permitting the transfer of personal identifying information to the DCC.
5. Study Procedures

5a. Subject Tracking General Information

Subjects in the COPDGene® study have had an opportunity to participate in the LFU program and have received regular updates about the study. More than 82% of the cohort has been contacted at least once since their initial visit, and the majority of those subjects have participated in regular reports of their health and symptoms.

A Phase 2 Subject List, including all subjects who are candidates for a Phase 2 visit, will be created by the DCC for each Clinical Center. In addition, the new Subject Tracking Report will further assist study centers with subject contacts and longitudinal follow-up (See Figure 5-1). Importantly, this system lists all subjects in order of Visit 2 start dates and current contact status. This system is integrated with the LFU system and will reflect any recorded updates or changes in subject contacts and completed LFU surveys.

The Subject Tracking Report is located on the COPDGene® website, under the Data Management tab. Each Clinical Center will have a unique report that categorizes participants based on LFU survey completion, vital status, and Visit 2 status and date.

![Figure 5-1. Subject Tracking, Full Report](image)

Subjects will be automatically categorized by the application as follows:

1) Current – subject has completed an LFU survey or had a contact within the past 12 months
2) Needs Contact – subject has not had a contact or the last LFU survey is older than 12 months
3) Preliminary Screening for Visit 2 has been done
4) Visit 2 has taken place
5) Deceased – missing Death Certificate, Next of Kin Interview and/or Medical Record will be flagged

5a.1. Subject Listed as Needs Contact

Subjects flagged as “Needs Contact” require an action from the clinical center coordinator. Attempts should be made to contact the subjects and update the DCC regarding their status using the Subject Contact Log on the Subject Tracking Report during the first six months of Phase 2. (See Figure 5-2.)

Since these subjects have not completed an LFU survey in over 12 months, they require a coordinator call, email, and/or mailed letter to re-establish contact. Once contact is made, update contact information, complete an LFU survey, and schedule a Visit 2, if appropriate. Subjects in need of contact may not be receiving automated LFU contacts due to inaccurate, missing or out-of-date contact information, or the subject may be deceased. Once updated contact information is obtained, the Subject Contact List should be updated for the next LFU upload. If a subject is found to be deceased, a Discontinuation Form must be submitted to the DCC. If a subject “Requests no further contact,” this does not exclude the participant from Phase 2 study visits. Please try to clarify this issue carefully, and do not discontinue a subject from the study if he/she only wants to stop doing the LFU survey.

Clinical Coordinators should work on their “Needs Contact” list in order of Visit 2 start dates. The Subject Tracking Report should be updated throughout the course of Phase 2, paying particular attention to subjects who have had no contact for the past 12 months. Establishing and maintaining contact is critical in order to schedule and complete Visit 2. We want to have regular contact with the subjects – if they are willing – to learn about exacerbations, hospitalizations and new illnesses. If the automated LFU system is not working for the subject, consider making periodic personal phone calls and completing the LFU contact manually for the subject.
Subject Contact Log for 10005Q

<table>
<thead>
<tr>
<th>Date</th>
<th>Contact Type</th>
<th>Spoke With</th>
<th>Result</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>03/18/2013</td>
<td>LFU Survey</td>
<td>subject</td>
<td></td>
<td></td>
</tr>
<tr>
<td>06/26/2013</td>
<td>V2 Screener</td>
<td>subject</td>
<td>preliminary</td>
<td></td>
</tr>
</tbody>
</table>

Hint: Open another browser window with LFU and complete a survey at the same time!

**Figure 5-2. Subject Contact Log**

**Discontinuation Form**
The coordinator will need to submit a Discontinuation form for the following situations:
1) Subject is deceased (Discontinuation form same as in the past).
2) Subject has requested no further contact from COPDGene®. This includes both Visit 2 and LFU contacts. Subject does not want to participate in the second Phase of COPDGene®.

The subject is NOT discontinued from the COPDGene® study if:
1) Subject does not want to continue with LFU.
2) Subject declines to participate in Visit 2 but still willing to participate in LFU surveys (moved away, too ill).
3) All primary AND secondary contacts have been exhausted without success and all methods of contact have been implemented (phone, email, mail, internet searches).

If a subject no longer wants to participate in the LFU portion of the study then the subject should be withdrawn from LFU via the LFU website.

**5b. Death Searching**

**Identification of Deceased Subjects**
Subjects may be identified as deceased by at least three different routes: 1. Informal sources,
including relatives or friends may inform a clinical coordinator that a COPDGene® subject is deceased, 2. A formal contact attempt to a subject by a coordinator call may result in information about a death, 3. The death may be identified from the process of “Death Searching.”

Whenever a death is identified, the clinical coordinator should record that information on the COPDGene® website via the Discontinuation Form. Please also make notes in your local records to describe how you identified the death. Currently (July 2013), the Phase 1 process asks that the coordinator provide whatever information he/she can about the cause of death. After the revised amendment is approved for your clinical center, you will complete the Discontinuation Form for all reported deaths and try to obtain additional information on the cause of death through the process of “Death Searching and Adjudication.” This process includes asking a family member, friend or next of kin for additional information about the events surrounding the subject’s death. You can also request the family to provide you with medical records regarding the events prior to the death. To complete our understanding of the cause of death we will ask that you obtain a copy of the death certificate.

**Phase 1 – Death Identification**

![Diagram of Death Identification Process]

**Figure 5-3. Phase 1 of Death Adjudication Process is identification of subjects who are deceased and transmitting that information to the Data Coordinating Center**

**Options in Phase 2 for Death Identification**

1) Local internet search: Subjects who are lost to follow-up (have not responded to LFU contacts for more than 12 months) should be tracked using their secondary contacts. Subjects who are lost to follow-up and fail to be tracked using secondary contacts should also be searched using standard internet tools including public websites and search engines. (See PowerPoint slides from October 2013 Meeting for more information).

2) SSDMF search using LFU server, pending IRB approval: In addition to searching for new addresses and phone numbers, subjects who are lost to follow-up should be added to the upload list for automated death searching. This automated death searching (if approved by your IRB) is done by the LFU server when the subject’s social security number is uploaded to the LFU server for death search. The LFU server temporarily uses the social security number to compare to the social security death master file (http://ssdmf.com). If the subject’s social security number is found on the death master
file, a report is sent to the local clinical center and the COPDGene® DCC. If you receive a report of a subject death you should complete the Discontinuation Form on the COPDGene® website and categorize the subject as deceased – death adjudication pending.

3) SSDMF search with local license: If your IRB does not approve the automated SSI searching using the LFU server, your local clinical center can do a manual search of the social security death master file by obtaining a subscription at http://ssdmf.com. Your clinical center may have a pre-existing subscription to the SSDMF. After obtaining a subscription you can search their files periodically for your subjects who are lost to follow-up by using a combination of name, address and social security number. A free website that will help to identify a subject as deceased is www.death-record.com. By entering in a subject’s SSN, coordinators can use this website to confirm a subject’s vital status.

4) SSDMF search by Administrative Core: In Phase 2 of the study we are requesting subjects who re-consent to continue in the study to allow their personal identifiers, including social security number, name, address and phone numbers, to be centrally stored in the DCC. This information will be used to do SSDMF searching in the Administrative Core.

Phase 2 - Obtaining Records for Adjudication
The next actions to take are:
1) Confirm the death by contacting the subject’s secondary contacts or if different and known, contact the “next of kin” or “personal representative.”

Rules and procedures vary from state to state and you will need to investigate your local procedures. An important fact to keep in mind is that HIPAA privacy protections for an individual remain after death for up to 50 years. Thus, you are not free to disclose protected health information about a research subject without his/her consent or IRB waiver of consent for research purposes. Operationally, this means that you cannot disclose to a family member or friend that the subject was a participant in a research project when you try to confirm death or obtain information about cause of death.

2) Obtain death certificate either from next of kin or state/local source.

3) Complete Informant Interview for death adjudication

For Phase 2 consented subjects, you should have consent to contact the next of kin. For Phase 1 consented only subjects, you may be limited in what you can obtain depending on your local state regulations and local IRB permissions.

4) Request hospital records/discharge summary. Request these records if the subject died in the hospital or was hospitalized within 28 days of death.

5) If not hospitalized prior to death, contact primary care physician for records or informant interview.

6) Send death certificate (de-identified or redacted if not approved by your IRB to transmit PHI), Medical Records, and Informant Interview to the Central COPDGene® Coordinator and record data collected on the Subject Tracking Report.
This process is completed by the local clinical coordinators for subjects who have enrolled and consented in Phase 1 of COPDGene® and have not been re-consented for Phase 2. For subjects who have not yet re-consented and signed a records release form, medical records and/or death certificate may have to be obtained through the next of kin depending on state and local regulations. In the case of subjects who are re-consented for Phase 2 and sign the release of records form, medical records and death certificate can be obtained directly.

After completing all phases of the record collection process, the coordinator should complete the Subject Tracking Report and fill in all relevant fields. Study Centers will be reimbursed on a quarterly basis for Death Certificates, Informant Interviews, and Hospital Records obtained and sent to the Administrative Core.

Obtaining Death Certificates
Death certificates are obtained from a state office that manages vital records (births and deaths typically) and may often be associated with the public health office. States vary widely in their rules on who may obtain a death certificate and what identification is required. Clinical centers should review the subject information for all of their enrolled COPDGene® subjects and determine which states their subjects reside in. For each state where your center has subjects living, you should query that state’s office of vital records (or the equivalent) regarding the procedures FOR RESEARCH STUDIES. In many states, having an IRB-approved study that is doing longitudinal tracking of subjects is a legitimate reason to request either the death certificate, or if you have a large number of subjects, the ICD-10 codes. The state may provide you with a dataset listing the ICD-10 codes and diagnoses associated with the specific subject or social security number. It is likely that you will need to make personal contact with a specific person in the vital records office and give him/her a copy of the IRB approval in order to get information about this option.

If your state does not limit access to death certificates, then you should simply request the certificate for each deceased subject. This may include filling out a request form and a small payment. The subject’s name, date of birth, address and social security number are often
requested to identify the individual. For common names you should check that the social security number, age, gender and address match properly to your records. If you are unsure of whether the death certificate correctly matches, you should note that on the Death Summary Form.

If you are absolutely unable to obtain death certificates directly from the state office, the final option is to obtain a copy of it from the family or next of kin. You may need to inform the next of kin about the procedure for obtaining the death certificate in your state.

**Obtaining Hospital Discharge Summaries and Other Medical Records**
After completing the Next of Kin interview, you should attempt to obtain medical records on the subject if he/she died in the hospital or had been hospitalized within 28 days of death. During the interview with the next of kin, you should determine and record the name and address of the hospital and the approximate dates of hospitalization. Contact the medical records department of the hospital for information on obtaining those records. Hospitals allow release of records on deceased individuals for research purposes. These requests are typically reviewed by the hospital Privacy Officer and the medical record department will often have a specific form for research requests. The death certificate and information about the study along with a copy of IRB approval may be requested by the hospital. You should request a discharge summary at a minimum. The full records of the most recent admission can be requested but may be a fairly large document.

If the hospital does not allow direct release of records on a research basis, you can still ask the next of kin to obtain those records for you. Each hospital may have different requirements for who can obtain records on a deceased individual and what documentation is required, but a common expectation would be that the hospital would provide records to the next of kin when he/she presents a copy of the death certificate (listing the name of the next of kin) and photo ID for the next of kin to prove his/her identity. Thus, for obtaining these kinds of records, the assistance of the next of kin is critical.

**Phase 3 – Central Adjudication**

![Central Adjudication Process](image)

*Figure 5-5. Central Adjudication Process after Records and Death Summary Form is completed.*
Phase 3. Death Adjudication
The records and Death Summary Form for each deceased subject will be collated by the central coordinator and provided to the Death Adjudication Committee. This committee will meet by conference call monthly – or as needed – to review each subject based on the Principles of Mortality Adjudication Document. Each subject will have a final cause of death or a determination that cause of death is unknown recorded and sent to the DCC.

Principles of Mortality Adjudication
The Morbidity and Mortality Committee will designate cause of death by probable cause. Causes of death will be grouped by general categories (e.g., Respiratory, Cardiovascular, Cancer, or Other). If a cause of death cannot be ascertained, the cause of death will be classified as Unknown. The general principles used in this classification are listed:

1) All diagnoses of cancer should be corroborated by the primary medical record. If the primary medical record cannot be obtained to confirm the diagnosis, this should be affirmatively stated in the documentation, and the committee will determine a diagnosis based on their best judgment.

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

Based on the medical information, patients who have cancers that are not expected to result in death from complications of the disease or treatment, such as localized non-melanoma skin or urogenital cancer, may be considered to die of other causes.

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

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

4) The primary cause of death should be attributed to the disorder that causes the patient to present for medical treatment. This should be distinguished from terminal events that are the immediate cause of death.

• For example, if a patient is admitted to the hospital with a COPD exacerbation, from which he/she does not fully recover, and the patient subsequently develops complications such as pneumonia, respiratory failure, renal failure, sepsis, cardiac arrhythmia or myocardial infarction, the primary cause of death will be attributed to COPD.

• For example, if a patient undergoes surgery for cancer and dies from complications of the surgery or during the immediate post-operative period, the primary cause of death will be attributed to cancer, even if the cancer was potentially curable by the surgery.

• For example, if a patient is admitted to the hospital with pneumonia and develops complications such as respiratory failure, gastrointestinal bleeding, etc., the cause of death will be attributed to pneumonia. If it is unclear if a patient is admitted with a COPD exacerbation or pneumonia, the cause of death will be based on the hospital
admission chest radiograph. If pneumonia is present on the admitting chest radiograph (or within 48 hours of presentation), the cause of death will be designated pneumonia.

If pneumonia is present only on subsequent chest radiographs (beyond 48 hours after presentation), the cause of death will be designated as COPD.

• If a patient is admitted to hospice care for a designated chronic terminal condition (e.g., COPD, CHF), then the terminal condition will be the designated cause of death.

5) Sudden death is defined as death that occurs within 24 hours of being observed alive and without evidence of a deteriorating medical condition. Sudden cardiac death is defined as death that occurs within 1 hour of being observed alive and without evidence of a deteriorating medical condition. If the interval between death and last being observed alive is greater than 24 hours and there is no other known cause of death, the cause of death will be classified as unknown.

6) In cases of out of hospital death, the site coordinator or site physician should interview family or witnesses to ascertain the following information (if approved by your IRB):

• When was the person last known to be alive?
• When was the person found to be deceased?
• What were the events surrounding the death?
  Did the decedent have any symptoms or change in health status that preceded the death?
  Special reference should be made to dyspnea, febrile illnesses, chest pain, abdominal pain, syncope, seizures, paralysis and change in mental status.
• Were there recent medical visits or recent changes in medication?
• Was an autopsy performed?
• Permission to obtain medical records should be requested from next of kin if the death occurred in the hospital or within 28 days of hospitalization.

**Completion of Death Searching and Clinical Center Payments**

In the ideal situation all subjects who are deceased will have adequate information collected to allow cause of death to be determined. Optimally this will include death certificate information supplemented by Informant Interview and Discharge Summary/ medical records.

Clinical Center reimbursement for the process of obtaining death information will be capitated at $400 and based on two levels of completion. Minimum information for center payment is to obtain a death certificate or state data transfer of ICD-10 codes recorded on the death certificate. Each death certificate or ICD-10 codes obtained is reimbursable for $200. Completion of the Informant Interview and/or obtaining hospital discharge summary/ records results is another $200, for one or the other, not to exceed $400. Payments for death records will be sent out quarterly along with the LFU payments.
5c. Clinical Center Notification of Upcoming Visit 2

The web-based Subject Tracking Report can be sorted by Projected Visit 2 date to allow coordinators to check and make sure all subjects are current in time to schedule their visit. Subjects that are recently noted to have failed to respond to LFU contacts should be tracked again to determine whether there has been a hospitalization, move to assisted living/nursing facility or death.

It is recommended that subjects be contacted three months prior to their Visit 2 target date (five years after their first COPDGene® visit) to schedule Visit 2. At the time of contact for scheduling, a Preliminary Visit 2 Screening Form should be completed for the subject.

5d. Preparing for Phase 2 Subject Visits in COPDGene®

The following information is provided to assist study personnel who are enrolling subjects in COPDGene®. It is strongly advised that these items be carefully considered and addressed prior to starting the study.

Determine where subjects will be seen for evaluation and testing. Consider the following:
- Privacy for subject
- Quiet location for optimal subject-coordinator communication
- Comfortable seating for subject and coordinator
- Electrical power for computer
- Computer connection to internet
- Proximity to blood drawing and processing
- Proximity to six-minute walk test course
- Proximity to CT scan
- Proximity to oxygen supply if needed for COPD subjects using oxygen
- Space for diffusing capacity equipment – ndd EasyOne Pro™ and associated compressed gas supply
- Size of diffusing capacity compressed gas tank based on number of subjects to be seen and available space. Consider assistance from Respiratory Therapy or Pulmonary Function Department
- Freezer - minus 80 degree Centigrade

Check to make sure these pieces of equipment are available and located in an area convenient to where subjects will be seen. Order equipment if needed.
- Stadiometer (preferably measuring height in centimeters, cm)
- Pulse Oximeter
- Blood Pressure Cuff (have available a variety of cuff sizes for larger subjects)
- Scale (preferably measuring weight in kilograms, kg)
- Diffusing capacity machine, ndd EasyOne Pro™
- Gas tank for diffusing capacity
Computer (PC): It is highly recommended that you have a computer available during the Study Visit. (See sections below for information on how to assure inclusion and exclusion criteria are met and how to complete questionnaires and forms)

- Password-protection is required on computers.
- Internet access is necessary to complete on-line “live” Eligibility Assessment Form that assures immediate access to whether subjects meet inclusion and exclusion criteria.
- Internet access is necessary to download and transmit forms, to upload spirometry results and to transfer CT images.
- A full version of Adobe Acrobat needs to be installed on the study computer. Appropriate current versions include Adobe Acrobat X Standard or Professional. Adobe Reader is not sufficient. Contact the DCC if you require further information on currently available products.
- EasyWare™ version 2.24 software for the spirometer should be installed on the computer. 
  Note: no other versions of EasyWare are allowed and automatic updates for the software should not be routinely done. 
  Note: EasyWare™ software for spirometry can only be installed on a PC. All other study-related procedures and questionnaires can be processed and completed on either a PC or Mac computer.
It is highly recommended that spirometry be performed while the spirometer is connected to the computer.

- Microsoft Excel™ is the suggested program to locally maintain contact information about each study subject using a Subject Contact Form available on the study website. Alternate forms using other programs that can capture and store similar information for use only at the Clinical Center may be used. Such information includes secondary contact name, phone, address, and email.
- Imaging Core DICOM transfer software, provided by the Imaging Core, will anonymize subject CT scans and transfer subject and phantom scans to the Imaging Core laboratory
- A laser printer, or access to a laser printer, is necessary to print barcode labels and study questionnaires and forms. Laser printers are preferable to ink jet printers.

Order Materials and Supplies:
- Paper, pens, clipboard, printer supplies
- NDD EasyOne™ Spirometer Spirettes™ (mouthpieces)
- Nose clips for spirometry
- Diffusing capacity (DLCO) supplies – gas tank with specified gas concentrations, gas regulator, tubing, ndd disposable Barriettes™
- Albuterol MDI and Aerochamber® spacer
- Stop watch for six-minute walk test
- Tape measure, retractable steel blade builder’s type, for arm span
- “Blue” Masking Tape to mark arm span on wall
- Tape measure, cloth or soft tailor/sewing type, for waist circumference

Blood Processing and Shipping Supplies:
- Blood drawing supplies: tourniquet, needle, alcohol wipe, band-aid, gloves
- Blood tubes, plastic
• Centrifuge
• Tubes to aliquot serum/plasma
• Urine Pregnancy Test collection and testing supplies or order forms

**Chest CT Scans:**
• Have Radiology Department complete and send the CT Scan Site Survey Form to the Imaging Core prior to scanning any subjects.
• Monthly – Send a CT scan of the COPDGene custom lung phantom to the Imaging Core. Regular monthly phantom scans are required for each approved scanner. Initial phantom scans must be done and approved by the Imaging Core prior to scanning any subjects.
• Ensure Radiology Technologists have completed PowerPoint slide training and test prior to scanning any subjects. Scan and email completed tests to Imaging Core to document completion of training prior to scanning any subjects. Only approved technologists will be permitted to scan subjects.
• Daily – subject CT scans must be transmitted to the Imaging Core within 2 days of CT scan acquisition.
• Know the radiologist at your site who will be most involved in COPDGene.
• Know the radiology technologists who will be performing CT scans at your site in COPDGene.
• Establish process for uploading subject and phantom CT scans to Imaging Core using DICOM transfer software.

**Spirometry and DLco Certification:**
• Each coordinator must perform three tests on three naïve subjects
• Name the Patient ID “Cert1a”, “Cert2a”, and “Cert3a”. THIS IS VERY IMPORTANT! Any other names will be rejected as invalid and the data will not be loaded into our system. DO NOT enter this into the Name Field!
  o Always identify the Patient ID as “Cert” followed by a number and letter. If there are multiple coordinators, the Cert ID’s must be unique to determine whether every coordinator has completed 3 Certification tests. Please label as follows:
    ▪ For Coordinator 1: Cert1a, Cert2a, Cert3a
    ▪ For Coordinator 2: Cert1b, Cert2b, Cert3b
    ▪ For Coordinator 3: Cert1c, Cert2c, Cert3c
  o If a particular Cert ID fails grading, and a coordinator needs to complete additional certification tests, please use a NEW Cert ID. For example:
    ▪ Cert1a & Cert2a fail. Upload new Cert ID’s: Cert4a & Cert5a
    ▪ Cert3b fails. Upload a new Cert ID: Cert4b
• Each coordinator has a 3-letter Technician ID (example: SWB). Enter your Tech ID on each test.
  o On spirometer:
    ▪ Perform Test
    ▪ Select “New” test
    ▪ Enter Patient Data. Enter all fields until you get to Tech ID
    ▪ Enter your Tech ID into the Tech ID field.
OR, on computer:
- Select “Edit” from the menu bar
- Select “New Patient”
- Under the **Tech ID** field, enter your 3-letter ID.
- Leave the Name Field BLANK

On DLco device, enter your **Tech ID** into the **Referred by** field:
- Select “New Patient”
- Select the “History” tab
- In the “Referred by” field, enter your **Tech ID**

Once certification tests have been received and have passed quality review for each technician, research coordinators will then be certified to perform spirometry and DLco on COPDGene® subjects.

**COPDGene® Study Website and Study Contacts**
- Become familiar with website use for obtaining study forms, completing Visit 2 Screening Form and downloading subject questionnaires and forms.
- Locate contact information for COPDGene® Administrative Core and Data Coordinating Center personnel and other study personnel.

**COPDGene® Forms**
- Read and become familiar with all study forms and questionnaires.
- Know how to complete all study forms including the Visit 2 Screening form.
- Know how to transmit study forms and questionnaires to the COPDGene® Data Coordinating Center.
  - Complete study form on COPDGene® website
  - Submit completed form to DCC
  - Save completed electronic form
  - Print form (optional)
- A printed-paper copy of all completed forms, records, and signed informed consent should be maintained at the Clinical Center in the subject’s folder. These should be maintained in a secure area – locked file cabinet in a locked room.

**COPDGene® Questionnaire Administration**
- **Questionnaires should always be administered one-on-one by the coordinator reading the questionnaire to subjects and recording subject responses.**
- If the Clinical Center has Internet access during the study visit, direct computer entry of data into online forms is acceptable. Steps include: fill out form online, print form (optional) and submit form. To save an electronic version of a completed form locally, save it after it has been submitted to the DCC. Test saving forms to determine the best sequence of steps for your particular site.
- If the Clinical Center does not have Internet access during the study visit, paper entry of data should be done.
- Unsupervised and group visits for study subjects to complete questionnaires are not acceptable.
COPDGene® Protocol

- Download the current protocol from website.
- Read and know key details of the study.
- Understand in detail COPDGene® inclusion and exclusion criteria.

Manual of Operations

- Print and read the Manual of Operations and maintain a copy that is readily available during Study Visits.
- Print and read the ndd EasyOne Pro™ diffusing capacity manual and EasyOne™ spirometry manual and maintain copies that are readily available during Study Visits.
- Contact the Administrative Core with questions (regane@njhealth.org).

Practice Subject

- Consider using a colleague as a practice subject to become familiar with all study procedures, questionnaires, and physical assessment prior to enrolling any subjects in COPDGene®.

Locked File Cabinet

- Required for Subject Forms and source documents
- In a locked room

Transmission of Collected Study Visit Data

- **Data that are collected during Phase 2 MUST be transmitted in a timely manner to the Data Coordinating Center.**
- The following test data MUST be transmitted daily – i.e., the same day the information is collected: spirometry, diffusing capacity, and chest CT scan. The Lung Function Core, Imaging Core and Data Coordinating Center will review this information within 24 hours of receipt. Lung function tests that are not reproducible will lead to an email to the coordinator and PI requesting that the data be re-collected. CT scans that are not processed according to the COPDGene® Manual of Operations will lead to an email to the coordinator, PI and radiologist requesting the appropriate processing algorithm be used and the information be re-transmitted.
- Clinical Centers should check the Missing Items report at least once a week to ensure all forms for a given subject have been submitted.
- Data reports of missing or invalid key elements will be posted weekly for Clinical Centers to review and address.

5e. Materials Needed for a Study Visit

Prior to each Study Visit with a COPDGene® subject, you should have the following prepared for each subject:

- Subject Identification Number – this is a unique number for each study subject. Each subject will have been assigned this number during Visit 1 and will retain the same number for Visit 2. You will have already received a list of subject ID numbers that are ready to return for Visit 2 and connected the ID number with your subject information. The subject must provide reliable identification (drivers license, voters registration, passport, green
card, etc.) to confirm his/her identity at Visit 2 to assure the subject is the same subject who participated in Visit 1.

- Your local IRB-approved consent form (2 copies)
- Questionnaires and Forms – on computer (if your site has internet access) or printed except as noted
  - Visit 2 Informed Consent and Permissions Form
  - Visit 2 Screening Form – The Final Visit 2 Screening Form must be completed on the computer and will require an internet connection.
  - Hospital Anxiety and Depression Scale (HADS) – This form must be completed on the computer and will require an internet connection.
  - Safety Assessment Form
  - Visit 2 Demographics and Physical Characteristics Form
  - Visit 2 Spirometry Form
  - Visit 2 Respiratory Disease Questionnaire
  - Visit 2 Medication History Questionnaire
  - Visit 2 Medical History Questionnaire
  - Visit 2 Residential and Occupational History
  - Visit 2 Socioeconomic Questionnaire
  - Visit 2 COPD Assessment Test (CAT)
  - Visit 2 Women Only Form
  - St. Georges Respiratory Questionnaire
  - SF-36 Questionnaire
  - 6-Minute Walk Test Form
  - E-Cigarette Questionnaire
  - Blood Collection Form
  - Visit 2 CT Assessment Scoresheet with barcode label
  - CT Acquisition parameters report with barcode label
  - Subject Contact Information Form (new)
  - Clinically Significant Findings (new)
  - Discontinuation Form
  - Cancer Data Collection Form (as required)
  - Limited Follow up Questionnaire (as required)
  - Adverse Event Form (as required)
  - Severe Adverse Event Form (as required)

- Computer with software: EasyWare™ spirometry software, Adobe Acrobat
- EasyOne™ Spirometer
  - Spirettes™
  - Nose clip
  - Albuterol HFA
  - Spacer for albuterol administration, Aerochamber®
  - Connecting cable from EasyOne™ spirometer to computer
- EasyOne Pro® for Diffusing Capacity
  - Barriettes®
  - Spirettes™
  - Nose clip
• Additional labels printed and created at your clinical center (i.e., Avery Software Label Maker). These are in addition to the barcode labels provided by BWH to label source documents.
• Stopwatch for walk test
• Oxygen – for subjects using oxygen
• Tape measure, retractable steel blade builder’s type, for arm span
• “Blue” Masking Tape to mark arm span on wall
• Tape measure, cloth or soft tailor/sewing type, for waist circumference
• Pens
• Extra paper for notes
• Folder labeled with barcode and subject ID for forms
• Blood drawing supplies
  o Barcode labels
  o Blood tubes, plastic
  o Blood tube adapters
  o Alcohol pads
  o Tourniquet
  o Needles and tubing
  o Bandages
  o Gauze
  o Centrifuge
  o Refrigerator for storing samples
  o Shipping materials (see Biorepository section for details)
  o Blood Collection Form
  o Blood Sample Federal Express™ shipping form
• Chest CT scan supplies
  o CT order form for your center (varies at each site depending on local procedures)
  o Barcode labels
  o Approved method for transferring subject scans to the computer that transmits the scans to the Imaging Core (options include CD, DVD, USB drive, external hard drive, clinical PACS transfer)
  o Approved method for maintaining backup copies of subject scans at the Clinical Center (options include CD, DVD, USB drive, external hard drive, storage server)

5f. Subject Identification Number

The subject ID consists of a 5-digit number followed by a character. The character is a check-digit that catches transposition of numbers in the numeric portion of the ID. In order to facilitate identification of the Center at which a subject is enrolled, a 3-character Clinical Center prefix is attached automatically to the ID: for example, NJC_99999Z.

5g. Informed Consent Administration

COPDGene® Study Visit 2 is a continuation of the initial COPDGene® study. Visit 2 should be explained to potential subjects who pass the preliminary Visit 2 Screening (if IRB approved at
the Clinical Center to permit use of this form before informed consent is obtained; otherwise the Visit 2 Screening Form can be obtained after informed consent is obtained). Subjects should be allowed to ask questions and may request additional time to review the informed consent and study it with family members prior to providing informed consent. The informed consent form should be reviewed thoroughly with the subject. The coordinator must assure that the subject understands the study prior to providing informed consent and signing the informed consent.

5h. Screening Form

Prior to the Study Visit: A Preliminary Visit 2 Screening Form may be completed prior to the Study Visit, if approved by the Clinical Center IRB. Subjects are eligible to return for Visit 2 if more than four years and 9 months (i.e., five years + / - 3 months) have passed since their initial COPDGene® Visit. Subjects may still be seen if more than 5 years + 3 months has elapsed since their Phase 1 Visit. Visit 2 Screening may be done at first contact with the subject by phone or in person. Check on the “Preliminary” button on the Screening Form only when entering information for screening prior to an in-person Study Visit. This information may be saved for later review and should also be printed as a source document. To save the preliminary information, check the box to confirm all responses, and click on “Save Preliminary.”

If preliminary data is entered, this information can be retrieved at a later time for that subject, as long as it has been saved. To retrieve the Preliminary Eligibility Assessment, re-enter the subject ID, select “Preliminary screening,” and click on “Edit Preliminary.” The data entered previously for this subject will be shown on the screen.

At the In-Person Study Visit: A Final Visit 2 Screening must be performed to assure that the subject does not need to delay the visit.

