

Genetic Epidemiology of COPD

Clinical Center Manual of Procedures (MoP)

Phase 3 Study Visits

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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 develops 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: U01 HL089897 and U01 HL089856), has created a large cohort of subjects enrolled in Phase 1.

COPDGene® Phase 3

The third phase of COPDGene® is designed to continue 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 and second visits will be repeated. Additional data will be collected including a sit to stand test, physical activity questionnaire (PROactive and DASI), a COPD population screener (CAPTURE), cognitive testing, and some additional questions.

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.

The following items are required before a clinical center can start enrollment in Phase 3:

1. IRB approval of protocol amendment, consent, questionnaires, scripts, etc.
2. Signed contract amendment
3. Completed CT phantom to the correct COPDGene® protocol
4. Site training/PFT certifications by staff, and a Go-Live Call with the COPDGene® Administrative Core.

1b. Subjects

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

The total number of subjects who had a follow up in Phase 2 is 6,209. In Phase 2, 349 new nonsmokers were also enrolled.

Any subject still in the study, alive, and having a Phase 1 visit will be eligible to participate in Phase 3. Additionally, up to 800 of these subjects will be identified by the Data Coordinating Center (DCC) and invited by the sites for an additional follow up visit. This is called the Short Term Follow Up Visit.

1c. Specific Aims

The initial data collected in the Phase 1 and Phase 2 visits, including longitudinal follow up data will be used to accomplish the following Specific Aims for Phase 3:

Specific Aim 1: Disease Progression

All subjects who return for a 10-year visit and those who expire between the 5 and 10-year visits will be analyzed to confirm prognostication of clinical disease progression. We estimate that 6,500 subjects will be analyzed in this aim; 4,500 subjects who return for a 10-year visit and 2,000 who expire before that visit.

Specific Aim 2: Mortality and Incident Disease

All 10,371 subjects enrolled in Phase 1 will be included to identify genetic, transcriptomic, and proteomic determinants of susceptibility and progression of specific COPD subtypes. All these subjects have had an initial visit but may or may not have visits at 5 and 10 years.

Through the longitudinal follow-up (LFU) program conducted twice a year since the initial visit, we have obtained follow-up data from 82.3% of the original 10,371 subject cohort by a combination of telephony, web survey or coordinator calls. We will continue LFU on all of the original 10,371 subjects who are alive. All subjects will continue to be followed to assess vital status. We will perform death searches at least yearly to identify subjects that have expired.

Death certificates, medical records and informant interviews will be obtained to determine cause of death.

Specific Aim 3: Rapid Disease Progression Subtypes (Short Term Follow-up Study)

To test high-risk subtypes for rapid COPD progression, approximately 800 subjects from the full COPDGene[®] cohort will participate. These subjects will be invited back for a Short Term Follow up Study visit approximately one year after the Phase 3 visit.

Subjects participating in the Short-Term Follow-Up study will be identified by the Data Coordinating Center and a list will be provided to each participating clinical center.

1d. Study Structures and Websites

The COPDGene[®] Study has nine Core Units (Administrative, Data Coordinating Center, Genetic Analysis and the Sequencing and Bioinformatics, Biorepositories, Imaging, Pulmonary Function, Biomarkers, Subtyping, Mortality Adjudication and Epidemiology). In addition, there are twenty Clinical Centers (listed on page 1).

COPDGene[®] Websites

There is a COPDGene[®] *study website*: that provides study investigators, radiologists and

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

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

There is also a COPDGene® public website: that provides general information about the study and COPD. It provides links to related sites for subjects and interested non-participants.

<http://www.copdgene.org/>

Finally, there is the COPDGene® longitudinal follow-up survey website: this is the website the subjects access to log in to complete their 6-month follow-up surveys via email. This is also the website coordinators log in to each month to complete the LFU Monthly excel upload and work off the coordinator task list. This is covered in detailed in the Longitudinal Follow Up Section of this manual (Section 9. Longitudinal Follow-up: Coordinator Guide for Participant Contact).

<http://www.copdgenestudy.org/>

Utilizing REDCap for Electronic Data Capture (EDC) for COPDGene® Phase 3

REDCap (Research Electronic Data Capture) will be used to enter data for Phase 3 of COPDGene. REDCap is a secure, web-based application designed to support data capture for research studies. REDCap is maintained by the [REDCap Consortium](#) which is comprised of over 2000 institutional partners including National Jewish Health and is administrated locally by Research Informatics Services.

Data Security and Privacy

- Complete suite of features that support HIPAA compliance
- Access to database requires user authentication with password
- Data access based on individual's role on project
- Logging and audit trails on all data interactions
- All data stored on a secure server, and backups are encrypted
- Twice daily automated backups of REDCap servers

A full user training is required to gain access to the REDCap application and this is completed online at the following link (<https://redcap.njhealth.org/redcap/surveys/?s=YC7CPA7JHC>). Once completed, you will be granted access to the National Jewish Health REDCap site by the REDCap Administrator. Please work with the Administrative Core or the DCC for more specific training or REDCap support.

<https://redcap.njhealth.org/redcap/>

1e. Site Personnel

All new staff working on COPDGene must be trained by either the Clinical Center director or delegate or the COPDGene Administrative Core. The Administrative Core must be notified of all new personnel being added to the study. To do this complete the REDCap survey at the following weblink. Contact the COPDGene Administrative Core if an in-person visit is needed to train new staff.

<https://redcap.njhealth.org/redcap/surveys/index.php?s=RE44KLJPYK>

2. Human Subject Protection

Each clinical center is required to submit an application to their local governing Institutional Review Board for Human Subjects (IRB). The Phase 3 submission should be submitted as an amendment of Phase 2. 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>.

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. Send to Sara Cummings at cummings@njhealth.org or 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. Please request this from the Administrative Core.

Written local IRB approval of the application is necessary before any subjects can be enrolled in Phase 3 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 3. 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 protection of 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>. 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. *Informed Consent Forms must be sent to the COPDGene® Administrative Core for approval prior to submission to the local IRB.* Questions about IRB issues should be directed to the Administrative Core.

2b. Informed Consent Process

No study procedures can be performed on any subject prior to the subject signing the informed consent form or giving verbal consent if the site has approved the phone script(s).

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 or give their verbal consent over the phone. Research staff may then co-sign the consent statement acknowledging subject understanding and consent to participate, if the site's IRB requires study staff to sign the form. Clinical Centers are encouraged to document the informed consent process in each subject's source document folder.

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 subject protection rules.

The importance of establishing rapport with each subject is of paramount importance to maintain long-term contact with subjects. This study 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.
 - 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.

2d. Source Documents

All sites must maintain a folder for each subject. The folder should contain the original informed consent form as well as any paper questionnaires/ data entry forms that have been completed.

REDCap has the capability to have subjects answer the questionnaires directly on a computer or tablet via the “Survey” function. If subjects are completing documents on paper and pen, the coordinator must review them prior to the subject leaving for completeness, and then file the originals in the source folder. REDCap can download blank copies of all of the instruments.

However, COPDGene[®] has provided copies of source documents for clinical centers who wish to do the visit on paper and pen that better reflect branching logic in the questions.

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 Matt Strand, 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 Procedures should be addressed to the Administrative Core.

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 compile information, and to track transmission of spirometry and diffusing capacity results, shipment of CT scans, and shipment of blood samples. The COPDGene[®] website will no longer be used for data entry in Phase 3, as REDCap will be utilized for that.

In Phase 3, coordinators will still use the COPDGene[®] study website for the following:

- Home Page: datasets, IRB documents, newsletters, MoP, etc.
- Data Management
 - Subject Tracking
 - Supplies tracking and receipt
 - CT shipment tracking and receipt
 - Uploading PFT files
 - Missing Items Review
 - Invoicing Report
 - Enrollment Report
 - Non Smoker Enrollment Table

Contact information for all study personnel is on the website (Directory link from the home page). All changes in study personnel including additions and deletions should be reported promptly to the Administrative Core (email to: cummings@NJHealth.org) at National Jewish Health.

Each COPDGene[®] investigator and coordinator is required to have a unique login identity and password to use the website. **Passwords and logins 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 ([cummingss@NJHealth.org](mailto:cummings@NJHealth.org)) before they request a log-on. In order to obtain your log-on identity and password, please contact 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 REDCap 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. REDCap also has functions to do many in-time queries (which will query out of range data at the time of data entry).

Responses to DCC queries should be provided promptly and always within 7 working days.

4. Phase 3 Nonsmoker Controls

COPDGene® is not currently funded to recruit new nonsmoker control subjects for Phase 3. The overall goal, once funding is available, is to recruit up to 500 more nonsmoker controls. Once funding is obtained, the Administrative Core will notify the clinical centers and conduct training as needed.

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 previous participants who do not live with the subject and are not exposed regularly to second-hand smoke
- Radio ads, clinical center website

A recruitment poster has been provided by the COPDGene® Administrative Core. Each center should obtain IRB approval and use in recruitment efforts.

Recruitment Goals

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.

Current Nonsmoker Enrollment				
	NHW		AA	
Age	M	F	M	F
45-54	0	0	0	0
55-64	0	0	0	0
65-74	0	0	0	0
75-85	0	0	0	0

*Red = FULL

Figure 4-1. This table, located on the “Get a Subject ID” hyperlink 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 and the cell will be written in red bold.

4b. Subject Inclusion/Exclusion Criteria for Nonsmoker

Controls

Inclusion Criteria

Age 45-85 years (for nonsmokers)

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

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

Participation in the following studies: COPDGene® Phase 1, ECLIPSE, Boston Early-Onset COPD Study, Boston COPD Exacerbations Study, Denver Genetics Study, GlaxoSmithKline International COPD Genetics Network, NCI: National Lung Screening Trial, NIH: COPD Clinical Research Network: Macrolide and Leukotriene Trials, NIH: Long-Term Oxygen Therapy Trial, NIH: Lung Health Study, NIH: Lung Tissue Research Consortium, NIH: SPIROMICS, Pittsburgh SCCOR, MESA, MESA-Lung and CARDIA

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)

No place of permanent residence for the prior three months Alpha-1 Antitrypsin deficiency

Regular use of an inhaled medication

Regular marijuana use (more than once per week) History of employment in underground mining Body mass index greater than 35

Temporary Exclusion Criteria

Subjects with the following may not have a study visit performed but may be re-screened at a later time.

- 1) Pregnancy or suspected pregnancy. (These subjects will be re-scheduled for a visit at least three months after childbirth or after they are no longer suspected of pregnancy.)
- 2) Use of antibiotics for a respiratory infection within the past month. (These subjects will be rescheduled for a visit at least 4 weeks after completion of the antibiotics.)
- 3) Use of systemic corticosteroids (new prescription or increased dose) for a respiratory disorder within the past month. (These subjects will be rescheduled for a visit at least 4 weeks after completion of the steroids.)
- 4) Chest or abdominal surgery in the past three months. (These subjects will be rescheduled for a visit at least three months after surgery.)
- 5) Heart attack in the last three months. (These subjects will be rescheduled for a visit at least three months after the heart attack.)
- 6) Detached retina or eye surgery in the past three months. (These subjects will be rescheduled for a visit at least three months after surgery.)
- 7) Hospitalization for any other heart problem in the past month. (These subjects will be rescheduled for a visit at least 4 weeks after hospital discharge.)

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. The process for obtaining a subject ID in Phase 3 is similar to Phase 2. The subject ID number will be obtained from the COPDGene® website.

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®.

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. This will hold the subject a place in a age/race/gender group until a final screener is obtained.

1. Log on to the COPDGene® website and go to the forms page (<https://dccweb.njhealth.org/sec/COPDgene/Forms.cfm>).
2. Click on ‘New SubjectId’

Manual of Procedures

Manual of Procedures (separate web page)

Phase 3 Miscellaneous Forms	
New SubjectId	New Never-smoked

3. You will see an up to date enrollment table from this page. Follow the prompts to obtain a new Subject ID.
4. Once you have successfully obtained a subject ID you can move forward with the Eligibility form in REDCap.
5. You will first need to add the given subject ID to REDCap. Log into the “COPDGene® Nonsmokers-Phase 3” Project and click on “Add-Edit Records”

REDCap
 Logged in as **penchevs** | Log out

My Projects
 Project Home
 Project Setup
 Project status: **Development**

Data Collection [Edit Instruments](#)

Manage Survey Participants
 - Get a public survey link or build a participant list for inviting respondents

Record Status Dashboard
 - View data collection status of all records

Add / Edit Records
 - Add new records or edit/view existing ones

Applications

- Calendar
- Data Exports, Reports, and Stats
- Data Comparison Tool
- Logging
- Field Comment Log
- File Repository
- User Rights and DAGs
- Data Quality

COPDGene Nonsmokers - Phase 3

Project Home | Project Setup | Other Functionality | Project Revision History

Project status: **Development** Completed steps

Main project settings
 Not started
 Disable Use surveys in this project? [?](#) [VIDEO: How to create and manage a](#)
 Disable Use longitudinal data collection with defined events? [?](#)
 I'm done!
 Modify project title, purpose, etc.

Design your data collection instruments & enable your surveys
 Not started
 I'm done!
 Add or edit fields on your data collection instruments (survey and forms). This may be done either using the Online Designer (online method) or by uploading a Data Dictionary (offline method). You may then enable your instruments to be used as surveys in the Online Designer. Quick links: [Download PDF of all instruments](#) OR [Download the current Data Dictionary](#)
 Go to [Online Designer](#) or [Data Dictionary](#)
 You may also browse for pre-built data collection instruments in the [REDCap Shared Library](#)
 Have you checked the [Check For Identifiers](#) page to ensure all identifier fields have been tagged?

Define your events and designate instruments for them

- Then type the new Subject ID you were given from the COPDGene® website into the REDCap field, “Enter a new or existing Subject ID” and click “Enter” on your keyboard.

COPDGene Nonsmokers - Phase 3

Add / Edit Records

You may view an existing record/response by selecting it from the drop-down lists below. To create a new record/response, type a new value in the text box below and hit Tab or Enter. To quickly find a record without using the drop-downs, the text box will auto-populate with existing record names as you begin to type in it, allowing you to select it.

Total records: 1

Choose an existing Subject ID

Enter a new or existing Subject ID

Data Search

Choose a field to search (excludes multiple choice fields)

Search query

Begin typing to search the project data, then click an item in the list to navigate to that record.

- You will then be able to start data entry, but first be sure to click on the “Register Subject Id” form

NEW Subject ID 12345A

Data Collection Instrument	New Nonsmoker Phase 3	Other
Register Subject Id	<input type="radio"/>	
Eligibility	<input type="radio"/>	
Informed Consent	<input type="radio"/>	
Safety Assessment	<input type="radio"/>	
Demographics	<input type="radio"/>	
Spirometry Administration	<input type="radio"/>	
Medication History	<input type="radio"/>	
Six Minute Walk	<input type="radio"/>	
Medical History Nonsmokers (survey)	<input type="radio"/>	

- Then you will just change the form status to “complete”. Save and Exit the form and you will then be able to enter data for the rest of the forms.

Register Subject Id

Adding new Subject ID 12345A

Event Name: **New Nonsmoker Phase 3**

Subject ID 12345A

clinical center

Form Status

Complete? Complete **Complete**

4d. Preliminary Study Visit Procedures

First, obtain a Subject Identification Number as described above and enter it into REDCap.

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 eligibility form, click the button at the bottom of the form to confirm you have reviewed all responses, change the form status from “incomplete” to “unverified”, then click “save and exit form”. The status button for this subject’s form will now be colored yellow, indicating that data has been entered, but has not been verified and finalized. The data entered previously for this subject will be saved and shown each time that form is accessed.

The screenshot shows the bottom portion of a REDCap eligibility form. At the top, there is a confirmation question: "Please confirm that you have entered all the responses correctly. Are you ready to submit?" with radio buttons for "Yes" and "No". Below this is a text input field labeled "Eligible for study" containing the number "1", with a "View equation" link and a note "1=Eligible, 0=Not Eligible". A green box displays the message "This subject is ELIGIBLE to participate." Below this is a yellow box labeled "Form Status" containing a dropdown menu currently set to "Incomplete". At the bottom, there are three buttons: "Save & Exit Form", "Save & ...", and "-- Cancel --". A yellow box on the left contains the word "Eligibility".

Figure 4-2. This shows the bottom of the eligibility form in REDCap. Once all preliminary questions are answered, the form status should be changed from “incomplete” to “unverified” using the drop down arrow. Once the final eligibility is completed, the coordinator will change this status from “unverified” to “complete” using the same drop down arrow. To the right is an example of the form status button. It will be red if status is “incomplete” yellow if “unverified” and green if “complete”.

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. This is typically done on site after informed consent.

When completing a Final Eligibility Assessment in REDCap, the study coordinator should perform this assessment one-on-one with the participant during the Study Visit. The coordinator will access the same form used to collect the preliminary eligibility responses. At the time of the final eligibility assessment, the coordinator will change the eligibility screening status at the top of the form from “Preliminary” to “Final”, then ask the questions again, and update the subject responses as needed. The coordinator will have to obtain the subject’s actual height and weight (to calculate BMI for inclusion) for entering on the final eligibility assessment form. This step is required before any study procedures take place.

This form incorporates the inclusion and exclusion criteria for the study and certifies that subjects are eligible for the study prior to any evaluations. REDCap will automatically calculate the subject’s eligibility based on responses to the screener questions and will display a green box

stating “Subject is ELIGIBLE to participate.” Subjects who do not pass the Final Eligibility Assessment are considered to have failed screening. In cases when the subject fails screening, the REDCap eligibility form will display a red box at the bottom stating “This subject is NOT eligible to participate in the study. Please stop the visit at this time.”