When completing a Final Visit 2 Screening on the website, the study coordinator should perform this assessment based on information obtained during the face-to-face Study Visit from the potential study subject. This step is required before any blood is drawn, before questionnaires are administered, before spirometry, and prior to any testing. Even if a Preliminary Visit 2 Screening was completed prior to the in-person Study Visit, a Final Visit 2 Screening MUST be completed with the patient after the informed consent is obtained to assure it is accurate and correct. For example, a subject may have had a COPD exacerbation between the time of the Preliminary Visit 2 Screening and the in-person visit – this would exclude the subject from study procedures. (Note: Subjects who have had a recent exacerbation may be studied at a later date after the exacerbation is resolved – one month or more after completing antibiotics or steroids prescribed for the exacerbation.) Do NOT click the FINAL button until you are ready to reenter all of the eligibility information. Clicking on FINAL will clear all data.

Follow this process for the Final Visit 2 Screening during the in-person Study Visit.

a. Enter the subject ID and click on “Final.”

b. Complete all fields.

c. At the bottom of the form, there is a checkbox to confirm that data has been reviewed (to reduce input errors). Confirm you have entered the information correctly and click on the “Confirm” button.
d.  This will then bring up the Print and Submit buttons.
e.  “Print” the form for your on-site records.
f.  “Submit” the form to the DCC.

**CRITERIA for CT Scan**
All Subjects will have chest CT scan done with the following exclusion:

**Exclusion**
1)  History of a lung transplant since the initial COPDGene® visit.
6. Study Visit 2 Evaluation Sequence

The order of these initial procedures during the Study Visit is mandatory:

1) Obtain informed consent from the subject
2) Complete Informed Consent and Permissions Form (on-line form)
3) Complete the FINAL Visit 2 Screening Form to determine if subject can complete study visit at this time
4) If a pregnancy test is required, you should do it at this point prior to spirometry and albuterol.
5) Complete Demographics-Physical Exam Form including resting heart rate, oxygen saturation, blood pressure, height and weight, arm span, and waist circumference
6) Complete Safety Assessment Form
7) Spirometry, before and after albuterol
8) Diffusing Capacity

6a. Screening Form

Based on responses on this form, some subjects may be delayed for the Phase 2 visit (see COPDGene® protocol page 9). Responses that will result in a delay for Phase 2 include pregnancy or suspected pregnancy; receiving treatment of a COPD exacerbation within the previous four weeks; chest or abdominal surgery, heart attack, eye surgery or detached retina, or hospitalization for a heart problem within the past three months.

Based on responses on the Screening Form, some subjects will not have a chest CT scan; these subjects are still eligible to come in to the Clinical Center for the Phase 2 visit (minus CT scan):

- History of a lung transplant since the initial COPDGene® visit

6b. Blood Pressure

Blood pressure equipment should be calibrated on a regular basis on a schedule to be determined by the manufacturer’s recommendation and the local Clinical Center Bioengineering Department. Records of calibration should be maintained by the COPDGene® staff and located with other COPDGene® records. Coordinators should be adequately trained and certified in measurement of blood pressure.

Blood pressure should be measured prior to spirometry testing, albuterol administration, and the Six-Minute Walk Test. The subject should be resting and seated for at least five minutes prior to measurement of blood pressure. A subject’s BP should be measured three times, waiting one minute between each measurement, with the subject at rest and seated. The measurements should be performed on the same arm, for consistency. Record the three BP measurements on the Demographics and Physical Characteristics Form.

6c. Safety Assessment Form

The Safety Assessment Form should be completed prior to spirometry testing, albuterol administration, and the Six Minute Walk Test. This Form only needs to be completed one time.
and is administered after the Demographics and Physical Characteristics Form. The Safety Assessment provides guidelines for when an investigator should be contacted prior to spirometry testing, administration of albuterol and the Walk Test. Coordinators may ask additional questions not on this form in order to assist the local physician investigator (PI) in interpreting the subject’s answers. For example, there is a question on this form about chest pain. In assessing chest pain, if the subject knows their chest pain is based on non-cardiac causes, the coordinator should collect and transmit this information to the PI, who will make a final determination of whether the subject may proceed with COPDGene® testing. Based upon the PI’s review of the Safety Assessment Form and possible interview with the potential subject, a decision should be made about the safety of continuing with the COPDGene® procedures.

If the Safety Assessment Form identifies concerns that will delay the study visit or prohibit procedures during the study visit, the coordinator in collaboration with the PI, should decide whether to proceed or delay the visit. If the PI delays a study visit due to identified safety concerns, the coordinator should plan to reschedule the study visit for a later date.

If a subject cannot do a procedure due to medical problems, they should come back once treated and deemed appropriate by the PI. Subjects are not discontinued if they cannot have a complete visit, they should still participate in LFU.

6d. Questionnaires, Forms, Walk Test, CT Scan and Blood Draw

The remainder of the procedures may be performed in the order most convenient for the subject, coordinator, Radiology Department and local Clinical Center operations. The order of the remaining procedures should also be based on these additional considerations:

- Potential subject fatigue, especially those who are older or have more severe COPD.
- Subject ability to concentrate on questionnaires for long periods of time.
- Questionnaires might be interspersed with other procedures like walk test and CT scan. Questionnaires may be administered after albuterol administration and before post-albuterol spirometry. Questionnaires may be administered during the waiting time between repeated diffusing capacity measurements.
- Ability of subjects to walk for long distances to other procedures like spirometry (pre/post bronchodilator testing), the chest CT scanner and six-minute walk course
- Potential subject fatigue after the Walk Test
- Potential subject fatigue after spirometry
- Scheduling of Chest CT scanner- Schedule CT scan ahead of time to ensure that the subject is scheduled on the correct scanner (see CT section of MOP-specifically PVS CT Acquisition Report)

Consideration should be given to assure that subjects are not overly taxed physically or mentally and that sufficient time is given to allow a rest if walking between testing sites is required. For example, subjects should not be required to walk a long distance to the six-minute walk test course and then immediately perform the walk test. Rather, a rest may be indicated prior to starting the walk test, at which time questionnaires may be administered. Alternatively, a wheelchair can be used to transport the subject to the Walk Course. Subjects may become mentally fatigued if required to spend a long time without breaks completing questionnaires.
Alternating questionnaires with other tests such as blood draw, walk test and spirometry will avoid excessive mental fatigue.

Coordinators should plan tests in a sequence to be as efficient as possible and minimize patient time and coordinator effort. It is suggested that one or more questionnaires be administered during the time between albuterol administration and post-bronchodilator spirometry. Because of potential side effects from albuterol, the questionnaires administered during the immediate post-albuterol period should be those that do not ask about respiratory symptoms or health status. Thus, questionnaires about medications, medical history, residential/occupational history and socioeconomic history are appropriate immediately post-albuterol.

Spirometry should not be performed immediately following blood sampling. The Walk Test should be done at least 20 minutes after the albuterol administration and at least 15 minutes after the post-bronchodilator spirometry.

As an example, one test sequence of the remaining questionnaires and procedures that will not interfere with the prior testing and allow maximize efficiency is:

1) Visit 2 Medication Questionnaire
2) Visit 2 Medical History Questionnaire
3) Residential and Occupational
4) Socioeconomic
5) Hospital Anxiety and Depression Scale (HADS)
6) St. George’s Respiratory Questionnaire, SGRQ
7) Visit 2 Respiratory History Questionnaire
8) SF-36 Questionnaire
9) COPD Assessment Test (CAT)
10) Women Only
11) Six-minute Walk Test (If the distance the subject must walk to get to the walk course is lengthy, then walking to the course and resting prior to starting the test may be helpful. During the resting time, the medical history and medication questionnaires may be administered.)
12) E-Cigarette Questionnaire
13) Blood Sampling
14) Chest CT Scan

If a subject fails spirometry and is brought back to the Clinical Center for a repeat, then on the day of the repeat a new Safety Assessment and Spirometry form must be completed and sent to the DCC. No other forms should be re-done.
7. Questionnaires

Questionnaires can be completed on a computer (if Clinical Center has internet access during visit) or on a printed copy of the questionnaire.

- If you are completing Forms and questionnaires using a printed copy, print the forms and place the Subject Identification Number on each form prior to the Study Visit. After the questionnaires are completed, they must be entered via the website and transmitted to the Data Coordinating Center. Data entry for questionnaires should be performed within one week of questionnaire administration. Double entry of data is not necessary, but quality control of entry of printed forms will be performed periodically. Maintain the original form completed by the subject as a Source Document.

- If you are completing Forms and questionnaires on the computer, create a folder on the computer with the Subject Identification Number. Place the completed electronic Form in the folder and label each Form with name of the Form and the Subject Identification Number. Use a name for the Forms in a consistent manner that is most convenient for you and allows you to identify the Subject and the Form in the future; for example you might re-name the COPDGene® Spirometry Form as “NJ_C_99999Z Spirometry.”

Materials for Administering Questionnaires:

- Computer with Internet connection (at least 15 inch screen suggested if the subject is completing the questionnaire on the computer)
- Adobe Acrobat (Standard or Professional Edition) installed on computer. This is not a free program; rather it must be purchased for each computer used for the study

Study questionnaires and forms are in Adobe Acrobat™ pdf format and require purchase and installation of a full version of Adobe Acrobat™ on each computer that will be used for subject interviews. For more information see the Adobe website: http://www.adobe.com/products/acrobat/.

Questionnaires are posted on the study website:

https://dccweb.njhealth.org/sec/COPDGene/MainPage.cfm

The coordinator must administer each questionnaire and fill in the subject’s responses on the form during the visit. The coordinator MUST review all completed questionnaires with the subject to assure that the subject answers all questions.

Important Note for Administering Questionnaires:

All questionnaires must be administered as objectively as possible. The coordinator must keep “clinical judgment” out of assessing the subject’s responses. Use the exact wording of each question. If the subject 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.”

If coordinator is entering a date where exact month and day are unknown, then month and day should be captured as July 1st. For example, if a subject knows the last time they took albuterol was five years ago, but they don’t know exact day, then capture the date as 07/01/2009.
Decimal Points, forward slashes and colons: Decimals, forward slashes (/), and colons must be typed on the forms. Even though the form may have a decimal on it, its purpose is more of a reminder that the value will likely have a decimal. Ensure to type the decimal when you enter PFT values, weight, height, and CBC values.

7a. Contact Information

A Microsoft Excel spreadsheet is provided on the study website to facilitate collection of demographic information at the Clinical Center. This information should be kept at the Clinical Center. This information will be used by the site to contact the subject for future studies twice a year. This contact may be in the form of a phone call, a newsletter with a reply card, and/or an email with a required response.

In Phase 2 (if approved by your IRB) name, address, phone number, social security number and email address will be transmitted to the Data Coordinating Center on the Subject Personal Information Form. This data will be stored separately and securely by the DCC.

All subjects must have the following demographic information collected and stored at the Clinical Center and maintained in a secure manner:

- name,
- social security number
- permanent address,
- email address,
- two telephone numbers
- date of birth,
- primary care physician name, address and phone number.

In order to facilitate contact with the subject for longitudinal data collection and vital status, the following information must also be collected:

- For a close relative:
  - name,
  - address,
  - home telephone,
  - cell phone,
  - email address (if available).

- For a second close relative not living with the subject:
  - name,
  - address,
  - home telephone,
  - cell phone,
  - email address (if available).

7b. Visit 2 Medical History Questionnaire

A medical history questionnaire will be administered to all subjects. This will be used to obtain a history of other physician-diagnosed medical conditions. If a participant is found to have cancer
while completing the Medical History Questionnaire, a Cancer Data Collection Questionnaire should be administered during the study visit to collect additional data on the cancer diagnosis.

7c. Visit 2 Medications Questionnaire

At the time the study visit is scheduled, subjects should be instructed to bring all current medications with them to the study visit. A reminder call should be made to the subject the day before their study visit to assist them in remembering this. Medications that require refrigeration or special handling should not be brought to the study visit but a box with the prescription information should be substituted. It is important to remind the subjects that medications may include injectable medications, those that are administered at a doctor’s office or infusion center, and inhaled medications. All medications prescribed by a health care provider (physician, nurse practitioner, physician assistant) must be captured on this questionnaire. Remember that oxygen is a medication that should be included on this form even if the subject does not bring it to the Study Visit.

The easiest way to complete this form is to start at the bottom and write all the medications prescribed by a health care provider that are currently being taken by the subject. The coordinator must take care to copy the medication name correctly and not guess at spelling based on the patient’s pronunciation of the drug.

For all prescribed non-respiratory medications, the coordinator should write the medication in the text field. Either brand or generic names may be used. Only the medication should be recorded; doses and frequency of daily use are not to be entered. Include both medications taken on an as needed basis (prn) and medications taken on a regular schedule. If the subject is using a combination medication (e.g., Advair™, Symbicort™, Combivent™), answer affirmatively to the questions regarding each component of the medication as well as the combination itself.

After the Study Visit, the coordinator should then complete the questions regarding classes of respiratory medications using the list of all medications recorded during the Study Visit. For respiratory medications, classes of medications are recorded; the listed drugs are examples of the class. If there are questions about a medication that is not listed, the coordinator should consult the local investigator to confirm the correct class of respiratory medication. If a question remains about a drug the investigator or Clinical Center Coordinator should contact the Clinical Center Director, Barry Make MD (makeb@njhealth.org; 303-398-1720).
Inhaled Short-acting beta-2 agonist

- Albuterol (ProAir®, Ventolin®, Proventil®), Salbutamol, pirbuterol (Maxair®), Terbutaline (Brethine), Levalbuterol (Xopenex®), Albuterol sulfate (AccuNeb®)

Ipratropium inhaler

- Ipratropium (Atrovent™)

Combination short-acting inhaled medication

- Ipratropium/albuterol combination (Combivent™, DuoNeb™)

Long-acting beta-2 agonist (including combination preparations that contain a long-acting beta agonist bronchodilator)

- Salmeterol (Serevent™), Formoterol (Foradil™, Performomist™), Arformoterol tartrate (Brovana®), Indacaterol (Arcapta™)

Long-acting anticholinergic (muscarinic antagonist)

- Tiotropium (Spiriva®)
  - Aclidinium (Tudorza ™)

Inhaled corticosteroid

- Flunisolide (Aerobid®, Aerospan™), Mometasone furoate (Asmanex Twinhale®), Triamcinolone acetonide (Azmacort®), Flucason propionate (Floven®), Budesonide (Pulmicort®, Pulmicort Respules®), Benclomethasone dipropionate (QVAR®), Fluticasone propionate, fluticasone furoate, budesonide

Combination inhaled corticosteroid + long-acting beta agonist

- Fluticasone / salmeterol (Advair®), Budesonide / formoterol (Symbicort®) Fluticasone / vilanterol (Breo®), Mometasone/formoterol (Dulera®)

Combination long-acting beta-agonist + long-acting muscarinic antagonist

- Umeclidinium / vilanterol / (Anoro™)

Oral theophylline

- Theophylline (Theo-dur™)

Table 7-1: For respiratory medications, classes of medications are recorded; the listed drugs are examples of the class. The numbers before the class of medication name correspond to the number on the Medication History Form.

7d. Visit 2 Respiratory History Questionnaire

These questions have been taken from the ATS Adult Respiratory Questionnaire and have been reworded to clarify that most questions are asking about symptoms or behaviors “since your last COPDGene® visit approximately five years ago.” The coordinator should ask the subject the questions and mark the responses on the computer form.

General Guidelines for Administration of the Questionnaire

- The questionnaire can be administered by interviewers or reviewed by interviewers in the presence of the participant who completed the questionnaire. The Clinical Center Coordinator should review each subject’s questionnaire individually to obtain consistency.

- Always ask each question the same way every time you ask it. Read each question slowly and clearly. You can read the question again if the subject says that he/she does not understand you.

- Do not bias the subject with your comments. Do not interpret the question for the subject. For clarification, you should read the question again slowly and refer to the specific guidelines below.
• Always read the question as it is written on the questionnaire. Do not shorten or add anything to the question. When asking the same question repeatedly, you might be tempted to make your own minor modifications – please do not.
• Some questions may seem repetitive; they are asked for quality control. Instruct the subject to answer the question even if it seems similar to a question they have already answered.
• Do not give “uncertain” as an option—you would like them to answer YES or NO. If they truly cannot answer the question, then put “Don’t Know” where applicable or if there is no area to indicate a “don’t know” then answer “NO.”
• Fill out the questionnaire carefully and legibly. Make sure all the questions have been asked and that the responses are consistent.
• Check over the questionnaire before the subject leaves.
• If you need to make a change upon reviewing a printed copy of the questionnaire, cross out the incorrect response, circle the correct response, and write your initials next to that questionnaire item. Save the original hard copy of all questionnaires as Source Documents.

Respiratory Symptoms

Question 2 – “On getting up” may be at night for those who work at night.

Question 4 – Phlegm. Emphasis should be placed upon phlegm as coming up from the chest; postnasal drip does not count as phlegm. This may be clarified with the follow-up question: “Do you raise it up from your lungs, or do you merely clear it from your throat?” Some subjects admit to phlegm without admitting to cough. This claim can be accepted without changing the replies to “cough”; however, if they indicate that they cough up phlegm after responding negatively to the cough questions, the cough questions can be reviewed with the subject. Phlegm coughed up from the chest but swallowed counts as a positive response. Include, if volunteered, phlegm with first smoke or “on first going out-of-doors.” “On getting up” may be at night for night workers.

Question 7 – Periods of cough and phlegm. This question is to identify persons with exacerbations (periodic worsening) of their symptoms that are beyond the normal daily variation for the individual subject. Wording on this question is reliant on the previous two questions whereas the answers each individual gives will determine whether you include “increased” in question phrasing. If a person answers “Yes” to a usual cough AND phlegm, then include “increased” in the wording of the question. However, if the subject had said “No” to the previous questions about cough and phlegm, only ask … “periods or episodes of cough and phlegm…” omitting the “increased.”

Question 8 – Wheezing. Subjects may confuse wheezing with snoring or bubbling sounds in the chest. A demonstration “wheeze” may help if the subject requests further clarification.

Severity of COPD Exacerbations in the Last Year

Complete this section even if the subject responded “no” to the questions in the last section on COPD Exacerbations in the Last Year. If the subject responds “yes” to the first question in this section, go back and ask the subject to reconsider responses to the questions in the last section on COPD Exacerbations in the Last Year.
Respiratory Conditions

**Questions 1 through 4** – Chronic Bronchitis, Emphysema, COPD. We are interested if they have been labeled, in the past five years, with the diagnosis of chronic bronchitis, emphysema or COPD, rather than giving them a clinical definition or basing the responses from the section on current respiratory symptoms.

Cigarette Smoking

**Question 5 – In the past five years**, average cigarettes per day. Record a number. In order to clarify the concept of average (mean number of cigarettes smoked over period from age first started to age finally stopped smoking), you may state “Recognizing that sometimes you smoked more and sometimes you smoked less, on the average of the entire time you smoked, how many cigarettes did you smoke per day?” If the subject is a nonsmoking control, ask if the subject has smoked less than 100 cigarettes, 52 cigars or 12 oz. of pipe tobacco in his/her lifetime. If the subject is not sure, ask his/her to give you a general idea of his/her smoking habits. Assess whether the subject has smoked recently or only a few times in the past.

Pipe Smoking

**Question 1.** A YES answer requires smoking more than 12 oz. of tobacco in a lifetime (or 8 pouches of tobacco, where one pouch equals 1.5 oz.).

7e. **St. George’s Respiratory Questionnaire**

This health-related quality of life measure was developed specifically for patients with chronic respiratory disease. The coordinator can ask the subject the questions and note the responses on the computer form. If self-completion by the participant is performed, the research coordinator should check to be sure all questions are answered; subjects should be asked to provide answers to all questions. If the questionnaire is administered as a hard printed copy, the original should be kept as a source document.

7f. **SF-36 Questionnaire**

The SF-36 is a widely used and validated quality of life instrument that will reliably assess quality of life in both the nonsmoking controls and the existing groups. It will provide complementary information to the St. George instrument for the COPD subjects and will allow us to compare COPD subjects to other diseases. The MOS SF-36 can be completed by the average subject in 5 minutes and consists of 36 questions reflecting 8 domains of health-related quality of life. We are now enrolling nonsmoking controls who are not likely to have respiratory symptoms and thus will have enough missing data on the St. George Respiratory Questionnaire (SGRQ) that we may not be able to get valid scores of their health related quality of life (HR QoL). HR QoL is associated with severity of illness in COPD.

7g. **Residential / Occupational Questionnaire**

Environmental and occupational exposures can influence the development and progression of lung disease. The Residential / Occupational Questionnaire has been designed by COPDGene® to capture these influences on COPD, if approved by the Clinical Center IRB for transmission to
the COPDGene® Data Coordinating Center. The residential portion of the questionnaire asks for current address, the address where the subject lived during the first COPDGene® visit, and the address where the subject lived the longest and the address lived prior to age 13 at the time the subject’s lungs were developing and vulnerable to environmental influences.

The Occupational History queries employment where the subject may have been exposed to dusts, gases, vapors, fumes and smoke that may have been harmful to the lungs. For the main occupation questions, write in an answer the subject provides. Then ask the subject which code best describes that occupation. Since subjects have environmental exposures at work, the addresses where the subject worked should be collected. Lifetime occupational history collects information about the duration of exposures.

7h. Socioeconomic Questionnaire

The Socioeconomic Questionnaire will help COPDGene® understand the impact of these factors on the subject’s lung health. Access to health care, living situation, and exposure to children may influence morbidity from COPD exacerbations and mortality.

7i. Hospital Anxiety and Depression Scale (HADS)

Depression and anxiety are common in people with COPD. This questionnaire will inform the presence of these conditions. The questionnaire MUST be completed on-line, and the scores must be obtained by the coordinator prior to the completion of the visit. The HADS cannot diagnose depression; the diagnosis of clinical depression can only be made by a qualified health care professional. To assure COPDGene® subjects have further evaluation and potentially therapy for depression if appropriate, subjects will be told if their score (16 or greater) indicates possible depression and will be informed to seek further care from their personal physician. The HADS score will be immediately available to the Research Coordinator and if abnormal the Research Coordinator will inform the subject in person before the study visit is ended. In addition, this information will be mailed, if IRB-approved at the Clinical Center, to the subject’s primary care provider who will be asked to perform a clinical evaluation to determine the possible need for further evaluation or treatment for depression. The Data Coordinating Center will collect information from the study coordinators to verify that subjects and their physicians have been informed about such scores.

7j. COPD Assessment Test (CAT)

The COPD Assessment Test assesses respiratory symptoms and symptoms of activity performance, sleep, energy and confidence in going out of the house. The CAT is designed for patients with COPD and is recommended as a patient assessment tool by the Global Initiative for Obstructive Lung Disease.

7k. Women’s Only Questionnaire

The Women’s Only Questionnaire has been designed by COPDGene® to assess the potential role of women’s hormones on the development and progression of COPD.
7l. **E-Cigarette Questionnaire**

The E-Cigarette Questionnaire has been designed by COPDgene® to assess amount of use and attitudes. It will be administered to all subjects.

7m. **Cancer Data Collection Form(s)**

The Lung Cancer Data Collection Form is designed to collect additional information on the diagnosis of lung cancer among participants found to have lung cancer. This form should be completed by participants upon findings of lung cancer from the LFU Survey and/or from the Medical History Questionnaire.

Other Cancer Data Collection Forms may be provided throughout the study.

7n. **Clinically Significant Findings Form**

The Clinically Significant Findings Form will be completed for every study visit and subject. Use this form to record abnormal findings that have been judged by the local Clinical Center Director to represent a significant abnormal result that shall be conveyed to the subject so that decisions can be made by the subject and his/her personal physician about further care or evaluation. Notify a subject of significant abnormal findings from a HADS, blood, CT, or other result as these findings are known. These results shall be communicated to the subject by telephone and to the subject and his/her physician (if available) by letter sent by postal mail. If direct phone contact is not obtained, a delivery receipt that can be returned and stored in the patient record shall be used when the letter is sent by postal mail. Enter information about significant abnormal findings as they are known, but submit this form to the DCC only after all clinical results are known. Please submit the form prior to receiving subject response to being informed about any clinically significant finding. The subject response questions (such as “signed confirmation that letter was received” by subject) can later be edited through the Data Management webpage.

7o. **Blood Sample Form**

The Blood Sample Form will be completed for every study visit. Coordinators will use this form to record the date of blood collection, time of blood collection, time samples are frozen, and the number of tubes collected. The form must be submitted for every study participant, prior to shipping the samples. Use this form to record any issues with the blood collection process.

Refer to the Blood Shipment PowerPoint and Biorepository section of the MOP for further instructions on how to collect, aliquot, and ship blood samples.
8. Physical Characteristics

8a. Height

Height and weight should be measured prior to performance of spirometry.

**Technique**

Measure the subject’s height in centimeters (cm) to the nearest cm while the subject is standing erect, bare-footed or in stocking feet with their head looking straight ahead. A stadiometer is the recommended device for height measurement.

First, have the subject stand up straight against the backboard with the body weight evenly distributed and both feet flat on the platform. Instruct the subject to stand with the **heels together and toes apart**. The toes should point slightly outward at approximately a 60° angle. Check that the back of the **head, shoulder blades, buttocks, and heels make contact with the backboard**.

**NOTE:** Depending on the overall body conformation of the individual, all four contact points – head, shoulders, buttocks, and heels – may not touch the stadiometer backboard. For example, frequently elderly subjects may have kyphosis, a forward curvature of the spine that appears as a hump at the upper back. In particular, dowager’s hump is a form of kyphosis that creates a hump at the back of the neck. Additionally, some overweight subjects cannot stand straight while touching all four contact points to the backboard. In such instances it is important to obtain the best measurement possible according to the protocol. In instances where a subject may unable to stand to obtain height, coordinator should use arm span to estimate height. When this is done the coordinator should check “arm span was used to estimate height” on the Demographics and Physical Characteristics form. This should only be checked when height was unable to be obtained and was estimated from arm span.

The subject should be encouraged to stand as straight as possible with the feet and knees together and the knees straight. The examiner should ensure that the head is held in the Frankfort horizontal plane. The head is in the Frankfort plane when the horizontal line from the ear canal to the lower border of the orbit of the eye is parallel to the floor and perpendicular to the vertical backboard (Figure 8-1). Many people will assume this position naturally, but for some subjects the examiner may need to gently tilt the head up or down to achieve the proper alignment.

Next, lower the stadiometer headpiece so that it rests firmly on top of the participant’s head, with sufficient pressure to just compress the hair. Instruct the subject to stand as tall as possible, take a deep breath, and hold this position. The act of taking a deep breath helps straighten the spine to yield a more consistent and reproducible stature measurement. Notice that the inhalation will cause the headpiece to rise slightly. Record the height.

**Be sure to denote the correct units of measurement (inches or centimeters) on the Physical Characteristics Form.**
8b. Arm Span

**Technique:**
Have the subject stand against the wall in a corner of the room, with one outstretched arm touching the corner wall and the subject facing out into the room. Have the subject stretch the arms in opposite directions and attain the maximal distance between the tips of the middle fingers. The arm and body should form a 90-degree angle in the frontal plane, and the arms should be held straight out to the sides (not in front or behind the body) (See Figure 8-2). Place a piece of “blue” masking tape on the wall to note the location of the finger of the outstretched hand. Consider using a retractable, steel builders type tape measure and measure the distance from the tip of the long finger of the hand in the corner of the room to the blue tape indicating the tip of the other long finger with the fingers and hands fully extended.
For clinical centers that use the same space consistently an alternate procedure may be convenient: secure a piece of paper to the wall and have the subject stand against the wall with their arms stretched fully to the right and left. Mark the tip of the long finger on the right and left hand on the paper with the subject’s initials, have the subject step away from the wall and then measure the distance between the two marks with a measuring tape.

Be sure to denote the correct units of measurement (inches or centimeters) on the Physical Characteristics Form. The “arm span was used to estimate height” selection on the form should only be selected when height could not be obtained for a subject (ex. the subject was in a wheelchair).

8c. Weight

The subject’s weight should be measured using an accurate scale with the subject barefooted or in stocking feet. Outer clothing including coats and jackets should be removed. Weight is required for body mass index determination for the calculation of the BODE index but is not required for most reference values for spirometry. Weight should be recorded in kilograms (kg) to nearest 0.5 kg.

Be sure to denote the correct units of measurement on the Demographics and Physical Characteristics Form.

8d. Pulse Oximetry and Heart Rate

Pulse oximetry should be obtained prior to spirometry and immediately following and one minute after the Six-Minute Walk Test. Pulse oximetry should be obtained with the subject in the seated position. Pulse oximetry will be recorded after the subject has remained at rest in the seated position for at least five minutes. The pulse oximeter will be placed on a finger without nail polish and will be considered valid only if a strong pulse is demonstrable. The apparent
median value obtained while observing the monitor over a one-minute observation period should be recorded.

If the subject is using oxygen, the pulse oximeter should be placed on the subject’s finger first. Next, the subject’s oxygen should be discontinued while monitoring the oximeter for a period of five minutes. If the pulse oximeter reading falls to 82% or less, oxygen will be replaced and a reading of 82% will be recorded as the subject’s oximetry. The apparent median value obtained while observing the monitor over a one-minute observation period should be recorded.

The heart rate obtained by the pulse oximeter should also be recorded. The apparent median value obtained while observing the monitor over a one-minute observation period will be recorded.

8e. Blood Pressure

Blood pressure should be measured three times, waiting one minute between each measurement. Record the three BP measurements on the Demographics and Physical Characteristics Form. The subject should be seated and at rest for at least five minutes prior to the BP measurements. In subjects using supplemental oxygen, the oxygen will be withheld and subjects will breathe room air for 10 minutes prior to recording oxygen saturation. If resting oxygen saturation falls below 82% or the subject becomes dyspneic prior to 10 minutes without oxygen, oxygen therapy will be restarted as a safety precaution. If heart rate is less than 50 or greater than 110 or if the blood pressure is greater than 170/110, a study physician will evaluate the subject to determine if it is safe to conduct spirometry, administer albuterol and perform the Six-Minute Walk Test.

8f. Waist Circumference

Explain to the subject that you will be measuring his or her waist.

Position the subject: Instruct the participant to gather his or her shirt or gown above the waist, cross the arms, and place the hands on opposite shoulders. Demonstrate the desired position of the arms. It may help to tell the subjects to think of giving themselves a hug. If necessary, lower the pants and underclothing to slightly below the waist. Again, always tell the subject what you are going to do before you do it.

Mark the measurement site: Stand on the subject’s right side. Palpate the hip area to locate the right ilium of the pelvis. With the cosmetic pencil draw a horizontal line just above the uppermost lateral border of the right ilium. Cross this mark at the midaxillary line, which extends from the armpit down the side of the torso. Figure 8-3 shows the measurement site correctly marked for the waist circumference.