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. To save the final eligibility form, change the form status at the bottom from “Unverified” to “Complete”, then save and exit form. This will change the form status button from yellow to green, indicating the final eligibility form is complete. The form status can be viewed from the Record Status Dashboard, or the subjects record home page.

4f. Study Visit Procedures for NS Controls

The nonsmoker control study visits will follow the same steps and procedures as the standard study visits with a few minor exceptions (described in section 4g).

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. The REDCap project for new nonsmokers is kept separate from the Phase 3 return visit.

The new nonsmoker forms which differ from the Phase 3 return subject forms are: eligibility, Medical History, Respiratory Disease, Socioeconomic, Residential and Occupational, and CT Assessment Form.

4g. 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 completion of Informed Consent and Permissions Granted Form
- 2) Obtain actual height and weight on subject (will be recorded on Final Eligibility as well as Demographics Form).
- 3) Final Eligibility, Stop if subject BMI >35 (exclusion criteria)
- 4) Pregnancy Test, if applicable
- 5) Demographics Form
- 6) Safety Assessment Form
- 7) Pre-Bronchodilator Spirometry
- 8) Questionnaires while waiting 20 minutes after albuterol
- 9) Post-BD Spirometry

- 10) DLco
- 11) Remaining questionnaires, Six-Minute Walk, Sit to Stand Test, Blood Sampling, CT.

4h. 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 enrolled a subject you will need to update the Master Excel Spreadsheet for the LFU Monthly upload with the newly subject contact information, (subject first and last name, a primary and secondary phone number(for the subject) if available, an email address if available, an optional email password for accessing the Web Survey, and an option for manual contact only). The Clinical Coordinator will need to remember to add any newly enrolled NS subjects to their internal site list 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 and also for each time there is a change to contact information.

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 an email so they can do their LFU surveys online. 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 Section (9. Longitudinal Follow-up: Coordinator Guide for Participant Contact), for greater detail on the LFU system.

4i. 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. 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.

4j. Study Visit Payments

New nonsmoker controls will be reimbursed the same amount as the return study subjects (\$125). 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 3 Subject List, including all subjects who are candidates for a Phase 3 visit, will be created by the DCC for each Clinical Center and provided in the Subject Tracking Report. This 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 3 start dates and current contact status. This system will automatically reflect any successful LFU surveys done by the LFU system within 24-48 hours of completion.

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 current contacts, vital status, and Visit 3 status and date.

Center	Return for Phase 3						Unavailable		Total Return Sids	P3 New Never-Smoked
	Need Contact	Current (LFU or contact)	Phase 3 screened	Phase 3 completed	Cannot Locate	Subtotal Returning	Deceased	Subj: No more contact		
	208	768	0	1	91	1068	288	66	1422	0

Reports:								Search for Subject:	
<input type="button" value="Full Report"/>	<input type="button" value="Projected Visit Date"/>	<input type="button" value="Need Contact"/>	<input type="button" value="Deceased"/>					<input type="text"/>	<input type="button" value="Search"/>
<input type="button" value="Cannot Locate"/>	<input type="button" value="Referrals"/>	<input type="button" value="No Further Contact"/>							

Projected Visit Date										
Sid	Current Status	Projected Phase 3	Phase 2 Date	Last Survey Date	Contact Log		Visit 3 status	Death Info		
					Successful	Unsuccess.		Death Cert Received	Informant Interview	Medical Record
10008W	Cannot Locate	01/18/2018	no			02/15/2017				
10010J	Current	01/25/2018	onsite 08/13/2015	10/11/2017	08/25/2016	01/16/2015				
10031R	Current	02/22/2018	onsite 07/24/2013	10/24/2017	08/25/2016	05/08/2015				

Figure 5-1. Subject Tracking, Full Report

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, and the Preliminary Screening form is out of date. This status will show as ‘preliminary out of date’ and highlighted in orange once 2 months has passed from the initial preliminary screener.
- 4) Phase 3 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 Subject Tracking Log regarding their status using the Subject Contact Log throughout the study period. (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 Phase 3, 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, be sure to update all subject personal information files you are keeping, including the Master LFU Excel upload file.

If a subject is found to be deceased, a Discontinuation Form must be submitted in REDCap. If a subject “Requests no further contact,” 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. Subjects can be withdrawn from LFU without being withdrawn from the main study.

The Clinical Center coordinators should take certain actions to try to locate subjects who are presumed to be lost. The following steps should be taken:

- **Phone:** Coordinators should try to call the subjects primary phone number three times, at different times each day. One or more of the calls must take place on a weekend and/or evening. Coordinators should leave voicemails if given the option.
- **Email:** If an email address is known, coordinators should attempt to contact the subject by email.
- **Mail:** A letter should be mailed to the subject’s address if he or she cannot be reached by phone. If a response isn’t received from the first mailing, the coordinator should try to send a certified letter with a signature requested.
- **Secondary Contacts:** If these attempts are not successful, the coordinator should then try to locate the subject via the secondary contacts that the subject provided in Phase 1 or Phase 2.
- **Searches:** Coordinators should search EMR and Google for updated contact information. The COPDGene[®] Administrative Core has purchased a subscription for a platform called Microbilt. Microbilt searches various databases to find updated phone numbers and mailing addresses. COPDGene[®] can search for each Clinical Center’s lost subjects centrally if your Clinical Center is IRB approved to transfer subject identifiers under Phase 1 consent or subjects have signed a Phase 2 Consent or Mail Consent. If new contact information is discovered, attempt phone and letter contacts as above.

Clinical Coordinators should work on their “Needs Contact” list in order of Phase 3 start dates. The Subject Tracking Report should be updated by the clinical center throughout the course of the study, 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 Phase 3. 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 completing the LFU contact manually for the subject.

Click on the “Click here to expand/collapse Phase 2” link to see subject tracking activity done in Phase 2.

Phase 3

Subject Contact Log for 10010J

[Return to Subject List](#)

[Click here to expand/collapse Phase 2](#)

Contact Log - Phase 3				
Date	Contact Type	Spoke With	Result	Notes
10/11/2017	LFU Survey	subject		
Date	Contact Type	Spoke With	Result	Notes
<input type="text"/> mm/dd/yyyy	<input type="radio"/> primary: subject phone nbr(s) <input type="radio"/> secondary: friend/rel contacts <input type="radio"/> mail (normal) <input type="radio"/> mail certified <input type="radio"/> in-person (ex. patient visit) <input type="radio"/> internet <input type="radio"/> Microbilt <input type="radio"/> physician call <input type="radio"/> medical record	<input type="radio"/> subject <input type="radio"/> friend/relative/ physician <input type="radio"/> wrong number <input type="radio"/> voicemail <input type="radio"/> nobody/ no answer/ web/ disconnected/ mail unconfirmed	<input type="radio"/> Ok to continue contact <input type="radio"/> Deceased <input type="radio"/> Not interested in returning <input type="radio"/> Geographically distant (specify state in notes) <input type="radio"/> Requests no further contact <input type="radio"/> Found: web/Microbilt/ medical rec/Mail Cert. <input type="radio"/> Contact no longer valid/ Returned letter <input type="radio"/> Status unknown <input type="radio"/> Exhausted all methods; cannot locate	<input type="text"/>
<input type="button" value="Save"/>				

Figure 5-2. Subject Contact Log

Discontinuation Form

The coordinator will need to submit a Discontinuation form for the following situations only:

- 1) Subject is deceased
- 2) Subject has requested withdrawal from COPDGene®. Subject does not want to participate in COPDGene® visits or LFU. In this case, the Clinical Center coordinator should try to obtain a limited follow up questionnaire over the phone prior to discontinuing the subject.

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 Phase 3 but still willing to participate in LFU surveys (moved away, too ill)
- 3) Subject is lost- If all primary AND secondary contacts have been exhausted without success and all methods of contact have been implemented (phone, email, mail, internet searches); subject is thought to be lost. This should be documented in the COPDGene® Subject Tracking Log as “Exhausted All Methods: Cannot Locate.”

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 or LFU 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 must record that information in REDCap via the Discontinuation Form. Please also make notes in local records to describe how the death was identified. Once a clinical center is aware of the death, they should 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 (Informant Interview). Coordinators should also ask a hospital or 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 also want the clinical centers to obtain a copy of the death certificate for all deceased subjects.

The Administrative Core will utilize the Social Security Death Index (SSDI) or the National Death Index to confirm all deceased subjects. The Administrative Core will search these databases for all transferred subject information (as IRB approved). If a subject is identified as deceased from one of these databases, a report will be sent to the local clinical center for follow-up. If a clinical center receives a report of a subject death they should complete the Discontinuation and categorize the subject as deceased. You should then take steps to obtain records for adjudication.

Local internet search is an option to identify deceased subjects. Subjects who are lost (have not responded to LFU contacts for more than 12 months) and a social security number is unavailable should be tracked using their secondary contacts. Subjects who are lost and fail to be tracked using secondary contacts should also be searched using standard internet tools including public websites and search engines. A simple Google search of the subject’s name and the word ‘obituary’ should be done.

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

- 4) Request hospital records/discharge summary. Request these records if the subject died in the hospital, or other facility, or was hospitalized within 28 days of death
- 5) Complete Informant Interview for death adjudication with next of kin or primary care physician.
- 6) You may be limited in what you can obtain regarding informant interviews and medical records depending on your local IRB permissions, so please be sure to review this.
- 7) Send death certificate (de-identified or redacted), Medical Records (de-identified or redacted), and Informant Interview to the COPDGene® Administrative Core and record data collected on the Subject Tracking Report (click on the applicable subject ID first). Death certificates and Medical Records should be redacted to remove identifying information such as names, SSN, addresses, etc. The COPDGene® Clinical Center and subject ID should be written on each one. The date of death should not be redacted as this information is needed for adjudication.

Death Data Collection for 1.0010J	
Death Certificate	
<input type="radio"/> Request submitted to state <input type="radio"/> Received and copy sent to COPDGene Admin Date: <input type="text"/> mm/dd/yyyy <input type="radio"/> Cannot obtain	
COPDGene Admin only: Date Received by Admin Core: <input type="text"/> mm/dd/yyyy	
Informant Interview	
Informant Interview form not yet submitted.	
If not possible: (check reason)	
<input type="radio"/> Refused <input type="radio"/> Cannot locate	
Medical Record	
Date Medical Records Sent: <input type="text"/> mm/dd/yyyy	
-- or --	
<input type="radio"/> Medical Record Not Possible	
COPDGene Admin only: Date Received by Admin Core: <input type="text"/> mm/dd/yyyy	
<input type="checkbox"/> Medical records inadequate for Cause Of Death <input type="checkbox"/> Informant Interview inadequate for Cause Of Death	
COPDGene Admin only: <input type="checkbox"/> Exhausted all sources; no more data	
Record	

Figure 5-3: Where to track death document information

Subjects that have signed the Phase 2 consent should have already consented for you to collect informant interview and medical records surrounding time of death. The subject should also have signed a medical record release form as part of the Phase 2 visit.

Study Centers will be reimbursed on a quarterly basis for Death Certificates, Informant Interviews, and Hospital Records obtained and sent to the Administrative Core.

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.

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 other facility, 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. This information should also be present on the death certificate. 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 or consent 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. In Phase 2, subjects should have been asked to sign a Medical Record Release form. This should be provided to the facility when requesting the medical records.

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



Figure 5-3. Central Adjudication Process after Records and Death Summary Form is completed.

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 to review each subject. 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 perform two separate adjudication processes to designate cause of death by probable cause. The first is meant to mimic the process performed in the TORCH study and the second for COPDGene. These principles will be maintained in a Principles of Mortality Adjudication document by the Death Adjudication committee.

5c. Clinical Center Notification of Upcoming Phase 3 Visit

The web-based Subject Tracking Report from the COPDGene® website can be sorted by Projected Phase 3 visit date to allow coordinators to check and make sure all subjects are current in time to schedule their visit. Subjects that 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 six to three months prior to their Phase 3 target date (ten years after their first COPDGene® visit) to schedule the Phase 3 visit. At the time of contact for scheduling, a Preliminary *Phase 3 Screening Form* should be completed for the subject.

5d. Preparing for Phase 3 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. If you have internet access you can have subjects complete the questionnaires on the computer or tablet via the survey function in REDCap.
- EasyWare® version 2.25 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. The exception to this is that version 2.25 is allowed for

computers with Windows 10. There are detailed directions for installation on windows 10 provided on the COPDGene website, so be sure to follow and share with your IT personnel when needed.

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.

- A program that can capture and store complete subject contact information information for use only at the Clinical Center must be in place. 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 printer, or access to a printer, to print study questionnaires and forms.

Order Materials and Supplies:

- Paper, pens, clipboard, printer supplies
- ndd EasyOne[®] Spirometer Spiquettes (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 and Sit to Stand 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
- Filters obtained from ndd for all PFTs for the duration of the COVID-19 pandemic

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 center Radiology Department complete CT Site Survey Form to the Imaging Core. A CT Phantom must be received and approved 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 training and a test prior to scanning any subjects. Completed tests can be uploaded to the Send Tool for the Imaging Core to

review 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.
- Establish process for timely collection of the CT Assessment forms.

Spirometry and DLco Certification:

- Each new coordinator must perform **three** tests on three **naïve** subjects. If the coordinator was certified in Phase 2, only two certification tests will need to be performed.
- Name the **Patient ID** “C-Three Digit Tech Initial1.” For example: C-SJP1, C-SJP2, C-SJP3. *Always be sure to use a three digit tech initial. 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!**
 - Always identify the Patient ID as described above. If there are multiple coordinators, the Cert ID’s must be unique by the three digit tech ID to determine whether every coordinator has completed 3 Certification tests.
 - If a particular Cert ID fails grading, and a coordinator needs to complete additional certification tests, please use a NEW Cert ID. For example: use a 4 and 5 after C-SJP4, C-SJP5
- Each coordinator will also use their 3-letter Technician ID (example: SJP). Enter your Tech ID on each test.
 - 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 Phase 3 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 and REDCap

- Read and become familiar with REDCap, including all study forms and questionnaires.
- A printed-paper copy of all completed forms (if done with paper/pen), 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 may be administered one-on-one by the coordinator reading the questionnaire to subjects and recording subject responses or by the subject completing themselves via paper and pen or directly on the computer (preferred).
- If the Clinical Center does not have Internet access during the study visit, paper entry of data should be done as internet access is needed for REDCap.
- 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 Procedures

- Print and read the Manual of Procedures and maintain a copy that is readily available during Study Visits.
- Contact the Administrative Core with questions.

Practice Subject

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

Locked File Cabinet

- Required for Subject source documents
- In a locked room

Transmission of Collected Study Visit Data

- *Data that are collected during Phase 3 MUST be transmitted in a timely manner to the Data Coordinating Center (7 business days).*
- *The following test data MUST be transmitted daily – i.e., the same day the information is collected: spirometry and diffusing capacity. The CT scan must be transmitted within 2 days. 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 Procedures will lead to an email to the coordinator, PI and radiologist requesting the appropriate processing algorithm be used and the information be re-transmitted. CT scans must not be repeated if not done correctly.*
- 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 to the COPDGene® website weekly for Clinical Centers to review and address.

5e. Materials Needed for a Study Visit

Prior to each Study Visit, you should have the following prepared for each subject:

- Subject Identification Number – this is a unique number for each study subject. Each return subject will have been assigned this number during Visit 1 and will retain the same number for each phase. You will have already seen a list of subject ID numbers that are ready to return for Phase 3 (in the Subject Tracking Log and in REDCap) and you will be responsible to connect the ID number with your internally housed subject information. The subject must provide reliable identification (drivers license, voters registration, passport, green card, etc.) to confirm his/her identity at Phase 3 to assure the subject is the same subject who participated in previous visits.
- Your local IRB-approved consent form (2 copies)
- PPE for the COVID-19 pandemic
- Questionnaires and Forms – on computer (if your site has internet access) or printed except as noted- all should be the unique forms for Phase 3- do not copy forms from previous phases!
 - Informed Consent and Permissions Form
 - Screening Form – The Final Visit 3 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
 - Demographics Form
 - Spirometry Form
 - Respiratory Disease Questionnaire
 - Medication History Questionnaire
 - Medical History Questionnaire
 - Residential and Occupational History
 - Socioeconomic Questionnaire
 - COPD Assessment Test (CAT)

- CAPTURE Questionnaire
- PROactive Questionnaire
- DASI (Duke Activity Status Index) Questionnaire
- St. Georges Respiratory Questionnaire (SGRQ)
- SF-36 Questionnaire
- Cognitive Assessment Testing Data Collection Form (must have clock page printed- see Section 7p- Cognitive Screen Tests)
- Six-Minute Walk Walk Test Form
- Sit to Stand Test Data Collection Form (includes hand grip strength)
- eCigarette Questionnaire
- Cannabis Use Questionnaire
- PTOA (if your site has approval)
- COVID Questionnaire
- Dried Blood Spot kit (if needed for that participant)
- Blood Collection Form
- CT Assessment Scoresheet
- CT Acquisition Form (not in REDCap- obtained from COPDGene® website)
- Subject Contact Information Form (not in REDCap- obtained from COPDGene® website)
- Clinically Significant Findings
- Discontinuation Form (as required)
- Limited Follow up Questionnaire (as required)
- Adverse Event Form (as required)
- Serious 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
 - Filter (for use during the COVID-19 pandemic)
- EasyOne Pro® for Diffusing Capacity (with USB in back)
 - Barriettes
 - Spirettes
 - Nose clips
 - Filter (for use during the COVID-19 pandemic)
- 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 the Channing Lab for blood supplies and should be used to label source documents.
- Stopwatch for walk test and sit to stand 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
 - Barcode labels
 - Blood tubes, plastic
 - Blood tube adapters
 - Alcohol pads
 - Tourniquet
 - Needles and tubing
 - Bandages
 - Gauze
 - Centrifuge
 - Refrigerator for storing samples
 - Shipping materials (see Biorepository section for details)
 - Blood Collection Form
 - Blood Sample Federal Express™ shipping form
- Chest CT scan supplies
 - CT order form for your center (varies at each site depending on local procedures)
 - CT acquisition form
 - 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® Phase 3 study visit is a continuation of the previous phases of COPDGene®. Phase 3 should be explained to potential subjects who pass the preliminary screening (if IRB approved at the Clinical Center to permit use of this form before informed consent is obtained; otherwise the final 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 or getting a verbal consent over the phone.