Take the measurement: Extend the measuring tape around the waist. Position the tape in a horizontal plane at the level of the measurement mark. Use the wall mirror to ensure the horizontal alignment of the tape. Check that the tape sits parallel to the floor and lies snug but does not compress the skin. Always position the zero end of the tape below the section containing the measurement value. Take the measurement to the nearest 0.1 cm at the end of the subject’s normal expiration.
Record the result: Be sure to denote the correct units of measurement (inches or centimeters) on the Physical Characteristics Form

Figure 8-3. Location to obtain waist circumference measurement at the top of the iliac crest identified by palpation of the bone.
9. Longitudinal Follow-up: Coordinator Guide for Participant Contact

Introduction
The Longitudinal Follow-up (LFU) program is the central mechanism in the COPDGene® study to maintain contact with subjects over time. It provides a way to get updates on the subject’s health and also allows us to track changes in address and contact phone numbers. The goal of this document is to provide a detailed overview of the roles and responsibilities of the Clinical Coordinators involved in the COPDGene® Study in managing participant follow-up contacts. Longitudinal follow-up in COPDGene® is an important aim of the study and involves multiple components in managing and maintaining subject contact to acquire longitudinal follow-up survey data. This guide includes how to work with the LFU system to correctly maintain and upload the participant spreadsheet, how to use the COPDGene® Study LFU website (www.copdgenestudy.org), and information on the reports available to the Coordinators.

Although the system is designed to do direct contacts to subjects by telephony (automated phone calls) or email/web data entry, for Clinical Centers who are not able to participate in the full LFU program because of IRB limitations, it is feasible for those centers to input subject responses to the LFU questionnaire from coordinator phone calls.

Questions regarding the LFU process can be directed to Sara Penchev, Manager of Longitudinal Follow-up, at penchevs@njhealth.org or 303-398-1142 or Elizabeth Regan MD, PhD, Associate Director, COPDGene®, at regane@njhealth.org or 303-398-1531 or the COPDGene® Project Manager.

Part I: Description of System

The LFU process is conducted by a combination of three primary methods including automated telephone contact (Telephony), web-based questions (Web Survey), and coordinator phone calls (Manual Follow Up) which follows a sequential order. Subjects will be contacted twice a year. In the event that a subject has either reported cancer or a possible cancer has been observed in their COPDGene® CT scan, subjects may be contacted additional times. When each subject was enrolled he/she agreed to be contacted for the purpose of longitudinal follow-up as part of the study participation.

Obtaining an email address on the COPDGene® subjects greatly enhances the process of maintaining longitudinal contacts and makes it easier to get these updates on the subjects’ health.

Frequency of Subject Contact
Enrollees in the COPDGene® Study sign an Informed Consent form that describes the frequency of contact and the possibility that their secondary contacts will be used to find them in the case that they are initially lost to us. Subjects enrolled in the study early in Phase 1 (approximately before July 2009) have agreed to contacts twice each year and the majority of subjects enrolled after July 2009 have consented to contacts four times per year. Regardless of which consent the subjects signed, we are contacting subjects only twice a year for LFU in Phase 2; however, we may contact them at other times to inform them about the COPDGene® study and about clinical
research projects for which they potentially may be eligible. Clinical coordinators do not need to manage the frequency of subject contact in the longitudinal follow-up system as the computer system will do this automatically.

**Master Spreadsheet**
At each clinical site, the Clinical Coordinator will maintain an Excel file that contains subject information as noted in Part II: filling out the Master Excel Spreadsheet.

The LFU website and Master Excel spreadsheet will allow the Web System to keep track of contact attempts and successes for each subject.

**File Upload**
On the first Friday of every month, the Clinical Coordinator must upload the current version of the Master Excel file to the COPDGene® Longitudinal Follow-up Web System. On the Thursday prior to the first Friday of each month, Clinical Coordinators will receive an email reminding them to upload the Master Excel spreadsheet the next day. The LFU system will track when a subject was last contacted and will only initiate a contact if the subject is scheduled for a contact that month. **THUS, SUBJECTS WILL ONLY BE CONTACTED IN THE MONTH THEY ARE SCHEDULED FOR A CONTACT EVEN THOUGH THE MASTER SPREADSHEET WITH ALL SUBJECTS WILL BE UPLOADED MONTHLY.**

After three weeks of attempted contact, the COPDGene® Follow-up system will permanently purge all identifying subject information. The information must be re-uploaded by the Clinical Coordinator every month to start a new round of contacts. **For more information on master spreadsheet maintenance, please see the Spreadsheet section under Part II.**

**LFU Reports**
The LFU System will generate several reports detailing the outcome of the follow-up attempts. Reports are available for: 1) individuals (Indiv report), 2) all the subjects (status report), or 3) the center as a whole (summary report). For more information, see the Part II: Reports section.
Overview of Subject Contact Process

1. Coordinator receives reminder email for monthly upload. Upload to occur the first Friday of every month.

2. Master Excel file reviewed to make sure all applicable additions and deletions for subjects have been made.

3. Revised Master Excel file uploaded to LFU Web System through secure study site login and password.

4. LFU System sorts Master Excel file into subjects to be contacted for that month. Subjects with email addresses are also sorted to receive email contact first.

5. LFU System initiates telephony. Completed Surveys are stored in LFU System Data Base.

6a. Subjects unable to contact via telephony or email placed in Web System study center Work List for manual follow up.

6b. Survey data sent to DCC and private subject information purged from Web System.
Monthly Timeline of Events

1) On the Thursday prior to the first Friday of every month, Clinical Coordinators at each clinical center receive a reminder email instructing them to upload the Master Excel file.

2) On the first Friday of every month each Clinical Coordinator uploads the Master Excel file containing new and old subject information.

3) System begins telephony sequence and sends Web Survey log-in information to subjects with email addresses. Subjects without email addresses are called by the automated telephony system. Subjects identified by the LFU System for follow-up can now call into the toll-free LFU phone line to complete the survey.

4) 10 to 14 days after the initial file upload, Clinical Coordinators should log onto the LFU website and begin manual follow up via LFU Work List (see details in Manual Contact section).

5) By end of 30 days, all manual contacts should be completed and Work List cleared for new file upload. If a subject is not contacted by a Clinical Coordinator before the 30 days are up, the subject will remain on the LFU Work List until all attempts have been exhausted.

Data Procedures and Security
After subject data is uploaded to the Telephony system, it will remain there for three weeks, after which it will be purged from the system. During the three weeks, identifying subject information will only be accessible by the Clinical Coordinator for the clinical site and Inventive Labs. Protected identifying subject data must remain with the System for the length of subject contact attempts in order to identify and track subject responses. To maintain a level of personalization, the Telephony and Web Survey employ the use of the subject's name when contacting him/her. Identifiable information that includes name, telephone numbers and mail address is kept for these reasons. At the termination of three weeks, completed survey data will be identifiable by subject ID only and will be sent to the COPDGene® Data Coordinating Center (DCC) at National Jewish Health.

When the Telephony, Web Survey, and manual attempts have been exhausted for each subject queued for contact on the initial upload, a de-identified cumulative data summary of contact results will be generated and available via the secure COPDGene® Longitudinal Follow-up website. Clinical Coordinators will have access to de-identified data reports from their subjects only, while access to all of the sites reports will be limited to the LFU manager within the COPDGene® administration.

Data Transmission Security
Interaction with the host site operates through a web browser that uses secure sockets technology (SSL). The public key certificate was issued by a valid secure certification authority. Transmission of data employs 128-bit encryption or greater using the HTTPS protocol on port 443.

Physical Security
The host computer system is located in a secure data facility at 600 W. 7th Street, Los Angeles, CA 90017. This is a secure and controlled facility with employees on site 24 hours per day. The
facility offers uninterruptable power (UPS) and diesel generator power back-up. Servers are kept behind locked doors with access only to authorized personnel.

Data Storage and Confidentiality
All confidential and identifying data is stored in a separate encrypted database using the Microsoft SQL Server 2005 product. All confidential data is purged shortly after the survey has been completed, after attempts to contact the subject have been exhausted, or after three weeks following the initial upload to the system. Any information provided to the COPDGene® DCC has been de-identified and contains only the COPDGene® subject ID number. The system complies with all National Jewish Health procedures for maintaining the security and confidentiality of patient data. These standards are in accordance with federal regulations for handling this type of data. The database is stored behind an industry standard firewall. There is daily backup of all data. For increased security, the system uses 'time-outs' activated on open screens that require password sign-on after 40 minutes of non-activity. All server access and databases are password protected and periodic checks of activity logs are run to guard against hacking.

Part II: Using the Longitudinal Follow-up System

The Longitudinal Follow-up system is designed to efficiently collect health information from subjects without excessive manual calls from coordinators. The Clinical Coordinator will log into the System through a secure password-protected portal and upload the file to the system on the first Friday of every month, which will commence the round of automated follow-up contacts. Transmission of subject information will be secured through password protection of the website using a password login specific to each study site.

To accomplish a subject contact, LFU attempts will start through the automated routes of web contact and telephony. If a subject has provided COPDGene® with an email address and that email address has been added to the LFU Master Excel spreadsheet, then the System will attempt to first contact a subject through email. Upon monthly file upload, an email will automatically be generated and sent to the subject inviting him/her to take the survey and giving him/her an individual password and login for the website. The email will appear to be from the study center where the subject was seen and not from the general LFU system. Subjects will then go to the COPDGene® Study LFU website and log into the site to access the survey. When a subject is due for a survey and an email is generated, subjects will have several weeks to go online or call into the telephony system to complete the survey. After several weeks however, the LFU system will purge all subject information limiting follow-up participation to a manual Clinical Coordinator call only, this information is captured on the web-based Work List.

Subject information will also be purged automatically after a survey has been completed.

Step 1) Filling Out the Master Excel Spreadsheet
The first step in LFU is getting all subjects onto one Master Excel spreadsheet. Newly recruited subjects will be added to this spreadsheet as they are recruited to the study. Each center will keep one main or master version of this spreadsheet to which all changes and updates must be made and saved. Each month the Clinical Coordinator will upload the Master Excel spreadsheet, which includes both the old and new subjects. The LFU computer system will keep track of who is due
for contact. Because the LFU system purges all of the subject’s personal information at the end of each month, it is critical that the Clinical Coordinator save changes to the subject’s information on the Master Excel file. **Clinical Coordinators will also be responsible for amending the Master Excel document when new information on the subject becomes available. The LFU system cannot amend the Master spreadsheet automatically.** Thus, it is extremely important that each Clinical Center amend its Master spreadsheet for changes such as new subject phone numbers, email addresses, and subject participation status. It is strongly suggested that the Clinical Coordinator follows adequate back-up procedures for this file. If the file is lost, it will have to be re-created by the Clinical Center.

An LFU spreadsheet template was created and sent to each Clinical Center. This exact template must be used with the format for date, name, and other fields exactly like the example on the spreadsheet template. It is also important to note that the name of the worksheet within the spreadsheet file should be called “Sheet1” without any spaces. For example, “Sheet 1” and “Sheet2” will cause the upload to fail. The spreadsheet contains 11 data fields, which hold important information about the subject.

### COPDGene® ID
should list the six-character SID without the center code.

### Salutation
Enter Mr./Miss./Mrs.

### First Name
Enter the first name that the subject goes by. **Do not enter middle names or middle initials here.**

### Last Name
Enter the last name of the subject. **Do not enter middle names or middle initials here.**

### Primary Phone
Enter the first phone number you have on file for the subject. The format should look exactly like the template where digits are separated by a dash. Any changes to a phone number must be updated on the Master Excel spreadsheet as they will not be captured in the system.

### Secondary Phone
Enter any other phone numbers you have on file for the subject.

### Email
Enter the email address of the subject if you have one. Any changes to a subject’s email address must be updated on the Master Excel spreadsheet.

### Date Completed
Enter the date that subject was first seen at the clinical center. Date must be in the exact format mm/dd/yy

### New Consent
If the subject signed the ‘new’ version of the Informed Consent document (implemented summer of 2009) than they have consented to up to 4 contacts per year. If the subject has signed the new version, enter a ‘Y’ here. If the subject signed the old consent version limiting contact to only twice a year, enter a ‘N’ here. The exact date that the new consent form
was implemented will depend on when each center received IRB approval to implement the new consent.

Password: This is for subjects with email addresses only. If a subject requests a specific password that they can use to log into the system to take the survey, then you may enter it here. If this is left blank, the subject will be sent an email inviting them to take the survey where their log in is their email address, and their password is their six-character COPDGene® Subject ID. In most cases, this column will be left blank. For subjects with an email address on the spreadsheet, an email invitation containing a username and login password allowing them to take the survey online will be sent to them shortly after the upload of the Master Excel spreadsheet. If a subject forgets his/her Web Survey login information, he/she may retrieve it by following the “Forgot your password?” link.

Cord Call Only: If a subject refuses to participate in the automated phone call, the subject can be diverted directly to the Coordinator Work List for a manual call by entering a ‘Y’ in this column. By entering a ‘Y’ here, the computer will still keep track of when the subject should receive a call for a survey completion, but he/she will appear on the Work List immediately following a spreadsheet upload instead of receiving three calls from the automated system. In most cases, this column should be kept blank.

When the master spreadsheet is uploaded, only subjects scheduled to be contacted for that cycle will be contacted by the System.

Step 2) Paper Letter
Before a newly enrolled subject is contacted by LFU for the first time, a letter must be generated and sent to the subject’s home address explaining in detail the process of LFU contact. The COPDGene® Administrative Core provided a template of this letter for all sites. Each site is required to amend the letter and include the name and telephone number of the Lead Clinical Coordinator at that site. When LFU is initiated for the first time, a large batch of letters must be generated to the entire cohort. Subsequent letters will be mailed to subjects as they are enrolled in the study. Clinical Coordinators should mail the initial LFU contact letter no more than two months after the initial study date. New non-smoking controls will follow this procedure as well.

Step 3) Using the COPDGene® LFU Web Site
The public COPDGene® Study Web site (separate from the DCC COPDGene® website) has a unique login portal for Clinical Coordinators (“staff login”). Once logged into the site, Coordinators can upload their Master Excel spreadsheet, access and manage their individual Coordinator Follow Up screen, and view reports. Login name and passwords will be provided by Sara Penchev. If you lose or forget your name or password, please contact Sara at PenchevS@njhealth.org.

Login
Coordinators can login to the portal by going directly to https://www.copdgenestudy.org/Login.aspx or by clicking the ‘Staff Login’ link found in the upper right corner on the home page of the COPDGene® Study:
Uploading the Spreadsheet

The first Friday of every month, Coordinators are required to upload the Master Excel spreadsheet that contains both old and new subject information. To access the Upload screen, simply click on the Upload link found at the top menu of the Coordinator Follow Up screen.

When you see the Upload screen, use the Browse button to find the Master Excel spreadsheet for your center, the spreadsheet should be saved on your computer as an .xls file. Click the “Upload File” button.

After a successful upload, you should receive e-mail notification that your file has been uploaded correctly. The email will provide you with a summary of the data on your spreadsheet. Below is an example of what the email will look like.

```
The file was processed at: 07-22-09 09:39 AM and had the following statistics:

Total Subjects uploaded: 134
New Subjects: 81
Existing Subjects: 53
```
Step 4) Completing a Follow-up Survey: Overview

There are many quick and convenient ways for a subject to complete the COPDGene® Study longitudinal follow-up survey. Subjects can complete the survey online at https://www.copdgenestudy.org, through the automated telephony voice response system, or complete the survey over the phase through a manual call by a Coordinator.

Automated Email – Web Survey via Email

If the subject has a valid email address, the subject will first be contacted through an email that invites them to take the LFU Survey online. The email will provide the subject with personal login information so that the subject may sign into the secure Web Survey. The login for the subject will be their email address, and the generated password will be the unique COPDGene® SID designated for the subject. An example of this email is below.

Dear “Subject,”

Thank you for your participation in the COPDGene® study. You have indicated that you would prefer this follow-up contact to be over the web. Below is a link to our website where we would like you to complete a brief questionnaire concerning your recent health. Please log into the site using the user name and password provided in this email and complete the survey within four days of this letter. If we do not hear from you after four days, we will attempt to contact you by phone.

https://www.copdgenestudy.org/SurveyLogin.aspx (includes email and password)

We understand that your time is valuable, and we greatly appreciate your participation in this study. Thank you for working with us to advance the knowledge and future treatment of COPD!

Sincerely,
COPDGene® Study

If a subject does not respond to the sent email by taking the survey online within 7 days, the System will attempt to collect a survey through the telephony system. Subjects who did not initially provide email addresses will be defaulted to the telephony system for contact. The telephony system will make three call attempts per phone number. Each call will occur at a different time of day; one in the late morning, one in the early afternoon, and one at dinnertime. Telephony responses from subjects will be captured using the touchtone keypad. Subjects have the option of not responding to any or all questions via a built in option presented at each question.
Automated Calls – Telephony
The first phone call to a subject occurs at 6pm (their local time.) If an email was sent and the subject did not complete the Web survey, then the first phone call will occur at 6pm seven days after the email was sent. The second phone call occurs at 2pm the following day unless the subject requested in the survey to call back tomorrow evening in which case the call is dialed at 6pm local time. The third phone attempt will occur at 10am on the third consecutive day. Each phone number in the upload file is attempted 3 times; the Primary phone number 3 times, then the Secondary number 3 times.

If an answering machine is reached, the telephony system will leave a message with a call back number. Subjects may call into the telephony system to complete the survey only until the end of the month. After that time, a survey can only be collected by a manual call from a Clinical Coordinator. In order for the subject to be recognized by the automated system when they call in, they will be asked to enter one of the phone numbers that we have on file for them (the same phone numbers that are listed on the Master Excel spreadsheet for the subject). Call-in surveys can be collected either by the subject calling the COPDGene® survey line from one of the recognized phone numbers or by the subject entering one of the ‘known’ numbers after hearing a prompt to do so. The automated system links the ‘known’ phone number for a subject, with their COPDGene® SID so that we know who is taking the survey.

Troubleshooting Tip: Subject is angry at being on an automated call list. If a subject is dissatisfied with being put on the automated telephony call list, a subject can bypass the telephony and be scheduled for a manual call only. By putting ‘Y’ in the ‘Cord Only Call’ column on the Master Excel spreadsheet, the System will place the subject on the Work List immediately following an upload when it is time for the subject to take a survey.

Manual Contact – Coordinator Follow-up
After the Telephony and Web System have made all attempts to the subjects scheduled to take the survey, the remaining subjects who did not take the survey, or subjects who require further attention, will show up on the ‘Coordinator Work List’. The main role of the COPDGene® Study
Coordinator is then to go to the Work list and evaluate each case, selecting a result for each contact attempt. Every subject that appears on the Work List is linked to a short description that outlines the reason for his or her appearance on the list. We call this description the ‘Action Needed’ column. After appropriate action is taken to address the subject on the Work List, a result must be selected and submitted. Submitting a result for each subject is how the System is able to track the progress and activity of a Clinical Center for longitudinal follow-up. Do not forget to select “submit” after selecting a result from the drop down.

Subjects on the Work List will receive three manual calls by the Clinical Coordinator before going off the work list. Once removed from the work list, a survey can still be collected by the coordinator once contact is made by selecting the “take a survey for call back link” (picture below); however, email/telephony will not initiate for another 6 months. Attempts should be made to contact a subject for a survey by secondary contacts and mailings; however, this will be tracked from the COPDGene® Subject Tracking log and not in the LFU system.

The coordinator needs to input the progress of the manual attempts by entering the results of the contact after the call on the LFU website. The System will record the number and outcome of attempts made for each subject. Subjects will disappear from the Work List if the following ‘results’ are submitted:

1) A survey is completed through a manual call
2) The subject is found to be deceased
3) A subject is unable or unwilling to complete the survey
4) The subject requests to be removed from the LFU portion of the study
5) The subject’s phone number is found to be bad
6) After three unsuccessful manual contacts are made

When an unsuccessful manual call attempt is made and the result submitted on the System, the subject will move to the bottom of the Work List and the subject will re-appear with a ‘1’ marked in the ‘Number of Attempts’ column.

When a subject is reached and new contact information is received or changes to study participation or other important changes occur, the System will ask the coordinator to update the Master Excel spreadsheet. All changes to subject information must be made on the Master Excel Spreadsheet by the Clinical Coordinator in order to be saved.

When a successful manual contact is made, coordinators will take the survey for the subject online by reading the questions to the subject and entering the answers into the computer. Details on this procedure are outlined in the following sections.

If a subject is also a patient at the clinical site where he/she completed the initial study visit, then the Clinical Coordinator should try to obtain the follow-up survey when the subject comes into the clinic for a visit if the visit is within the LFU time allowance. It is also suggested that the Clinical Coordinator obtains a survey at the time of preliminary eligibility/scheduling in the event that the subject does not show up for his/her visit. The survey can be given to the subject in paper form but to save the coordinator time, it is preferable to administer the survey online.
Below is a sample of a typical Coordinator Follow Up screen:

<table>
<thead>
<tr>
<th>COPDGene id</th>
<th>Action Needed</th>
<th>Last attempt</th>
<th>Voice mail</th>
<th>Take Survey</th>
<th>Update Email</th>
<th>Attempts</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1055BL</td>
<td>Voice Mail-Update Email Address</td>
<td>5/14/2009</td>
<td>9:10 PM</td>
<td></td>
<td></td>
<td>0</td>
<td>Select a result</td>
</tr>
<tr>
<td>10480U</td>
<td>Subject Requested Contact</td>
<td>7/22/2009</td>
<td>2:56 PM</td>
<td></td>
<td></td>
<td>0</td>
<td>Select a result</td>
</tr>
<tr>
<td>10630D</td>
<td>Voice Mail-Update Email Address</td>
<td>7/22/2009</td>
<td>5:01 PM</td>
<td></td>
<td></td>
<td>0</td>
<td>Select a result</td>
</tr>
</tbody>
</table>

‘Action Needed’: How to Work the Screen
Each subject on the Work List should be addressed based on the description of the Action Needed column for the subject. Below are descriptions of the Action terms.

Voice Mail-Update Email: In this instance, a subject has attempted to leave a voice mail for the coordinator with their email address on it. This usually means that the subject would like to take the web survey instead of the telephony survey in the future or they have a changed email address. The coordinator can listen to this voice mail by clicking on the green telephone icon for that subject. A separate screen with a wav. file will appear. Press the play button and listen to the voice mail. After the new email address has been written down, the new email must be entered on the Master Excel Spreadsheet.

Troubleshooting: Message is silent or impossible to understand. Sometimes a subject does not intend to leave a message but activates the automatic voice recorder on the telephony system by accident. If there is no message, or the message is impossible to understand, you should try and call the subject to get the email address. If you cannot contact the subject, you may ‘task complete’ them.

Voice Mail-Cannot Be Contacted: If a phone number is bad or a subject is no longer living at the residence attached to the phone number, then the person who the telephony system calls has the option of leaving a voicemail letting us know why the subject cannot be contacted. Listen to the voicemail by pressing on the green phone icon. The voicemail may give a Coordinator valuable information about a subject such as relocation information or subject death.

Voice Mail – Update Contact Information: Subjects have the option of updating their contact information with us through the Telephony System by leaving a voicemail. To listen to the voicemail, click on the green telephone icon. Remember to update the Master Excel Spreadsheet with the new information.
**Send Email Survey:** If a subject has refused to take a survey through the phone but would like to take the survey through the web, he/she can be sent an email invitation to take the Web survey through this option. When the orange email button is pushed, a new screen will appear (see below).

Enter the new email, then click the “Save” button. This will automatically send an email to the subject inviting him/her to take the survey online. **Remember that you must also update your Master Excel spreadsheet with the new email address, as all confidential information is purged from the system after phone call attempts are completed.** After the new email address is entered onto your Master spreadsheet, the subject will henceforth be invited to take the survey through the web. Please note that the email option can only be used if the subject is scheduled to take the survey.

**Take Survey:** When a subject needs to complete a survey, the ‘Take Survey’ icon will appear blue. A survey may be taken over the phone when a Coordinator calls a subject. To take a survey for a subject, click the ‘Take Survey’ button that links directly to the survey for that subject. When you have completed the survey for the subject, the System will automatically save the results and send them to the DCC. Ensure to refresh the page after exiting out of the survey page.

- **Telephony Unable to Contact:** The telephony system was unable to reach the subject and now three manual attempts are required. If a coordinator calls the subject and is unable to reach him or her, the ‘Unable to Contact’ result should be selected from the drop-down menu followed by ‘submit’. The System records the number of attempts that are made, and the time and date the last attempt was made.

**Troubleshooting:** The Subject is willing to take the survey when they receive a personal call. Sometimes ‘unwilling in telephone survey’ can occur by mistake if the subject presses the wrong button, or sometimes an individual who is not the subject answers the phone instead. In either case, the subject needs to be called in order to accurately evaluate the subject’s needs.
• **Unwilling in Telephony Survey**: This action term will appear when the telephony system has contacted a subject and the subject has indicated that they are unwilling to complete the survey through the automated system. A Coordinator should contact the subject to find out why he/she is unwilling to complete the survey and take the appropriate action. A subject can select that he/she is unwilling to participate through a question asked in the automated telephony system.

• **Invalid Subject ID**: A subject ID was entered incorrectly and as a result that subject could not be identified and did not receive LFU calls. Coordinator should correct the subject ID on the Master Spreadsheet. Upon the following upload, the subject will be contacted to complete the survey.

**Troubleshooting: the LFU System is reporting that a subject ID is incorrect but I know it is correct.** Every SID that is on the Master Excel Spreadsheet gets cross-checked with the DCC when it is uploaded monthly. Sometimes if a subject has recently been recruited to the study, the DCC has not yet validated the subject and the subject ID will show up as being incorrect even though it is the right number. In these cases, make sure that the SID in question is correct. Next, ‘task complete’ these subjects. Next month when the upload is done again, the subjects should appear as being correct and start receiving calls from the telephony system. This error message can also be received if a subject is transferred to a new Clinical Center but the initial Clinical Center has not yet removed the SID from its Master Excel file. In this case, the original Clinical Center should remove the SID from its Master Excel file prior to the next upload.

• **Manual Call**: A subject can be scheduled to bypass the automated system by entering a ‘Y’ in the last column of the Master Excel spreadsheet under the ‘manual call only’ column. If a subject is listed as a manual call only case, the system will automatically send the subject to the manual work list when the subject is scheduled for a call. The action term will appear on the work list as Manual Call.

**Selecting Results from Manual Follow Up**
Each time a call is made the results from the call need to be entered into the system. Entering a result allows us to keep a record of the call outcome as well as keep track of how many times the subject has been contacted. Logging a record of a manual call is important for tracking manual call attempts both for the Coordinator and for COPDGene® payment to the center for their efforts.

After making a manual call attempt, use the drop-down menu to choose the appropriate result, then click ‘Submit.’ Submitting a result will allow the System to automatically keep track of how many times a subject has been manually contacted. When a subject has had a successful survey completion or has been called three times, the subject will disappear from the work list. The number of attempts that have been made can be seen on the Work List in the ‘attempts’ column.
The Results drop down menu will reflect options that are specific to the reason the subject is on the Work List. An example of the Results drop down menu is below:

![Results Menu](image)

**Results Terms**

- **Unable to Contact**: Select this result when a call is made to a subject but there is no answer. If an answering machine is reached, the Coordinator should leave a message asking the subject to call back. Every time an answering machine is reached, a message should be left. After the third unable to contact attempt, the subject will be removed from the work list and telephony will re-initiate six months from the last failed date. The Coordinator should continue to try to make contact with the subject by utilizing the COPDGene® DCC Subject Tracking website.

- **Deceased**: If a Coordinator discovers that a subject is deceased, a Discontinuation Form should be submitted to the DCC immediately. When the Deceased option has been selected, a reminder note will appear to complete the discontinuation form and an automated email will be sent to the Clinical Coordinator. Deceased subjects must then be manually removed from the Master Excel spreadsheet to discontinue contact.

- **Bad Phone number**: If a subject’s phone number is no longer working or someone other than the subject now uses the phone number, this option should be selected. The bad phone number should be removed from the Master spreadsheet and an LFU letter sent to the subject. The subject will be removed from the Work List. The Clinical Coordinator should work from the DCC Subject Tracking Log website to re-establish contact with the subject.

- **Cannot complete this cycle**: If a subject does not wish or is unable to complete the survey anytime in the next six months, then this option should be selected. Some common reasons for this may include the subject being in the hospital or on a vacation. No further action is needed, and the subject will be automatically contacted again the following cycle.

- **Withdrawn from LFU Only**: If a Coordinator speaks to a subject in person, and the subject requests to be withdrawn from the LFU portion of the study, then the Coordinator will select this option. The Coordinator should also remove the subject information from the Master Excel spreadsheet. If the subject expressly states they wish to be withdrawn from the entire study, then the Coordinator should complete a Discontinuation form to submit to the DCC immediately. Withdrawn subjects must then be manually removed from the spreadsheet to discontinue contact.

- **Task Complete**: Select this option for the successful completion of the task.

**Finding a Subject on the Work List**

If a subject has disappeared from the work list but is still due to take a survey, or if the Coordinator is having trouble locating the subject on the Work List, the COPDGene® SID can be
used to be directed to the subject-specific survey page. Above the Work List table on the left hand side the ‘Take a Survey for Call back’ link will be seen in yellow.

By clicking on the ‘Take a survey for callback’ link, the following screen will appear.

By entering the subject ID for in this window and then clicking ‘go’, you will be directed to the survey screen where you can take a survey for a subject.

**Manually Enter Subject Information**
Select the ‘manually enter subject information’ yellow link when you cannot locate a subject from the task list and the subjects has taken a survey in the past six months. Various actions can be taken from this link.

**Discontinuation**
Subjects should **not** be discontinued from the study in the event that they do not want to participate in LFU. If a subject does not want to participate in LFU, the center should “manually withdraw from LFU only” on the LFU website for withdrawal from the LFU program. If a subject requests to be discontinued from the study and wants to be removed completely from the study or if the subject is deceased, then a discontinuation form needs to be completed and submitted to the DCC. If a subject is found to be deceased, it is important to try and collect information on the cause of death. After a discontinuation form is submitted, the subject needs to be removed from the Master Excel spreadsheet.

If a subject is ‘accidentally withdrawn’ or withdrawn for any reason and needs to be added back to LFU, the coordinator can add them back in by selecting “Manually Update Discontinuation”
and then entering the subject ID. Upon entering the subject ID the coordinator should then enter
the current date and select “Remove from discontinued.” A screenshot for this is below.

A Discontinuation Form should NOT be submitted in the event that a subject is lost to
follow-up. Subjects who are unreachable or lost to follow-up should have their information
removed from the Master Spreadsheet.
Manual Follow-up Procedures

Coordinator accesses LFU Work List from Study Survey website
- Failed contacts
- E-mail updates
- Request contact

Coordinator calls subjects on Work List
- Call 3 times with message
- Track attempt on website
- When subject is reached, fill out survey online

If subject phone number incorrect or discontinued initiate secondary contacts
- Call each contact up to three times
- Leave message

If subject is deceased complete Discontinuation Form
- Retrieve information on cause of death
Reports
At the top of the Follow Up screen in the main menu, three reports are accessible; the Indiv (individual) report, Status Report and the Summary Report. These reports are designed to give real-time information on the status of LFU for individual subjects and pooled data of centers. All reports are downloaded in an Adobe PDF format and are for viewing only.