5h. Screening Form

Prior to the Study Visit: A *Preliminary* Phase 3 Screening Form may be completed prior to the Study Visit, if approved by the Clinical Center IRB. Subjects are eligible to return for Phase 3 if approximately ten years (years +/- 6 months) have passed since their initial COPDGene® Visit.

There must be at least three years in between the Phase 2 and Phase 3 visits. Subjects may still be seen if more than 10 years + 6 months has elapsed since their Phase 1 Visit. Visit 3 Screening may be done at first contact with the subject by phone or in person and will be data entered as a preliminary screener in REDCap.

At the In-Person Study Visit: A *Final* Phase 3 Screening must be performed to assure that the subject does not need to delay the visit.

This step is required prior to any study procedures or testing (except informed consent). Even if a *Preliminary* Screening was completed prior to the in-person Study Visit, a *Final* 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 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.)

Follow this process to complete the Final Phase 3 Screening during the in-person Study Visit.

Both the preliminary and final screener are found on the same REDCap form (called “Screener”). Near the top of the form, the coordinator will click either ‘preliminary’ or ‘final’ for the Phase 3 Screener status. When completing the preliminary screener, once the form is completed, at the bottom change the form status from ‘incomplete’ to ‘unverified’ then save and exit the form. The status button for this subject’s form will now be colored yellow when viewing from the record home page or the Record Status Dashboard. When completing the final screener, the coordinator will access that same form, change the Phase 3 screener status to ‘final’, then ask the questions again, modifying the answers as needed. After the final screener is completed, the coordinator will need to change the form status from ‘unverified’ to ‘complete’. The status button for this form will change from yellow to green indicating the form is complete.

Subject ID	10005Q
Interviewer's initials	<input type="text"/>
Date	<input type="text"/> Today M-D-Y
Phase 3 Screener status	<input type="radio"/> Preliminary <input type="radio"/> Final

Figure 5-4. The top section of the screener form in REDCap. The coordinator should select “preliminary” when conducting the preliminary screener over the phone. When completing the final screener the coordinator will access this same form, change the status to “final” and ask all screener questions again.

CRITERIA for CT Scan

All Subjects will have chest CT scan done with the following exclusion:

Exclusion

- 1) History of a lung transplant since their previous COPDGene® visit.

If a subject has metal in the chest, such as a cardiac pacemaker, defibrillator, or otherwise, this does not exclude this subject from having a chest CT scan.

5i. COVID-19 Modified Visits

During the COVID-19 pandemic, COPDGene will stop in-person visits in order to protect both the subjects and staff; centers may continue in-person visits at their discretion. All subjects currently alive, enrolled in the study from Phase 1 or Phase 2 (never-smokers), and who have not yet completed a Phase 3 visit will be invited to participate in a virtual visit over the phone to answer some of the questionnaires. Later, those subjects will be brought on-site to complete in-person portion of the visit.

For the virtual phone visit, a phone call will be made to each subject to schedule a time when they can complete the questionnaires over the phone. During this scheduling call, the participant will be asked to assemble their contact information (email, other phone numbers) if they need to look it up.

During the modified phone visit, the coordinator will read a consent script to the participant before beginning to administer the questionnaires. At the in-person portion of the modified visit, the study staff will review the informed consent form as in a regular visit.

Phone Visit	Later, in-person visit
Screener	Screener
Informed Consent Permissions Form	Informed Consent Permissions Form
Subject Personal Information Form	Safety Assessment Form
Medical History Form	Demographics/Physical Characteristics Form
PTOA Questionnaire	Spirometry
Respiratory Disease Questionnaire	DLco
CAPTURE Questionnaire	Medication History Form
CAT	Respiratory Disease In-Person Questionnaire
SF-36 Questionnaire	Six Minute Walk
SGRQ	SF-36 Questionnaire

Socioeconomic Questionnaire	HADS
eCigarette Questionnaire	Cognitive Screen Items
Cannabis Questionnaire	Sit to Stand
	Blood Sample
PROactive Questionnaire	CT
DASI Questionnaire	Medication History Form
Optimism Questionnaire	COVID Questionnaire (if needed)
Residential and Occupational History Questionnaire	
COVID Questionnaire (if needed)	

Also, during this time, increased contact with the subject will occur to track COVID-19-related illness. This will be tracked using a brief questionnaire that the subject can choose to answer over the phone with a coordinator or through email, or if the site is allowing in-person visits to occur, then the subject can answer the questionnaire at the time of the visit. The subject will be contacted quarterly for the duration of the study. The participant will be mailed a dried blood spot kit that will allow them to prick their finger for a blood sample and send that sample back to determine if they have formed antibodies to COVID-19; if the participant is on site for their visit at the time the finger-prick is due, then they may opt for the coordinator or a nurse to assist. The subject will consent to this increased contact, the collection of blood, and COVID-19 medical records release at the time of consent for the modified visits for the Phase 3 Virtual visit and/ or (for those not scheduled for a phase 3 visit) a separate contact for COVID-19 tracking survey.

The participant will consent to the dried blood spot on the phone or by signing a mailed consent form that they will send back to COPDGene Administrative Core with their dried blood spot card. The COPDGene Administrative core will then send the consents to the appropriate site. The mailed consent will have the SID and name of the participant; this information will remain confidential. Note: All dried blood spot cards have a distinct Biospecimen ID number (BID #) associated with them. Prior to mailing out the dried blood spot card to an eligible participant, or completing on site, COPDGene clinical coordinators MUST enter the BID # into REDCap to ensure accurate identification.

Type of consent for the COVID-19 portion of Phase 3 may be obtained using a written consent in person or through mail, or a verbal consent over the phone. The Phase 3b visits will be modified to include subjects who experienced a respiratory exacerbation reported on the patient's surveys will be included in the 3b visits as a group potentially at risk for rapid progression. These

subjects will be identified by the DCC and the centers will be asked to invite the subjects to return for a phase 3b visit.

APPENDIX A: Virtual Visit in REDCap

Data Collection Instrument	Phase 3 visit	Virtual 10-year visit	In-Person Finish to Virtual
Six Minute Walk	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Medical History (survey)	<input type="radio"/>	<input type="radio"/>	
Respiratory Disease (survey)	<input type="radio"/>	<input type="radio"/>	
CAPTURE (survey)	<input type="radio"/>	<input type="radio"/>	
COPD Assessment Test CAT (survey)	<input type="radio"/>	<input type="radio"/>	
SF-36 (survey)	<input type="radio"/>	<input type="radio"/>	
SGRQ (survey)	<input type="radio"/>	<input type="radio"/>	
HADS (survey)	<input type="radio"/>		<input type="radio"/>
Socioeconomic (survey)	<input type="radio"/>	<input type="radio"/>	
eCigarette (survey)	<input type="radio"/>		
Ecigarette 92 (survey)	<input type="radio"/>	<input type="radio"/>	
Cannabis Use (survey)	<input type="radio"/>	<input type="radio"/>	
PROactive Questionnaire (survey)	<input type="radio"/>	<input type="radio"/>	
DASI (survey)	<input type="radio"/>	<input type="radio"/>	
Optimism (survey)	<input type="radio"/>	<input type="radio"/>	
Cognitive Screen Items	<input type="radio"/>		<input type="radio"/>
Sit To Stand Test	<input type="radio"/>		<input type="radio"/>
Residential And Occupational History	<input type="radio"/>	<input type="radio"/>	
Blood Sample Collection	<input type="radio"/>		<input type="radio"/>

Use only the questionnaires under the virtual visit column.

Make sure to mark questionnaires as “Complete” and save the forms.

APPENDIX B: COVID-19 in REDCap

Record ID **99012A**
NJC

[Table not disp](#)

Data Collection Instrument	Baseline	Dried Blood Spot	Year1 C4R	Quarterly 1	Quarterly 2	Quarterly 3	Quarterly 4	Week 4	Week 8
Enrollment Consent (survey)									
Amendment 9.4 Consent									
Covid19 Questionnaire (survey)									
Dried Blood Spot Collection									
C4R Covid19 Survey (survey)									

COPDGene COVID-19

Record Home Page

The grid below displays the form-by-form progress of data entered for the currently selected record. You may click on the colored status icons to access that form/event.

[Choose action for record](#)

Legend for status icons:

- Incomplete
- Incomplete (no data saved) ?
- Unverified
- Partial Survey Response
- Complete
- Completed Survey Response

Subject ID **99001A**
AVA

No upcoming calendar events

Data Collection Instrument	Baseline Month 0	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52
Enrollment/Consent														
COVID-19 Questionnaire														
Contact Information														

APPENDIX C: Redaction Methods

Section 5, Study Procedures, COPDGene MOP

Directions for the Redaction of Medical Records and Death Certificates Using the Safe Harbor Method

We use the Safe Harbor Method ([Methods for De-identification of PHI | HHS.gov](https://www.hhs.gov/hipaa/for-professionals/safe-harbor)) and a three step process to de-identify medical records and death certificates. Under the Safe Harbor Method the following 18 identifiers need to be removed to make a de-identified data set.

Section 164.514(a) of the HIPAA Privacy Rule provides the standard for de-identification of protected health information. Under this standard, health information is not individually identifiable if it does not identify an individual and if the covered entity has no reasonable basis to believe it can be used to identify an individual.

§ 164.514 Other requirements relating to uses and disclosures of protected health information.

(2)(i) The following identifiers of the individual or of relatives, employers, or household members of the individual, are removed:

(A) **Names**

(B) **All geographic subdivisions smaller than a state**, including street address, city, county, precinct, ZIP code, and their equivalent geocodes, except for the initial three digits of the ZIP code if, according to the current publicly available data from the Bureau of the Census:

(1) The geographic unit formed by combining all ZIP codes with the same three initial digits contains more than 20,000 people; and

(2) The initial three digits of a ZIP code for all such geographic units containing 20,000 or fewer people is changed to 000

(C) **All elements of dates (except year) for dates that are directly related to an individual**, including birth date, admission date, discharge date, death date, and all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of “age 90 or older”

(D) **Telephone numbers**

(L) **Vehicle identifiers and serial numbers**, including license plate numbers

(E) **Fax numbers**

(M) **Device identifiers and serial numbers**

(F) **Email addresses**

(N) **Web Universal Resource Locators (URLs)**

(G) **Social security numbers**

(O) **Internet Protocol (IP) addresses**

(H) **Medical record numbers**

(P) **Biometric identifiers, including finger and voice prints**

- (I) **Health plan beneficiary numbers**
- (Q) **Full-face photographs and any comparable images**
- (J) **Account numbers**
- (R) **Any other unique identifying number**, characteristic, or code, except as permitted by paragraph (c) of this section [Paragraph (c) is presented below in the section “Re-identification”]; and
- (K) **Certificate/license numbers**

Directions:

First Pass by the Site Coordinator:

1. Read all notes to identify any PHI that falls under the list above. Be sure to look in headers, footers, and hand-written notes. If the file is electronic, use the Find feature to do a first run (e.g. find /20 for dates, last name), but a final redaction needs to be done with a thorough reading of the file.
 - a. Look for partial dates, like month/day or alternative date formats that would be missed using a search.
 - b. ‘Account numbers’ and ‘other unique identifying numbers’ could include, prescription IDs, CT accession numbers, lab order identification numbers, etc.

Records for Death Adjudication:

- c. Under the Data Collected and Data Handling section starting on page 15 of the Central Protocol, COPDGene is permitted to collect identifiers including dates of death from death certificates.
 - d. There is no explicit requirement to remove the names of providers or workforce members
2. Choose redaction tools: Use digital tools such as Adobe Acrobat's "Redaction Tool," or if digital redaction is not possible, use manual tools such as black markers.
3. Mark the identified PHI with a black marker or use the redaction tool to cover it.
4. Make sure that the redaction has completely covered the PHI and that no part of the information is visible or shows through the marker ink. Digital tools can be used to verify the redaction.
5. Store the redacted record in a secure location.
6. Send the redacted file to the COPDGene DCC using a secure file transfer system.

Examples:

- a. Encrypted file upload, such as the File Upload feature in REDCap forms, for example the C4R COVID-19 Medical Record Tracking form, or the File Depot file transfer, which encrypts the file. These systems require user authentication.
- b. Secure email system, which requires user/password login and file encryption
- c. LiquidFiles™ file sharing software, which requires user authentication and provides file encryption.

Second Pass by the NRCs:

1. Carefully read through the redacted file to look for any remaining 18 identifiers.
2. Choose redaction tools: Use digital tools such as Adobe Acrobat's "Redaction Tool" on the received scanned PDF documents.

3. Use the redaction tool to cover any remaining PHI.
4. Make sure that the redaction has completely covered the PHI, and that no part of the information is visible. Digital tools can be used to verify the redaction.
5. The NRCs will store the redacted record in a secure location either on the secure file server used for COPDGene study data or the File Depot file application, which encrypts the files and stores them on a secure file server.

Third Pass by the DCC:

1. Carefully read through the redacted file to look for any remaining 18 identifiers.
2. Choose redaction tools: Use digital tools such as Adobe Acrobat's "Redaction Tool" on the received scanned PDF documents.
3. Use the redaction tool to cover any remaining PHI.
4. Make sure that the redaction has completely covered the PHI, and that no part of the information is visible. Digital tools can be used to verify the redaction.
5. The DCC will use the secure file server used for the COPDGene study data and/or the File Depot file server, as described above.

6. Phase 3 Study Visit (and post COVID “in person” part 2 visit) Evaluation Sequence

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

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

*Do not complete the Sit to Stand test until after the Six-Minute Walk test is performed and it is a good idea to separate the two tests with questionnaires.

6a. Screening Form

Based on responses on this form, some subjects may be delayed for their study visit (see COPDGene® protocol for temporary exclusions). Responses that will result in a delay for the visit 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 visit (minus CT scan):

- History of a lung transplant since the previous 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, DLco, the Six-Minute Walk Test, and the Sit to Stand 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 Form.

6c. Safety Assessment Form

The Safety Assessment Form should be completed prior to spirometry testing, albuterol administration, DLco, the Six-Minute Walk Test and the Sit to Stand test. The Safety Assessment provides guidelines for when an investigator should be contacted prior to spirometry testing, administration of albuterol, DLco, the Six-Minute Walk Test and the Sit to Stand 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. A Safety Assessment form should be completed again in the event that a visit is rescheduled. The responses will just be updated in REDCap.

If a subject cannot do a procedure due to medical problems, they should come back once treated **and deemed appropriate by the PI**. At that time the safety form should be updated. **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 Six-Minute Walk Test and Sit to Stand test

- NOTE: the Sit to Stand test should not be completed until after the Six-Minute Walk test and time should be given to the subject in between the two tests (for example, time to complete questionnaires sitting down)
- 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 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 Six-Minute Walk Test should be done at least 20 minutes after the albuterol administration and at least 15 minutes after the post-bronchodilator spirometry. The CT is to be completed after Spirometry and albuterol.

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 listed below. Questionnaires marked with a * are available to be conducted as a survey in REDCap (to be completed by the subject on a computer or lap top).

- 1) Medication History Questionnaire
- 2) Medical History Questionnaire *
- 3) Respiratory Disease *
- 4) CAPTURE *
- 5) COPD Assessment Test (CAT) *
- 6) SF-36 Questionnaire *
- 7) St. George's Respiratory Questionnaire (SGRQ) *
- 8) Spirometry Administration
- 9) DLco
- 10) Hospital Anxiety and Depression Scale (HADS) *
- 11) Socioeconomic *

- 12) eCigarette Questionnaire*
- 13) Cannabis Use Questionnaire *
- 14) COVID Questionnaire (if subject is due)
- 15) 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.
- 16) PROactive Questionnaire *
- 17) DASI Questionnaire *
- 18) Cognitive Screen Items
- 19) Sit to Stand Test
- 20) Residential and Occupational
- 21) Blood Sampling
- 22) 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. No other forms should be re-done.

6e. Querying in REDCap – Data Resolution Workflow

In most instances, REDCap will do in time data querying. However, there may be a need for a clinical center to respond to a query after the form has been completed.

The DCC is incorporating REDCap’s Data Resolution Workflow in to the COPDGene® Phase 3 Data Quality Process.

When you click on “Data Rprts” on the Main COPDGene® web page, you are still be brought to a list of Data Quality Reports. However, a link to REDCap has replaced a Range Checks report in the first column.

NATIONAL JEWISH COPDGene: Genetic Epidemiology of COPD
Clinical Center Data Reports

[Home](#)
Forms
PFT Files
[Phase 3 Certification](#)
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Data Mgmt
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Data Quality Reports
 Updated on 02/28/2018

AVA:	REDCap Queries	Missing Forms	Visit Discrepanies	Subject Follow-up
BAY:	REDCap Queries	Missing Forms	Visit Discrepanies	Subject Follow-up
BWH:	REDCap Queries	Missing Forms	Visit Discrepanies	Subject Follow-up
COL:	REDCap Queries	Missing Forms	Visit Discrepanies	Subject Follow-up
DUK:	REDCap Queries	Missing Forms	Visit Discrepanies	Subject Follow-up
FAL:	REDCap Queries	Missing Forms	Visit Discrepanies	Subject Follow-up
HAR:	REDCap Queries	Missing Forms	Visit Discrepanies	Subject Follow-up
HPR:	REDCap Queries	Missing Forms	Visit Discrepanies	Subject Follow-up
HVA:	REDCap Queries	Missing Forms	Visit Discrepanies	Subject Follow-up
JHU:	REDCap Queries	Missing Forms	Visit Discrepanies	Subject Follow-up
MSM:	REDCap Queries	Missing Forms	Visit Discrepanies	Subject Follow-up
MVA:	REDCap Queries	Missing Forms	Visit Discrepanies	Subject Follow-up
NJC:	REDCap Queries	Missing Forms	Visit Discrepanies	Subject Follow-up
PIT:	REDCap Queries	Missing Forms	Visit Discrepanies	Subject Follow-up
TEM:	REDCap Queries	Missing Forms	Visit Discrepanies	Subject Follow-up
TXS:	REDCap Queries	Missing Forms	Visit Discrepanies	Subject Follow-up
UAB:	REDCap Queries	Missing Forms	Visit Discrepanies	Subject Follow-up
UTA:	REDCap Queries	Missing Forms	Visit Discrepanies	Subject Follow-up
UMC:	REDCap Queries	Missing Forms	Visit Discrepanies	Subject Follow-up
UMN:	REDCap Queries	Missing Forms	Visit Discrepanies	Subject Follow-up
USD:	REDCap Queries	Missing Forms	Visit Discrepanies	Subject Follow-up

Range checks are now being done in REDCap's Resolve Issues Application

Click on the “[REDCap Queries](#)” link and you’re directed to the Open/Unresolved issues within REDCap. Click on the comment button on the far left to open a data query.

Data Quality

Resolve Issues 1 **Resolution Metrics**

[VIDEO: Data Resolution Workflow](#) or [Read introduction to Data Resolution Workflow](#)

This page displays all data queries that are currently unresolved or have already been resolved using the Data Resolution Workflow. Some issues may have been initiated by users on data collection instruments, and others may have been initiated after executing Data Quality rules on the Find Issues tab. The table lists the name of the record and the specific field or Data Quality rule to which the data query belongs, as well as the user assigned to the query (if applicable), the number of days the data query has been open, and a brief snippet of the query’s first and last comment. The results in the table can be filtered by the query status type (e.g., open, closed), by certain fields or Data Quality rules, and also by users assigned to it. Each data query may be viewed by clicking the button to its left.

Data Resolution Dashboard		Filters: Open / unresolved issues (1)				
Export		<input type="text" value="All fields and rules"/> <input type="text" value="All events"/> <input type="text" value="All data access groups"/> <input type="text" value="User assigned (all users) or not assigned"/>				
Click button to view data query	Record (Sorted by DAG)	Data Quality rule and/or Field	User Assigned	Days Open	First Update	Last Update
1 comment	99999N Phase 3 visit (NJC)	Field: platelets (Platelets)	-	0	KnowlesR (03/05/2018 10:24am): "Please re-check out-of-range value and edit if needed. If correct, please include the field and va..."	[same as first update]

A window will pop up that will give you more information.

If a value is NOT correct

If the queried value needs to be edited, click on the Subject ID and you will be sent to the form with the value so you can correct it.

Data Resolution Workflow

[VIDEO: Data Resolution Workflow](#)

This pop-up displays the Data Resolution Workflow for the specified record for a given field and/or Data Quality rule. Users with appropriate user privileges may open data queries to begin a documented process of resolving an issue with the data. Opened data queries may thus be responded to by users with appropriate privileges, and then they may be closed once the issue has been resolved. All data queries can also be viewed on the Resolve Issues page in this project.

Subject ID: **99999N**
Event: **Phase 3 visit**
Field: **platelets** ("Platelets")
Status: **Open / Unresolved** (unresponded)

Date/Time	User	Comments and Details
03/05/2018 10:17am	knowlesr	Data Changes Made: platelets = '461'
03/05/2018 10:24am	KnowlesR	Action: Opened query Comment: "Please re-check out-of-range value and edit if needed. If correct, please include the field and value in your comment. For example, "HR of 125 is correct.""
03/05/2018 11:03am	ruthietest	Reply with response: -- choose response -- Upload file (optional): Upload document Comment:

Respond to query Cancel

A pop-up that states “Save and then open Data Resolution Pop-up” will be hovering by the value. Enter the correct value and then click the pop-up.

RCC * must provide value	<input type="text"/>	<input type="button" value="Save & Exit Form"/> <input type="button" value="Save & ..."/> ▾ <input type="button" value="-- Cancel --"/>
MCV * must provide value	<input type="text"/>	
MCH * must provide value	<input type="text"/>	
MCHC * must provide value	<input type="text"/>	
Platelets * must provide value	<input type="text" value="416"/>	
Form Status		
Complete?	<input type="text" value="Complete"/> ▾	
		<input type="button" value="Save & Exit Form"/> <input type="button" value="Save & ..."/> ▾ <input type="button" value="-- Cancel --"/>

🔔 Save and then open Data Resolution Pop-up

Next, choose from the “Reply with response:” drop-down list, provide a comment, and then submit by clicking “Respond to query”.

Data Resolution Workflow
✕

[VIDEO: Data Resolution Workflow](#)

This pop-up displays the Data Resolution Workflow for the specified record for a given field and/or Data Quality rule. Users with appropriate user privileges may open data queries to begin a documented process of resolving an issue with the data. Opened data queries may thus be responded to by users with appropriate privileges, and then they may be closed once the issue has been resolved. All data queries can also be viewed on the Resolve Issues page in this project.

Subject ID: [99999N](#)
 Event: **Phase 3 visit**
 Field: **platelets** ("Platelets")
 Status: 🗨️ **Open / Unresolved** (unresponded)

Date/Time	User	Comments and Details
03/05/2018 10:17am	knowlesr	Data Changes Made: platelets = '461'
03/05/2018 10:24am	KnowlesR	Action: Opened query Comment: "Please re-check out-of-range value and edit if needed. If correct, please include the field and value in your comment. For example, "HR of 125 is correct.""
03/05/2018 11:12am	ruthietest	Data Changes Made: platelets = '416'
03/05/2018 11:12am	ruthietest	<div style="display: flex;"> <div style="flex: 1;"> <p>Reply with response:</p> <p>Upload file (optional):</p> <p>Comment:</p> <div style="border: 1px solid gray; height: 20px; width: 100%; margin-top: 5px;"></div> </div> <div style="flex: 1; border: 1px solid gray; padding: 2px;"> <p>-- choose response --</p> <p>Corrected - Data missing</p> <p>Corrected - Typographical error</p> <p>Corrected - Wrong source used</p> <p>Verified - Confirmed correct (no error)</p> <p>Other</p> </div> </div>

Respond to query
Cancel

If the value IS correct

Provide a comment that includes the field and value.

🔔 **Data Resolution Workflow**
✕

[🎥 VIDEO: Data Resolution Workflow](#)

This pop-up displays the Data Resolution Workflow for the specified record for a given field and/or Data Quality rule. Users with appropriate user privileges may open data queries to begin a documented process of resolving an issue with the data. Opened data queries may thus be responded to by users with appropriate privileges, and then they may be closed once the issue has been resolved. All data queries can also be viewed on the Resolve Issues page in this project.

Subject ID: **99999N**
 Event: **Phase 3 visit**
 Field: **platelets** ("Platelets")
 Status: 🚫 **Open / Unresolved** (unresponded)

Date/Time	User	Comments and Details
03/05/2018 10:17am	knowlesr	Data Changes Made: platelets = '461'
03/05/2018 10:24am	KnowlesR	Action: Opened query Comment: "Please re-check out-of-range value and edit if needed. If correct, please include the field and value in your comment. For example, "HR of 125 is correct.""
03/05/2018 10:55am	ruthietest	Reply with response: -- choose response -- Upload file (optional): + Upload document Comment: <div style="border: 1px solid gray; padding: 5px; margin-top: 5px;"> Platelets of 461 is correct </div>

Respond to query
Cancel

And choose one of the options from the “Reply with response:” drop-down list and click “Respond to query”.

Data Resolution Workflow

[VIDEO: Data Resolution Workflow](#)

This pop-up displays the Data Resolution Workflow for the specified record for a given field and/or Data Quality rule. Users with appropriate user privileges may open data queries to begin a documented process of resolving an issue with the data. Opened data queries may thus be responded to by users with appropriate privileges, and then they may be closed once the issue has been resolved. All data queries can also be viewed on the Resolve Issues page in this project.

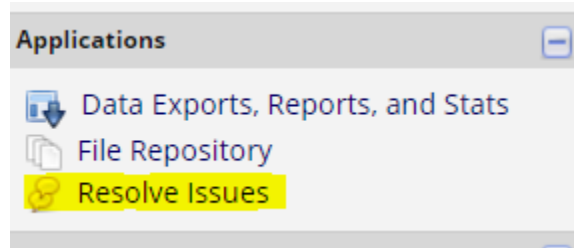
Subject ID: **99999N**
 Event: **Phase 3 visit**
 Field: **platelets** ("Platelets")
 Status: **Open / Unresolved** (unresponded)

Date/Time	User	Comments and Details
03/05/2018 10:17am	knowlesr	Data Changes Made: platelets = '461'
03/05/2018 10:24am	KnowlesR	Action: Opened query Comment: "Please re-check out-of-range value and edit if needed. If correct, please include the field and value in your comment. For example, "HR of 125 is correct.""
03/05/2018 10:55am	ruthietest	Reply with response: -- choose response -- Upload file (optional): Comment: Platelets of 461 is corr

Corrected - Data missing
 Corrected - Typographical error
 Corrected - Wrong source used
 Verified - Confirmed correct (no error)
 Other

Respond to query Cancel

To access these data queries from within REDCap, click on “Resolve Issues” under Applications.



7. Phase 3 Short-term/COVID-19 Follow-up Procedures

To test high-risk subtypes for rapid COPD progression, approximately 800 subjects from the full COPDGene® cohort will participate. These subjects will be invited back for a Short Term Follow-up Study visit approximately one year (12-15 months) after the Phase 3 visit.

During the COVID-19 pandemic, the short-term follow-up visit will, instead, be used to call back individuals who have been identified for a COVID-19 follow-up visit.

Subjects participating in the Short-Term/COVID-19 Follow-Up study will be identified by the Data Coordinating Center and a list will be provided to each participating clinical center.

Follow the Phase 3 Study Visit Evaluation Sequence outlined in pages 42-45 of this MoP. All procedures will be the same as the 10 year Phase 3 visit except there may be no: CAPTURE Questionnaire, Cognitive Screen Questionnaire, Cannabis Use Questionnaire, PTOA Questionnaire, Socioeconomic Questionnaire, Optimism Questionnaire, Residential and Occupational History, or Food Frequency Questionnaire.

8. Questionnaires

Questionnaires can be completed on a computer (this is preferred but can only be done 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 into REDCap. 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.

Materials for Administering Questionnaires:

- Computer with Internet connection

Questionnaires are posted on the study website:

https://dccweb.njhealth.org/sec/COPDGene/Files/COPDGenePhase3_Forms_05%20Dec%202017.pdf

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 07/01/2018.

8a. Contact Information

All centers are responsible for maintaining and updating the full contact information for their subjects.

In Phase 3 (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 on the COPDGene® website on the Forms page. (this data will not be transmitted via REDCap).

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).

8b. 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.

8c. PTOA Questionnaire

The PTOA questionnaire will help investigators determine if COPDGene cohort is experiencing post-traumatic osteoarthritis.

8d. 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 Clinical Center Coordinator should discuss with their local investigator.

CLASS OF MEDICATION	EXAMPLES
(b) Inhaled Short-acting beta-agonist	Albuterol [®] , ProAir [®] , Ventolin [®] , Proventil [®] , Maxair [™] , Xopenex [®] , AccuNeb
(c) Ipratropium inhaler	Atrovent [™]
(d) Combination short-acting inhaled medication	Ipratropium/albuterol combination (Combivent [®] , DuoNeb [®])

(e) Long-acting beta-agonist	Serevent™, Brovana®, Arcapta™ Perforomist®, Striverdi Respimat®
(f) Anticholinergic bronchodilator	Spiriva®, Aclidinium (Tudorza®), Incruse Ellipta®, Seebri®, Lonhala®, Yupelri®
(g) Corticosteroid	Aerobid®, Aerospan®, Asmanex Twisthaler®, Azmacort®, Flovent®, Pulmicort®, QVAR®, Arnuity®, Alvesco®
(h) Combination inhaled corticosteroid + long-acting beta agonist	Fluticasone / salmeterol (Advair®), Budesonide / formoterol (Symbicort®) Fluticasone / vilanterol (Breo®), Mometasone/formoterol (Dulera®) Fluticasone furoate, umeclidinium, vilanterol (Trelegy) fluticasone propionate 113 mcg and salmeterol 14 mcg (AirDuo®)
(i) Combination long-acting beta-agonist + long-acting muscarinic antagonist	Anoro®, Stiolto®, Bevespi Aerosphere®, Utibron®
(j) Theophylline	Respbid, Slo-bid, Theochron, Theo-24
(k) Macrolide antibiotic	Daily or chronic: Azithromycin Zithromax Zmax
(l) Phosphodiesterase inhibitor:	Daliresp®
(m) Oral corticosteroids	Daily or chronic: Deltasone Medrol Prednisolone Prednisone

Figure 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.

8e. Respiratory Disease 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.” 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.).

A modified, shorter version of this questionnaire is administered during the in-person to finish virtual portion of the visit for the COVID-19 modified visits.

8f. St. George's Respiratory Questionnaire (SGRQ)

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.

8g. 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.

8h. Residential / Occupational Questionnaire

Environmental and occupational exposures can influence the development and progression of lung disease. The Residential / Occupational Questionnaire has been designed to capture these influences on COPD, if approved by the Clinical Center IRB for transmission to the COPDGene® Data Coordinating Center.

8i. 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.

8j. 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.

8k. 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.

8l. CAPTURE Questionnaire

The CAPTURE Questionnaire is a COPD screener. Over 24 million Americans may have COPD, but only 15 million are diagnosed each year. Spirometry is not routinely used by primary care doctors. Use of a screening questionnaire has been proposed to assist in making the correct diagnoses in those currently undiagnosed.

8m. eCigarette Questionnaire

The eCigarette Questionnaire has been designed by COPDGene[®] to assess amount of use and attitudes. It will be administered to all subjects and asks questions about eCigarettes and vaping.

8n. Cannabis Use Questionnaire

The Cannabis Use Questionnaire has been designed by COPDGene[®] to assess amount of use and attitudes. It will be administered to all subjects and asks questions about Cannabis and vaping.

8o. PROactive and DASI Questionnaires

The PROactive and Duke Activity Staus Index (DASI) questionnaires are instruments used to measure physical activity and frailty in patients with COPD. Patients with COPD are inactive and this is associated with mortality. COPDGene[®] has an aging population and aging is associated with decreased activity. We are administering these to look at if clinical features we are measuring are related to lung disease or just aging. There currently is no consensus on measuring physical activity with a questionnaire in a COPD population. The PROactive and DASI coupled with the Six-Minute Walk and Sit to Stand test should give investigators a good assessment of both physical activity and frailty in COPDGene[®] subjects.

8p. Sit to Stand Test

Purpose: To test leg strength and endurance

Equipment:

- A chair with a straight back without arm rests (seat 17" high)
- A stopwatch

Contraindications:

- BP greater than 170/100
- High fall risk, specifically amputees without prosthesis
- Individuals who need an assistive device for ambulation
- Individuals with a short term lower extremity impairment
- Subjects who have had a previous stroke with significant residual deficits in balance or proprioception
- Use of > 6 L/min oxygen flow with activity

Instructions to the Patient

- 1) Sit in the middle of the chair.
- 2) Place your hands on the opposite shoulder crossed at the wrists.
- 3) Keep your feet flat on the floor.
- 4) Keep your back straight and keep your arms against your chest.
- 5) On “Go,” rise to a full standing position and then sit back down again.
- 6) Repeat this for 30 seconds.



- On “Go” begin timing.
- If the patient must use his/her arms to stand, stop the test. Record “0” for the number and the score.
- Count the number of times the patient comes to a full standing position in 30 seconds.
- If the patient is over halfway to a standing position when 30 seconds have elapsed, count it as a stand.
- Record the number of times the patient stands in 30 seconds. This is the score.

*A below average score indicates a high risk for falls. Below Average Scores

Age	Men	Women
60-64	<14	<12
65-69	<12	<11
70-74	<12	<10
75-79	<11	<10
80-84	<10	<9
85-89	<8	<8
90-94	<7	<4

Cited from: www.cdc.gov/injury /STEADI

If the Sit to Stand test is not completed, the form must still be completed in REDCap. There is an option in the form to indicate why this test was not performed.

Did the subject attempt the Sit Stand Test?

Yes
 No, safety concern noted on Safety form
 No, non-ambulatory
 No, subject refused, no safety concern

reset

Figure 7-2: For the Sit to Stand test, the coordinator can select from the above options, depending on whether or not the test was performed, and if not for what reason.

8q. Hand Grip Strength Test

Centers will be provided with a Jamar dynamometer for measuring hand grip strength.