• **Indiv Report (individual report):** Gives LFU information on an individual subject. Each page of this report holds the cumulative LFU contact summary for a single subject. Every row on the report represents one cycle of LFU contacts. The Clinical Coordinator can look to this report to see how many surveys a subject has completed, and by what method (manual call, telephony etc.). This report is designed to be printed and placed in a subject’s COPDGene® Study subject file.

• **Status Report:** The status report looks similar to the Master Excel file except it includes information on when each subject last completed the survey.

• **Summary Report:** This reports provides an overall picture of LFU at each center for a given date range. The center can review common statistics such as percentages of manual survey collection, percentages of failures and deceased, and get a number breakdown of how surveys were successfully collected (web, manual call, telephony). This report will also allow a center to do a direct comparison with the collective totals from all the other centers involved in LFU for COPDGene®. To access this report, select a date range of activities to view. A PDF report will then be generated with the statistics for the selected date range.

Logoff
Use the Logoff link at the top right of the Follow Up screen to log out of your session. If you need to log back in, simply use the login link to go back into the system.
10. Spirometry

10a. Overview

Spirometry is a test that measures function of the respiratory system. It is one of the simplest, most effective tests available for the assessment of lung function. The spirometer registers the amount of air a subject breathes in and out and the rate at which the air moves. The most common spirometric test requires that the subject take a full, deep breath and then exhale as forcefully as possible. This effort is called the forced expiratory maneuver and measures the amount and speed of air that is exhaled.

COPDGene® uses a spirometer (the ndd EasyOne™ Spirometer) that measures flow and volume by ultra-sound transit time. This spirometer meets 2005 American Thoracic Society spirometry standards.

Because the results of spirometry testing are used to determine the presence and severity of COPD, the measurement must be performed according to strict standards by technicians who have been properly trained and certified in how to conduct the maneuver. In addition, the equipment must be in good operating order and the calibration regularly checked. All spirometric maneuvers will be reviewed by a central reading laboratory (COPDGene® Pulmonary Function Core) to assure optimal quality of the data and to provide ongoing feedback to the pulmonary function technicians regarding the adequacy of the maneuvers.

10b. Summary of Measures

The following measurements will be obtained through spirometry testing during the COPDGene® clinic visits:

A. **Forced Vital Capacity (FVC)** is the total volume of air, expressed in liters, exhaled in a forced expiratory maneuver (the act of exhaling as hard and fast as possible after a maximal inspiration). The FVC is useful for detecting restrictive disorder, since lower than expected results may be a sign that the lungs cannot inflate as fully as normal. The FVC may also be reduced in people with more severe COPD and other obstructive disorders.

B. **Forced Expiratory Volume at One Second (FEV₁)** is the amount of air, expressed in liters, that a person breathes out during the first second of a forced expiratory maneuver. This is reduced in people with airflow limitations such as COPD and asthma. The FEV₁ may also be reduced in patients with restrictive disorders.

C. **The ratio of FEV₁ to the FVC (FEV₁/FVC)** is the most sensitive and specific index of airflow limitation measured by a spirometer. It is obtained by dividing the FEV₁ by the FVC, and is expressed as a percent (i.e., 100 x FEV₁/FVC). Note that the FEV₁/FVC ratio is the ratio of the absolute FEV₁ and absolute FVC in liters and is not usually expressed as a percent of predicted.

D. **Forced Expiratory Volume at Six Seconds (FEV₆)** is the amount of air that a person breathes out during the first six seconds of a forced expiratory maneuver. Increasing interest is being shown in the FEV₆, and more particularly in the FEV₁/FEV₆ ratio, as an
alternative to the FEV₁/FVC ratio. Use of the FEV₆ may be easier to obtain, particularly for patients with severe airflow limitation with long forced exhalation times.

E. The ratio of FEV₁ to the FEV₆ (FEV₁/FEV₆) is an alternative to the FEV₁/FVC ratio. One of the secondary objectives of COPDGene® is to evaluate the utility of the FEV₁/FEV₆ ratio, particularly with respect to the assessment of COPD.

10c. Setting for Spirometry Testing

Spirometry testing ideally should be performed in a private, temperature-controlled room. All of the instruments necessary for the test should be in the room. The room should be well lit and located in a quiet area. These conditions will improve the quality and reproducibility of the results. For safety, the participant should be seated in a chair with no wheels; preferably the chair should have arms.

For some sites, it may be that testing will be done in non-clinical settings. The ndd EasyOne™ Spirometer is portable and has been shown to perform well in the field. Nonetheless, this document assumes that testing will be done in a centralized clinic facility. Sites planning to do otherwise should develop corresponding local procedures detailing off site considerations and document them in their local Manual of Procedures.

Clean mouthpieces (Spirettes™), nose-clips, and spacers should be available in the room, as should be a container to collect used Spirettes™ and used spacers. A box of facial tissue paper, paper plate or some type of container to place dentures on or in (if needed), and a trashcan should be placed close to the participant. It also may be helpful for a source of drinking water to be nearby, as some subjects may get dry mouth as they are performing the maneuvers.

The ndd EasyOne™ Spirometer does not need calibration. However, a calibration check should be carried out daily to ensure that the spirometer is reading accurately. Instructions for performing the calibration check are in the ndd EasyGuide™ technical manual and appear in section 10n. The calibration syringe and adapter should always be stored next to the spirometer so that the temperature of the syringe and the spirometer are the same. This will avoid having large differences between room temperature and the spirometer temperature that could affect the results of the calibration tests. If there is the potential for a large temperature difference between the calibration syringe and the spirometer, the technician should pull and push the piston on the syringe several times to correct the problem. If spirometry is done in the field (outside of a clinical center), it is preferable to keep the spirometer and calibration syringe together overnight to avoid temperature differences at the time of calibration.

10d. Setting up the ndd EasyOne™ Spirometer

Prior to conducting the spirometry measurement, the technician should assure that the configurations of the EasyOne™ are set according to the specifications outlined under the “ndd Configuration Settings for Use in COPDGene®” below in sections 10j and 10p. Failure to have the correct settings may result in lost or deleted maneuvers, which will result in the participant being excluded from analysis in COPDGene®. Ideally, a single person should be designated as responsible for configuration of the EasyOne™ at each Clinical Center.
10e. EasyWare™ Setup and Data Upload

Install the EasyWare™ software version 2.24 from the flash drive provided to you by National Jewish Health on all PC computers that will be used for spirometry. Note that a Macintosh computer CANNOT be used with the spirometer. It is strongly recommended that the spirometer be connected to a PC with software installed during performance of spirometry in COPDGene®. This enables visual confirmation and feedback to both technician and participant during the test.

10e.1. Setting up your spirometry EasyWare™ master database

Every time you plug your spirometer into your computer, the software will sync the spirometer tests with a “Master Database” on your computer. To make your Master Database easier to find, we recommend creating a special folder on your computer.

Note: DO NOT plug in your spirometer until step 3 below.

1. Creating a new folder on the C:Drive
   a. Go to My Computer
   b. C: Drive
   c. File: New-> Folder
   d. Name this folder COPDGene2_EZWare

2. Setting up the EasyWare software to write to this Folder (COPDGene2_EZWare)
   a. Open ndd EasyWare from your desktop
   b. Go to File-> Preferences
   c. Click on the “Browse” key to open the “Database path and name” (See Figure 10-1)
   d. Look in: Local Disk (C:)
   e. Select the COPDGene2_EZWare folder (See Figure 10-2)
   f. Under File Name, enter: Centercode_COPDGene_Spiro (See Figure 10-3)
      *Enter your 3-letter center code in the file name. Example: NJC_COPDGene_Spiro
   g. Click “Open”
   h. Returns user to EasyWare Preferences (See Figure 10-4)
   i. Click “OK”
   j. Pop-up box, “The program must be restarted”: Click “OK” (See Figure 10-5)
   k. Reopen ndd EasyWare from your desktop
   l. Pop-up box, “New database will be built”: Click “OK” (See Figure 10-6)
   A new database is created and located on your C:Drive

3. NOW, plug in your spirometer and then reopen EasyWare. You will see all of your spirometry tests loading into your New Master Database (See Figure 10-7)
Figure 10-1. Setting up EasyWare to Write to COPDGene2_EZWare Folder

Figure 10-2. Finding your New Folder on the C: Drive
Figure 10-3. Enter File Name: Centercode_COPDGene_Spiro

Figure 10-4. New EasyWare Database Master File Location
10f. Medication Use Prior to Testing

The subject’s recent bronchodilator use needs to be recorded on the COPDGene® Spirometry Form. Some commonly used currently available bronchodilators and their classes are listed in the table in section 7c. In COPDGene®, bronchodilators should not be withheld prior to the Study.
Visit. The reason for NOT withholding bronchodilators is to allow for all of the procedures to be completed in a single Study Visit at which time the informed consent will be signed immediately followed by all study procedures. While the assessment of bronchial hyper-responsiveness may be biased because bronchodilators are not withheld, the post-bronchodilator measurements should be unaffected, and for COPDGene® it is the post-bronchodilator measurements that are used to define and assess the Stage of COPD.

10g. Bronchodilator Administration

In order to provide an assessment of bronchial hyper-responsiveness and to establish a diagnosis of COPD and the spirometric stage of COPD, a “Post” bronchodilator spirometry will be performed in addition to the “Pre” bronchodilator test. In COPDGene® study, only Albuterol will be used as the bronchodilator. The brand names of some currently available albuterol HFA formulations are ProAir™ and Ventolin HFA™.

10h. Contraindications

The “Demographics and Physical Characteristics” and “Safety Assessment” forms should be completed prior to performing spirometry to assure that administration of the test or the bronchodilator does not pose a potential health risk. Since COPDGene® requires post bronchodilator assessment for COPD determination, if the participant is unwilling or unable to provide a post bronchodilator measurement, the subject will be excluded from the study. Specifically, spirometry testing should not be done if the subject has or reports any of the following:

- chest or abdominal surgery in the past three months
- a heart attack in the last three months
- detached retina or eye surgery in the past three months
- hospitalization for any other heart problem in the past month
- a resting pulse rate more than 120 beats/minute (participant should be sitting for at least 5 minutes prior to pulse rate determination)

In addition, if the participant exhibits any other co-morbidity (such as unstable angina or pneumonia) that, in the opinion of a site clinician, may affect the performance of the test or jeopardize the participant’s safety, then spirometry testing should not be done. Indicate this on the Safety Assessment Form.

Note that the presence of a respiratory tract infection treated with an antibiotic in the four weeks prior to the visit is a contraindication to testing in the COPDGene® study; this is an issue of not only infection control but also for accurate diagnosis and spirometric staging of COPD.

Ideally, sites could reschedule testing at a later date when the above situations are resolved. If participants are brought back later for spirometry testing, the site should contact the Data Coordinating Center for instructions on processing the data.
10i. Conducting the Visit

A detailed description of the use and operation of the ndd EasyOne™ spirometer, together with instructions for coaching the participant, are included in the ndd EasyGuide™ users’ manual. See the ndd website (www.ndd.ch) for current version of users’ manual. All pulmonary function technicians are expected to have read this document and to be familiar with its contents. A copy of this document should be kept with each spirometer in case questions about the use of the EasyOne™ spirometer arise during testing.

10i.1. Safety checks

Complete the Demographic and Physical Characteristics Form and the Safety Assessment Form prior to testing. Contact the Clinical Center investigator to review the results if prompted to do so on the Safety Form.

For safety purposes, measure each participant’s pulse rate prior to spirometry testing. Resting pulse rate is determined by having the participant sit and rest for 5 minutes prior to the measurement. Testing should not be done on subjects whose resting pulse is more than 120 beats per a minute without prior approval from a physician investigator.

Coordinators should ask the safety questions that are included on the Safety Assessment Form. If required by the Safety Assessment Form, the PI will determine if the subject should continue with Albuterol administration or not. Clearly document actions taken on page 2 of the Safety Assessment Form.

10i.2. Preparing to conduct the spirometry maneuver

In order to minimize the risk of cross-contamination, technicians should wash their hands before the start of the test and should use the Spirette™’s packaging to remove a mouthpiece (the Spirette™) from its storage container for the participant to use. Insert the clean Spirette™ into the spirometer. Be careful to ensure that the arrow on the Spirette™ is lined up with the arrow on the spirometer.

Testing should be conducted with the participant in the sitting position. A chair with arms and without wheels should be used for the testing, and the participant should sit erect with chin slightly elevated. The purpose of the chair is to support the participant in case she/he faints during the maneuver.

Instruct participant to loosen any tight clothing that might restrict maximal inspiration. Some individuals may have difficulty doing the spirometry maneuver due to urinary incontinence. Offer the participant a chance to use the bathroom prior to testing.

Dentures should be left in place if they are not loose to help keep a tight seal around the mouthpiece. If they are loose, have participant remove them and provide a paper plate or clean container to place them on or in.

All maneuvers should be performed with the participant wearing a nose clip. This clip prevents air from moving through the nose during the test. Noseclips should be cleaned with alcohol.
wipes between tests or disposed of after each use. Some participants do not tolerate nose clips, as an alternative the participant can hold their nose with their fingers during the test.

10i.3. Enter the participant data into the spirometer

Prior to conducting the test, participant information must be entered into the EasyOne™. It is easiest to do this via the EasyWare™ software on your computer (the spirometer must be connected to the computer while you do this). Choose the “Edit” menu and the “New Patient” option. Below are instructions for each field:

• ID field: Enter the participant’s COPDGene® ID number. This must be done in order to link the participant’s questionnaire data with their spirometry data.
• Name field: Leave blank. Please do NOT enter the participant’s name into the spirometer.
• Tech ID: Enter the 3-letter initials of the coordinator performing the test.
• Other fields: Enter the subject’s age, height, weight, ethnic category, gender.
  o Ensure to use appropriate units requested on device when entering height and weight. Failure to enter all these data will result in incomplete data that may not be usable in COPDGene®.

10i.4. Explain the purpose of the spirometry test

Explain that the purpose of the test is to check on the health of the participant’s lungs. Emphasize that, although the procedure does not hurt, in order to get useful and valid results he/she must breathe as hard and as fast as possible when told to do so and will need to repeat the procedure a few times. Depending on the cultural setting in which the testing is done, subjects may need repeated assurances that spirometry does not hurt them or damage anything.

10i.5. Demonstrate the maneuver

Explain that the participant should:

• Take in as deep a breath as possible
• When his/her lungs are totally full, quickly position the mouthpiece
• BLAST out the air as hard and as fast as possible.

A vigorous demonstration of the maneuver by the technician will help to prevent wasted time and effort caused by the participant’s lack of understanding. Demonstrate the correct placement of the mouthpiece. The technician should take a deep breath and emphasize the maximal depth of inhalation. He/she should then demonstrate the proper positioning of a demonstration Spirette™ mouthpiece and dramatically blast the air out as fast as possible. The technician should also demonstrate at least six seconds of exhalation so that participant understands the actual length of the blow.

10i.6. Coaching the participant and troubleshooting problems

Because the adequacy of these maneuvers is highly dependent on participant effort, the technicians must guide the participant through the breathing maneuvers. It is extremely important to inhale maximally and to exhale forcefully and maximally for a minimum of six (6) seconds. Tell the participant when to start taking in a deep breath and to put the mouthpiece in his/her mouth. Then tell the participant to blast out the air and to continue exhaling for at least 6 seconds.
Observe the body language of the participant as he/she attempts to follow the instructions, and encourage the participant to continue blowing out smoothly without re-breathing. Instruct the participant to remain erect and not to bend over during the maneuver, and to keep their feet flat on the floor.

10i.7. Pre-bronchodilator test

After instructing the participant about the procedure for spirometry testing, proceed with the actual testing, following the procedures outlined in sections 5.2 to 5.4 of the ndd EasyGuide™ Users’ Manual and the detailed steps in this Manual of Procedures on page 84.

The initial series of maneuvers is performed BEFORE administering the bronchodilator. Follow the computer prompts until a successful test session has been obtained. A successful test session is defined as at least three acceptable maneuvers, with the two best FEV₁s and the two best FVCs from these maneuvers both within 150 milliliters of each other.

10i.8. Administer the bronchodilator

After at least 3 acceptable and 2 reproducible maneuvers (see below for definitions of “acceptable” and “reproducible”) are obtained, administer two puffs of bronchodilator (albuterol, a short-acting beta-agonist) to the participant using a spacer. A large-volume spacer (Aerochamber™ preferred) should be used. A timer should be set up to sound 15 minutes after the last administered puff of bronchodilator. During the waiting time, the coordinator may administer the study questionnaires. The effect of the bronchodilator will persist, and actually slightly increase, for at least the next 30-40 minutes. Coordinators may therefore choose to fully complete the questionnaires between the pre- and post-BD maneuvers, but should not wait more than 40 minutes from the last administered puff to do the post-BD spirometry.

10i.9. Post-bronchodilator maneuver

The post-bronchodilator (post-BD) maneuver can start anytime after the 15-minute wait, but is preferred to be within 15-20 minutes after administering the bronchodilator. Twenty minutes post-BD is the optimal amount of time to wait before administering the post-BD spirometry test. The same criteria of at least 3 acceptable and 2 reproducible maneuvers should be followed. It is not critical that the post-BD maneuver be done immediately at 15 minutes, but rather that it be done at least 15 minutes but not more than 40 minutes after the last administered puff of bronchodilator.

10i.10. Print results

Print the results for each subject and maintain a hard copy at the Clinical Center as a source document.

Clinical Centers wishing to give participants a hardcopy printout of their results can do so (if IRB approved) following the instructions in the ndd EasyGuide™ Users’ Manual. Clinical Centers choosing to give such printouts to their participants are encouraged to provide guidelines for interpreting the results. It is strongly suggested that Clinical Centers provide reports to subjects’ primary care physician (with subject consent and IRB approval).
10j. Step by Step Spirometry Instructions

10j.1. Verify EasyOne™ calibration
   a. Power on the EasyOne™.
   b. Choose “Check Calibration” from the main menu on the spirometer.
   c. Insert calibration Spirette™ into EasyOne™, matching arrows on both (designate one Spirette™ for calibration use only).
   d. Connect 3L syringe to Spirette™ using adapter.
   e. Press ENTER on EasyOne™ to start the verification.
   f. When tone is heard, withdraw one full pump stroke then inject one full pump stroke.
   g. Ensure “Calibration Check Passed” message appears on EasyOne™ screen.
   h. Choose “Quit.”

10j.2. Conduct the pre-bronchodilator spirometry

Note: The subject must have already completed and passed the Safety Assessment and if necessary been approved for albuterol use by one of the site’s Investigators prior to spirometry.
   a. Connect the EasyOne™ USB cable to the computer’s USB port.
   b. Launch the EasyWare™ software via the desktop icon.
   c. First time only: Choose “File,” then choose “Preferences,” and ensure that “Screen Connector” is selected.
   d. Power on the EasyOne™ and connect it to the cable. (“Device Connected” will display at the bottom of the EasyWare™ window.)
   e. From the Edit menu, choose New Patient, and enter the subject identification numbers, three-letter Tech ID, date of birth, height, weight, gender, asthma status, ethnicity, and smoking status. Confirm with OK.
   f. Insert a new Spirette™ into the EasyOne™, matching the arrows on the front of both.
   g. From the View menu, choose Test On-Line.
   h. To perform the Forced Vital Capacity maneuver, do the following on the EasyOne™ device keypad:
      i. Use (>) to highlight ‘Recall’ and press ENTER to choose it
      ii. Use ENTER to choose “Last Test”
      iii. Verify the subject ID number and press ENTER.
      iv. Press ENTER to choose FVC (Expiratory)
      v. **It is extremely important that prior to the first test, the spirometer flow is zeroed.** In order to zero the spirometer, the EasyOne™ will prompt to “block the Spirette™.” At the prompt,
         (1) place the spirometer on a flat surface so that it is not moving,
         (2) block the expired end of the Spirette™, and
         (3) then press ENTER
         (4) after a few seconds the unit will indicate it is ready to test
      vi. When prompted, with “Blast Out,” assist participant in applying nose clips and instruct them to execute a forced expiratory maneuver.
vii. View results on computer. Review computer screen to assess adequacy of spirometry. Reinstruct subject if necessary.

viii. Highlight “Retry” and press ENTER when ready to continue.

ix. Repeat steps vi through vii until three acceptable and reproducible efforts have been recorded, in accordance with 2005 ATS criteria (highest two FEV$_1$ and FVC volumes within 150 mL of one another), or until 8 efforts have been made. **Note: The EasyOne™ software may consider a session complete before these criteria have been met. If that is the case, choose the ADD option to continue the session.**

x. If the “Acceptable” message appears, use (>) to highlight ‘Post’ and press ENTER to choose it, which prepares the device for post-bronchodilator efforts.

xi. If you do not see the “Acceptable” message, Use (>) to highlight ‘Quit’ and press ENTER to choose it. Then Use (>) to highlight ‘Post’ and press ENTER to choose it, preparing the device for post-bronchodilator efforts.

xii. It is not necessary to include the pre-bronchodilator FVC and FEV1 on the Spirometry form. However, you should retain at least one hard copy of all data at your site.

### 10j.3. Bronchodilator administration

Once three acceptable, reproducible efforts have been made, use the spacer to administer two puffs of Albuterol.

a. Instruct participant to exhale before each puff. Once dose is administered, instruct participant to inhale slowly and deeply, and hold his/her breath for 10 seconds.

b. Record the time of bronchodilator administration on the Spirometry form. The post-bronchodilator spirometry should be done 15-40 minutes later.

### 10j.4. Post-bronchodilator spirometry

a. Power on the EasyOne™ if it has shut itself down

b. To perform the Forced Vital Capacity maneuver, do the following on the EasyOne™ device keypad:
   i. Choose ‘Perform Test’ with ENTER
   ii. Use (>) to highlight ‘Recall’ and press ENTER to choose it
   iii. Use ENTER to choose ‘Last Test’
   iv. Verify that the info on the screen matches the participant you are testing
   v. Press ENTER to choose this participant
   vi. Ensure that the test says “FVC Post Med.”
   vii. Choose ADD to add a post-bronchodilator session to this test.
   viii. In order to zero the spirometer, the EasyOne™ will prompt to block the Spirette™ – do so, and press ENTER. The spirometer will zero in a couple of seconds and indicate it is ready to test.
   ix. When prompted, with “Blast Out,” assist participant in applying nose clips and instruct them to execute a forced expiratory maneuver after correctly placing the Spirette™ in their mouth.
   x. View results on computer. Review computer screen to assess adequacy of spirometry. Reinstruct subject if necessary.
xi. Select RETRY when ready to continue.

xii. Choose Next to begin the next maneuver.

xiii. Repeat steps ix through xii until three acceptable and reproducible efforts have been recorded, in accordance with 2005 ATS criteria (best two FEV1 and FVC volumes within 150 mL of one another), or until 8 efforts have been made. **NB: The EasyOne™ software may consider a session complete before these criteria have been met. If that is the case, choose ADD to continue the session.**

xiv. Quit when the session is complete.

xv. Look at the computer and complete the Spirometry form. Use the best values of the post-bronchodilator FVC and FEV1 from the acceptable tests (see below). The FVC and FEV1 do NOT need to be from the same test.

For new nonsmoker controls only, complete the Assignment to GOLD group form on the COPDGene® website. Enter the post-bronchodilator values for FVC and FEV1. Also enter the predicted values for FVC and FEV1 (the values are obtained from the pre-bronchodilator tests)—the percent predicted will be calculated from these values.

**Failed Spirometry Tests**
If a participant does not receive a passing grade during the study visit (a grade of A, B, or C), after eight trials, it is the coordinator’s responsibility to inform the participant of a possible return visit. The coordinator should alert the participant to the possibility of a return visit to re-test the subject in spirometry. This may not be required after the PFT Core reviews the failed tests, but it is better to notify the participant at the time of the study visit.

**Test Session Quality Grades**

- **A** 3+ acceptable, best 2 match within 100ml
- **B** 3+ acceptable, best 2 match within 150ml
- **C** 2+ acceptable, best 2 match within 200ml
- **D** only one acceptable maneuver, or reproducibility > 200 ml
- **F** no acceptable maneuvers

Daily reports will be sent to the clinical centers for subjects who have failing grades from the Utah grading and review. If you receive a failing grade from this review, you will need to schedule a second study visit to retest the participant in spirometry.

**10j.5. Print your results**

a. On the computer in EasyWare™, highlight the row that contains the subject’s tests.

b. Go to file, select print.

c. Print the test.

d. Save a hard copy at the Clinical Center as a source document.
10j.6. Making a copy of the master database to upload to the PFT file depot

All data that the PFT Core needs is in the "Easyware.mdb" file. Make a copy of the file, rename the file with today’s date and your center ID (see steps below). **You must rename the .mdb file at each new upload.**

a. Connect the Spirometer to you computer
b. Go to My Computer
c. Open the C: Drive
d. Select the COPDGene2_EZWare Folder
e. Select the Centercode_COPDGene_Spiro.mdb file
f. Go to File-> Copy
g. Go to File-> Paste, to paste the copy into your Folder
h. Rename the file to Centercode_COPDGene_Spiro_MM_DD_YYYY.mdb

*Centercode is your 3- letter clinical center code (NJC, MSM, JHU, etc.)*

*You must rename the .mdb file for each new upload to the File Depot!*

For example: Uploading a file from Iowa on July 14, 2013, you would name the file the following:

"UIA_COPDGene_Spiro_07_14_2013.mdb"

This will provide a unique name for every site on every day that they upload. (If you fail to rename the files, it will overwrite existing files.) If your center uploads spirometry data from multiple sites, the center code should have a 1 or 2 after the site name to distinguish between the two locations. Please use the following format:

Center 1: “PIT1_COPDGene_Spiro_07_14_2013.mdb”
Center 2: “PIT2_COPDGene_Spiro_07_14_2013.mdb”

**Upload Spirometry Test to the COPDGene® Website**

a. Open your internet web browser and go to the COPDGene® website (https://dccweb.njhealth.org/sec/COPDGene/MainPage.cfm).
b. Log into the website. If you have lost your log-in information, contact Ruthie Knowles (KnowlesR@NJHealth.org) at the DCC.
c. On the left panel, click on “PFT Files.”
d. Log into the website again.
e. Click on the button across from the group called “COPDGene®: Your Site.”
f. Click on the Choose file button and locate the new spirometry file you just saved (see the directions below if you cannot find it).
g. Click on the .mdb file and choose to open it.
h. Click “Add File Now.” You should now see your file in the table.
i. Use the comment section on the spirometry form to include information on the test you upload.
If you are unable to find the .mdb file on your computer, follow these steps:

a. Open the EasyWare™ software on your computer.

b. Click on File.

c. Click on Preferences.

d. In the text box below Database Path and Name, is the place where your .mdb file is located.

e. The location for your database file is: C:\COPDGene\EZWare\COPDGene_Spiro_CenterCode.mdb. You should find your file in this location, unless you or someone else has changed the settings for the software.

10k. Acceptable and Reproducible Maneuvers

For the purpose of spirometry testing, “acceptable” is defined as a maneuver that is free from error. “Reproducible” is defined as being without excessive variability between maneuvers. The following are some errors that can be seen or calculated from a forced expiratory maneuver and that can affect acceptability: hesitation or false starts, cough, variable effort, glottis closure, early termination, and leaks.

Three acceptable maneuvers are needed to determine reproducibility. The two highest values for FVC and FEV₁ taken from acceptable forced expiratory maneuvers must show minimal variability (preferably within 150 milliliters of the second highest FVC and FEV₁). It is also important to inspect the volume-time curves to determine if the size and shapes of the curves are reproducible.

The American Thoracic Society defines FEV₁ and FVC as the highest measurements from acceptable and reproducible maneuvers. **It is not necessary that they all come from the same maneuver.** The FEV₁/FVC and FEV₁/FEV₆ ratios are computed as the ratio of the individual measurements. In order to obtain these results, select the “best value” setting from the system configuration menu (see section 8 of the EasyGuide™ Users’ Manual).

When errors occur, review common errors with the subject before proceeding with additional maneuvers.

Ask the participant to watch the technician perform the FVC maneuver again. The technician should demonstrate the correct placement of the mouthpiece, emphasize the maximum depth of inhalation, and then blast out the air. If the participant tries again and the reproducibility criteria are not met, the technician should continue administering the test as needed (up to a total of eight maneuvers), assuming that the subject is able to continue.

Some participants will never be able to provide three acceptable and having two reproducible maneuvers is OK. The goal is to meet the acceptability and reproducibility criteria, but these are not absolute requirements for data to be used. Previous studies have shown that inability to perform reproducible spirometry, even with good coaching, is an important risk factor in predicting future health.
10. Reference Values

To interpret spirometric results, they must be compared either to a subject’s previous results or to a published set of “predicted reference values.” Such predicted reference values typically describe the average lung function for an individual of a given age, height, and sex, and such equations have been published for a variety of racial groups.

Typically, lung function measurements are expressed as a percent of predicted. One hundred percent of predicted represents the average value for the population, but normal, healthy individuals will exhibit a wide range of values about this level. In general, values of 80% or greater for FEV₁ and FVC are considered to be in the normal range. Individuals whose test results are below this level may have an abnormality.

The ndd EasyOne™ spirometer offers a number of published predicted values, most of which were derived from studies of largely white participants. Four ethnic correction settings are available that allow you to customize the amount of adjustment that is made for selected racial groupings. Consult the EasyGuide™ users’ manual, sections 8 and 12, for more information regarding the use of prediction equations. For COPDGene®, we will use the reference values that were derived from the 3rd National Health And Nutrition Examination Survey (NHANES III) in the United States (Hankinson et al., AJRCCM 1999; 159:179-187). This study used a large, randomly selected subset of the entire U.S. population, which included a variety of ethnic groups and strict attention to quality control according to current American Thoracic Society guidelines.

Choice of reference values in the ndd EasyOne™ spirometry software only affects the printouts available from the spirometry software, which sites may choose to give to the participants. For the official COPDGene® dataset for each site, the COPDGene® Operations Center will create local prediction equations based on healthy never smokers at that site. In addition, the official COPDGene® dataset will contain additional prediction equations based on the United States NHANES III equations for white participants.

10m. Implementation of Spirometry Quality Control

The Epidemiology Standardization Project, the American Thoracic Society spirometry standards, and recent evaluations of commercially available spirometers emphasize the importance of spirometry quality control (QC) procedures.

10m.1. Factors Affecting Spirometry Quality

a. Participant: A subject may not take as deep a breath as possible or exhale as forcefully as possible at the start of the maneuver. Several possibilities will prevent a maneuver from being acceptable: an involuntary epiglottis closure, temporarily cutting off the flow of air; an early termination of the maneuver, preventing the achievement of a plateau; or a variable effort. Coughing during the maneuver or a leakage due to the participant’s inability to keep a tight seal around the mouthpiece also will prevent you from obtaining a good maneuver. To address these sources of error, it is very important to have technicians trained to watch the participant closely during the test performance and accurately review
the displayed flow-volume curves on the computer monitor. The technician thus can guide and explain the source of error to the participant.

b. **Technician:** Improper coaching or non-standardized coaching procedures will negatively affect the quality of the spirometry testing. The technician should clearly instruct the participant on how to perform this test, demonstrate the maneuver, and watch the participant closely during the performance to avoid unacceptable errors and obtain the best effort from the participants. He/she must be trained to recognize patterns of unacceptable maneuvers and perform equipment checks. COPDGene® will monitor and provide periodic feedback on each technician’s performance.

c. **Equipment:** Leaks in the system, differences in temperature, and poor calibration are all factors that affect the quality of the test results. Daily spirometer calibration checks should be performed using a 3.00 Liter syringe as the “gold standard.” Refer to section 14 of the EasyGuide™ users’ manual for instructions.

d. **Analysis:** A combination of all factors may affect the quality of the results. Results from the calibration factors, technician’s impression of test session quality, and the QC supervisor’s impression of test session quality are all integrated to obtain the final FEV₁ and FVC results used in the study.

**10n. Spirometry Calibration, Maintenance, and Hygiene**

The EasyOne™ spirometer is designed to minimize the need for cleaning and maintenance (see sections 13 and 14 in the EasyGuide™ Users’ Manual). The surface of the spirometer and cradle may be cleaned by wiping with a damp cloth. If a more thorough cleaning is desired, the spirometer and its Spirette™ cavity may be cleaned with an alcohol wipe or a soft cloth that has been lightly moistened with isopropyl alcohol. **Do not let liquids flow into the Spirette™ cavity of the spirometer while cleaning.** The disposable Spirette™ eliminates the need for cleaning the spirometer between patients. The Spirettes™ are designed for single patient use only, and must be removed and disposed of after each patient.

Additional guidelines for hygiene and infection control are provided by the American Thoracic Society and include the recommendation that the technician and patient wash their hands after testing and that proper attention be given to environmental controls in settings where tuberculosis or other diseases spread by droplet nuclei are likely to be encountered. Participants with evidence of obvious upper respiratory infections should not be tested, but rather rescheduled for testing at a later date.

Beyond battery replacement and the calibration check described below, no periodic maintenance is required or recommended on the spirometer or cradle. No service should be performed on the spirometer except by manufacturer-authorized personnel.

*On each day a subject will be tested, and prior to the first participant tested, the spirometer calibration should be checked with a 3.00-Liter calibration syringe that has been stored next to the spirometer. The calibration procedure requires the ndd calibration adapter to connect the syringe with the spirometer.*
To clean the nose clips, they should be wiped with alcohol after each use or discarded.

10o. Trouble Shooting

Refer to the section 15 of the EasyGuide™ Users’ Manual for troubleshooting tips.

10p. ndd EasyOne™ Configuration Settings for Use in COPDGene®

When setting up your EasyOne™ spirometer, use the following settings for compliance with COPDGene® protocol.

Test Settings:
1) Predicted = “NHANES III”
2) Add Ped = “Blank”
3) Value Sel = “Best Value”
4) Interpretation = “-- -- --”
5) Lung Age = “OFF”
6) Automatic QC = “ON”
7) FVC Selection = “FVC”
8) PEF unit = “L/sec”
9) African ethnic = 88%
10) Asian = 100%
11) Hispanic = 100%
12) Other ethnic = 100%
13) Curve Storage = “3 Best Curves” <Very Important!!! >

General Settings:
1) Time Format = 24 hr
   Date Format = “MM/DD/YY”
2) Date = Enter correct date
3) Time = Enter correct time
4) Alpha-ID = “YES”
5) Tech ID = “YES”
6) Syringe Vol = 3.0 Liter
7) Height Unit = “m/cm”
8) Weight Unit = “kg”
9) Age/Birth = “AGE”
10) Contrast = 8 or adjust as needed
11) Language = “ENGLISH”
12) Altitude = 0 or set to approximate (100 meter increments)
13) Op Mode = “DIAGNOSTIC”
14) Temp = “C”
15) Rel Humidit = Best average guess (0 to 100%)

Report Settings:
1) Printer Type = “Via PC”
2) Result Data = “3 Best Data”
3) Number of Curves = “3 Best Curves”
4) Graph Types = “Small FV & VT”
5) Header 1 to 4 = “Text that you want to print on the report” Some centers may choose to enter their Center’s 3 letter code and COPDGene®

10q. Spirometry Checklist

Clinical Center Coordinators are encouraged to print and use this checklist as an aid during performance of the spirometry testing.

Subject Identification Number:_______ Test Date:_______

<table>
<thead>
<tr>
<th>Action</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calibrate spirometer</td>
<td>□</td>
</tr>
<tr>
<td>Safety Assessment Form administered</td>
<td>□</td>
</tr>
<tr>
<td>Prepare to conduct spirometry</td>
<td>□</td>
</tr>
<tr>
<td>Confirm race/ethnicity of participant</td>
<td>□</td>
</tr>
<tr>
<td>Explain purpose of test</td>
<td>□</td>
</tr>
<tr>
<td>Demonstrate maneuver</td>
<td>□</td>
</tr>
<tr>
<td>Complete pre-bronchodilator test</td>
<td>□</td>
</tr>
<tr>
<td>Administer bronchodilator</td>
<td>□</td>
</tr>
<tr>
<td>Wait 15-40</td>
<td>□</td>
</tr>
<tr>
<td>Complete post-bronchodilator test</td>
<td>□</td>
</tr>
<tr>
<td>Print results</td>
<td>□</td>
</tr>
</tbody>
</table>

10r. Common Questions and Answers for the ndd Spirometer

This document summarizes various problems that have been reported by sites when using the ndd spirometer. If you are experiencing problems with the ndd, review this document to see if your problem is described and see if the proposed solution takes care of the problem. If not, then contact the PFT Core or ndd directly.

1. CALIBRATION CHECK ERRORS

Problem: Unable to obtain an acceptable calibration check.

Explanation: It is not possible for the user to change the calibration in the EasyOne™. EasyOne™ will not change its calibration since it uses ultrasound transit time measurement. To enable customers to check the calibration, however, EasyOne™ includes a calibration check program. The procedure for this calibration check is described in the manual. Potential reasons for failed calibration checks are summarized below, with potential solutions noted below.
a. The calibration syringe may be defective.

Solution: The syringe itself may be defective, or it may require a special adaptor to properly attach to the Spirette™. Hans Rudolph makes a calibration syringe specifically designed for use with the ndd, and we recommend that sites use this syringe. An advantage of the Hans Rudolph syringe is that it can be properly connected to the Spirette™ without the need for a flexible tube, which can be an additional source of calibration errors.

b. Faulty ndd device.

Solution: We are aware of at least one instance where the ultrasound transducer was not mounted correctly in the factory and therefore resulted in excessive variability (up to 10%) during calibration tests. If you suspect you may have a faulty device, notify the Operations Center, which will in turn notify ndd. If the unit is indeed defective, ndd will replace it.

c. The grey calibration adapter is broken or has been used without the necessary second screen inside. This can cause an increased variation in the calibration check.

Solution: This problem only applies for instruments with a serial number below 46000. All EasyOne™ with serial number 46000 and higher use an improved calibration adapter design that solves this problem. However if you have an older device this may still be an issue and we recommend that you use a more recent instrument if possible.

d. The room is very ‘windy’ because the windows and the doors are open to supply cooling or the spirometer is close to a heating/cooling vent.

Solution: This can interfere with the calibration checks, especially regarding the inspiratory values. During the cal check staff should make sure that there is no noticeable air draft in the room.

e. Additional reasons for an inadequate calibration check are that the baseline was not set correctly at the beginning of the cal check (see below) or that the syringe was not pulled in or out completely

Solution: Check for these issues and repeat the calibration.

In addition to the calibration check routine, it is also possible to do a calibration check in the FVC program. However, this is discouraged for the following reasons:

There is a 4% BTPS correction built into the test that causes an over estimation of the flow and the volume by 4%. The reason for this correction is that the gas in the lung is warmer than when it arrives in the sensor. This cooling down of the gas also causes a volume reduction.

FEV₁ values will be different since in human tests the FEV₁ calculation needs to follow ATS algorithms. If there is slow flow before the actual start of the blow, this would cause a lower FEV₁. To correct for this, the t-zero point is calculated by back extrapolation from the maximum volume increase in the Volume Time Curve. FEV₁ values are therefore hardly comparable between the syringe and the EasyOne™. The better the syringe stroke simulates a human spirometry test, the closer the two FEV₁ values will be.
The flow parameters (PEF) can usually vary more than the Volume parameters. In the ATS waveform test a variation of +/- 12% is allowed for PEF. This is because gas can be compressed and resistance between syringe and sensor can influence the result.

2. **SETTING ZERO FLOW BASELINE**

**Problem:** The EasyOne™ does not stop at the end of the test, or volume parameters are inaccurate in the calibration.

**Explanation:** Prior to every FVC test or calibration check, the zero flow baseline needs to be set. You should see the message “setting baseline. Block Spirette™ to avoid flow” on the screen. The technician should make sure that there is absolutely no flow through the Spirette™ while the baseline is set. Hold the instrument still and block the Spirette™ or hold the instrument close to the body to make sure there is no flow. If the baseline is not set correctly, there is an offset in the flow measurement. This causes an inaccuracy in all of the measured FVC values. The longer the measurement takes, the bigger the error in the result. If there is a 20 ml offset, the error after 8 seconds in the FVC value is 160 ml. In the FEV$_1$ value the error is only 20 ml.

If EasyOne™ does not stop at the end of the maneuver, there is most likely an offset in the baseline and the instrument continues to accumulate volume. If the volume-time curve shows a very long test, and there was a very low volume accumulation over many seconds, the baseline was probably not set correctly.

3. **SMALL CURVES**

**Problem:** Technicians have sometimes observed that there are sometimes small curves between normal maneuvers. Quality Grades were poor even though the maneuvers look good.

**Explanation:** The test was started too late. The instrument was started by pressing ENTER after the patient had already started blowing. Only a part of the maneuver was captured by the EasyOne™. This could happen because the instrument was not held by the patient but by the technician. Most of these curves are not selected as best curves since the FVC is too low. The flow volume curves look strange on the printout since they start immediately with the peak flow, and of course it was smaller since the total volume measured was smaller. This problem can be very frustrating for the participant since it triggers a bad reproducibility of maneuvers message even though the patient gave their best.

This problem can be easily avoided if the patient holds the instrument themself. The instrument is very robust and there is no need to fear that the patient might break it, for instance by dropping it. The technician should start the instrument and hand it over to the patient. EasyOne™ automatically recognizes when the actual test starts. EasyOne™ will recognize an incorrect trial and give a coaching message.

4. **“ERROR 6” MESSAGE**

**Problem:** Some instruments have occasionally displayed an “error 6” message on the screen. The message prevents further test maneuvers from being performed on the patient.
**Explanation:** This problem should have been fixed with the Firmware Version 1.20. The “error 6” message means that a database conflict came up without reason. This should only be possible in very rare cases, but ndd reports that it could reproduce the effect. Fortunately no data are lost when the message comes up, although as noted it is not possible to add further trials or a post test to the session. If the problem does occur, it is strictly a software issue and does not indicate a problem with the spirometer device itself.

5. **EASYONETM WON’T ACCEPT ADDITIONAL TRIALS**

**Problem:** Some technicians have reported that they have tried to add more trials but the equipment does not seem to take the new data.

**Explanation:** EasyOne™ allows up to 15 trials per test session. Since ATS recommends stopping after 8 trials if no good results can be achieved, 15 seems to be a safe maximum number. If after 5 trials, the patient has reached a QC Grade C, the instrument considers the test session to be sufficient and suggests ending the test. However, it is certainly possible to add more trials at this point.

One reason for this perceived problem may be a misunderstanding of the device display and its operation: The following screen is shown after a trial:

![Screen](image)

The information on the display depends on the test status:
- If the test is **not finished** the display shows the **best** and the **current** curve. The numeric results to the right are also from these curves.
- If the test session is **finished**, the results from the **two best** curves are shown.

This means that if a curve is added after the EasyOne™ thinks the session is finished and the result of this trial is lower than the two previous best results, the screen only shows the two best tests. Staff also need to understand the criteria EasyOne™ uses to determine a test session is finished. The ndd software considers the session to be finished, and hence recommends stopping:
- As soon as a quality grade of A or B is reached, or
- If, **after 5 trials**, a quality grade of **at least C** has been reached

As noted previously, even though the ndd EasyOne™ device deems the session to be finished, the technician can still add additional tests, up to a maximum of 15, in order to get a better QC grade. The technician just needs to realize that the results from the new curve will only be displayed in this case if it is one of the two best curves in the session. Even if the display does not change, the curve is stored in the database. Only when 15 trials are reached it is not possible to add any more trials.

As soon as a POST test has been started, it is no longer possible to add trials to the PRE test. However an additional 15 trials may be conducted for the POST test, for a total of 30 overall. (see also #10)
6. "KEEP GOING...” MESSAGE

Problem: Sometimes the tests do not stop and the “Keep going…” message is shown.

Explanation: In most cases this happens due to incorrect baseline setting (see #2 above). At the beginning of a new test session make sure the user blocks the Spirette™ to avoid flow. If this is not done carefully, a wrong flow offset can be set which leads to the described behavior.

7. POWER DOES NOT TURN ON/OFF CORRECTLY

Problem: the device cannot be switched on or off.

Explanation: ndd has not been able to reproduce this problem, and would appreciate more information in order to properly investigate the issue. If the problem occurs, please supply the following information: does the issue always happen with the same device, how often does it happen, and under what circumstances does it happen? In the meantime, if the problem does occur it should be remedied by replacing the battery. No data can be lost by removing the batteries.

8. FLOW-VOLUME CURVES HAVE STRANGE SHAPE

Problem: Some of the flow-volume curves have a strange shape and the FEV₁ and FVC values are low (see curve marked with red and heavy line below). (See also #3 above)

Explanation: This happens if the patient blows before the device is ready to accept flow; it should not happen for the very first trial since the baseline is required to be set for this maneuver. The problem appears to result from the manner in which the tests are performed at some sites. The operator would hold the device while the patient inhaled through it prior to the exhalation. At the end of the inhalation the operator would press the ENTER key to start a new trial.

The ndd EasyOne™ has a delay of approximately one second between pressing the ENTER key and the device being ready to measure flow. The spirometer beeps when it is ready. If the patient is already exhaling when the key is pressed or shortly after that, this leads to the unusual curves. This also leads to strong variations in the measurement results.
These bad curves are usually not accepted in the final results since the parameters are all low. However it is frustrating for the interviewer/technician and the patient when they do not get acceptable results. The interviewer should make sure that the instrument is started early enough, at least one second prior to the forced exhalation. (see also #3 above)

9. QUALITY GRADE GETS WORSE

Problem: It can happen that the quality grade changes from A or B to C (e.g., gets ‘worse’).

Explanation: This can happen if an acceptable trial is added that has substantially better values than the previous best trial, thus causing the variability between the two best maneuvers (the difference between the two best values) to increase. Depending on the magnitude of the difference, the quality grade can even change to a D. (see also #5 and #11)

In some cases the screen will display the message “Deeper Breath” when this happens. In this particular case the message is misleading and should probably state, “Great effort. Do another just like it!” The technician should be aware of this and coach the participant accordingly. ndd hopes to change this message in a future version of the software.

10. EASYONE™ WON’T ACCEPT POST TEST DATA

Problem: Sometimes the wait after administering a BD is so long that the device automatically switches off. If the test is recalled then, it is sometimes impossible to do a POST test and only the selection NEW and EXIT is available instead of ADD, POST and NEW.

Explanation: This effect is caused not by the time delay, but by the way the software currently handles PRE tests with 15 trials. Due to a software error, no POST test can be added when doing a recall of a pre test with 15 trials. This problem does not occur as long as there are less than 15 trials in the pre session. This problem has been fixed as of Firmware Version 1.20 of the EasyOne™ software.

Please alert the Operations Center if this occurs with the current version of EasyOne™ or if it occurs in other circumstances than described above with earlier versions of the software.
11. **EASYONE™ Accepts Bad Tests**

**Problem:** Occasionally the EasyOne™ accepts bad curves, which can result either in inappropriate values for FEV₁ and FVC or in inappropriate QC grades.

Specific examples of the situations in which apparently unacceptable curves have been reported as being accepted by the EasyOne™ software are summarized below.

a. A double inspiration due to cough or hesitation in starting

b. Variable effort or cough during a trial

**Explanation:** ndd is aware of this problem and is working on a fix. Please notify the Operations Center of all such instances as they occur so that we can pass them onto ndd for further analysis. In versions of the EasyOne™ software prior to 2.3, there is no way to allow technicians to exclude inappropriate tests on their own. In version 2.3, it is possible to switch off the QC grade function under the “Configuration” menu. When you do this, the device allows you after every trial to reject an acceptable trial or to accept an unacceptable trial. The disadvantage of this option is that you don’t see the QC grades during the test and on the report. Other than this, the test procedures and messages are the same as when the QC grade function is turned on.

With the EasyWare™ you are able to see the QC grades on the screen. (Note that any decisions regarding acceptability or unacceptability may be overridden by the spirometry reading center.)

12. **STAFF DISAGREE WITH GOOD QC RATING**

**Problem:** Even though tests display a grade of A, the technician may disagree with this grade.

**Explanation:** ndd is aware of this problem and is working on a fix. Please notify the Pulmonary Function Core of all such instances as they occur so that we can pass them onto ndd for further analysis (see also #11). In the meantime it is likely that such curves will be detected as part of the central QC review.

**Related Pulmonary Function Documents:**

11. Carbon Monoxide Diffusing Capacity (DLco)

11a. Overview

DLco is a test that measures another aspect of the respiratory system, which is the ability of the lungs to perform gas exchange. It is an important measurement that allows for better and earlier diagnosis of the condition of the lung.

COPDGene® will use a DLco instrument (the ndd EasyOne Pro™) that measures flow and volume by ultra-sound transit time and gas concentrations by both infrared spectroscopy and by ultra-sound molar mass. This instrument meets 2005 American Thoracic Society/European Respiratory Society standards for a DLco instrument.

The results of the DLco testing are used to determine the rate at which gases move across the lung, from the alveolus to the pulmonary capillary blood. It thus assists in evaluating the presence and severity of COPD. The DLco test must be performed according to strict standards by technicians who have been properly trained and certified in how to conduct the maneuver. In addition, the equipment must be in good operating order and the calibration regularly checked. All DLco maneuvers will be reviewed by a central reading laboratory (COPDGene® Pulmonary Function Core) to assure optimal quality of the data and to provide ongoing feedback to the pulmonary function technicians regarding the adequacy of the maneuvers.

11b. Summary of Measures

The following measurements will be obtained through DLco testing during the COPDGene® clinic visits:

A. **DLco (ml CO/min/mmHg)** is the rate at which carbon monoxide (CO) moves through the lung into the hemoglobin in the blood. DLco is lowered in the presence of COPD and other diseases of the lung.

B. **VA (liters)** is the volume of the "alveolar" region of the lungs. This is effectively the Total Lung Capacity (TLC) less the volume of regions that do not participate in gas exchange with the blood (e.g., trachea and larger airways as well as diseased regions that are not ventilated) VA is determined by analysis of helium (He) dilution. VA is often increased in people with air-flow limitations such as COPD and asthma. The VA may also be reduced in patients with restrictive disorders.

11c. Setting for DLco Testing

DLco testing ideally should be performed in a private, temperature-controlled room. All of the instruments necessary for the test should be in the room. The room should be well lit and located in a quiet area. These conditions will improve the quality and reproducibility of the results. For safety, the participant should be seated in a chair with no wheels; preferably the chair should have arms.
For some sites, it may be that testing will be done in non-clinical settings. The ndd EasyOne Pro™ is somewhat portable and has been shown to perform well in the field. Nonetheless, this document assumes that testing will be done in a centralized clinic facility. Sites planning to do otherwise should develop corresponding local procedures detailing off site considerations and document them in their local Manual of Procedures.

Clean mouthpieces (Spirettes™) and nose-clips should be available in the room, as should be a container to collect used Spirettes™. A box of facial tissue paper, paper plate or some type of container to place dentures on or in (if needed), and a trashcan, should be placed close to the participant. It also may be helpful for a source of drinking water to be nearby, as some subjects may get dry mouth as they are performing the maneuvers.

Prior to each test, the ndd EasyOne Pro™ automatically performs a full three-point automatic gas (CO and He) calibration. Therefore, the devise does not need calibration by the technician.

11d. Setting up the ndd EasyOne Pro™ Instrument

Prior to conducting the DLco measurement, the technician should assure that the configurations of the EasyOne Pro™ are set according to the specifications outlined under the “ndd Configuration Settings for Use in COPDGene®” below in section 10j. Failure to have the correct settings may result in lost or deleted maneuvers, which will result in the participant’s DLco results being excluded from analysis in COPDGene®. Ideally, a single person should be designated as responsible for configuration of the EasyOne Pro™ at each Clinical Center. Clinical Centers are strongly urged to set up the DLco device to turn on Mini-Flush to eliminate minor leaks and add the message code parameter to the device. Message codes contain information about errors and warnings associated with the trial and a possible resolution.

11e. Starting the EasyOne Pro

See the ndd manual for power cord placement and power switch. The ndd EasyOne Pro™ is a self contained unit with its own windows based computer and dedicated software, and therefore does not require a separate computer for operation. Once the unit is powered up it will take about 30 seconds for the software to load and to perform some self-checks to ensure that unit is functioning properly. You will then see the main screen. To power the unit on see Figure 11-1 below for the location of the front panel power switch (item d). The "Main" power switch must also be on. This is located on the rear panel of the unit (item q). See Figure 11-2.

The unit will perform a number of self-tests and diagnostics and will alert you if a hardware or software condition exists that will prevent the unit form working properly.

EasyOne Pro™ can be operated under the following ambient conditions:

- temperature +5 to +40 °C (41 to 104 °F)
- relative humidity 15 to 95%, no condensation
- atmospheric pressure 700 to 1060 hPa. (525 to 795 mmHg)
Figure 11-1. EasyOne Pro™

- a Sensor holder, extendible
- b Sensor cable connection
- c Connection for gas supply tube to sensor
- d ON/OFF switch
- e Touch stylus
- f Sensor (see Fig. 10-3)
11f. Medication Use Prior to Testing

The subject’s recent bronchodilator use needs to be recorded on the COPDGene® Spirometry Form. Some commonly used currently available bronchodilators and their classes are listed in the table in section 7c above. In COPDGene®, bronchodilators should not be withheld prior to the Study Visit. The reason for NOT withholding bronchodilators is to allow for all of the procedures to be completed in a single Study Visit in which the informed consent will be signed immediately followed by all study procedures. Post-bronchodilator measurements should be unaffected, and for COPDGene® DLco will only be measured post-bronchodilator.
11g. Bronchodilator Administration

DLco will be performed in addition to the “Pre” and "Post" bronchodilator spirometry tests. In the COPDGene® Study only Albuterol will be used as the bronchodilator. The brand names of some currently available albuterol HFA formulations are ProAir™ and Ventolin HFA™. DLco will be tested only after "Post" bronchodilator spirometry has been performed and a slow vital capacity (SVC) value has been obtained to help judge the quality of the DLco test.

11h. Contraindications

The “Demographics and Physical Characteristics” and “Safety Assessment” forms should be completed prior to performing DLco to assure that administration of the test or the bronchodilator does not pose a potential health risk.

Specifically, DLco testing (as in spirometry testing) should not be done if the subject has or reports any of the following:

- chest or abdominal surgery in the past three months
- a heart attack in the last three months
- detached retina or eye surgery in the past three months
- hospitalization for any other heart problem in the past month
- a resting pulse rate more than 120 beats/minute (participant should be sitting for at least 5 minutes prior to pulse rate determination)

In addition, if the participant exhibits any other co-morbidity (such as unstable angina or pneumonia) that, in the opinion of a site clinician, may affect the performance of the test or jeopardize the participant’s safety, then DLco testing should not be done. Indicate this on the Safety Assessment Form.

Note that the presence of a respiratory tract infection treated with an antibiotic in the four weeks prior to the visit is a contraindication to testing in the COPDGene® study; this is an issue of not only infection control but also for accurate diagnosis and DLco assessment.

Ideally, sites could reschedule testing at a later date when the above situations are resolved. If participants are brought back later for DLco testing, the site should contact the Data Coordinating Center for instructions on processing the data.

11i. Conducting the Visit

A detailed description of the use and operation of the ndd EasyOne Pro™, together with instructions for coaching the participant, are included in the ndd EasyOne Pro™ Operating manual. See the ndd website (www.ndd.ch) for current version of users’ manual. The exact web address of the manual is:

All pulmonary function technicians are expected to have read this document and to be familiar with its contents. A copy of this document should be kept with each EasyOne Pro unit in case questions about the use of the EasyOne Pro™ DLco instrument arise during testing.

11i.1. Safety checks

Complete the Demographic and Physical Characteristics Form and Safety Assessment Form prior to testing. Contact the Clinical Center investigator to review the results if prompted to do so on the Safety Assessment Form.

For safety purposes, check each participant’s pulse rate prior to DLco testing. Resting pulse rate is determined by having the participant sit and rest for 5 minutes prior to the measurement. Testing should not be done on subjects whose resting pulse is more than 120 beats per minute without prior approval from a physician investigator.

Coordinators should ask the safety questions that are included on the Safety Assessment Form. If required by the Safety Assessment form, the PI will determine if the subject should continue with Albuterol administration or not. Clearly document actions taken on the bottom of the Spirometry Form.

11i.2. Preparing to conduct the DLco maneuver

In order to minimize the risk of cross-contamination, technicians should wash their hands before the start of the test and should use the Spirette’s™ packaging to remove a mouthpiece (the Spirette™) from its storage container for the participant to use. Insert the clean Spirette™ into the DLco device. The same Spirette™ can be used for spirometry and DLco testing. Be careful to ensure that the arrow on the Spirette™ is lined up with the arrow on the DLco sensor, see Figure 11-3.
Testing should be conducted with the participant in the sitting position. A chair with arms and without wheels should be used for the testing, and the participant should sit erect with chin
slightly elevated. The purpose of the chair is to support the participant in case she/he faints during the maneuver.

Instruct participant to loosen any tight clothing that might restrict maximal inspiration. Some individuals may have difficulty doing the DLco maneuver due to urinary incontinence. Offer the participant a chance to use the bathroom prior to testing.

Dentures should be left in place if they are not loose to help keep a tight seal around the mouthpiece. If they are loose, have participant remove them and provide a paper plate or clean container to place them on or in.

All maneuvers should be performed with the participant wearing a nose clip. This clip prevents air from moving through the nose during the test. Noseclips should be cleaned with alcohol wipes between tests or disposed of after each use. Some participants do not tolerate nose clips, as an alternative the participant can hold their nose with their fingers during the test.

11i.3. **Enter the participant data into the EasyOne Pro™**

Prior to conducting the test, participant information must be entered into the EasyOne Pro™. First, enter your three-lettered center code into the DLco device. This will display in the top left corner of the saved pdf file.

- From the Main page, click on **Utilities**
- Click on **Configuration**
- Click on the main heading **General** and subheading **Header**
- In the Header 1 row, enter your center code (NJH)
- Click OK

**Adding a New Patient**

To enter new patient information, click on the **Select Patient** icon from the Main Menu screen and then select +**New Patient**.

- Enter a patient ID and press the TAB key or the Enter key (click 🖥️ to enter an automatically generated ID).
- Enter the last and first names in the same way.
- Click “a” (Figure 11-4) to select the gender and press the TAB key.
- Also, select the ethnic origin “b”.
- Enter the date of birth, height and weight.
  * **Note**: The information regarding gender, age, height, weight and ethnic origin must be correct because it is used to calculate the predicted values and to interpret the acquired data. Height and weight must be entered in cm and kg, respectively.

- Additional information can be entered on Smoking History (see Figure 11-4), History and Comment, tab “e” if needed.
**Entering your Tech ID**

To enter your individual technician ID for every new patient, after entering the New Patient information:

- Click on the *History* tab
- In the Referred by field, enter your three-lettered Tech ID (SWB)
- Close the window with OK.

The patient list will be displayed and the new patient is selected.

Failure to enter all these data will result in incomplete data that may not be usable in COPDGene®.

**11i.4. Explain the purpose of the DLco test**

Explain that the purpose of the test is to check on the health of the participant’s lungs. Emphasize that, although the procedure does not hurt, in order to get useful and valid results he/she must breathe out quickly, but not forcibly, continuing until their lungs are empty. After their lungs are empty they will be instructed by the technician to take a full breath to completely fill their lungs. They will hold their breath in for about 10 seconds and then, without force, exhale the air from their lungs. Depending on the cultural setting in which the testing is done, subjects may need repeated assurances that DLco does not hurt or damage the lungs.

**11i.5. Slow Vital Capacity (SVC)**

Before proceeding to the DLco test, a slow vital capacity (SVC) measurement is required. Exact instructions for performing the SVC test are found on section 3.4 of the Operator Manual, pages 50 to 54. You need to obtain the slow vital capacity measurement BEFORE you obtain the DLco tests, as the quality of the DLco tests rely on the subject inhaling at least 85% of his/her vital lung capacity. COPDGene® recommends two SVC tests and the EasyOnePro automatically default to two SVC tests.

Slow vital capacity measurements determine the vital capacity of the lungs, starting from tidal breathing.
SVC Test Procedures

1) Select the patient (see Adding a New Patient section 10.i.3).
2) Prepare the patient (see "Preparations" on page 46) and explain the test maneuvers to him or her.
3) Select Perform Test.
4) Select SVC.
5) Confirm Measured Values.
6) Take the spirette™ into the mouth with the lips sealing around the spirette™, taking care not to block its opening with the tongue or bite down excessively on the spirette™.
7) Instruct the patient to breathe calmly in and out (Tidal breathing).
8) When the start test prompt appears, take a maximum inspiration followed by an immediate, but unhurried, exhalation.
9) When three acceptable trials have been performed, the message Session complete! appears and a quality grade from A (optimal) to F is displayed. (See "Quality Messages and Quality Grades" on page 84 of Easy One Pro User Manual.)

The slow vital capacity acquisition screen appears as seen below.
Fig. 3-19 From the Easy One Pro User Manual page 57

a) Selected test parameters  
b) Predicted values  
c) Volume-time curve area  
d) Start button  
e) Test information and system interpretation area  
f) Click for a retrospective test evaluation or to expand the parameter list (see "Retrospective Test Assessment, Entering Comments" on page 97 of the Easy One Pro User's Manual)  
g) Click to view additional information  
h) Click to perform a new test, to view the patient's test list, to select a new patient and to print a test
11i.6. **Demonstrate the DLco maneuver**

Explain that the participant should:
- Take a few quiet breaths
- Exhale fully so that the lungs are empty
- When instructed, take one full breath in and hold
- Hold his/her breath for about 10 seconds
- After the 10 seconds have elapsed the technician will instruct them to exhale fully

A careful demonstration of the maneuver by the technician will help to prevent wasted time and effort caused by the participant’s lack of understanding. The technician should show all the steps in the DLco maneuver. He/she should then demonstrate the proper positioning of a demonstration Spirette™ mouthpiece and the breathing prior to the test, the inhalation, the 10-second breath hold and the non-forced exhalation.