Subjects should be tested in a *standing position* using the dominant hand unless the subject is not able to stand for the test. The elbow should be flexed (bent) to 90 degrees and the forearm in neutral rotation (thumb pointed up to the ceiling). Hold the device so the gauge is facing away from the subject (toward the coordinator).

The shoulder should be in neutral position with the elbow comfortably near the waist. If a chair is needed for subject safety or other limitations, the chair should not have an arm that interferes with the subject positioning. Subjects should be instructed to loosely grip the dynamometer and, when they are ready, squeeze it as hard as they can for approximately 3-4 seconds (long enough for the reading to stabilize). The dynamometer should be unsupported while the subject is doing the test. The coordinator should ensure that the instrument is set at zero prior to each measurement and record the value after the subject grips it. Values should be recorded in kg of force. The subject should do one practice grip and then be allowed 60 seconds rest. The testing is done three times with each value recorded and with a 60 second rest in between each test.

If the subject has artificial nails that extend 0.5 cm beyond the finger tip, this should be noted on the data entry form.

If the subject states that they have hand, wrist or finger arthritis, this should be noted on the data entry form.

Note on the form which is the subject's dominant hand. "Which hand do you use to write, eat and work with? Right Left Both equally

If the subject states that they use both equally then test the left hand, otherwise test the hand that is reported to be dominant. Record which hand was tested.

If the subject is unable to use the dominant hand (due to surgery, fracture, etc.), don't do the test unless the subject is fairly ambidextrous and can do non-dominant hand.

Coaching should be provided as follows:

"I want you to hold the handle like this and when you are ready squeeze as hard as you can."
The examiner demonstrates and then gives the dynamometer to the subject.

After the subject is positioned appropriately, the examiner says, “Are you ready? Squeeze as hard as you can.”

As the subject begins to squeeze, the examiner says, ‘Harder!... Harder!... Relax’

8r. Cognitive Screen Tests

There are three questions to be asked to subjects in the beginning of this form.

After the three questions is the MiniCog assessment. This is used a standardized cognitive screening tool. This test includes two components; a word list recall and a clock drawing task.

Coordinator Instructions:

Introduction to using the tool for coordinator and patient.

Be sure to have a stop watch to time the clock drawing.

Do not deviate from the instructions below (which are also in the REDCap form). These are standardized and validated and changing the instructions could affect the results.

1) Three Word Recognition:

Coordinator: Look at the person and say, "Please listen carefully. I am going to say three words that I want you to repeat back to me now and try to remember. The words are:

Banana

Sunrise

Chair

“Please say them for me now.”

If the person is unable to repeat the words after three attempts, move on to Step 2 (clock drawing).

2) Clock Drawing:

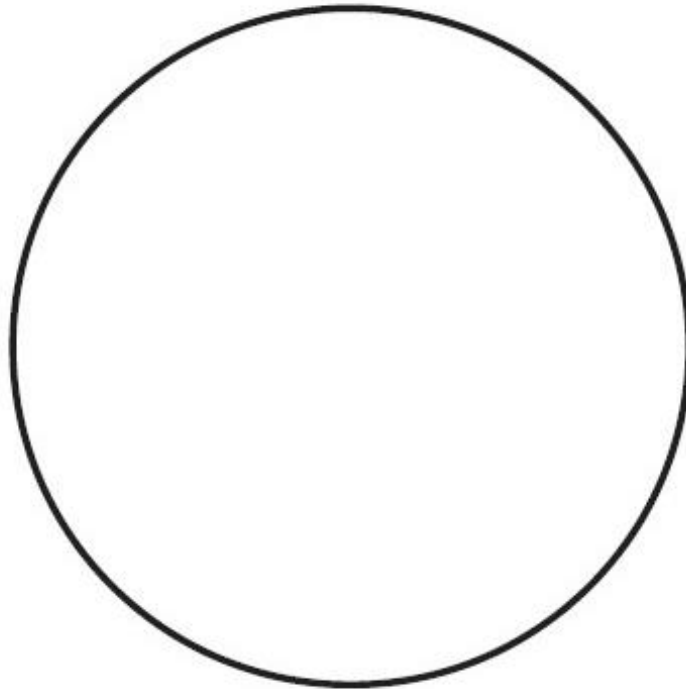
Coordinator: “Next, I want you to draw a clock for me. First, put in all of the numbers where they go.”

When that is completed, say: “Now, set the hands to 10 past 11.” (This phrasing must be used).

The coordinator must provide the preprinted circle (shown below) for this exercise. Repeat instructions as needed as this is not a memory test. Move to step 3 if the clock is not drawn within three minutes.

Clock Drawing

ID: _____ Date: _____



Once the clock drawing is done, the coordinator will go back to the three word recall.

3) Three Word Recall

The coordinator will now ask the subject to recall the three words that were stated in step 1.

Coordinator: “What were the three words I asked you to remember?” (Record the the person’s answers on the “Cognitive Screen Items” form in REDCap).

DO NOT CUE OR GIVE HINTS TO THE SUBJECTS.

Do not share the results of the correct words with the subject when done.

Mini-Cog Scoring:

- Word Recall (0-3 points): 1 point is given for each word spontaneously recalled in step 3 without cueing
- Clock Draw (0 or 2 points): A normal clock is given 2 points. For points to be given, the clock must be drawn with all twelve numbers in the correct sequence and approximately in the correct position (12, 3, 6, 9 are in their anchor positions), there are no missing or

duplicate numbers, and the hands are pointing to the 11 and the 2 (11:10). Hand length is not scored.

Total Score= Word Recall + Clock Draw score

The coordinator will need to scan and upload the clock drawing to REDCap as a .pdf file (can be done after the visit). This is because the clock scores will be adjudicated by a member of the Administrative Core prior to posting in the final dataset.

If a subject asks how they did you should instruct them that the test will be scored offsite and if they have any concerns about their memory they should discuss with their doctor.

The Mini-Cog is not a diagnostic test. It is a screening tool, and it needs to be followed up with other kinds of testing to determine the cause and effect of the problem.

For the Mini-Cog adjudicator (Internal use only):

The Administrative Core will have select personnel assigned to adjudicate the Mini-Cog final clock scores. The adjudicator will log into the REDCap project and click on each specific subject ID. They will then be able to download the clock and review and score. Once a final score is determined, the adjudicator will enter their name in the “Adjudicator Signature” line, the actual score, and the total score. This must be done for all subjects before including the clock scores in the posting of a study dataset.

8s. Optimism Questions

Optimism has been associated with longevity and cardiovascular health; prior studies have suggested that optimism is associated with slowed lung function decline and decreased mortality from chronic respiratory disease, even after adjustment for lifestyle choices and cigarette smoking (35). There is little understanding of the biological mechanisms that may drive the association between optimism and respiratory outcomes. The addition of the Life Orientation Test-Revised adds six questions to the COPDGene® Phase 3 study protocol will allow us to study both the epidemiologic and biologic associations between optimism and outcomes in smokers with and without COPD.

Please indicate the extent to which you agree or disagree with the following statements.

	Disagree strongly	Disagree a little	Neither agree nor disagree	Agree a little	Agree strongly
In uncertain times I usually expect the best.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
If something can go wrong with me, it will.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
I'm always optimistic about my future.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
I hardly ever expect things to go my way.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
I rarely count on good things happening to me.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Overall, I expect more good things to happen to me than bad.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Centers must have local IRB approval prior to asking these questions to the subjects. This questionnaire was added to protocol amendment version 9.1.

8t. Clinically Significant Findings Form

The Clinically Significant Findings Form will be completed for every study visit and subject. Use this form to record clinically significant findings that have been judged by the local investigator 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 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 mail. Enter information about significant abnormal findings as they are known but complete this form in REDCap only after all clinical results are known and actions have been taken. Please submit the form prior to receiving subject response to being informed about any clinically significant finding. One of the metrics calculated in COPDGene® is that all subjects with a clinically significant finding were notified within 3 months of the visit.

8u. Blood Sample Form

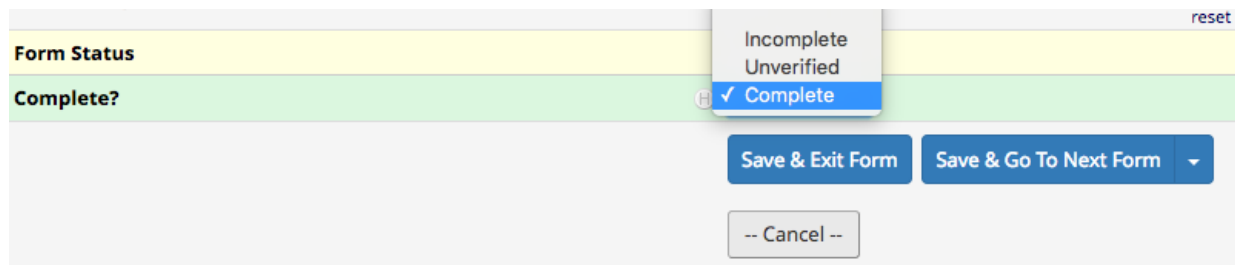
The Blood Sample Form will be completed for every study visit. Coordinators will use this form to record the date of blood collection, time of blood collection, time samples are frozen, and the number of tubes collected. The form must be submitted for every study participant, prior to shipping the samples.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

Refer to the Blood Shipment PowerPoint and You Tube videos which will be provided prior to study start for more information on blood processing.

New in Phase 3, we will be capturing a question regarding last meal on this form, we will ask the subject what time of day did they last eat and/or drink anything other than water; including candy/chewing gum, and collect this information.

8v. Completing Forms in REDCap

At the end of each form in REDCap you are able to update the status. The options are: incomplete, unverified and complete. We suggest that if all data has not yet been entered, you save the status to “Incomplete” and change to “complete” once the form is completely data entered. Forms will need to have a “complete” status in order to be eligible for payment. On the Record Status Dashboard” Red = Incomplete, Yellow=Unverified, and Green=Complete.



The screenshot shows a REDCap form completion status update interface. It features a table with two rows: 'Form Status' and 'Complete?'. The 'Form Status' row is highlighted in yellow and has a dropdown menu open with options: 'Incomplete', 'Unverified', and 'Complete'. The 'Complete?' row is highlighted in green and has a dropdown menu open with the option: 'Complete'. Below the table are three buttons: 'Save & Exit Form', 'Save & Go To Next Form' (with a dropdown arrow), and '-- Cancel --'. A 'reset' link is visible in the top right corner of the table area.

Figure 7-3 Screenshot from REDCap, updating form completion status and saving

Once complete, you can either Save and Exit, Save & Go To Next Form, or Save and Stay (by clicking on the arrow drop down next to Save & Go To Next Form). Remember to Save the status.

8w. Food Frequency Questionnaire (FFQ)

After the visit, each subject will be given a Food Frequency Questionnaire (FFQ) to complete at their convenience. A growing body of literature has linked diet with risk for COPD in smokers. However, few studies have addressed the association of additional COPD-related phenotypes such as emphysema in relation to diet. The Food Frequency Questionnaire (FFQ) has been extensively validated in large cohort studies and will provide new information about links between diet and COPD progression, severity and subtypes.

Each center will receive a FFQ package for each subject included in their blood supply shipments. The center will not need to do anything additional to modify these packets. The only thing that needs to be done is to give to the subject at the conclusion of the COPDGene® Visit.

The FFQ is 4 pages long. Each participant will receive the questionnaire, questionnaire instructions, a stamped envelope addressed to the Channing Division of Network Medicine at Brigham and Women's Hospital, and a #2 pencil in a postage paid addressed envelope.

The subject has the option to complete the FFQ at the end of the visit or to complete it at home and send it to the Channing in the mail. The instructions for the FFQ will be provided on a cover letter that will instruct the subject on proper completion of the questionnaire and also tell them not to write their name or any other identifying information on the questionnaire or return envelope. Each questionnaire will have the subject ID already listed on it before being provided.

If the FFQ is completed and left on site, the local clinical center should put it into the provided addressed/stamped envelope and mail it to the Channing. It will be data entered once received at the Channing and no data entry is required by site personnel.

This cover letter and FFQ must have local IRB approval prior to providing to the subjects. This assessment was added to protocol amendment version 9.1.

8x. COVID-19 Tracking Survey

COVID-19 related illness will be tracked using **this** brief questionnaire that the subject can choose to answer over the phone with a coordinator or through email. The subject will consent to this increased contact at the time of consent for the modified visits for the Phase 3 Virtual visit and/ or (for those not scheduled for a phase 3 visit) a separate contact for COVID-19 tracking survey.

If during the LFU call the participant answers that they had a COVID-19 diagnosis or illness, the coordinator will call the participant to consent for and administer the short-version COVID Questionnaire. If the phone consent is not possible, the coordinator will send the LFU contact

letter and the participant will call the coordinator, then the coordinator will administer the LFU COVID Phone script, then the short-version COVID Questionnaire.

8y. Blood Spot

A dried blood spot kit will be sent to the participants who have agreed to provide a blood sample. The kit will include an alcohol swab, lancets, sample collection card, card sleeve, band-aid, instructions, return envelope, and a copy of the informed consent.

Subsequent blood spot kits will be sent to participants who have had an inconclusive result on their previous antibody test(s) or lost/damaged the kit. Blood spot kit(s) will be sent to participants to survey for COVID antibodies at up to 12-month intervals when COVID remains in an epidemic status and extend into antibody surveys at up to 12-month intervals during the first five years of endemic circulation of COVID.

9. Physical Characteristics

9a. 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 be 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 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 Demographics Form.

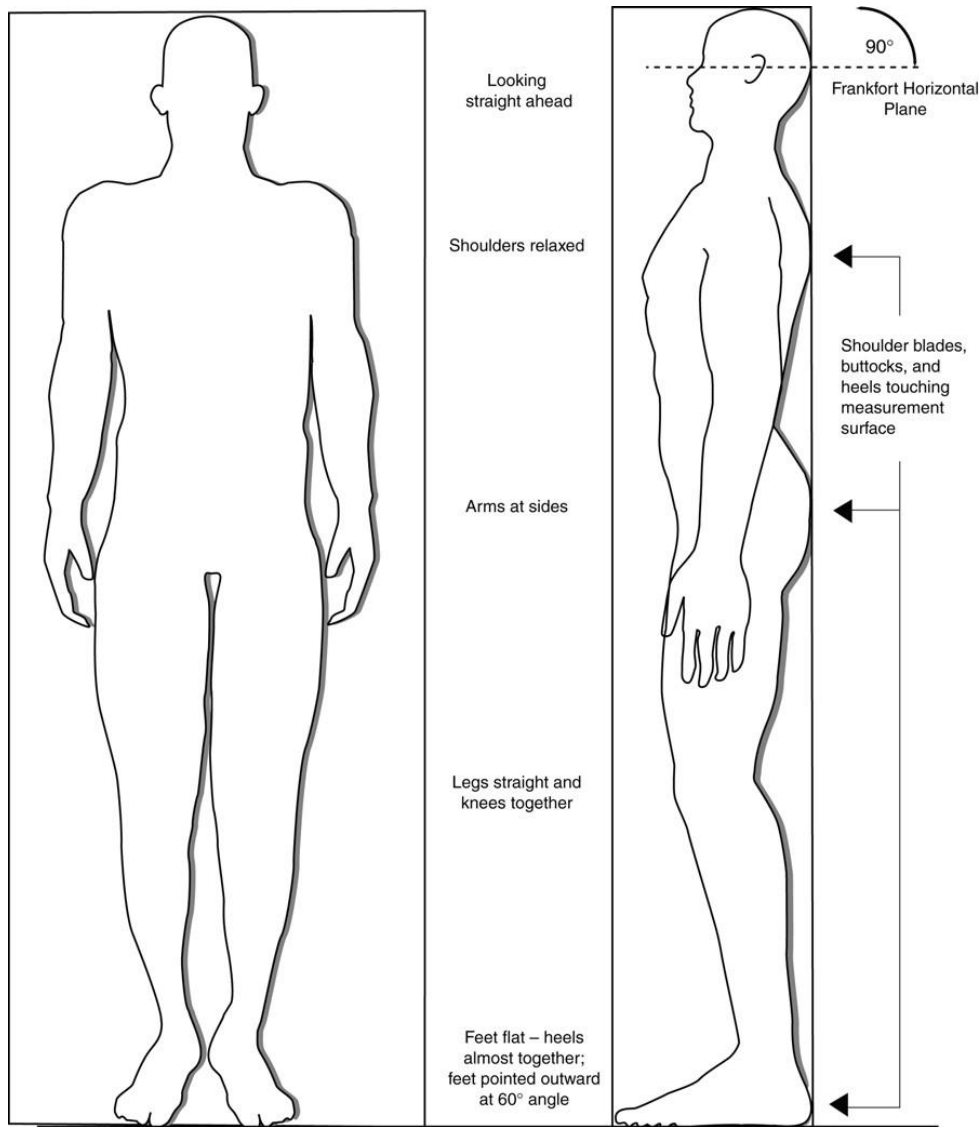


Figure 8-1. Measurement of Height

9b. 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.