11i.7. **Coaching the participant and troubleshooting problems**

The DLco maneuver is typically more easily performed than spirometry. There are a few critical aspects to get good results. First it is very important that the subject exhales fully. In the case of some patients with COPD this may take 10 to 15 seconds. Second, a full breath in is absolutely necessary to get accurate DLco measurements. Lastly, the breath hold must be between 8 and 12 seconds. Observe the body language of the participant as he/she attempts to follow the instructions, and encourage the participant to follow the instruction exactly and carefully observe to see that the instructions are properly followed.
11i.8. DLco test

After instructing the participant about the procedure for DLco testing, proceed with the actual testing, following the procedures outlined in sections 3.7 of the ndd EasyOne Pro™ Operation Manual and the detailed steps beginning on page 55.

At least two (2) DLco and no more than five (5) maneuvers are performed AFTER spirometry. Follow the computer prompts until a successful test session has been obtained or five maneuvers have been performed. A successful test session is defined as at least two (2) acceptable maneuvers within 3 ml/min/mmHg or within 10% of the highest value. Acceptable maneuvers are defined by:

1) Inspired volume > 85% of the SVC
2) Inspiratory time < 4sec.
3) Breath hold time 8-12 sec without evidence of leaks or Valsalva or Muller maneuvers
4) Expiratory time <4sec
5) Appropriate clearance of dead space as determined by inspection of the exhaled gases and adjustments of the collection bar as needed

11i.9. Print DLco results

Print the results for each subject and maintain a hard copy at the Clinical Center as a source document.

Clinical Centers wishing to give participants a hardcopy printout of their results can do so (if IRB approved) following the instructions in the ndd EasyOne Pro™ Operator Manual. Clinical Centers choosing to give such printouts to their participants are encouraged to provide guidelines for interpreting the results. It is strongly suggested that Clinical Centers provide reports to subjects’ primary care physician (with subject consent and IRB approval).

11j. Step by Step DLco Instructions

11j.1. EasyOne Pro™ Calibration

Power on the EasyOne Pro™.
The EasyOne Pro™ performs numerous self-tests at startup and prior to every DLco test the unit does an automated 3-point gas calibration. There is no need to do a calibration verification, as these calibration results are stored in the unit's database and are reset for each DLco test performed.

If the EasyOne Pro™ indicates there is a problem with the calibration you should first check the following:

- The Spirette™ is properly placed
- All fittings are secure and that the gas tank has been properly installed and is turned on
- That the cable from the sensor is plugged into the unit
If these fittings and cables are correct, please consult the EasyOne Pro™ Operator Manual for additional messages and remedies. See section 5.3, pg. 69 DLCO Quality Messages and Quality Grades in the EasyOne Pro™ Operator Manual.

If you are unable to proceed or resolve the problem after consulting the Operator Manual, you will need to contact ndd support for further assistance.

Table 11-1 shows how DLco quality grades are assigned for the EasyOne Pro™. The implemented quality grades are designed to provide guidance for determining the quality of DLco test sessions. Note that inspiratory volume, Breath Hold Time (BHT), sample volume, DLco variability, Inspiratory Time and the number of Acceptable trials is considered in determining a quality grade for DLco.

<table>
<thead>
<tr>
<th>Score</th>
<th>VI [%]</th>
<th>BHT [s]</th>
<th>Sample Volume [l]</th>
<th>DLCO Var. [ml/min/mmHg]</th>
<th>Inspiratory Time [s]</th>
<th>Accept. Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>&gt;90%</td>
<td>9.0 - 11.0</td>
<td>0.5 - 1.0</td>
<td>&lt;1</td>
<td>1.5 - 2.5</td>
<td>&gt;1</td>
</tr>
<tr>
<td>B</td>
<td>&gt;85%</td>
<td>8.5 - 11.5</td>
<td>0.5 - 1.0</td>
<td>&lt;2</td>
<td>1.0 - 3.5</td>
<td>&gt;1</td>
</tr>
<tr>
<td>C</td>
<td>&gt;80%</td>
<td>8.0 - 12.0</td>
<td>0.5 - 1.0</td>
<td>&lt;3</td>
<td>&lt;4.0</td>
<td>&gt;1</td>
</tr>
<tr>
<td>D</td>
<td>&gt;80%</td>
<td>8.0 - 12.0</td>
<td>Outside range</td>
<td>&gt;3</td>
<td>&lt;4.0</td>
<td>&gt;1</td>
</tr>
<tr>
<td>F</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

The score with the lowest value determines the overall score. For quality grading, all acceptable trials are taken into account.

- The following parameters determine the score and quality grades:
  o VI (inspiratory volume of DLco test) as a percentage of SVC target
  o BHT: Breath-hold time in seconds
  o DLco variability in absolute values
  o Inspiratory time in seconds
  o Number of accepted trials

In order to be minimally acceptable, a trial must meet the following criteria:

- VI >80% of SVC target
- Breath-hold time (BHT) of 8.0 to 12.0 seconds
- Inspiratory time ≤4 seconds

Note: The quality grades are recomputed if the user manually changes the sampling window position (repositioning of the collection bar)

11j.2. Print Your Results

a. On the computer in EasyOne Pro™, highlight the row that contains the subject’s tests.
b. Go to file, select print.
c. Print the test.
d. Save a hard copy at the Clinical Center as a source document.

11j.3. Export Patient Data from DLco device to Flash Drive

(EasyOne Pro™ Operator Manual Section 7, pg. 80)

Once a participant has completed the DLco test, you will need to save the patient data to either the flash drive provided by ndd or your own flash drive. You will use this flash drive to transfer the data from the DLco device to your computer.

a. Insert your flash drive into the back of the EasyOnePro™.
b. From the Main Menu screen, select Utilities -> Advanced
c. You will then need to enter the password, EOPTM (EasyOne ProTM) This password is case sensitive and should be entered in all capital letters.
d. Select Login
e. Choose Export
f. On the Data Export Selection screen, uncheck Option Settings, Logging Information and Installation Setting. Leave Patient Data as the only item checked.
g. Select Export
h. On the Browse For Folder screen, look for your flash drive, labeled “Removable Disk,” usually the F drive. Click on it to highlight it.
i. Select OK
j. On the Export Data To screen, when asked to replace the existing file, select Yes
k. Export successfully finished screen will appear
l. Select OK
m. Remove the flash drive and insert into your computer to upload the EasyOnePro.mdb file to the DCC.

11j.4 Upload the EasyOnePro File to the COPDGene® Website

Once you have removed the flash drive from the rear USB socket of the DLco device and inserted this into a computer, you will then upload the Patient Data to the DCC.

a. Locate and open the flash drive on your computer
b. Find the EasyWarePro.mdb file (see Figure 11-5)
c. File->Copy
d. File->Paste
e. Select the Copy
f. File-> Rename
g. Rename this file to: Centercode_COPDGene_DLco_MM_DD_YYYY.mdb
h. Next, open the COPDGene® website (https://biosweb.njc.org/sec/COPDGene/MainPage.cfm).
i. Log into the website. If you have lost your log-in information, contact Ruthie Knowles at the DCC.
j. On the left panel, click on “PFT Files.”
k. Log into the website again.
l. Click on the button across from the group called COPDGene: Your Site.
m. Click on the “Choose File” button and locate the ndd flash drive.
n. Click on the EasyWarePro.mdb file you renamed and select “Choose”.

o. You may use the comments section to include information on the test you upload

p. Click “Add File Now.” You should now see your file in the table.

Figure 11-5. Removable Flash Drive with DLco EasyWarePro.mdb master file

11k. Acceptable and Reproducible Maneuvers

For the purpose of DLco testing, “acceptable” and “reproducible” are defined in Section 11.i.6 above. “Reproducible” is defined as being without excessive variability between maneuvers. The following are some errors that can be seen or calculated from a DLco maneuver and that can affect acceptability: failure to exhale fully prior to inhaling the test gas, taking longer than 4 seconds to inhale the test gas, holding the breath for less than 8 seconds or longer than 12 seconds, exhaling at the end of the test too fast.

At least two acceptable maneuvers are needed to determine reproducibility. The average of the DLco measurements taken from at least two acceptable tests is used as the patient's DLco measured value.

When errors occur, review common errors with the subject before proceeding with additional maneuvers.

Ask the participant to watch the technician perform the DLco maneuver again. The technician should demonstrate the correct placement of the mouthpiece, emphasize the steps of doing a DLco test. If the participant tries again and the reproducibility criteria are not met, the technician should continue administering the test as needed (up to a total of five (5) maneuvers), assuming that the subject is able to continue.

Some participants will never be able to provide two acceptable maneuvers. The goal is to meet the acceptability and reproducibility criteria, but these are not absolute requirements for data to be used.

11l. Reference Values

To interpret DLco results, they must be compared either to a subject’s previous results or to a published set of “predicted reference values.” Such predicted reference values typically describe the average lung function for an individual of a given age, height, and sex, and such equations have been published for a variety of racial groups.

Typically, lung function measurements are expressed as a percent of predicted. One hundred percent of predicted represents the average value for the population, but normal, healthy
individuals will exhibit a wide range of values about this level. In general, values of 80% or greater for DLco are considered to be in the normal range. Individuals whose test results are below this level may have an abnormality.

The ndd EasyOne Pro™ unit offers a number of published predicted values, most of which were derived from studies of largely white participants. Four ethnic correction settings are available that allow you to customize the amount of adjustment that is made for selected racial groupings. Consult the EasyOne Pro™ Operator manual, sections 8 and 12, for more information regarding the use of prediction equations.

Choice of reference values in the ndd EasyOne Pro™ DLco software only affects the printouts available from the DLco software, which sites may choose to give to the participants. For the official COPDGene® dataset for each site, the COPDGene® Operations Center will create local prediction equations based on healthy never smokers at that site.

11m. Implementation of DLco Quality Control

The American Thoracic Society/European Respiratory Society DLco standards, and recent evaluations of commercially available pulmonary function equipment emphasize the importance of DLco quality control (QC) procedures.

11m.1. Factors Affecting DLco Quality

a. Participant: If a subject does not follow the steps in performing the DLco (tidal breathing, full exhalation, full inhalation of test gas, 10 sec breath hold and quick non-forced exhalation) the test may not represent the correct measured value. Coughing during the DLco maneuver will render the test invalid. Leakage due to the participant’s inability to keep a tight seal around the mouthpiece also will prevent you from obtaining a good maneuver. To address these sources of error, it is very important to have technicians trained to watch the participant closely during the test performance and accurately review the gas concentration and volume curves on the computer monitor. The technician thus can guide and explain the source of error to the participant.

b. Technician: Improper coaching or non-standardized coaching procedures will negatively affect the quality of the DLco testing. The technician should clearly instruct the participant on how to perform this test, demonstrate the maneuver, and watch the participant closely during the performance to avoid unacceptable errors and obtain the best effort from the participants. He/she must be trained to recognize patterns of unacceptable maneuvers and perform equipment checks. COPDGene® will monitor and provide periodic feedback on each technician’s performance.

c. Equipment: Leaks in the system and differences in temperature are two factors that affect the quality of the test results. Quality Control is discussed in section 10n below.

d. Analysis: A combination of all factors may affect the quality of the results. Results from the calibration factors, technician’s impression of test session quality, and the QC
supervisor’s impression of test session quality are all integrated to obtain the final DLco results used in the study.

11n. DLco Calibration, Maintenance, and Hygiene

American Thoracic Society/European Respiratory Society recommendations for equipment quality control are:

a. Gas analyzer calibration before each test (automatically done)
b. Daily volume calibration checks should be performed using a 3.00 Liter syringe as the “gold standard.” Refer to section 2, pages 93-95 of the EasyOne Pro™ Operator’s manual for instructions.
c. Quarterly gas analyzer linearity and timer check
d. Weekly biologic control testing

The EasyOne Pro™ DLco device is designed to minimize the need for cleaning and maintenance (see section 7 page 89 in the EasyOne Pro™ Operator Manual). The surface of the EasyOne Pro™ and cradle may be cleaned by wiping with a damp cloth. If a more thorough cleaning is desired, the spirometer and its Spirette™ cavity may be cleaned with an alcohol wipe or a soft cloth that has been lightly moistened with isopropyl alcohol. Do not let liquids flow into the Spirette™ cavity of the DLco sensor while cleaning. The disposable Spirette™ eliminates the need for cleaning the DLco unit between patients. The Spirettes™ are designed for single patient use only, and must be removed and disposed of after each patient.

Additional guidelines for hygiene and infection control are provided by the American Thoracic Society and include the recommendation that the technician and patient wash their hands after testing and that proper attention be given to environmental controls in settings where tuberculosis or other diseases spread by droplet nuclei are likely to be encountered. Participants with evidence of obvious upper respiratory infections should not be tested, but rather rescheduled for testing at a later date.

No periodic maintenance is required or recommended on the DLco device or cradle. No service should be performed on the EasyOne Pro™ except by manufacturer-authorized personnel.

To clean the nose clips, they should be wiped with alcohol after each use or discarded.

11o. Trouble Shooting

Refer to the section 9 of the EasyOne Pro™ Operator Manual for troubleshooting tips.

11p. ndd EasyOne™ Configuration Settings for Use in COPDGene®

When setting up your EasyOne Pro™ unit, use the following settings for compliance with COPDGene® protocol. Please refer to section 8 of the EasyOne Pro™ Operator Manual for assistance in making the settings. The following settings have been selected for the COPDGene® study. Each EasyOne Pro™ will come preconfigured to the requirements of the COPDGene®
study, however you should check to make sure the settings are correct prior to testing your first participants.

Test Settings:
The device was pre-configured by ndd prior to shipping. These settings should remain as programmed.

General Settings:
  a. Length Unit= m/cm
  b. Temperature= °C
  c. Weight Unit= kg
  d. Hb Unit= g/dl
  e. Pressure Unit= mmHg
  f. Language= English
  g. Date= MM/DD/YYYY

Report Settings:
Report settings are set to include curve data and trial values. These settings should remain as programmed.

11q. DLco Checklist

Clinical Center Coordinators are encouraged to print and use this checklist as an aid during performance of the DLco testing.

<table>
<thead>
<tr>
<th>Subject Identification Number:_____</th>
<th>Test Date:_____</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Action</strong></td>
<td><strong>Comments</strong></td>
</tr>
<tr>
<td>Safety Assessment Form administered</td>
<td>□</td>
</tr>
<tr>
<td>Prepare to conduct DLco</td>
<td>□</td>
</tr>
<tr>
<td>Confirm race/ethnicity of participant</td>
<td>□</td>
</tr>
<tr>
<td>Explain purpose of test</td>
<td>□</td>
</tr>
<tr>
<td>Demonstrate maneuver</td>
<td>□</td>
</tr>
<tr>
<td>Perform 2 to 5 additional DLco tests and wait 4 minutes between each test</td>
<td>□</td>
</tr>
<tr>
<td>Print results</td>
<td>□</td>
</tr>
</tbody>
</table>

11r. Answers to Common Problems with the EasyOne Pro™

If you are experiencing problems with the ndd EasyOne Pro™, review the Operator Manual and see if the proposed solution takes care of the problem. If not, then contact the PFT Core or ndd directly.
Related Pulmonary Function Documents:
12. Six-Minute Walk Test

The six-minute walk test is a timed walk involving a familiar activity and requiring minimal technical resources. It has been shown to be a reproducible objective indicator of functional capacity and is a part of the multi-component BODE index that correlates with survival. It is important to emphasize that this is a test of maximum exercise performance; subjects should be instructed and encouraged to push themselves to achieve maximal distance. Only one walk test will be done on each subject.

12a. Contraindications

- Proven or suspected unstable coronary artery disease or angina
- Resting heart rate of more than 120
- Exercise related syncope (fainting)
- Proven or suspected claudication (limping)
- Uncontrolled hypertension (resting systolic blood pressure > 200 mmHg or resting diastolic blood pressure > 110 mmHg)
- Resting bradycardia (< 50 beats/min), history of complex ventricular arrhythmia or sustained SVT
- Use of > 6 L/min oxygen flow with activity

12b. Facilities/Equipment

- Stopwatch
- Course pre-marked with distances in feet
- Portable oxygen delivery system if the patient is on oxygen (nasal cannula)
- Telephone (in case of emergency)
- Subject instructions below

12c. Walk Course

The path should be unobstructed, flat, and indoors. If a public corridor is used, ability to control traffic should be assured. Each site is encouraged to use the same course used during the first COPDGene® visit. The course description should be recorded on the walk test data collection form. The course should be designated as straight or circular, and the distance of the course should be included on the walk test form. Preferably, the walk course should be marked every 3 m to measure the total distance traveled and be 30 m (100 feet) in length.

12d. Procedure

When possible, the six-minute walk test should be performed after spirometry and within two hours after giving a bronchodilator. Oxygen saturation, heart rate, and blood pressure will NOT be monitored during the walk. Immediately and one minute after the end of the six-minute walk test, a subject’s heart rate and oxygen saturation will be measured using a pulse oximeter. A practice walk should not be performed prior to the 6-minute walk test.
12e. Patient Preparation

- Short acting bronchodilator may be used if so prescribed as part of the subject’s usual medications, but if taken they must be used at least 20 minutes before testing.
- A light meal 2 to 4 hours prior to testing is advised; at least 2 hours must have elapsed since the patient last ate a meal.
- The patient should rest in a sitting position for 10 minutes before testing.
- Patient should wear loosely fitting clothing and comfortable walking shoes.

12f. Subject Instructions

Pre-test instructions: Identical instructions should be given to each subject. Say to the subject: “You are now going to begin a six minute walking test. The object of this test is to walk as quickly as you can to cover as much ground as possible in six minutes. You may slow down if necessary. If you stop, we wish you to continue the walk again as soon as possible. Your goal is to walk as fast and as far as you can in six minutes.” Then review the course with the patient. Specific instructions on walking the course will differ somewhat between sites because of differences in the layout of each walking course. Finally, say “Wait until I say ‘Start’ before beginning. It is important that you not talk during the test unless you are having a problem. Do you have any questions?”

12g. Instructions during Walking

At the end of each minute the patient will be given the time remaining and a standard phrase of encouragement as follows:
- Minute 1 – “Do your best. You have five minutes to go.”
- Minute 2 – “Keep up the good work. You have four minutes to go.”
- Minute 3 – “You are doing well. You have three minutes to go.”
- Minute 4 – “Give it your all. You have two minutes to go.”
- Minute 5 – “Walk faster if you can. You only have one minute to go.”

It is important to use the same set of phrases with every participant so as not to bias the results. Only give encouragement every minute using the standard phrases above to be consistent in your test results.

12h. Research Coordinator Responsibilities

If the subject routinely uses oxygen during activity and if they prefer to perform the walking test with oxygen, they are advised to do so. The coordinator may walk behind the participant to carry the oxygen source. It is strongly advised not to walk in front of or beside the participant while carrying the oxygen supply. Begin by saying, “Start.” Provide standard instructions before the test and standard information and encouragement during the walk at set intervals as described above. Say “Stop” at the end of six minutes. Measure the distance walked to the nearest foot and record the distance walked on the 6MW form in feet only. Rest periods are not recorded in the total distance walked; a test lasts 6 minutes if the patient is on the course for 6 minutes; the patient need not walk continuously for 6 minutes for the walk to be considered to have a normal
termination. If the patient stops or takes a momentary rest on the course, during the recorded 6 minutes, do not stop your stopwatch; this will be included as part of their 6 minutes of walking.

**Do not walk with the participant during the test.** If supplemental oxygen is used, it is acceptable for the coordinator to walk behind the participant to carry the oxygen source. Only walk with the participant if it is requested by the participant or if this is an institutional safety guideline. Walking next to a participant could impact their walking pace and bias the results. If a participant walks with a rollator or walker, allow the subject to use this during the test.

If it is indicated on the Safety Assessment Form that a subject will not be doing the Six Minute Walk due to safety reasons, then the site should not submit the form.

For subjects who refuse to do the Six Minute Walk (NOT for safety reasons) the site should complete a Six Minute Walk form and collect all information. Zero “0” should be entered for distance, course should be marked, and checked whether mobility was limited. Post-SaO2 and heart rate should still be completed after waiting six minutes.

### 12i. Abnormal Test Termination Criteria

- Chest pain suspicious for angina
- Intolerable dyspnea (shortness of breath)
- Evolving mental confusion or lack of coordination
- Evolving lightheadedness
- Pale or ashen appearance, or excessive sweating
- Otherwise warranted based on clinical condition
13. Visit 2 Hierarchy Preference

In line with the study goal of maximizing the total number of return subjects from Phase 1, options have been added to the protocol to get subjects seen for Phase 2 even if the subject cannot return to the Clinical Center where he/she was seen for Phase 1. Despite the addition of these options, it is ultimately preferred to have a subject return to the Clinical Center where he/she was seen in Phase 1. Other options should be exercised only in cases where the subject is unwilling or unable to come to the Clinical Center for Phase 2. The site Principal Investigator and study coordinator should speak with subjects as needed to determine why he/she may not be able to return and determine the next best course of action. The Administrative Core must also be notified for each circumstance. IRB approval must be granted to utilize these other options. Figure 13-1 describes the order of preference that should be followed to determine other options that are available if a subject cannot return to the Clinical Center for Phase 2. A full Phase 2 visit at the Clinical Center a subject was seen in Phase 1 is the first preference. If the subject has moved and is closer to a different Clinical Center, the subject may be seen at that center. A home visit may take place when the subject is unable to come to the Clinical Center due to long-term inability to travel. If a home visit is not an option, then the next alternative would be to administer study questionnaires over the phone. Finally, if none of these options is feasible, then the Clinical Center should administer the Limited Follow-Up Questionnaire to the subject over the phone. These procedures are described in detail below.

Figure 13-1 illustrates the order of preference of procedures in the event that a subject cannot return to the Clinical Center for their Phase 2 visit. As a general principle, a full Phase 2 visit at the Clinical Center is preferred.

13a. Subject has moved and is closer to a different Clinical Center for Phase 2

In the event that a Phase 1 subject has moved away from his/her local Clinical Center and to an area closer to another participating COPDGene® Clinical Center, the subject may elect to complete Visit 2 at this closer Center rather than traveling long distance to their original Center. If they live between two centers, it is preferred to return to the original center the subject was seen for Phase 1.

Please review Figure 13-2 or contact the Administrative Core with any questions related to finding a geographically proximate center.
13a.1. Procedure

The Clinical Center where subject was seen for Phase 1 visit will ask the subject for verbal approval to send their name and contact information to the new Clinical Center. Once the subjects verbal approval is obtained, the Clinical Center from Phase 1 should complete the web-based COPDGene® Subject Referral Form. The form includes the Subject ID, Interviewer, date, Phase 1 Clinical center where subject was seen, Phase 2 Clinical Center where subject is proposing to be seen, subject name and phone number. The 5 digit number + letter Subject ID will remain the same for the subject throughout the study.

Upon completion of this form to the DCC, an automatic email will be sent to the “new” clinical center, notifying them of the change. At the point the subject may be called and scheduled by the “new” center.

13a.2. Longitudinal follow up when a subject has changed centers

If the coordinator is notified by a subject that he/she has moved and it is determined he/she will be seen at a different Clinical Center for Phase 1 then they were seen for Phase 2, then the coordinator should complete a LFU survey with the subject at that time. This should be done prior to referring the subject to another center.

When a subject has been seen at a different Clinical Center for Phase 2, the “new” Clinical Center will take over longitudinal follow up for this subject. In the event a manual coordinator call needs to occur for LFU, it will be completed by the new center, as long as the subject has already been seen there.

The subject should be removed from the Phase 1 Clinical Center master excel upload file and it will be added to the new Clinical Center master excel upload file after the visit occurs (as updated contact information will have been obtained at the visit.)
13b. Home Visit

The home visit should be considered an option to get the subject seen for the Phase 2 Visit, but bringing the subject back to the Clinical Center for the Phase 2 Visit is preferred over a home visit.

The home visit is not applicable for enrollment of new nonsmoker control subjects.

When IRB and local center approved, Clinical Centers are permitted to conduct a visit in the subject’s home only when the subject is unable to come to the Clinical Center due to long term physical inability to travel. If subject is temporarily ill, that does not qualify the subject for a home visit as he/she should be able to have a visit at the Clinical Center at a later date.

Procedure:
Home visits consist of administration of:
- Home Visit Informed Consent and HIPAA
- All questionnaires (including vitals)
- Pre and post bronchodilator spirometry
- Blood draw


Subjects should be notified that if they are ever able to come to the Clinical Center to complete the visit they should call the coordinator.

A printable home visit final screener checklist is available to assist the coordinator (Appendix B) at the site if Internet access is not available.

If preferred by the local IRB and Clinical Center, the center may mail the informed consent to the subject for review prior to the visit. The center should discuss the visit procedures over the phone before the visit (the consent must still be signed at the home visit).

For home visits, there must be a total of three screeners: 2 preliminary and 1 final.

The first preliminary screener should be conducted when scheduling the visit. The second should be completed in the Clinical Center by calling the subject 24 hours before the visit. The final will be done at the subject home visit (if the subject does not have internet access this can be completed back at the Clinical Center within 24 hours of the visit).

The home visit selection should be chosen at the bottom of the final screener eligibility (Figure 13-3).
Clinical centers should have site Standard Operating Procedures to follow when conducting home visits.

### 13c. Completing Questionnaires with subject over the phone

It is preferred to have a phase 2 clinical center visit. If the subject cannot do that, a home visit is preferred prior to completing all COPDGene® Questionnaires over the phone.

For Phase 2, IRB approval was requested to be able to complete questionnaires over the phone (under Phase 1 consent), for subjects who are unable to come to Clinical Center or have a home visit conducted. Clinical Centers may administer questionnaires over the phone when given IRB approval to do so.

**Procedure:**

The order listed below should be followed when conducting questionnaires over the phone. It is anticipated to take approximately 2 hours to do all questionnaires. This may be accomplished over multiple calls. The coordinator may stop administering at any time the subject does not wish to continue. It is suggested all questionnaires be written and completed with pen and paper while the subject is on the phone. Later the forms will be entered and sent to the DCC through the COPDGene® website. If a subject requests to stop prior to completion of the questionnaire, you may do so. However, only complete questionnaires can be sent to the DCC. While the subject is on the phone you should update the subjects personal information.

1. Final Screener (ensure to select ‘phone’ for Question 9)
2. Respiratory Disease
3. Medical History
4. Medication History
5. St. George’s Respiratory Questionnaire
6. COPD Assessment Test
7. Socioeconomic Questionnaire
8. SF-36 Health Survey
9. Residential and Occupational History
10. Women Only
13d. Limited Follow-Up Questionnaire

The Limited Follow-Up Questionnaire is not to be administered during the COPDGene® study visit. With IRB approval, this questionnaire is to be administered over the phone to subjects who are unable to come to the Clinical Center for the Phase 2 visit, to have a home visit, to answer the questionnaires over the phone, or to participate in additional follow up. The purpose of the Limited Follow-Up Questionnaire is to gather longitudinal information on the subject related to respiratory symptoms, exacerbations, and comorbidities.
Appendix A, Part 1: Home Visit Preparation Checklist

Home Visit Preparation Checklist:

☐ Complete Visit 2 Preliminary Screener online with subject at scheduling and 24 hours prior to visit
☐ Confirm if Subject has home Internet access
  (If not, a printable Final Screener and HADS should be printed for the visit)
☐ Laptop and charging cable, for spirometry and if subject has Internet access
☐ Subject Folder for ICF, questionnaires, etc.
☐ Measuring tapes (steel and sewing)
☐ Portable Scale for weight
☐ Blood Pressure Equipment (various cuff sizes)
☐ Blue tape for arm span measurement and height measurement
☐ Pulse Oximeter

Supplies for Questionnaires
☐ Pens
☐ 2 copies Printed ICF and HIPAA (have subject sign 2 and leave one signed document with subject)
☐ Printed Questionnaires before visit (See Appendix A, Part 2 – including the HADS Form, clicking the word “HADS” will pull up a printable pdf)
☐ Clipboard
☐ Extra Paper for Notes

Supplies for Spirometry
☐ Screen Connector (cord for spirometer)
☐ Spirometer (same ndd spirometer used for other COPDGene Phase 2 visits)
☐ Spirettes
☐ Nose Clips
☐ Albuterol
☐ Aerochamber

Supplies for Blood Draw
☐ Gloves
☐ Tourniquet
☐ Needle
☐ Alcohol Wipe
☐ Gauze
☐ Band Aid
☐ Biorepository Supplies (tubes, affix labels, biohazard bag)
☐ Blood Tube Rack
☐ Cooler and ice pack for transport. Can use “diaper” to avoid any potential messes in cooler.
☐ Transportable Sharps container (~ $8 online)
Appendix A, Part 2: Home Visit Procedures Checklist

Home Visit Procedures Checklist

- Visit 2 Final Screening Form (internet or on paper printable copy)
- Informed Consent Form and HIPAA Completion
- ICF and Permissions Granted Form
- Demographics and Physical Characteristics
- Safety Assessment Form
- Subject Personal Information
- Pre- BD Spirometry
- Administer Albuterol
- Wait 15-20 minutes for post-BD Spirometry (not more than 40)
- Post- BD Spirometry
- Spirometry Form
- Medical History Questionnaire
- Medication Questionnaire
- Respiratory Disease Questionnaire
- SF-36
- St. George's Respiratory Questionnaire
- COPD Assessment Test (CAT)
- HADS (if subject does not have home internet access complete at site after visit within 24 hours and inform subject separately)
- Residential and Occupational History
- Socio-Economic
- E-Cigarette Questionnaire
- Women Only
- Complete Blood Sample Collection Form and put Biorepository labels on tubes

Post Visit
- Deliver CBC directly to Local lab
- Process Blood
- Complete any questionnaires not sent to DCC at subject home (including Final Screener and HADS)
- Upload Spirometry Data
- Clinically Significant Findings Form
- Mail subject copies of spirometry tests, etc.

Notes:

________________________________________

________________________________________
Appendix B: Printable Visit 2 Screening Form

Printable Visit 2 Screening Form to be used for Home Visit
Coordinator: to be used for final determination screener when subject does not have Internet access. Must be completed within 24 hours of completion of the home visit.

Responses are required to all questions.

Center: 
Subject ID: 
Interviewer: 
Date (mm/dd/yyyy): 

Enter Screening Status:
[ ] Final Determination (required, to be completed day of visit)

1. Have you used a new or increased dose of antibiotics for any lung disease or infection within the past month?
   [ ] Yes  [ ] No

2. Have you been on a new or increased course of prednisone within the past month for any lung disease?
   [ ] Yes  [ ] No

3. In the last 3 months, have you had chest or abdominal surgery?
   [ ] Yes  [ ] No

4. In the last 3 months, have you had a detached retina or eye surgery?
   [ ] Yes  [ ] No

5. In the last 3 months, have you had a heart attack?
   [ ] Yes  [ ] No

6. In the past month, have you been hospitalized for any other heart problem?
   [ ] Yes  [ ] No

7. Have you had lung transplant surgery?
   [ ] Yes  [ ] No

8. Females Only:
   a. Have you had a hysterectomy?
      [ ] Yes  [ ] No  [ ] N/A (Male)
   b. If no, when was your last menstrual period?
      [ ] More than 12 months ago
      [ ] Less than 12 months ago
      [ ] N/A
   c. Are you currently pregnant or possibly pregnant?
      [ ] Yes
      [ ] No
      [ ] Don’t Know
      [ ] N/A

9. If Final: What type of visit is the subject doing for Phase 2?
   [ ] On-Site
   [x] Home
   [ ] Phone
14. Mail Consent

All Clinical Centers are requested to obtain IRB approval for the mail consent documents (includes: Additional Mail Authorization_Informed Consent Addendum, cover letter to subject, personal information update form, study participant memo, and authorization to release protected health information form).

These documents will currently only be implemented by Clinical Centers whose IRB did not approve transfer of subject identifiers under the Phase 1 consent, until further notice.

For the centers utilizing mail consent:
Prior to the Phase 2 return visit, subjects may be contacted by the Clinical Center via mail to request additional consent and authorization. This additional consent and authorization will request that the subject allow transfer of identifiers from the Clinical Center to the Data Coordinating Center at National Jewish Health. The mail consent provides permission for the Clinical Center to transmit the subject’s personal information (social security number, address, secondary contact address) to the DCC. A Personal Contact Information Update form will be sent with the mail consent, asking subjects to update contact information, including secondary contacts and primary care physician.

The information obtained will be used for central subject tracking, longitudinal follow up, vital status searching, and to obtain cost and utilization information on subjects from CMS databases. The mail consent also allows the Clinical Center to seek perimortem medical records and informant interviews about the circumstances around the subject’s death. Additionally the subjects will be invited to sign an “Authorization to Release Protected Health Information” medical record release form so that the Clinical Centers may obtain medical records.

Once the completed mail consent documents are signed by the subject and received back by the Clinical Center. The Clinical Center should make a copy and batch the copies to the COPDGene® Administrative Core for processing centrally. These may be scanned and emailed if allowed by Clinical Center. They must be mailed via traceable mail service, so the batch is suggested to save on money and time. The original documents should remain in the subject source folder.
15. Imaging

15a. Introduction

The Quantitative Imaging Laboratory (QIL) at National Jewish Health serves as the Imaging Core for the COPDGene® study. The QIL trains clinical center staff, provides CT acquisition protocols and certifies scanners, conducts visual quality assurance of CT images, evaluates CT protocol compliance, and works with the clinical centers to troubleshoot protocol deviations and quality issues. Additionally, the QIL provides quantitative CT analysis of all images and monitors individual scanner stability at each clinical center.

The CT scanning protocol for COPDGene® requires multi-detector CT (MDCT) images of the entire lung at full inspiration (TLC) and at expiratory Functional Residual Capacity (FRC). Although there are some variations among CT scanners, standardization of the acquisition parameters has been established across manufacturers and models so that reliable quantitative measurements may be made.

TLC and FRC scans were performed at the baseline visit for Phase 1 of COPDGene® and will be performed approximately 5 years later for Phase 2. Whenever possible, subjects who return for a follow-up visit will be scanned on the same CT scanner and with the same CT parameters (dose, display field of view (DFOV), etc.) used for the baseline CT scan. The images from the MDCT chest will be stored locally and will be transmitted to the Imaging Core via DICOM Send software (National Jewish Health), which de-identifies the scans in a consistent fashion.

15b. CT Training and Set-up

STEP 1: Site Survey

1) Site surveys completed by the clinical centers provide information regarding CT technologist staff and CT scanners for Phase 2.

2) Site surveys individualized for each center identify the specific CT scanners that were used for the baseline CT scans.

3) If a baseline CT scanner is known to be unavailable for Phase 2, the site survey is used to record information about the replacement CT scanner.

STEP 2: Personnel Training and Certification

1) COPDGene® CT technologists must review the training materials located on the COPDGene® website.

   **Training Materials:**
   a. COPDGene® Imaging Manual of Procedures (MOP)
   b. COPDGene® CT Protocol sheet for CT Technologists
   c. PowerPoint tutorial

2) One individual (usually a coordinator) is designated to generate the CT Scan Parameter Report and to use the DICOM Send software. This individual will receive
communications regarding image transfers, image quality issues and CT protocol compliance issues.

3) The lead technologist and every CT technologist expected to scan subjects for the study are identified on the site survey. These individuals must review the PowerPoint tutorial and sign the CT Technologist Training Log before scanning subjects. They will also receive communications regarding image quality issues and CT protocol compliance issues.

4) Only CT technologists who have reviewed the PowerPoint tutorial will be approved to scan subjects for Phase 2.

STEP 3: DICOM Send Software

1) The DICOM send software anonymizes subject CT scans and transfers CT images from the clinical centers to the Imaging Core. The software is included on the COPDGene® USB drive and can be provided on CD/DVD.

2) APPENDIX A provides installation instructions and instructions for use.

3) The Imaging Core will conduct a test image transfer with each clinical center using a phantom scan. If the software is unable to make a transfer, the Imaging Core will work with the IS Department at the clinical center to troubleshoot the issue.

4) In the event that a clinical center is unable to transmit images, a stand-alone version of the software is available to use for de-identification of images and to route de-identified images to an archive location.

STEP 4: CT Scanner Certification

1) Program the COPDGene® scanning protocol (1.7 CT Scanning Protocol) onto the scanner.

2) Properly set up and scan the COPDGene® Phantom with both inspiratory and expiratory settings.

3) Reconstruct the phantom scans using the COPDGene® reconstruction settings specified in the scanning protocol. The Display Field of View (DFOV) for each reconstruction must be 36.5 cm / 365 mm and the (x,y) reconstruction coordinates must be (0,0).

4) Scan the phantom on each CT scanner identified on the site survey. Certification phantom scans will be burned to DVD and shipped to the Imaging Core.

5) Phantom scans will be evaluated by the Imaging Core. Any issues identified through the phantom scans must be resolved before a CT scanner can be certified.

6) Only certified scanners are permitted for use in the COPDGene® study. Monthly phantom scans will be acquired for all certified scanners. Only certification phantom scans will be
sent on DVD. Regular monthly phantom scans will be sent to the Imaging Core using the DICOM Send software.

15c. **CT Scan Parameters for Visit 2**

1) The CT Scan Parameter Report is accessed through the COPDGene® website.

2) The report may be printed from the Visit 2 Screener page and also from the Data Management section under Review Data Records. Figure 12-1 and Figure 12-2.

3) For subjects who participated in Phase 1 of the study, the report identifies the CT scanner to be used for each subject’s Phase 2 scan (Figure 12-3). The report provides the CT protocol settings to use and specific DFOV and reconstruction kernel instructions based on the baseline CT scan settings. DFOV is the same for inspiratory and expiratory scans and for Recons 1 and 2.

4) The red text in Figure 12-3 includes an alert (IMPORTANT) that the baseline scan’s DFOV parameter was too large for optimum quantitative measures to be made from the scan. This alert will only be present for subjects whose baseline scans had a problematic DFOV. Phase 2 reconstructions at the baseline DFOV will be acquired and will be used for comparisons against the baseline scans. In cases where the baseline DFOV was too large, the report asks for an additional tighter DFOV reconstitution. Recons 1 and 2 of the inspiratory and expiratory scans use the original DFOV parameter and Recon 1b of the inspiratory and expiratory scans uses the tighter DFOV specified in the report. For Phase 2, reconstructed scans must be provided at these two fields of view when requested in the report. The DFOV for Recon 1b should be set so there is no more than a 1 cm margin outside of the lungs on either side of the scan where the lungs are the widest in the chest.

5) For subjects that did not have a Phase 1 CT scan the red text specifies that the DFOV for Recon 1 should be set so there is no more than a 1 cm margin outside of the lungs on either side of the scan where the lungs are the widest in the chest. The same DFOV should be used for all other inspiratory and expiratory reconstructions. Figure 12-4.

6) CT acquisition date, CTDIvol for inspiratory and expiratory scans, and the CT technologist name should be recorded on the CT parameters report at the time of CT acquisition.

![Figure 15-1. Visit 2 Screener Screenshot](image-url)
### Review Data Records

#### Figure 15-2. Review Data Records Screenshot

<table>
<thead>
<tr>
<th>Subject ID</th>
<th>NJC 10072F</th>
</tr>
</thead>
</table>

### Acquisition Parameters:

<table>
<thead>
<tr>
<th>Effort</th>
<th>Pitch</th>
<th>kVp</th>
<th>Exposure</th>
<th>Slice Thickness</th>
<th>Interval</th>
<th>Other Settings</th>
</tr>
</thead>
</table>
| Inspiratory| 1.0   | 120 | 200 mAs  | 0.75            | 0.5      | Rotation time: 0.5 s Care Dose OFF  
                                        |        |     |          |                 |          | HD mode: No  
                                        |        |     |          |                 |          | Iterative Reconstruction: No  
                                        |        |     |          |                 |          | Do not use IRIS or SAPHIRE |
| Expiratory | 1.0   | 120 | 50 mAs   | 0.75            | 0.5      |                |

### Reconstruction Parameters:

<table>
<thead>
<tr>
<th>Effort</th>
<th>Recon</th>
<th>Kernel</th>
<th>DFOV (cm)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insp</td>
<td>Recon 1</td>
<td>B31f</td>
<td>32.0 cm</td>
<td><strong>IMPORTANT:</strong> The Field of View for the baseline scan was too large. Need Recon 1b in addition to Recon 1 &amp; 2.</td>
</tr>
<tr>
<td>Insp</td>
<td>Recon 1b</td>
<td>B31f</td>
<td>* Tighter DFOV</td>
<td>Set DFOV to display lungs at TLC with only 1 cm margin outside lungs.</td>
</tr>
<tr>
<td>Insp</td>
<td>Recon 2</td>
<td>B45f</td>
<td>32.0 cm</td>
<td></td>
</tr>
<tr>
<td>Exp</td>
<td>Recon 1</td>
<td>B31f</td>
<td>32.0 cm</td>
<td><strong>IMPORTANT:</strong> The Field of View for the baseline scan was too large. Need Recon 1b in addition to Recon 1 &amp; 2.</td>
</tr>
<tr>
<td>Exp</td>
<td>Recon 1b</td>
<td>B31f</td>
<td>* Tighter DFOV</td>
<td>Use same DFOV as Insp. Recon 1b</td>
</tr>
<tr>
<td>Exp</td>
<td>Recon 2</td>
<td>B45f</td>
<td>32.0 cm</td>
<td></td>
</tr>
</tbody>
</table>

### Visit 2 Scan - Information below to be filled out by CT Technologist

<table>
<thead>
<tr>
<th>COPDGene Subject Id</th>
<th>NJC 10072F</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT Acquisition Date</td>
<td>mm/dd/yyyy</td>
</tr>
<tr>
<td>CT Dose Index (CTDI): Inspiratory (mGy)</td>
<td>Expiratory (mGy)</td>
</tr>
<tr>
<td>Imaging Technologist</td>
<td></td>
</tr>
</tbody>
</table>

**Baseline Scan:** 03/25/2008

Site Coordinator: Please record on CT Assessment form before delivering to radiologist.

#### Figure 15-3. COPDGene® Phase 2 CT Acquisition Form – Return Visit
Subject ID: NJC 30000N

Scanner to be used:

<table>
<thead>
<tr>
<th>Scanner ID</th>
<th>Scanner</th>
<th>Scanner Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>NJCD4</td>
<td>Siemens Definition AS+</td>
<td>A342</td>
</tr>
</tbody>
</table>

### Acquisition Parameters:

<table>
<thead>
<tr>
<th>Effort</th>
<th>Pitch</th>
<th>kVp</th>
<th>Exposure</th>
<th>Slice Thickness</th>
<th>Interval</th>
<th>Other Settings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inspiratory</td>
<td>1.0</td>
<td>120</td>
<td>200 mAs</td>
<td>0.75</td>
<td>0.5</td>
<td>Rotation time: 0.5 s Care Dose Off</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HD mode: No Iterative Reconstruction: No</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Do not use IRIS or SAPHIRE</td>
</tr>
<tr>
<td>Expiratory</td>
<td>1.0</td>
<td>120</td>
<td>50 mAs</td>
<td>0.75</td>
<td>0.5</td>
<td></td>
</tr>
</tbody>
</table>

### Reconstruction Parameters:

<table>
<thead>
<tr>
<th>Effort</th>
<th>Recon</th>
<th>Kernel</th>
<th>DFOV (cm)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insp</td>
<td>Recon 1</td>
<td>B31f</td>
<td>* Tight DFOV</td>
<td>Set DFOV to display lungs at TLC with only 1 cm margin outside lungs.</td>
</tr>
<tr>
<td>Insp</td>
<td>Recon 2</td>
<td>B45f</td>
<td>* Tight  DFOV</td>
<td>Use same DFOV as Insp. Recon 1</td>
</tr>
<tr>
<td>Exp</td>
<td>Recon 1</td>
<td>B31f</td>
<td>* Tight DFOV</td>
<td>Use same DFOV as Insp. Recon 1</td>
</tr>
<tr>
<td>Exp</td>
<td>Recon 2</td>
<td>B45f</td>
<td>* Tight DFOV</td>
<td>Use same DFOV as Insp. Recon 1</td>
</tr>
</tbody>
</table>

### Visit 2 Scan - Information below to be filled out by CT Technologist

<table>
<thead>
<tr>
<th>COPDGene Subject Id</th>
<th>NJC 30000N</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT Acquisition Date</td>
<td>mm/dd/yyyy</td>
</tr>
<tr>
<td>CT Dose Index (CTDI): Inspiratory</td>
<td>(mGy)</td>
</tr>
<tr>
<td>CT Dose Index (CTDI): Expiratory</td>
<td>(mGy)</td>
</tr>
<tr>
<td>Imaging Technologist</td>
<td></td>
</tr>
</tbody>
</table>

Baseline Scan: No baseline scan

Site Coordinator: Please record on CT Assessment form before delivering to radiologist.

---

**Figure 15-4. COPDGene® Phase 2 CT Acquisition Form – No Baseline Scan**

### 15d. De-Identification, Scan Reconstructions and Backup Storage

Subject scans may be acquired with the subject’s name in the Patient Name field and the CT Technologist should not de-identify any DICOM fields. The DICOM send software will de-identify all images before transferring them to the Imaging Core. The Patient Name field for phantom scans should read “COPDGene® Lung Phantom.”

The preferred method of transferring CT images to the coordinator is on a USB drive, external hard drive or PACS location. DVDs and CDs are acceptable if there is no other option. Original Images should be saved to the coordinator’s computer (preferably to a folder on the desktop). Coordinators will be given the option to save de-identified images following completion of the image transfer and a backup of de-identified images should be saved at the clinical centers. A
hard drive is the easiest storage solution to save images to from the DICOM send software. DVDs and CDs are also acceptable.

The Series Description should specify the series (Inspiration or Expiration) and reconstruction kernel. Only DICOM images will be accepted.

Here is an example of the labeling scheme for each of the four COPDGene® reconstructions:

<table>
<thead>
<tr>
<th>General Electric</th>
<th>Philips</th>
<th>Siemens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inspiration Standard</td>
<td>Inspiration B</td>
<td>Inspiration B31f</td>
</tr>
<tr>
<td>Inspiration Bone</td>
<td>Inspiration D</td>
<td>Inspiration B45f</td>
</tr>
<tr>
<td>Expiration Standard</td>
<td>Expiration B</td>
<td>Expiration B31f</td>
</tr>
<tr>
<td>Expiration Bone</td>
<td>Expiration D</td>
<td>Expiration B45f</td>
</tr>
</tbody>
</table>

15e. Subject CT Scan Lung Volumes

Scout scans will be used by the technologist to obtain the size of the subject and to position the CT scan over the lung field. Two different fixed-volume CT scans will be performed. The first volume is at Total Lung Capacity (TLC) and the second is at Functional Residual Capacity (FRC). The exposure factors (kV and mA) for the topograms should be set to the lowest available that still provide acceptable images. For example, settings of 80 kv and 20 mA in GE scanners are sufficient to achieve satisfactory scout image quality.

Scout scans will be obtained and must be performed at the lung volume for which anatomical boundaries are being evaluated. Scout scans are performed for TLC scans so that the full extent of the lung is acquired at the respective lung volumes and over-scanning is kept to a minimum (no more than 2 cm from the start of the scan to the thoracic inlet and no more than 5 cm from the lowest slice of lung to the end of the scan). GE scanners require separate scout scans for inspiration and expiration scans, while Philips and Siemens scanners do not. The expiration scan should be shorter than the inspiration scan for each subject. Inadequate scout scans may be repeated as permitted at the clinical center. Spiral scans may not be repeated.

15f. Subject Preparation

Prior to scanning, subjects should remove any jewelry that may be visible in the CT scans and any items from chest pockets. The COPDGene® CT protocol requires subjects to be scanned in the supine position with arms extended above the head. Subjects should be centered on the scanner bed with nothing under the body that would affect body position or alignment, such as pillows or cushions.

Perform a “Time Out” to make sure you have the Right Patient, Right Research Study, and Right Scan Protocol. You must do a "time out" before each exam and go over the 3 Rs.

1) **Right Patient:** Check patient’s Personal Identification (i.e. Driver’s License). Compare the name on the ID to the name on the COPDGene® CT Acquisition Report.
2) **Right Research Study:** Check that the patient is being scanned for the COPDGene® Study and that the CT Acquisition Form matches this description. Have the Imaging Manual of Procedures for COPDGene® Phase 2 as a reference guide during scanning.

3) **Right Scan Protocol:** Check that the correct CT scan parameters are selected for COPDGene® Phase 2.

15g. **CT Breathing instructions**

These are the instructions to be given by the Technologists at the time of scanning.

* Side notes for technologist in italics

It is important for the Technologist to ensure that the subject is able to follow the commands appropriately and also that the subject is appropriately coached PRIOR to performing the actual imaging procedures.

**GENERAL:** This study consists of 2 scouts (topograms) and 2 scans.

**CONTRAST:** Oral/IV. None.

**SUPINE INSPIRATION:**

Instruct the patient to breathe as follows:

“For the first part of this study you will be asked to hold your breath in for about 20 seconds. If you cannot hold your breath that long, try the best you can and then take very shallow, slow breaths if you need to.”

“For now, take several easy, deep breaths and relax while we prepare to take a CT scan of your lungs.”

Allow patient to breathe and relax for at least 15 seconds.

“I am now going to give you specific breathing instructions. Try to follow as best you can.”

“Take in a deep breath….and let it out.”

“Take in another deep breath….and let it out.”

“Take in another deep breath, and hold your breath in. Keep holding your breath!”

**Take the scout**

When the scout is completed, tell the study participant to “Breathe and relax!”

Allow patient to breathe and relax for at least 15 seconds.

**Repeat these breathing instructions.**

“I am now going to give you specific breathing instructions. Try to follow as best you can.”

“Take in a deep breath….and let it out.”

“Take in another deep breath….and let it out.”

“Take in another deep breath, and hold your breath in. Keep holding your breath!”

**Scan the patient in one breath-hold at full-inspiration.**

When the scan is completed, tell the study participant to “Breathe and relax!”
SUPINE EXPIRATION:

Instruct the patient to breathe as follows:
“For the second part of this study you will be asked to blow out your breath and hold it out for about 20 seconds. This is usually more difficult than holding your breath in, but do the best that you can. If you cannot hold your breath out that long, take a very slow shallow breath in if you need to.”
“For now, take several easy, deep breaths and relax while we prepare to take the last CT scan of your lungs.”

Allow patient to breathe and relax for at least 15 seconds.
“I am now going to give you more specific breathing instructions. Try to follow as best you can.”
“Take in a deep breath….and let it out.”
“Take in another deep breath….and let it out.”
“Take in another deep breath, let it out and hold your breath out! Do not breathe!”

Take the scout
When the scout is completed, tell the study participant to “Breathe and relax!”

Allow patient to breathe and relax for at least 15 seconds.
“I am now going to give you more specific breathing instructions. Try to follow as best you can.”
“Take in a deep breath….and let it out.”
“Take in another deep breath….and let it out.”
“Take in another deep breath, let it out and hold your breath out! Do not breathe!”

Scan the patient in one breath-hold at expiration as quickly as possible.
When the scan is completed, tell the study participant to “Breathe and relax!”
### 15h. CT Scanning Protocol

<table>
<thead>
<tr>
<th>CT Scanning Protocol</th>
<th>Inspiratory CT</th>
<th>Expiratory CT</th>
<th>Inspiratory CT</th>
<th>Expiratory CT</th>
<th>Inspiratory CT</th>
<th>Expiratory CT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Scanner Make</strong></td>
<td>GE</td>
<td>GE</td>
<td>GE</td>
<td>GE</td>
<td>GE</td>
<td>GE</td>
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<tr>
<td><strong>Scanner Model</strong></td>
<td>LS 16</td>
<td>LS 16</td>
<td>VCT 64 Slice</td>
<td>VCT 64 Slice</td>
<td>Discovery CT</td>
<td>Discovery CT</td>
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<tr>
<td><strong>Scan Type</strong></td>
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<td>Helical</td>
<td>Helical</td>
<td>Helical</td>
<td>Helical</td>
<td>Helical</td>
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<tr>
<td><strong>Scan FOV</strong></td>
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<td>Large</td>
<td>Large</td>
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<td>Large</td>
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<td><strong>Rotation Time (s)</strong></td>
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<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
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<tr>
<td><strong>Det. Configuration</strong></td>
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<td>16 x 0.625</td>
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<td>64 x 0.625</td>
<td>64 x 0.625</td>
<td>64 x 0.625</td>
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<tr>
<td><strong>Pitch</strong></td>
<td>1.375</td>
<td>1.375</td>
<td>0.984</td>
<td>0.984</td>
<td>0.984</td>
<td>0.984</td>
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<tr>
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<td>120</td>
<td>120</td>
<td>120</td>
<td>120</td>
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<td>120</td>
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<td><strong>mA Setting</strong></td>
<td>400</td>
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<td>100</td>
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<td><strong>Dose Modulation</strong></td>
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<td>Auto-mA OFF</td>
<td>Auto-mA OFF</td>
<td>Auto-mA OFF</td>
<td>Auto-mA OFF</td>
<td>Auto-mA OFF</td>
</tr>
<tr>
<td><strong>HD Mode</strong></td>
<td>OFF</td>
<td>OFF</td>
<td>OFF</td>
<td>OFF</td>
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<td>OFF</td>
</tr>
<tr>
<td><strong>Scan Time (s)</strong></td>
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<td>&lt;10</td>
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<tr>
<td><strong>30 cm Length</strong></td>
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<td><strong>Reconstructions</strong></td>
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<tr>
<td><strong>RECON 1 Algorithm</strong></td>
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<td>Standard</td>
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<td><strong>Additional Image Filters</strong></td>
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<td>No Selection</td>
<td>No Selection</td>
<td>No Selection</td>
<td>No Selection</td>
<td>No Selection</td>
</tr>
<tr>
<td>** Thickness (mm)**</td>
<td>0.625</td>
<td>0.625</td>
<td>0.625</td>
<td>0.625</td>
<td>0.625</td>
<td>0.625</td>
</tr>
<tr>
<td><strong>Interval (mm)</strong></td>
<td>0.50</td>
<td>0.50</td>
<td>0.50</td>
<td>0.50</td>
<td>0.50</td>
<td>0.50</td>
</tr>
<tr>
<td><strong>Iterative Reconstruction (Noise Reduction)</strong></td>
<td>Do Not Use ASIR</td>
<td>Do Not Use ASIR</td>
<td>Do Not Use ASIR</td>
<td>Do Not Use ASIR</td>
<td>Do Not Use ASIR</td>
<td>Do Not Use ASIR</td>
</tr>
<tr>
<td><strong>DFOV (mm)</strong></td>
<td>Parameters Report specifies DFOV to match baseline DFOV</td>
<td>Parameters Report specifies DFOV to match baseline DFOV</td>
<td>Parameters Report specifies DFOV to match baseline DFOV</td>
<td>Parameters Report specifies DFOV to match baseline DFOV</td>
<td>Parameters Report specifies DFOV to match baseline DFOV</td>
<td>Parameters Report specifies DFOV to match baseline DFOV</td>
</tr>
</tbody>
</table>

*If the DFOV from the baseline CT scan was too large, additional inspiratory and expiratory reconstructions will be requested using the RECON 1 algorithm and a tighter DFOV. The CT Scan Parameters Report provided by the coordinator will specify the required reconstructions.*
<table>
<thead>
<tr>
<th>CT Scanning Protocol</th>
<th>Inspiratory CT</th>
<th>Expiratory CT</th>
<th>Inspiratory CT</th>
<th>Expiratory CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scanner Make</td>
<td>Philips</td>
<td>Philips</td>
<td>Philips</td>
<td>Philips</td>
</tr>
<tr>
<td>Scanner Model</td>
<td>Brilliance 40 slice</td>
<td>Brilliance 40 slice</td>
<td>Brilliance 64 slice</td>
<td>Brilliance 64 slice</td>
</tr>
<tr>
<td>Scan Type</td>
<td>Spiral Helix</td>
<td>Spiral Helix</td>
<td>Spiral Helix</td>
<td>Spiral Helix</td>
</tr>
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<td>Scan FOV</td>
<td>No Selection</td>
<td>No Selection</td>
<td>No Selection</td>
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**Reconstructions**

- **RECON 1 Algorithm**: B
- **RECON 2 Algorithm**: D (YB if D not available)
- **Additional Image Filters**: Adaptive Filtering OFF
- **Thickness (mm)**: 0.67
- **Interval (mm)**: 0.50
- **Iterative Reconstruction (Noise Reduction)**: Do Not Use iDOSE
- **DFOV (mm)**: Parameters Report specifies DFOV to match baseline DFOV

*If the DFOV from the baseline CT scan was too large, additional inspiratory and expiratory reconstructions will be requested using the RECON 1 algorithm and a tighter DFOV. The CT Scan Parameters Report provided by the coordinator will specify the required reconstructions.*
<table>
<thead>
<tr>
<th>CT Scanning Protocol</th>
<th>Inspiratory CT</th>
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**Reconstructions**

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<td>Parameters Report specifies DFOV to match baseline DFOV</td>
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<td>Parameters Report specifies DFOV to match baseline DFOV</td>
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*If the DFOV from the baseline CT scan was too large, additional inspiratory and expiratory reconstructions will be requested using the RECON 1 algorithm and a tighter DFOV. The CT Scan Parameters Report provided by the coordinator will specify the required reconstructions.
<table>
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<tr>
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<td>Parameters Report specifies DFOV to match baseline DFOV</td>
<td>Parameters Report specifies DFOV to match baseline DFOV</td>
</tr>
</tbody>
</table>

*If the DFOV from the baseline CT scan was too large, additional inspiratory and expiratory reconstructions will be requested using the RECON 1 algorithm and a tighter DFOV. The CT Scan Parameters Report provided by the coordinator will specify the required reconstructions.
15i. **Subject CT Scan Quality Control and Safety Monitoring Plan**

The site study coordinator should accompany subjects to the imaging suite, verify with the technologist that the COPDGene® protocol will be followed and will preferably remain in the CT control room during scanning to assure that appropriate breath hold instructions are given. CTDIvol will be recorded for both the inspiratory and expiratory CT scans.

All COPDGene® subject and phantom CT scans will be transferred to the Imaging Core within two (2) working days of their acquisition. Scans will be evaluated for quality assurance and protocol compliance.

Once a scan is received, the Imaging Core will confirm that the radiation dose utilized was consistent with the radiation risk language in the site's Informed Consent. Protocol issues will be classified as “deviations” if they are related to radiation dosing. These deviations result in radiation exposure either greater or less than approved limits. Examples of deviations are excessive current or voltage, excessive scan length and repeating a scan.

In cases of deviations, the Imaging Core will immediately send an electronic deviation report describing the issue to the site PI, lead coordinator, site radiologist, lead technologist and Imaging Core Director. Two consecutive deviations or cumulative deviations of more than 5% of scans acquired will generate an immediate report to the Imaging Core Director, site PI, lead coordinator, radiologist, lead technologist, and Executive Committee. CT scanning will be suspended until a remediation plan is in place and agreed to by the site PI and the Executive Committee. All deviations should be reported to the relevant clinical center’s local IRB.

Other types of protocol errors will be classified as “Quality Control Notifications” and are protocol issues that do not result in non-approved radiation exposure. Examples of these quality control notifications are, whole lung not scanned, incorrect reconstruction kernel used, inspiratory or expiratory scan not performed, CT data lost, CT tech not certified, CT scanner not certified, etc.

Quality control issues will be reported to the site PI, lead coordinator, site radiologist, lead technologist and Imaging Core Director. The technologist responsible for the quality control issues will have to review the training materials with the site’s lead technologist in order to continue scanning subjects. Excessive quality control issues will be reported to the Executive Committee and a remediation plan will be developed for quality improvement.
15j. Examples of Image Quality Issues

Figure 15-5. Poor DFOV

Figure 15-6. Appropriate DFOV

Figure 15-7. Inappropriate scan length includes head

Figure 15-8. Scan does not include entire lungs
15k. CT Scanner Quality Control

CT scanners should be operated and maintained according to the recommendations of the manufacturer. This includes the use of weekly water phantoms and daily air calibrations. All CT scanners used in COPDGene® must be certified with a phantom scan. This phantom scan will provide checks for protocol adherence and proper calibration of the CT scanner.

Phantom scans not performed to protocol will be rejected by the DICOM Send software and a report will provide feedback regarding the nature of the failure. If it is a post processing issue, such as the wrong DFOV, slice thickness or slice spacing, the issue can be corrected without a rescan. If the problem is related to scan acquisition (e.g., wrong mA/mAs, kV, pitch, or exposure time), the phantom must be re-scanned to the correct parameter(s).

If a phantom scan reveals an issue with a CT scanner, the Imaging Core will work with the clinical center to troubleshoot the cause of the issue. CT scanners with significant quality issues will not be approved for use until the issues are resolved. Once scanners are approved and certified, monthly phantom scans must be acquired and transmitted via the DICOM Send software. Regular monthly phantom scans will be acquired throughout the course of the study.
15. COPDGene® Lung Phantom (* CTP674 Lung Phantom™)

Figure 15-9. COPDGene® Lung Phantom

Figure 15-10. Schematic Drawing
15m. COPDGene® Lung Phantom Description

The COPDGene® Lung Phantom is designed to allow comparative measurements between CT scanners. This phantom is not intended to replace current methods of comprehensive quality assurance testing. It is intended to offer additional density and geometrical information for CT scanners used in clinical “quantitative based” lung studies.