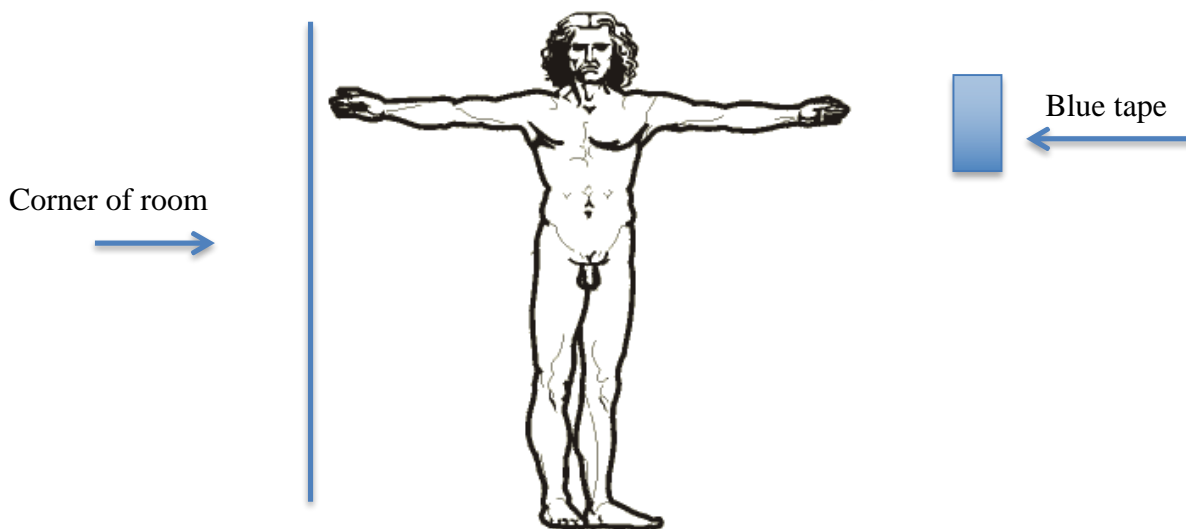


Figure 8-2. Arm Span

Be sure to denote the correct units of measurement (inches or centimeters) on the Demographics 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).

9c. 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 Form.

9d. Pulse Oximetry and Heart Rate

Pulse oximetry should be obtained prior to spirometry after the subject has remained at rest in the seated position for at least five minutes. Pulse oximetry will be obtained again immediately following and one minute after the Six-Minute Walk Test. Pulse oximetry should be obtained with the subject in the seated position. 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 ten 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.

9e. Blood Pressure

Blood pressure should be measured three times, waiting one minute between each measurement. Record the three BP measurements on the Demographics 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 bpm or greater than 120 bpm or if the blood pressure is greater than 170/100, a study physician will evaluate the subject to determine if it is safe to conduct spirometry, administer albuterol, perform the Six-Minute Walk Test, and perform the Sit to Stand Test.

9f. 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 Demographics Form

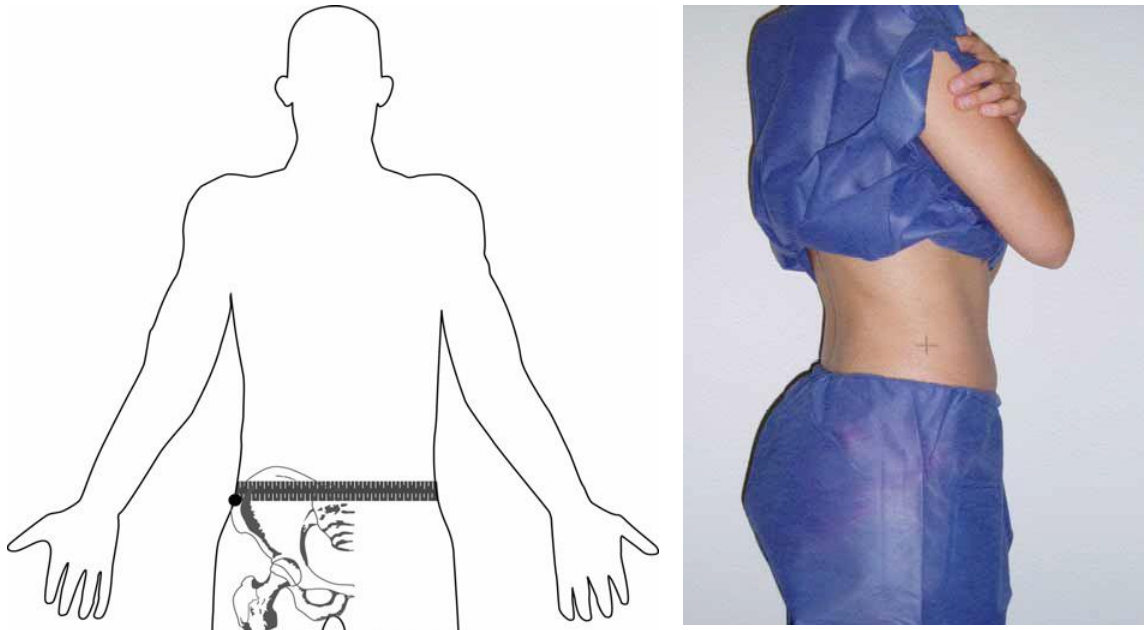


Figure 8-3. Location to obtain waist circumference measurement at the top of the iliac crest identified by palpation of the bone.

10. 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 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 the Administrative Core

Part I: Description of System

The LFU process is conducted by a combination of three primary methods:

- automated telephone contact (Telephony),
- web-based questions (Web Survey),
- and coordinator phone calls (Manual Follow Up).

Subjects will be contacted twice a year for LFU surveys. 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 COPDGene® signed 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; however, we may contact them at other times to follow up on cancer diagnoses, to inform them about the COPDGene®

study and to inform them 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 LFU computer program will do this automatically.

Master Spreadsheet

At each clinical site, the Clinical Coordinator must maintain an Excel file that contains subject information as noted below 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 (www.copdgenestudy.org).

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.

Note that if you require changes to who receives the reminder emails, contact the Administrative Core.

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 complete Master Excel file.
- 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*. Once data is purged, email links sent to the subjects will no longer work and the coordinator must obtain the survey from the subject over the phone. During the three weeks, identifying subject information will only be accessible by the Clinical Coordinator for the clinical site and Inventive Labs (the LFU programmer). 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.

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 using SHA-2 (2048-bit) key. Transmission of data uses this key to encrypt using the HTTPS protocol on port 443. State of the art Juniper Routers/Firewalls/Switches are employed to packet filter data to certain ports and certain protocols. Management is restricted to only access from specific IP addresses.

Physical Security

The host computer system is located in a secure data facility at 1950 N Stemmons Fwy, Dallas, Texas. 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. The facility is SSAE 16 compliant.

Data Storage and Confidentiality

All confidential and identifying data is stored in a separate encrypted database using the Microsoft SQL Server 2008 product. All confidential data is purged shortly after the survey has been completed, after attempts to contact the subject has 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 a limited amount of time to go online or call into the telephony system to complete the survey. After several weeks, the LFU system will purge all subject information limiting follow-up participation to a manual Clinical Coordinator call only. If a subject has not completed the survey by the time the identifying information is purged, their Subject ID will go on the Coordinator work list for a manual coordinator follow up.

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

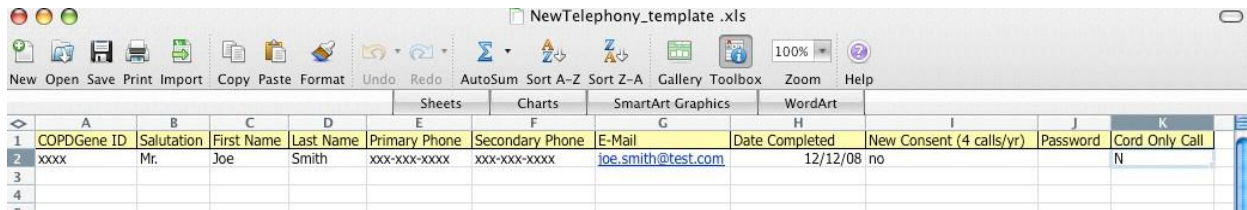
Step 1) Filling Out the Master Excel Spreadsheet

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 all active 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 in Phase 1. 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*. **DO NOT INCLUDE SECONDARY CONTACT INFORMATION ON THIS SPREADSHEET.**

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. **In Phase 3 we are encouraging the**

coordinators to try to obtain an email address for each COPDGene® subject (when available). Use of email to complete the LFU surveys greatly improves compliance and accuracy.

Date Completed: enter the date that subject was first seen in Phase 1 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

For new nonsmokers enrolled in Phase 3: 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.

Step 3) Using the COPDGene® LFU Web Site

The public COPDGene® LFU 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 Task List Follow Up screen, and view reports. Login name and passwords have previously been provided. If you lose or forget your name or password, please contact Sara Cummings at cummings@njhealth.org.

Login

Coordinators can login to the LFU website 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
Subjects with just Phone: 107
Subjects with just Email: 0
Subjects with Both: 27

Subjects with Neither: 0
Subjects loaded that were discontinued: 0
Subjects with New consent: 0
Subjects with Old consent: 134
Total Emails Sent: 20
Total Subjects Scheduled: 91
```

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 phone 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 [Mr./Mrs./Ms.],

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 email*. If we do not hear from you after four days, we will attempt to contact you by phone.

<http://www.copdgenestudy.org/SurveyLogin.aspx>

User name:

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.

Troubleshooting Tip: To take the Web survey, a subject is sent a login (which is the same as the subject's email address), and a password (which is the same as the subject's COPDGene® SID). If a subject cannot log into the system, ask the subject to make sure he/she is entering in the information correctly. For instance, a common mistake is to mix 'o' with zero. You can also see if the subject has already taken the survey (thus inhibiting the log in) by trying to log in for the subject. If the subject has completed the survey in the past 6 months, he/she is not allowed to take it again until the following 6-month period.

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 the coordinator 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.

Editing a Completed LFU Survey

Often, a subject (or the coordinator) will accidentally select the wrong answer in a survey. You may know at the time of survey completion or a subject may call or email you with a notification about the error. The coordinator has the ability to correct answers from the last survey completed by a subject. You can access the “Edit a survey” link from the main page.

Editing a Survey

Coordinator Follow Up

- [Take a survey for callback](#)
- [Edit a survey](#)
- [Manually enter subject information](#)
- [Manually update e-mail address](#)
- [Manually withdraw from LFU only](#)
- [Refresh](#)

Coordinators now have the ability to edit a completed survey. From the main screen you will see the link.

This can be done after you refresh the page after completing a survey.

Entering the SID will pull up the subjects last survey

Answer Review

If you need to change any of your answers, click 'Change' below:
 Survey Ended: 8/11/2017 5:04:14 PM
 COPD Gene ID: 25410E

Question		
Since we last talked, have you had an episode of increased cough and phlegm or shortness of breath, which lasted 48 hours or more?	No	Change
Do you still smoke cigarettes?	No	Change
<small>We would like to know if you have had any new conditions since we saw you last. Since we last spoke, have you been diagnosed with any of the following: heart disease, stroke, diabetes, blood clots, hip fracture, pneumonia or renal failure?</small>	No	Change

Editing a Survey

COPDGene Study Survey
Do you still smoke cigarettes?

Yes
 No

[Continue](#)

NOTE - Do not use the Back button to go back to a previous question. You will be able to review your answers at the end.

Answer Review
If you need to change any of your answers, click 'Change' below:
Survey Ended: 8/11/2017 5:04:14 PM
COPD Gene ID: 29410E

Question	Answer	Action
Since we last talked, have you had an episode of increased cough and phlegm or shortness of breath, which lasted 48 hours or more?	No	Change
Do you still smoke cigarettes?	No	Change
We would like to know if you have had any new conditions since we saw you last. Since we last spoke, have you been diagnosed with any of the following: heart disease, stroke, diabetes, blood clots, hip fracture, pneumonia or renal failure?	No	Change
Since your original COPDGene visit, have you been told by a physician that you have lung cancer?	No	Change
Since your original COPDGene visit, have you been told by a physician that you have a new cancer that is not lung cancer?	No	Change
Have you had any changes in your home address, telephone number, or friend and family contacts since we last spoke?	Yes	Change

[Survey Complete](#)

Utilize this feature as needed when an incorrect answer is selected on 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 to then 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 try to contact the subject again 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 (cannot complete this cycle)
- 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:

Coordinator Follow Up							
COPDGene Id	Action Needed	Last attempt	Voice mail	Take Survey	Update Email	Attempts	Result
10058L	Voice Mail-Update E-mail Address	5/14/2009 5:10 PM				0	Select a result <input type="button" value="Submit"/>
10480U	Subject Requested Contact	7/22/2009 2:56 PM				0	Select a result <input type="button" value="Submit"/>
10638D	Voice Mail-Update E-mail Address	7/22/2009 5:01 PM				0	Select a result <input type="button" value="Submit"/>

‘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.



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).

The screenshot shows the COPD Gene web interface. At the top left is the logo for COPD Gene, COPD Genetic Epidemiology. To the right of the logo are navigation links: Followup, Upload, Indiv Report, Status Report, Stats Report, and logof. Below the navigation is a section titled 'Update Email Address'. It contains a message: 'You must also update your spreadsheet so the system will have it for the next upload - as all confidential information is purged from the system after phone call attempts are completed.' Below this message is a text input field with the prompt 'Please enter the email address, then click the Save button:'. To the right of the input field are 'Save' and 'Cancel' buttons.

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.

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

- **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.
- **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

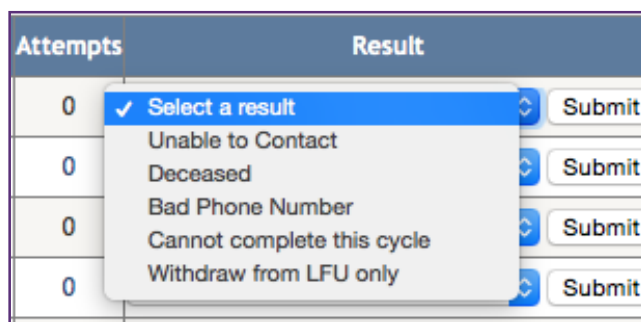
work list when the subject is scheduled for a call. The action term will appear on the work list as Manual Call.

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 Terms

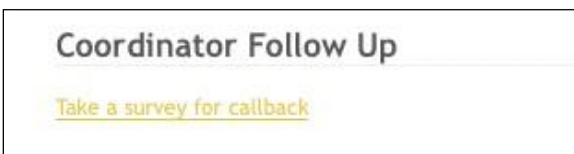
- **Unable to Contact:** Select this result when a call is made to a subject but there is no answer. If an answering machine is reached, the Coordinator should leave a message asking the subject to call back. *Every* time an answering machine is reached, a message should be left. After the third unable 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.

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

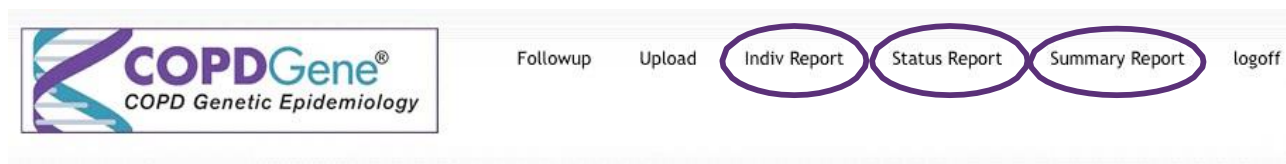


If subject is deceased complete Discontinuation Form

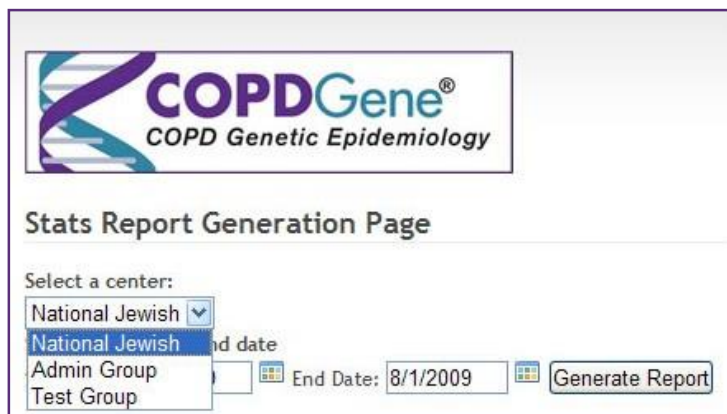
- Retrieve information on cause of death

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 COPD Gene® 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 report 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 COPD Gene®. 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.

11. Spirometry

11a. 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 or EasyOne Plus 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.

11b. 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.

11c. 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. For the duration of the COVID-19 pandemic, the appropriate filters from ndd should also be available. 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. The sites will be responsible for providing their own 3L calibration syringe. 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.

11d. 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 in Section 10p.

ndd EasyOne[®] Configuration Settings for Use in COPDGene[®]. 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.

11e. EasyWare® Setup and Data Upload

Install the EasyWare® software version 2.2525 provided to you by National Jewish Health on all PC computers that will be used for spirometry. This software is available from the COPDGene® Home Page -> Forms page, under "Phase 3 Quick Links" . 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.

11e.1 Setting up your spirometry EasyWare® master database

For Phase 3, we will continue to use the same file set up that is described below and was used for Phase 2.

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)

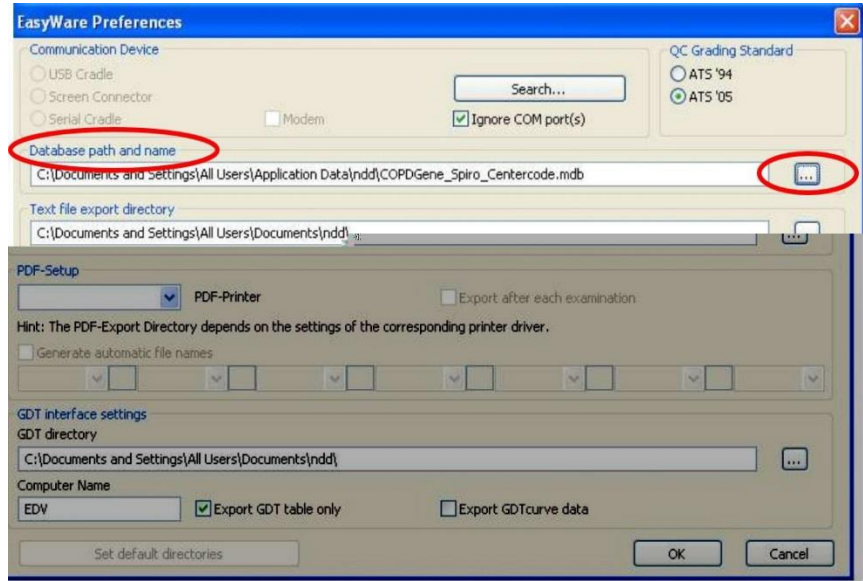


Figure 11-1. Setting up EasyWare to Write to COPDGene2_EZWare Folder

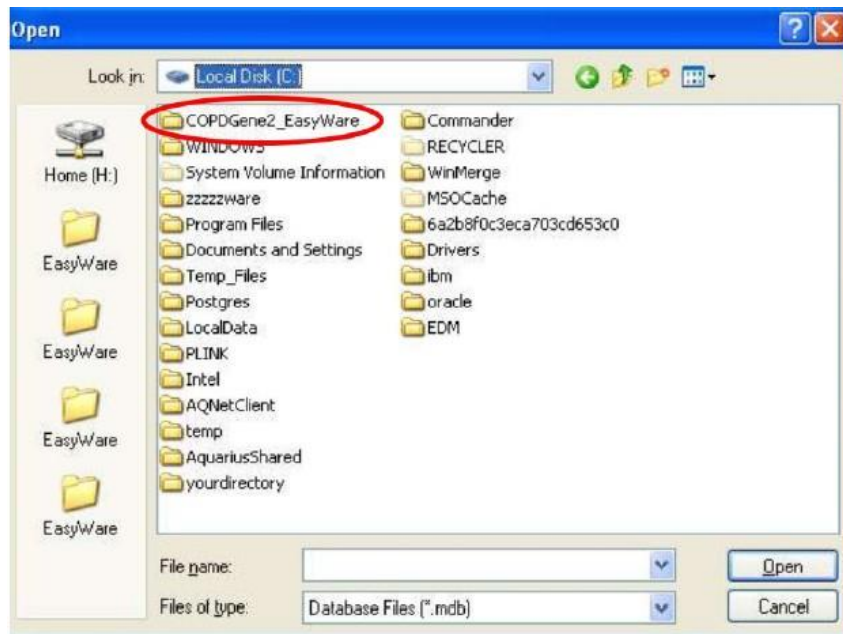


Figure 11-2. Finding your New Folder on the C: Drive

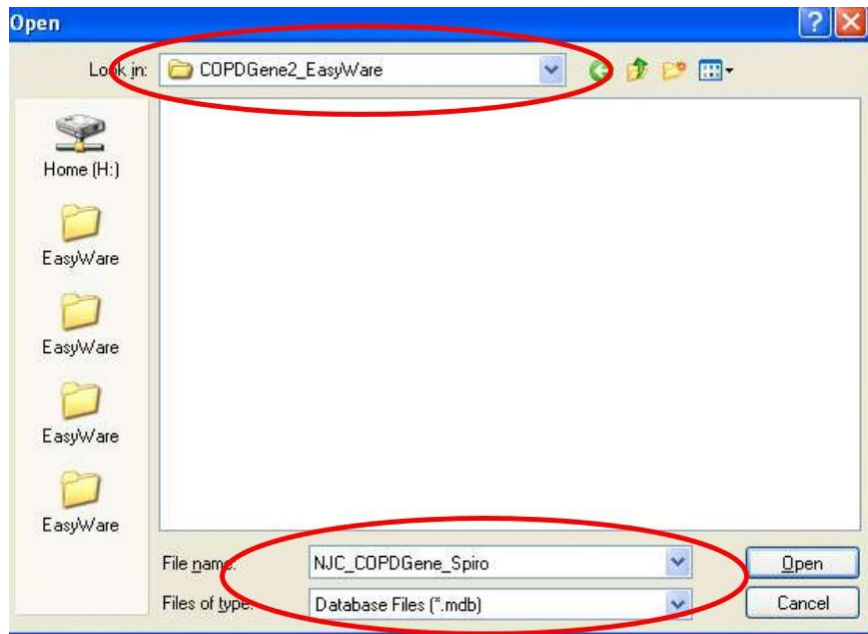


Figure 11-3. Enter File Name: *Centercode_COPDGene_Spiro*

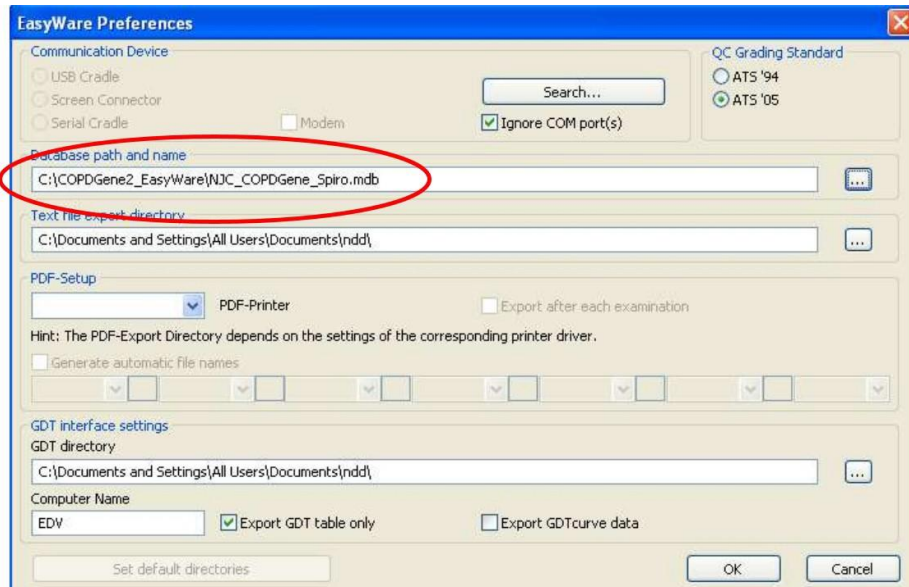


Figure 110-4. New EasyWare Database Master File Location

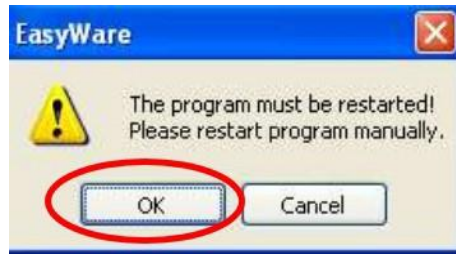


Figure 11-5. EasyWare software will shut itself down when you click “OK”



Figure 11-6. EasyWare recognizes new database name when it is restarted.

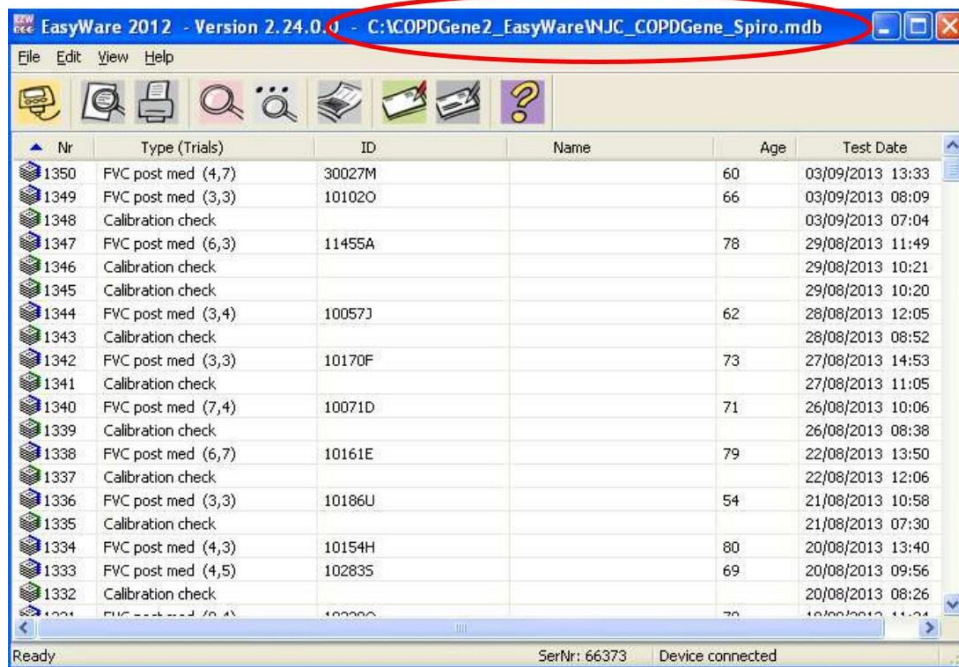


Figure 11-7. New Master Database

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 Figure 7-1. 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.

11g. 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®.

11h. Contraindications

The "Demographics" 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. 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)
- Elevated blood pressure

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.

11i. 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.

11i.1. Safety Checks

Complete the Demographics 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 the Safety Assessment Form.

11i.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.

11i.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. 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 (since DOB is a HIPAA identifier, use the convention 07/01/*subject birth year* when entering the date of birth), height, weight, ethnic category, gender.
 - 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[®].

11i.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.

11i.5. Demonstrate the maneuver

Explain that the participant should:

- Take in as deep a breath as possible
- When his/her lungs are totally full 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.

11i.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.

11i.7. Pre-bronchodilator test

After instructing the participant about the procedure for spirometry testing, proceed with the actual testing, following the procedures outlined in this manual of procedures. 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.

11i.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.*

11i.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.

110i.10. Print results