Each site must maintain its normal Standard Operating Procedures for regular calibration and maintenance of CT scanners.

The COPDGene® Lung Phantom consists of an outer ring (Catphan® Uniformity Material Ring) which simulates body tissue attenuation and a central oval insert which simulates lung attenuation. The reference materials used are air, water and acrylic. Figure 12 11.
15n. COPDGene® Lung Phantom Set-up and Scan Preparation

**Important:** Prior to scanning ensure that the water bottle is completely filled with DISTILLED WATER. The phantom should arrive at your site filled.

The blue line on the outer ring is to assist alignment of the phantom with the CT scanner’s alignment lights. Figure 15-12.

![Figure 15-12](image)

**Step 1:** The phantom will arrive to you without the legs of the base attached. Screw the legs into the acrylic plates. Figure 15-13.

![Figure 15-13](image)
**Step 2**: Prior to placing the phantom on the scanner table you must first ensure the water bottle top is sufficiently level with the back edge of the phantom. The bottle must be level with the phantom foam material not the protective plate.

**Step 3**: Place the phantom directly on the scanner table. The pad is removed for better leveling. There must be no other tables or boards below the phantom.

**Step 4**: Orient the phantom on the scanner table head-first, supine. The cap of the bottle is the head. The phantom is also marked with “H” for “head.”

**Step 5**: Align the phantom along both axes with the laser light on your scanner using blue line on phantom’s outer ring. Figure 12-12.

**Step 6**: Align the scanner crosshairs with the **“H” marking Head Position** on the front of the phantom. Figure 12-14.

**Step 7**: Move the scanner table. Do not allow the phantom to go past the detector center line.
15o. COPDGene® Lung Phantom Scan Acquisition

Phantom scan should include entire length of the phantom

Follow the CT Protocol for inspiratory and expiratory CT scans. Use 36.5 cm / 365 mm DFOV for all reconstructions and set (x,y) reconstruction coordinates to (0,0).

Figure 15-15

1) One scan using the COPDGene® CT Protocol inspiratory settings and one scan using the expiratory settings should be acquired for each COPDGene® certified scanner. Scanning must be accomplished with the phantom remaining in the same position for both scans.

2) Scan identification must have COPDGene® Lung Phantom in the Patient Name field.

3) “Patient” position should be head first, supine. Run the scout scan head to foot.

4) Reconstruct the images using each kernel specified in the CT scanning protocol. The Display Field of View (DFOV) must be 365 mm. and the (x,y) reconstruction coordinates must be (0,0) respectively.
Appendix A: DICOM Send Software

1) A copy of the DICOM send software zip file is located on the COPDGene® USB drive and is available on CD/DVD upon request.

2) A video tutorial for the software and a download link for the software are located at: http://copdsendtool.njh-imaging.org/

3) Open the zip file, extract the contents to your desktop and open the folder.

4) site.dic specifies the three letter designated site ID for use by the COPDSendTool.
5) To run the COPDSendTool:

   Windows:
   double-click run.bat

   OSX:
   double-click run.command

   Linux:
   double-click run.sh

6) Upon opening, the tool will connect to the QIL servers and download configuration parameters per your site.

7) When that is finished, click 'Browse' to locate your images.
8) Click 'Import' to scan for and import the images into the COPDSendTool.

9) A log will be maintained of the session actions.

10) Notice any invalid images/series will be listed with explanations in the log.
11) Studies found are listed in the upper left.

12) Series for the selected study are listed in the middle.
13) Assign the subject ID, CT tech and CTDI values for the selected study.

14) Click 'Apply' to submit these assignments.

15) Click 'Phantom' if the selected study is a Phantom study.

16) All subjects must have all values assigned before processing.

17) Phantom scans do not require CTDI values.

18) The log will list relevant errors when they occur.

19) Correct the mistakes until verification of the submission.
20) If you do not understand the error messages or you are not able to resolve errors, click ‘Email Support.’

   The software will email a detailed description of the problem to Technical Support.

21) After all studies have had their values assigned, click ‘Send’ to process and transfer the images.
22) As soon as image processing is finished, you may save the modified files locally.

23) After successful transfer, a notification email will be sent to the lab and site coordinators.
24) **Select 'Overwrite/Reset' to fix incorrect transfers.**

Unchecked, the COPDSendTool will simply re-process and resume interrupted transfers.

25) **If necessary, you may cancel/stop the import, send and save processes as needed.**
26) When finished, click ‘Quit’

If confirmed, The COPDSendTool will cleanup any temporary working files, save a log and quit.
Appendix B: Optional Calcium Calibration Phantom for Bone Density Ancillary Study

INTable™ CT Calibrations

The INTable™ Calibration Pad is intended to replace existing CT couch pads and to remain in place on the CT scanner. The small cross sectional samples do not interfere with other CT exams. The small (round) samples virtually eliminate streak artifacts, scatter, beam hardening, and the increased dose and noise of the older, larger QCT Calibration phantoms.

Each phantom sample is homogeneous and stable for long-term use. Calcium hydroxyapatite is the major component of human bone and vascular calcifications and has become the accepted standard for bone densitometry and calcium mass scoring. The Image Analysis proprietary software automatically finds the calibration samples on all slices and provides automated calibrations for either Calcium Scoring or Bone Densitometry.

DIMENSIONS: The Calibration pad is 51 in. (129 cm) long, and 16 in. (41 cm) wide. The contoured pad will fit all modern CT tables. Each sample rod is 0.625 in. (1.6 cm) diameter and 50 in. (127 cm) long.

CT-Water™: The base material is composed of our proprietary CT water equivalent solid compound.

CALIBRATION SAMPLES: Four sample concentrations of 0 mg/cc, 75 mg/cc, 150 mg/cc of calcium hydroxyapatite homogeneously (CaHA) blended into the CT-Water™ material. The fourth sample is fat equivalent.
Appendix C: Contact Information

**COPDGene® Imaging Core at National Jewish Health**

**General and Technical Information:**
Jordan Zach  
Research Associate, Department of Radiology  
(303) 270-2513  
*zachj@njhealth.org*  
Alex Kluiber  
Database Administrator  
(303) 270-2595  
*kluibera@njhealth.org*

**Shipping Address:**
Quantitative Imaging Laboratory – COPDGene® Study  
National Jewish Health  
1400 Jackson St., K012e  
Denver, CO 80206

**COPDGene® Phantom Analysis Laboratory at the University of Iowa**

**General and Technical Information:**
Jered Sieren  
Research Assistant III/CT Lab Manager  
(319) 384-7947  
*jered-sieren@uiowa.edu*

**Shipping Address:**
University of Iowa Hospitals and Clinics  
200 Hawkins Drive, cc-703 GH  
Dept. of Radiology, Div. of Imaging  
Iowa City, IA 52242
16. Collection of Blood Samples

16a. Purpose of COPDGene® Study Center Visit 2 Laboratory Manual

This manual serves to identify those involved with the COPDGene® Visit 2 Biorepository and to clarify standard operating procedures for work on this study. These procedures should be adhered to by all staff members and monitored by quality assurance and quality control activities.

16b. Biological Specimen Handling

16b.1. Labeling and Identification

Purpose: Ensure all collected samples are labeled accurately and adequately.

By Whom: COPDGene® Site Coordinator/phlebotomist

Procedure:
The COPDGene® site will use pre-barcoded labels, as provided by the Channing Lab Biorepository, to label all specimen collection containers, documents, etc. These labels include the laboratory barcode number, the COPDGene® ID number, and the tube type. An example of the label designed by the Biorepository is below:

![Label Example]

These labels will be used for all blood tubes and specimen transmittal documents for the lab. They can be used also for other COPDGene® study documentation. One blood tube package per subject will be provided with pre-printed barcodes for all blood tubes and aliquot tubes. Extra labels will be provided with the COPDGene® Subject ID.
Place label on tube from top to bottom. The bar code labels should be placed on both the blood collection tubes and on the Cryovial Aliquot tubes. Label all tubes prior to blood draw.

Note: When drawing blood for more than one subject on the same day, keep tubes from each subject separate and label tubes for one subject at a time.

16b.2. **Blood Draws/Phlebotomy**

**Purpose:** To ensure that venipunctures are performed following standard safety guidelines, and to ensure that blood samples are collected in the correct order and in accordance with study protocols.

**By Whom:** COPDGene® Site/Phlebotomist/nurse

**Procedure:**
The following table summarizes draw order and volume for the collection of blood samples into plastic vacutainer tubes.
<table>
<thead>
<tr>
<th>Draw Order</th>
<th>Tube Type</th>
<th>Tube Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EDTA purple top</td>
<td>10 ml</td>
</tr>
<tr>
<td>2</td>
<td>EDTA purple top</td>
<td>10 ml</td>
</tr>
<tr>
<td>3</td>
<td><em>EDTA purple top</em></td>
<td>4 ml or 5 ml</td>
</tr>
<tr>
<td>4</td>
<td>SST red-grey top</td>
<td>10 ml</td>
</tr>
<tr>
<td>5</td>
<td>Paxgene DNA tube</td>
<td>8.5 ml</td>
</tr>
<tr>
<td>6</td>
<td>Paxgene RNA tube</td>
<td>2.5 ml</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>46 ml</td>
</tr>
</tbody>
</table>

*EDTA 5ml Tube is drawn for CBC (complete blood count) analysis to be done at a local clinical laboratory

**Technique:**
Blood should be drawn using standard phlebotomy technique with tourniquet applied to identify vein and released after adequate blood flow is obtained.

Needle or catheter should preferably be no smaller than 21 gauge to minimize risk of hemolysis.

Be sure to wear appropriate PPE (Personal Protective Equipment) when handling blood and throughout blood processing. To safely handle blood, you need to wear latex or nitrile gloves, a laboratory coat, and a face shield.

**16b.3. Sample Processing**

Immediately after collecting the blood samples, ensure the barcode labels are on each tube and correspond to the correct study subject.

Make sure to keep samples at room temperature prior to sample processing. Do not put blood tubes on ice.

**EDTA Purple Top Tubes**

**Procedure:**
1. Mix EDTA purple top tubes thoroughly by inverting tube 5 times.
2. Send the 5 ml EDTA purple top to the local clinical laboratory for a Complete Blood Count with machine cellular differential. CBC must include automated differential.
3. Follow operator’s manual instructions for use of local centrifuge, insuring balance of tubes within the centrifuge.
4. Centrifuge at 2500 RPM or 1000 to 1300 g for 10 minutes.
5. Remove tubes from centrifuge. Note that the blood has separated into 3 layers:
   - Top: Plasma (yellow/transparent layer)
   - Middle: White Blood Cells (thin, delicate, white, membrane layer)
   - Bottom: Red Blood Cells (dark red, opaque layer)
6) Remove Rubber Stopper. Remove caps from Aliquot Cryovial Tubes. 

   **NOTE: During aliquoting, be careful not to disrupt the White Blood Cell layer. Leave a small portion of the plasma in the tube to ensure that no White Blood Cells were removed.**

7) Using a transfer pipet, aliquot as follows, using the markings on the transfer pipet to measure the volume (Note: If there is inadequate plasma volume for the specified aliquot below, create 6 aliquots with the available volume of plasma):
   - 6 aliquots with 0.5ml (500ul) Plasma

8) Re-cap the Purple Top EDTA blood tubes, and cap the Cryovial tubes.

9) Place EDTA blood tubes and aliquots into storage boxes and store samples at -80 degrees Celsius.
SST Red-Grey Top Tube

Procedure:
1) After obtaining the SST sample, allow sample to clot 30 minutes in a vertical position.
2) Follow manual instructions for use of local centrifuge, insuring balance of tubes within the centrifuge.
3) Centrifuge at 2500 RPM or 1000 to 1300 g for 10 minutes.
4) Remove Rubber Stopper. Remove caps from Aliquot Cryovial Tubes.
5) Using a transfer pipet, aliquot 0.5 ml of serum into 6 Aliquot Cryovial tubes, using the markings on the transfer pipet to measure the volume.
   • 6 aliquots with 0.5 ml Serum (aliquots may be smaller than 0.5 ml if inadequate volume of serum is obtained)
   • If there is not enough serum for six 0.5 ml tubes, then distribute the serum evenly among the tubes. The important point is to fill all 6 tubes with serum, not leaving a tube empty.
6) Discard the SST blood tube, and cap the Cryovial tubes.
7) Place the aliquots into storage boxes and store samples at -80 degrees Celsius.

Paxgene DNA and Paxgene RNA Tubes

Procedure:
1) After obtaining the Paxgene RNA and DNA tubes, mix thoroughly by inverting tube 10 times.
2) Allow the tubes to sit in an upright position at room temperature for 1-2hrs. Tubes need to incubate at Room Temperature in an upright position prior to freezing.
   Note: Paxgene tubes do not need to be centrifuged or aliquoted. Let these tubes sit at room temperature in an upright position while aliquoting plasma and serum from other blood tubes.
3) Place Paxgene RNA and Paxgene DNA tubes into the provided storage boxes and store samples at -80 degrees Celsius.

16c. Sample Distribution/Shipping

16c.1. Shipper Assembling and Packaging Instructions

Purpose: To ensure samples are correctly packaged and shipped according to specimen needs, study protocol, and IATA guidelines.

General Requirements
Technicians must be familiar with IATA guidelines outlined in the appendix. The packaging must be of good quality and strong enough to withstand the shocks and loadings normally encountered during transport – including trans-shipment between transport units and between transport units and warehouses as well as any removal from a pallet or over pack for subsequent manual or mechanical handling. Packaging must be constructed and closed so as to prevent any loss of contents that might be caused under normal conditions of transport, by vibration, or by changes in temperature, humidity or pressure.
The packaging must consist of three components:
  a) A primary receptacle: blood vacutainer tubes – EDTA, SST, Paxgene, and Aliquot Cryovial tubes
  b) A secondary packaging: specimen freezer storage boxes packed inside Saf-T-Pak envelopes.
  c) A rigid outer packaging: 19 ¾ x 16 ¾ x 15 ⅜ Thermosafe styrofoam shippers and cardboard outer box.

Primary receptacles (blood tubes and cryovials) must be packed in secondary packaging (specimen freezer storage boxes) in such a way that, under normal conditions of transport, they cannot break, be punctured or leak their contents into the secondary packaging. Secondary packaging must be secured in outer packaging (Styrofoam and cardboard box) with suitable cushioning material. Any leakage of the contents must not compromise the integrity of the cushioning material or of the outer packaging.

Step by step procedure:
A Power Point presentation outlining specific packing information for the blood and cryovial tube shipment has been developed and is available on the COPDGene® web site. All coordinators are expected to be familiar with this presentation. Shipping containers must be prepared in accordance with the steps shown in that presentation.

1) The Styrofoam container should be inserted inside the cardboard box.
2) Just prior to packaging the shipment, remove freezer boxes to be shipped from the -80 degrees Celsius freezer.
3) 2 large freezer boxes containing whole blood tubes plus 6 freezer boxes containing Aliquot Cryovials should be individually packed into Saf-T-Pak envelopes.
4) Place the freezer boxes into the shipping container.
5) Place approximately 5 pounds of dry ice over boxes, or fill until box is full. Be sure to cover boxes completely with dry ice, while still allowing enough room to tightly and securely close the Styrofoam container lid.
6) Place the top on the Styrofoam container.
7) Finally, seal the cardboard box with packing tape - do NOT seal so that the box is air tight.

    Note: Do not completely seal the Styrofoam box or the cardboard shipping box with tape. Sealing the box airtight can cause the package to explode. Dry ice needs ventilation because carbon dioxide gas is produced over time.

16c.2. Shipping to CHANNING BIOREPOSITORY LAB

**Purpose:** Ensure samples are correctly packaged and shipped according to specimen needs, study protocol, and IATA guidelines.

**By Whom:** COPDGene® Site/Study Coordinators
General Procedure:

**Note:** Specimens may only be shipped Monday through Wednesday to ensure arrival at the CHANNING LAB on a weekday. Avoid sending shipments that will be expected to arrive at CHANNING LAB on holidays.

**SHIP TO:**

Roxanne Kelly  
Channing Systems Genetics and Genomics  
Brigham and Women's Hospital  
221 Longwood Avenue  
EBRC Room 610  
Boston, MA, 02115  
617-732-5888

1) Refer to the previous section for detailed instructions on assembling and packaging the shippers.  
2) Place the specimen transmittal forms on the top of foam on the inside of the shipping box and seal the box.  
3) Complete the preprinted FedEx airway bill with DATE, PRIORITY OVERNIGHT, OTHER PACKAGING.  
4) Place the airway bill on the box, inside the clear plastic sleeve and call for FedEx pick up.  
5) Enter the shipment tracking number on the COPDGene® website, which will generate a shipment notification that will be sent to the lab.  
6) Specimens should be shipped on Monday – Wednesday only. Notices will be sent via email to coordinators one month prior to holidays to indicate any changes to lab and shipping schedules.  
7) Specimens should be shipped when you accumulate 24 subjects, or 2 full storage boxes of whole blood frozen tubes, plus 6 boxes of Aliquot Cryovials.  
8) Once shipments are received in the lab, the received date will be entered on the COPDGene® website by the lab staff. This will confirm and resolve the shipment. Problems or delays with the shipments will be handled on a case by case basis with clinical sites as well as logged on the COPDGene® website.

**Note:** Specimens may only be shipped Monday through Wednesday to ensure arrival at the Channing lab on a weekday.

### 16d. Supplies and Ordering

**By Whom:** Channing Lab and Clinical Center site technicians

<table>
<thead>
<tr>
<th>Sample Collection Supplies</th>
<th>Supplier</th>
<th>Catalog Number</th>
<th>Cost/Unit</th>
<th>To be supplied by</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purple top plastic EDTA tubes 10 ml</td>
<td>VWR</td>
<td>BD366643</td>
<td>case of 10x100 $270.81</td>
<td>Channing Lab</td>
</tr>
</tbody>
</table>
Red-Gray plastic SST tubes 10 ml | VWR | BD367985 | case of 10x100 | $543.55 | Channing Lab
---|---|---|---|---|---
Purple top plastic EDTA tubes 4 ml | VWR | BD367862 | case of 10x100 | $270.81 | Channing Lab
Paxgene DNA plastic tubes 8.5ml | VWR | 761115 | Case of 100 | $112.50 | Channing Lab
Paxgene RNA plastic tubes 2.5ml | VWR | 762165 | Case of 100 | $856.00 | Channing Lab
Butterfly needles 21 G (Preferred) | VWR | BD367281 | case of 4x50 | $249.75 | Site
Butterfly needles 23 G | VWR | BD367283 | case of 4x50 | $249.75 | Site
Tourniquets (reusable) | VWR | VT367203 | case of 20x25 | $186.95 | Site
Tube adapters | VWR | VT367290 | case of 10x100 | $317.86 | Site
Gauze | VWR | 82004-740 | case of 5000 | $126.54 | Site
Bandage | VWR | 56612-996 | case of 12x100 | $62.02 | Site
Alcohol pads | VWR | 15648-981 | case of 15x200 | $91.81 | Site
Hamilton Bell™ Vanguard Centrifuge | MarketLab | JL9576 | | $359 | Site
Tube/Document Labels | Brady | THT-125-499-3 | 3000 per roll, | $133.46 | Channing Lab

*Note: An alternative centrifuge can be used if available.

16e. Good Laboratory Practices

**Purpose:** To train all staff members in good laboratory practice and ensure these are followed in all laboratory activities.

**By Whom:** All laboratory staff members
- Eating, drinking, smoking, applying cosmetics, and handling contact lenses are prohibited in the laboratory working areas.
- Standard precautions should always be followed. Personal protective equipment (gown, gloves, eye protection) should be worn in the laboratory when handling and processing specimens and performing diagnostic testing.
- Physical containment devices should be used for all manipulations that may cause splashes or droplets of infectious materials.
- Mouth pipetting is forbidden.
- Contaminated materials must be disposed of in appropriate biohazard containers.
• Work surfaces must be decontaminated after any spill of potentially dangerous material using a bleach solution. Work surfaces and equipment should be decontaminated after specimens are processed.
• Personnel must wash their hands often – especially after handling infectious materials, before leaving the laboratory working areas, and before eating.
• Personal protective equipment must be removed before leaving the laboratory.
Biorepository Appendix

IATA Shipping Guidelines

Purpose: To ensure that all packages meet IATA guidelines for safe shipping.

By Whom: All staff members involved with shipping samples and reagents.

Disclaimer: This information is provided to each site as a quick reference to IATA shipping guidelines. Not all information provided in this section pertains to COPDGene® sites.

Procedure:
The Clinical Center (or shipper), not Federal Express™ (the transport company), is responsible for determining the hazard class and properly packaging and marking the hazard information on the shipment.

DIAGNOSTIC SPECIMENS
A diagnostic specimen is any human or animal material including, but not limited to, excreta, secreta, blood and its components, tissue fluids, and body parts being transported for research, diagnosis, investigational activities, disease treatment or prevention.

Diagnostic specimens transported under the IATA regulations are assigned the UN identification number 3373, and are subject to Packing Instructions 650. Any specimens shipped in dry ice must be labeled with the UN identification number 1845.

Labeling of shipping box:
• All diagnostic specimens must be labeled with a white diamond on point UN 3373 DIAGNOSTIC SPECIMENS label.
• If the shipper contains dry ice, there must be a Class 9 diamond on point label on the face of the shipper, as well as a DRY ICE UN 1845 label that includes the approximate weight (in kgs) of the dry ice included. Example of filled out dry ice label below:

  ![Dry Ice Label Example]

• The consignee and the shipper must be identified clearly on the face of the box.
PACKING INSTRUCTION 650

STATE VARIATIONS: DOG-03
OPERATOR VARIATIONS: AF-04, AO-03, AS-08, CO-07, CS-07, FX-09, LA-07, LH-12, OF-03

General Requirements
Diagnostic specimens must be packed in good quality packaging, which must be strong enough to withstand the shocks and loadings normally encountered during transport, including trans-shipment between transport units and warehouses as well as any removal from a pallet or over pack for subsequent manual or mechanical handling. Packaging must be constructed and closed so as to prevent any loss of contents when prepared for transport that might be caused under normal conditions of transport, by vibration, or by changes in temperature, humidity or pressure.

Primary receptacles must be packed in secondary packaging in such a way that, under normal conditions of transport, they cannot break, be punctured or leak their contents into the secondary packaging. Secondary packaging must be secured in outer packaging with suitable cushioning material. Any leakage of the contents must not substantially impair the protective properties of the cushioning material or of the outer packaging. Packages must be prepared as follows:

(a) For Liquids:
• The primary receptacle(s) must be leak proof and must not contain more than 500 ml;
• There must be absorbent material placed between the primary receptacle and the secondary packaging; if several fragile primary receptacles are placed in a single secondary packaging, they must be either individually wrapped or separated so as to prevent contact between them. The absorbent material, such as cotton wool, must be in sufficient quantity to absorb the entire contents of the primary receptacles and there must be a secondary packaging that must be leak proof.
• The primary receptacle or the secondary packaging must be capable of withstanding, without leakage, an internal pressure producing a pressure differential of not less than 95 kPa in the range of -40°C to +55°C (-40°F to 130°F).
• The outer packaging must not contain more than 4 L.

(b) For Solids:
• The primary receptacle(s) must be sift-proof and must not contain more than 500 g.
• If several fragile primary receptacles are placed in a single secondary packaging, they must be either individually wrapped or separated so as to prevent contact between them and there must be a secondary packaging that must be leak proof.
• The outer packaging must not contain more than 4 kg.

An itemized list of contents must be enclosed between the secondary packaging and the outer packaging.

Each completed package must be capable of successfully passing the drop test described in 6.6.1 except that the height of the drop must not be less than 1.2 m.

Packages must have one side with dimensions of not less than 100 mm x 100 mm (4 in x 4 in) or packages must be in an over pack that has one side with dimensions of not less than 100 mm x 100 mm (4 in x 4 in).
Each package and the “Nature and Quantity of Goods” box of the air waybill must show the text "DIAGNOSTIC SPECIMENS." Each package may also be marked in accordance with 7.1.5.8 to indicate that the shipper has determined that the packaging meets the applicable air transport requirements. The marking must be applied adjacent to the words "Diagnostic Specimens."

A Shipper’s Declaration for Dangerous Goods is not required.

Provided diagnostic specimens are packed in accordance with this Packing Instruction, no other requirements of these Regulations apply except for the definition in 3.6.2.1.4 and the reporting of dangerous goods accidents and incidents in 9.6.1. However, where carbon dioxide, solid (dry ice) or liquid nitrogen is used to keep specimens cold, all applicable requirements of these Regulations must be met.

Substances shipped refrigerated or frozen (wet ice, prefrozen packs, Carbon dioxide, solid [dry ice]): Ice Carbon dioxide, solid (dry ice) or other refrigerant must be placed outside the secondary packaging(s) or alternatively in an over pack with one or more completed packages. Interior support must be provided to secure the secondary packaging(s) or packages in the original position after the ice or Carbon dioxide, solid (dry ice) has been dissipated. If ice is used the packaging must be leak-proof. If Carbon dioxide, solid (dry ice) is used the outer packaging must permit the release of carbon-dioxide gas. The primary receptacle must maintain its containment integrity at the temperature of the refrigerant as well as at the temperatures and pressure of air transport to which the receptacle could be subjected if refrigeration were to be lost.

Substances shipped in liquid nitrogen: Plastic capable of withstanding very low temperatures must be used instead of glass receptacles. Secondary packaging must also withstand very low temperatures and in most cases will need to be fitted over individual primary receptacles. If multiple primary receptacles are placed in a single secondary packaging, they must be separated and supported to ensure that contact between them is prevented. Requirements for shipment of liquid nitrogen must also be observed. The primary receptacle must maintain its containment integrity at the temperature of the refrigerant 'used as well as at the temperatures and pressure of air transport to which the receptacle could be subjected if refrigeration were to be lost.

**Dry ice/carbon dioxide, solid**

PACKING INSTRUCTION 904.
STATE VARIATIONS: USG-13
OPERATOR VARIATIONS: HP-02, IC-08, VN-11

Carbon dioxide, solid (dry ice), when offered for transport by air, must be in packaging designed and constructed to permit the release of carbon dioxide gas and to prevent a build-up of pressure that could rupture the packaging.

The net weight of the Carbon dioxide, solid (dry ice) must be marked on the outside of the package. **Step by Step Diagrammatic representation of packaging and shipping COPDGene® samples using the Thermosafe shipper (15713-510).**
STEP 1.

Batch Shipment of Blood Tubes and Aliquots

- Items needed for blood shipment are (clockwise from upper left hand corner):
  - Styrofoam insulator box insert and top
  - FedEx Label, UN3373 Biological Substances Category A Label, Dry Ice Label, Biohazard Label.
  - 2 Blood Tube Freezer Boxes, containing frozen blood tubes.
  - 2 Saf-T-Pak Tyvek Bags for Blood Tube Freezer Boxes.
  - 6 Aliquot Freezer Boxes containing frozen aliquots.
  - 6 Saf-T-Pak Tyvek Bags for Aliquot Cytovial Tube Freezer Boxes.

STEP 2.

Batch Shipment of Blood Tubes and Aliquots:

- Log into blood shipment tracking site.
- Enter FedEx Tracking # and Ship Date
- Select Sample IDs to be shipped by clicking checkboxes

STEP 3.

Batch Shipment of Blood Tubes and Aliquots:

- Create Blood Sample Shipment Report
- Print this report, and include in shipment

STEP 4.

Batch Shipment of Blood Tubes and Aliquots:

- Just prior to shipment, remove Freezer Boxes from -80 degrees Celsius freezer
- Do not let samples sit out at room temperature for a long period of time!
- Samples MUST be kept FROZEN

STEP 5.

Batch Shipment of Blood Tubes and Aliquots:

- Place Aliquot Boxes into the small Saf-T-Pak Tyvek Biohazard Bags
- Remove adhesive tape from flap
STEP 6.

Batch Shipment of Blood Tubes and Aliquots:

- Press air out of bag and seal tightly

There will be 6 small Aliquot Freezer Boxes per shipment

STEP 7.

Batch Shipment of Blood Tubes and Aliquots:

- Place Large Blood Tube Freezer Boxes into the Large Saf-T-Pak Biohazard Bags.

Be sure to use the large bags for the Blood Tube Boxes

2 Large boxes per shipment

STEP 8.

Batch Shipment of Blood Tubes and Aliquots:

- Place sealed boxes upright into Styrofoam container

2 Large Blood Tube boxes plus 6 small aliquot boxes per shipment

STEP 9.

Batch Shipment of Blood Tubes and Aliquots:

Cover Boxes with 5 pounds of Dry Ice, fill box and cover completely so that samples stay frozen during shipment

STEP 10.

Batch Shipment of Blood Tubes and Aliquots:

Seal Cardboard Box with ONE Piece of Tape across Flap Seams.

*Do NOT tape box Air-Tight Shut!!

Dry Ice requires ventilation because it releases Carbon Dioxide Gas!!

STEP 11.

Batch Shipment of Blood Tubes and Aliquots:

Fill out FedEx waybill and secure to the top of the package
STEP 12.

Notes:

- Shipment should only be sent Monday through Wednesday. Do not ship specimens on Thursday or Friday!
- Samples should not be shipped the day before a national holiday.
- Shipping Address:
  Roxanne Kelly
  Channing Systems Genetics and Genomics
  Brigham and Women’s Hospital
  221 Longwood Avenue
  EBRC Room 610
  Boston, MA, 02115
  617-732-5888

STEP 13.

Clinical Center Contact Information

- Please remember to keep up to date emergency contact information with the Biorepository and Administrative Core.
- If you anticipate a change in personnel, notify the Administrative Core (Lori Stepp at steppl@njhealth.org)

STEP 14.

Questions?

Contact the Biorepository:

- Roxanne Kelly: 1-617-732-5560 or rerkk@channing.harvard.edu
- Aimee Garcia: 1-617-525-7829 or reaig@channing.harvard.edu
- Dan Cossette: 1-617-732-5888 or redac@channing.harvard.edu

2015 BIOREPOSITORY OBSERVED HOLIDAY CALENDAR

<table>
<thead>
<tr>
<th>Holiday</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>New Year’s Day</td>
<td>Thursday, January 1, 2015</td>
</tr>
<tr>
<td>Martin Luther King Day</td>
<td>Monday, January 19, 2015</td>
</tr>
<tr>
<td>President’s Day</td>
<td>Monday, February 16, 2015</td>
</tr>
<tr>
<td>Memorial Day</td>
<td>Monday, May 25, 2015</td>
</tr>
<tr>
<td>Independence Day</td>
<td>Saturday, July 4, 2015 (falls on weekend)</td>
</tr>
<tr>
<td>Labor Day</td>
<td>Monday, September 7, 2015</td>
</tr>
<tr>
<td>Columbus Day</td>
<td>Monday, October 12, 2015</td>
</tr>
<tr>
<td>Thanksgiving</td>
<td>Thursday, November 26, 2015</td>
</tr>
<tr>
<td>Christmas</td>
<td>Friday, December 25, 2015</td>
</tr>
</tbody>
</table>