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

Clinical Centers should give participants a hardcopy printout of their results as per the Phase 3 consent. Clinical Centers are encouraged to provide guidelines for interpreting the results. In Phase 3 subject have the option in the consent to allow these results to be sent to their primary

care provider (with subject consent and IRB approval). Results that are considered to be clinically significant by the local Clinical Center Director will automatically be sent to the subject's primary care provider.

11j. Step by Step Spirometry Instructions

11j.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."

11j.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 (using the convention '07/01/*subject birth year*'), 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 FEV₁ 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.

11j.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.

11j.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.

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.

11j.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.

11j.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 your computer
- b. Go to My Computer
- c. Open the C: Drive
- d. Select the COPDGene2_EZWare Folder
- e. Select the Centercode_COPDGene_Spiro.mbd 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:\COPDGene2_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.

11k. 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.

11l. 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. The official COPDGene[®] dataset will utilize additional prediction equations based on the United States NHANES III equations.

11m. 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.

11m.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.

11n. 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.

11o. Trouble Shooting

Refer to the section 15 of the EasyGuide® Users' Manual for troubleshooting tips.

11p. Add 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!!! > If using an Easy one Plus spirometer, be sure to select "All curves" here

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®

11q. 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: _____

Action		Comments
Calibrate spirometer	<input type="checkbox"/>	
Safety Assessment Form	<input type="checkbox"/>	
Prepare to conduct spirometry	<input type="checkbox"/>	
Confirm race/ethnicity of participant	<input type="checkbox"/>	
Explain purpose of test	<input type="checkbox"/>	
Demonstrate maneuver	<input type="checkbox"/>	
Complete pre-bronchodilator test	<input type="checkbox"/>	
Administer bronchodilator	<input type="checkbox"/>	
Wait 15-40	<input type="checkbox"/>	
Complete post-bronchodilator test	<input type="checkbox"/>	
Print results	<input type="checkbox"/>	

11r. 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 Administrative 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 Administrative 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.

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 FEV₁ 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.

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 themselves. 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.

“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.

EASYONE® 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:



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)

“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.

POWER DOES NOT TURN ON/OFF CORRECTLY

Problem: the device cannot be switched on or off.

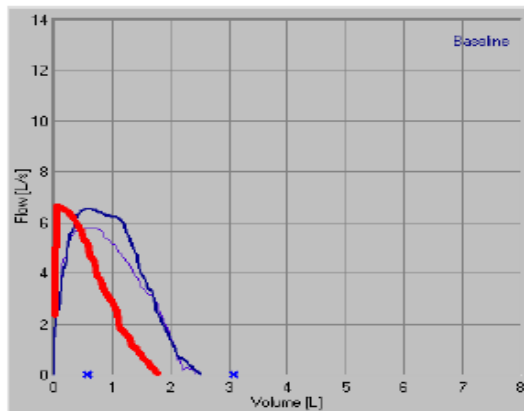
Explanation: ndd has not been able to reproduce this problem, and would appreciate more information in order to properly investigate the issue. If the problem occurs, please supply the following information: does the issue always happen with the same device, how often does it happen, and under what circumstances 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.

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)

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.

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 Administrative 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.

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 Administrative 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.)

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:

1. American Association for Respiratory Care Clinical Practice Guideline: Static lung volumes. *Respir Care* 1994; 41:629-636.
2. Clausen JL, Coates A, Quanjer PH. Measurement of lung volumes in humans: reviews and recommendations from an ATS/ERS workshop. *Eur Respir J* 1997; 10:1205-1206.
3. Coates AL, Reslin R, Rodenstein D, Stocks J. Measurement of lung volumes by plethysmography. *Eur Respir J* 1997; 10:1415-1427.
4. Newth CJ, Enright P, Johnson RL Jr. Multiple-breath nitrogen washout techniques: including measurements with patients on ventilators. *Eur Respir J* 1997;10:2174-2185.
5. American Thoracic Society: Lung function testing: selection of reference values and interpretive strategies. *Am Rev Respir Dis* 1991; 144:1202-1218.

6. Stoller JK, Basheda S, Laskowski D, Goormastic M, McCarthy K. Trial of standard versus modified expiration to achieve end-of-test spirometry criteria. *Am Rev Respir Dis* 1993; 148:275-280.
7. Enright P. Can we relax during spirometry? *Am Rev Respir Dis* 1993; 148:274.

12. Carbon Monoxide Diffusing Capacity (DLco)

12a. 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.

12b. 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.

12c. 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. For the duration of the COVID-19 pandemic, the appropriate filters from ndd should also be available. 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 device does not need calibration by the technician.

12d. 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 below in section 11p. ndd EasyOne[®] Configuration Settings for Use in COPDGene[®]. 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 must 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. The instrument must have been upgraded to software 3.7.1.9 in order to use the filters needed post-COVID-19.

12e. 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 from 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)

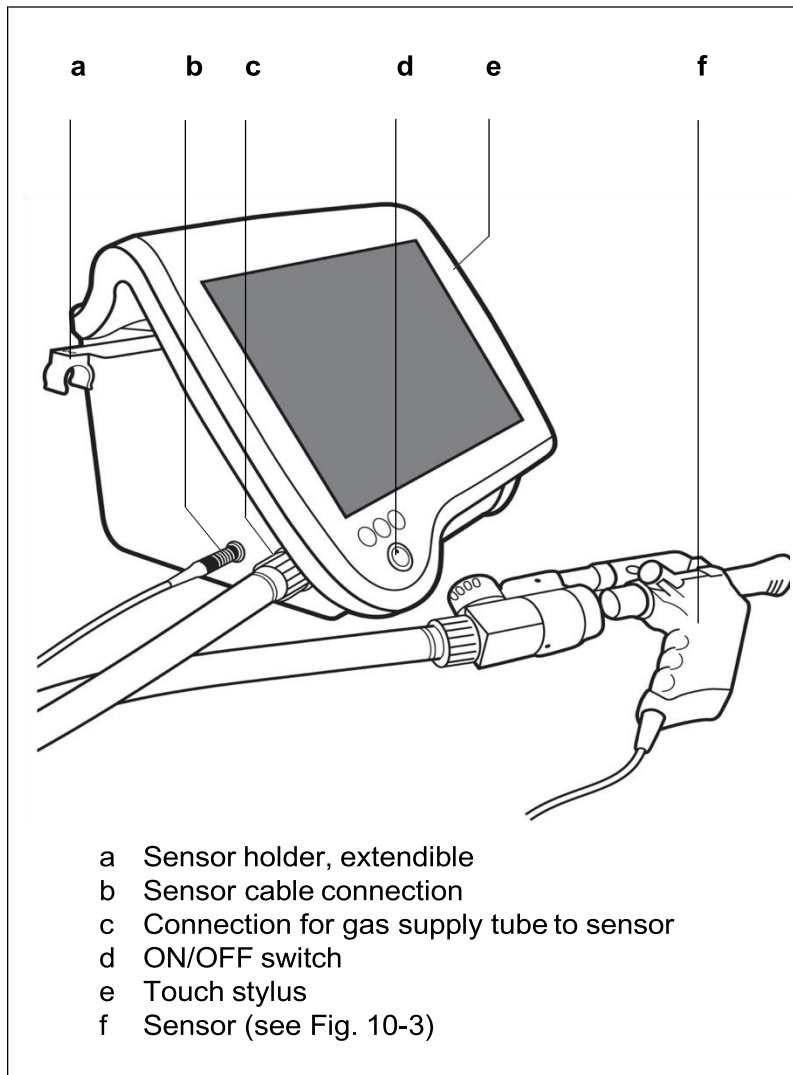


Figure 11-1. EasyOne Pro[®]

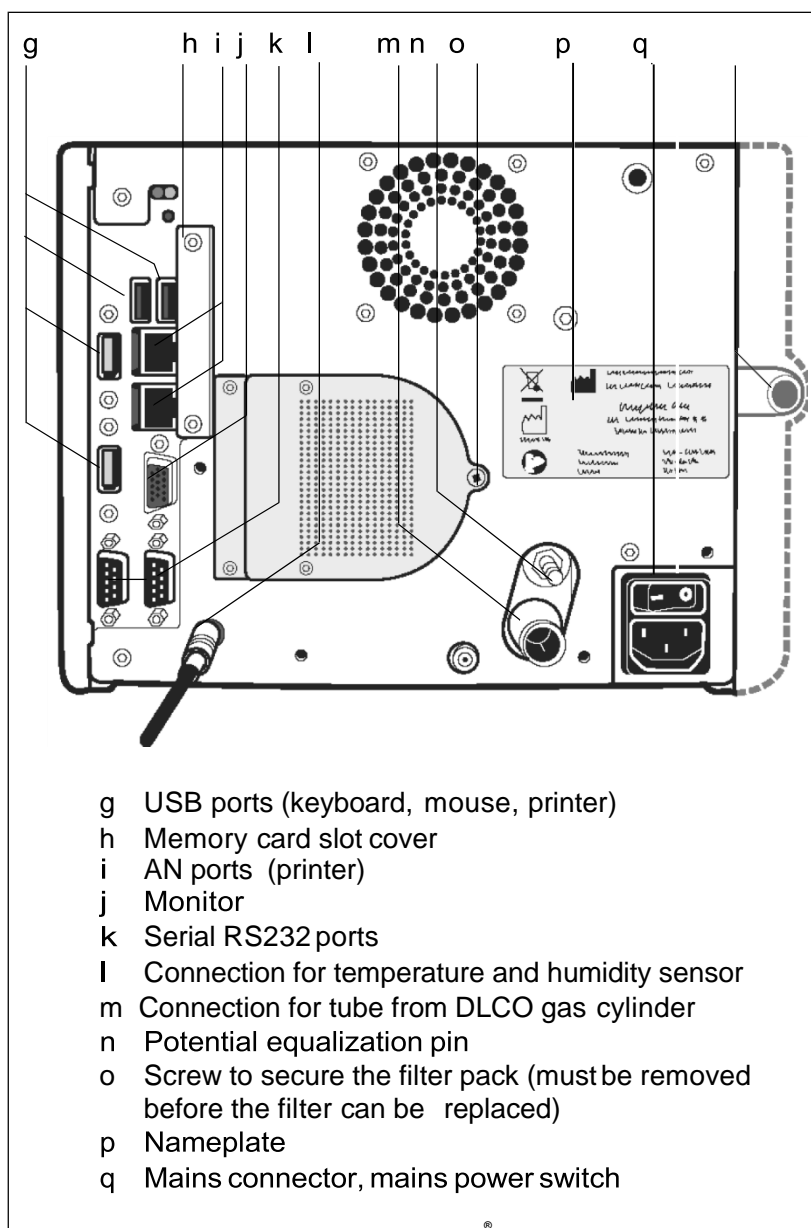


Figure 11-2. EasyOne Pro[®], rear panel

12f. Medication Use Prior to Testing and withholding supplemental O2

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 Medications table in section 7 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 be measured post-bronchodilator. If there are reasons for withholding the bronchodilator, the clinical center should still proceed with conducting the DLco maneuvers unless the clinician indicates there is a safety contraindication.

In subjects using supplemental oxygen, oxygen will be removed and subjects will breathe room air for 10 minutes prior to the test. If resting saturation falls below 82% or the subject becomes dyspneic prior to 10 minutes without oxygen, oxygen therapy will be restarted as a safety precaution and the test will be performed without the ten-minute oxygen washout. To obtain 2 reproducible measures, the test may be repeated up to 5 times.

12g. 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. If bronchodilator is withheld, the clinical center should still proceed with conducting the DLco maneuvers unless the clinician indicates there is a safety contraindication.

12h. Contraindications

The “Demographics” 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 and Spirometry 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.

12i. 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:

<https://www.ndd.ch/en/product/easyone-pro.html#downloads>

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.

12i.1. Safety checks

Complete the Demographics 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.

12i.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 12-3.

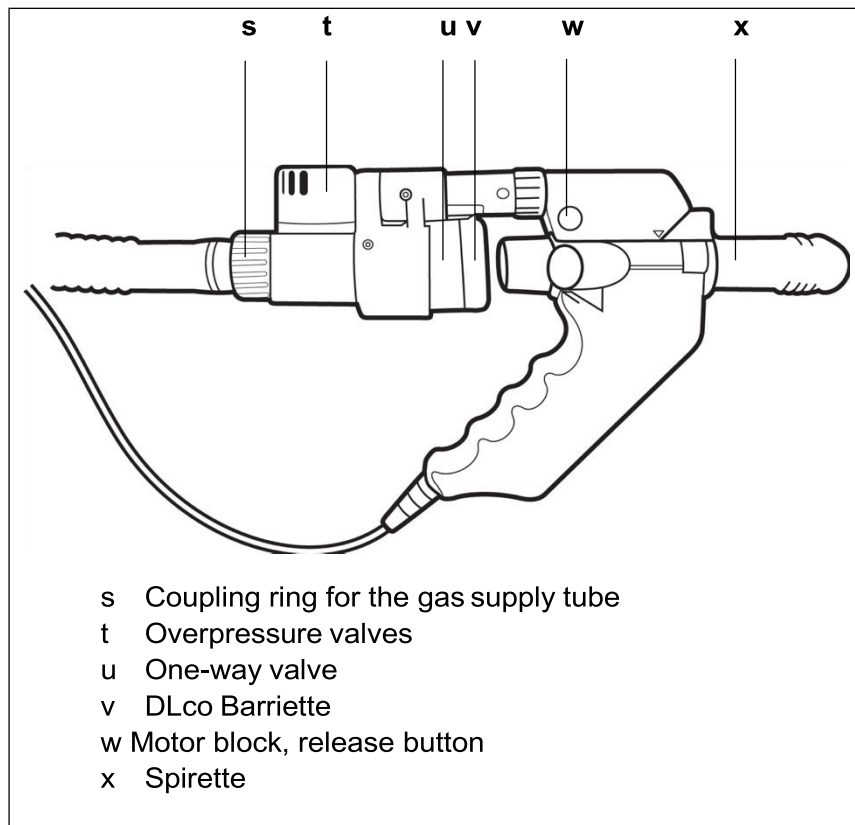
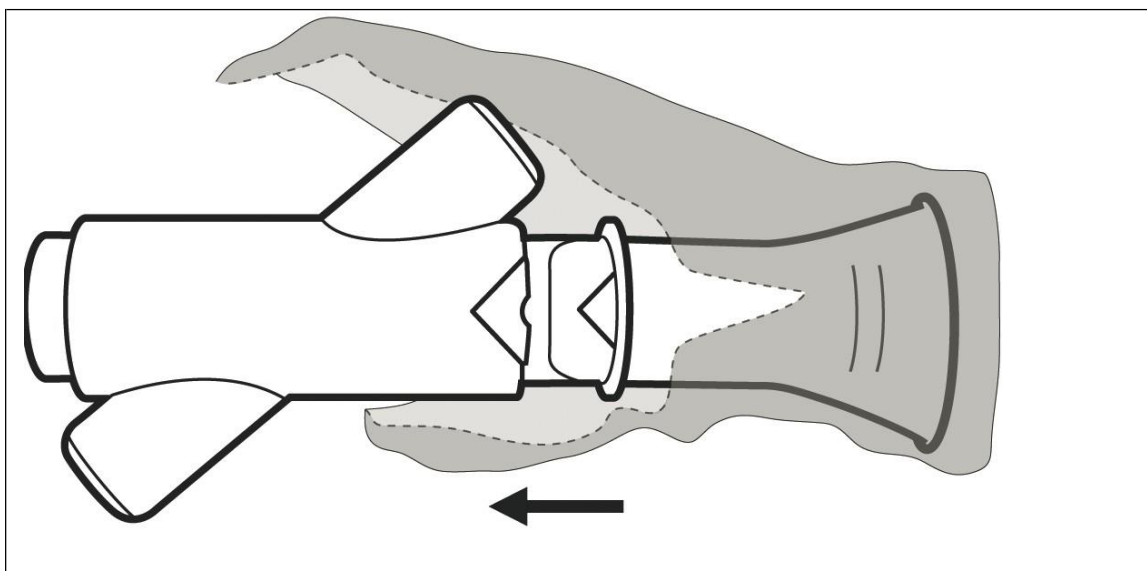


Figure 12-3a. Sensor

Figure 12-3b. Proper orientation of the Spirette



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.

12i.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
 - CAUTION: If you get the message “ID already exists” or “Value not unique”, do NOT use the alternate numeric code instead. This message means that the subject id is already in the list. Search for the id, and start a new test under the existing id. The system is designed to allow multiple tests for one patient.
 - If you are doing a Short-term 1-year visit, you may add a new id with “3B” at the end, like 12345Z3B, or you may use the existing id in the system.
- Do NOT enter patients name, leave “Last name” and “First Name” fields blank.
- Click “a” (Figure 12-4) to select the gender and press the TAB key.
- Also, select the ethnic origin “b”.
- Enter the date of birth (since DOB is a HIPAA identifier, use the convention ‘07/01/*subject actual birth year*’ when entering 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 12-4), History and Comment, tab “c” 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.

a b c

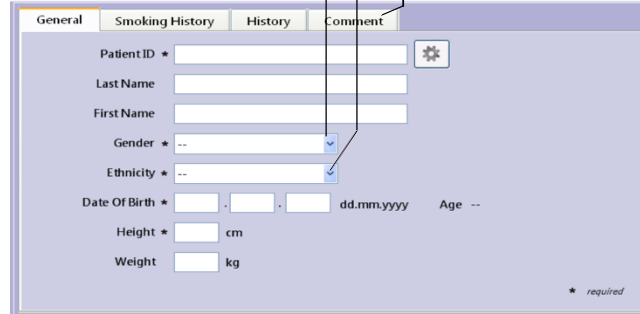


Figure 12-4. Patient data window

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

12i.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.

12i.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 11.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 display (See "Quality Messages and Quality Grades" on page 84 of EasyOne Pro® User Manual)

The slow vital capacity acquisition screen appears as seen below.

Slow Vital Capacity Acquisition Screen

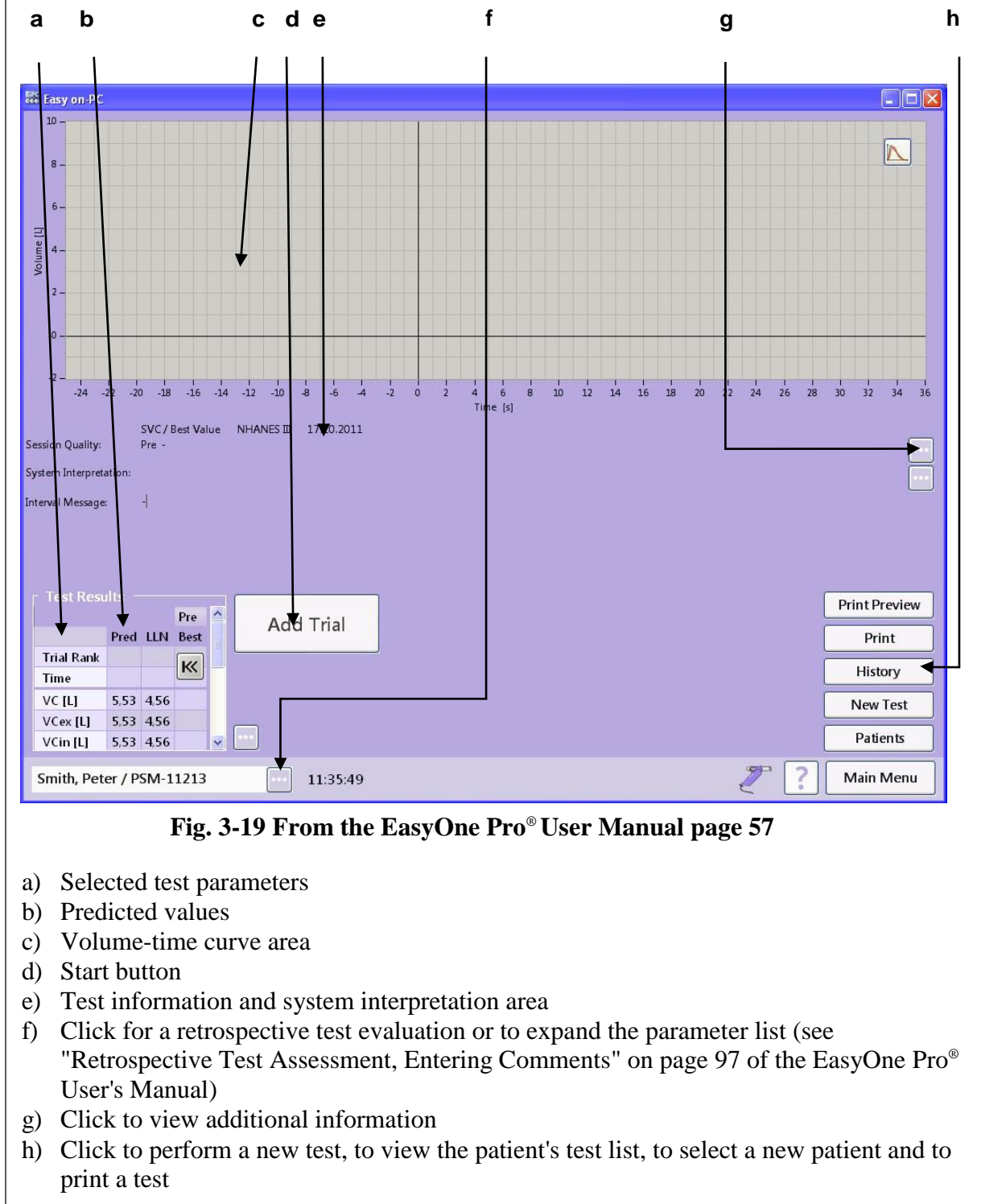
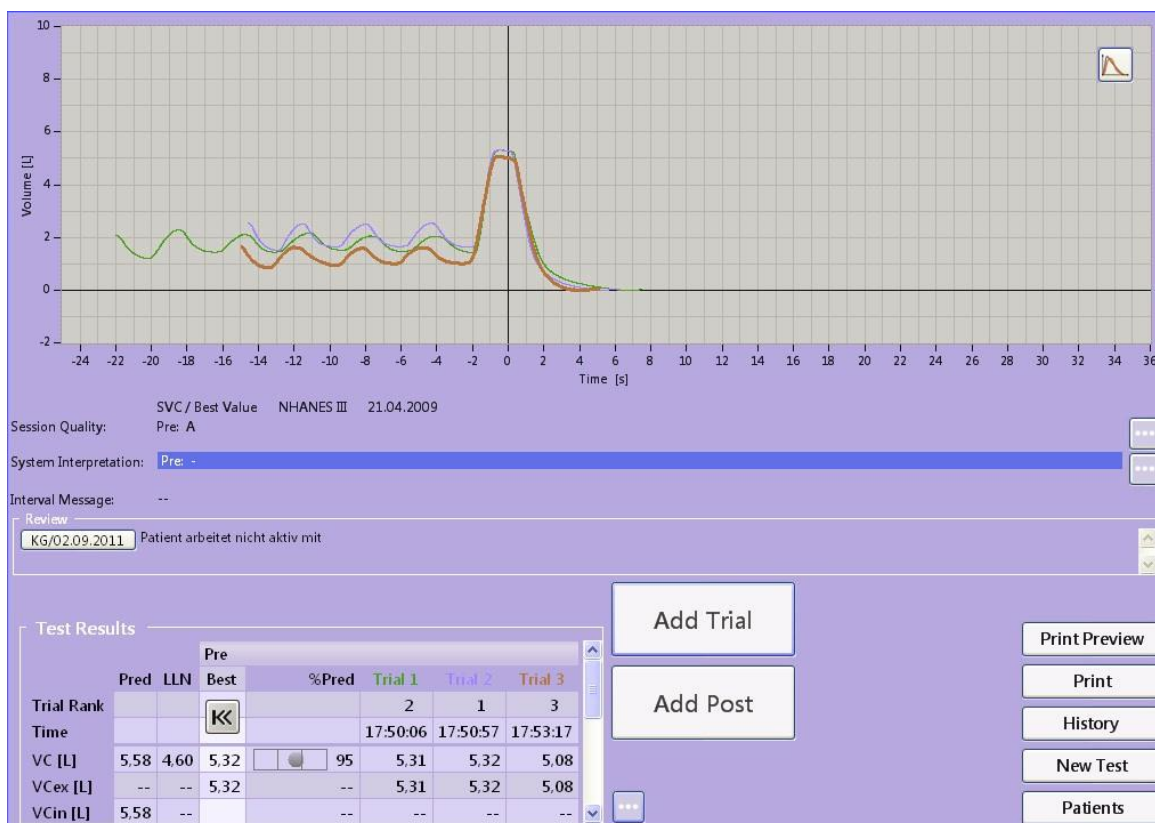


Fig. 3-19 From the EasyOne Pro® User Manual page 57

- 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 EasyOne 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



12i.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.

12i.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.

12i.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

12i.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.

12j. Step by Step DLco Instructions

12j.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 12-1 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 12-1. DLco Quality Grades for a Testing Session						
Score	VI [%]	BHT [s]	Sample Volume [l]	DLco Var. [ml/min/mmHg]	Inspiratory Time [s]	Accept. Trials
A	>90%	9.0 - 11.0	0.5 - 1.0	<1	1.5 - 2.5	>1
B	>85%	8.5 - 11.5	0.5 - 1.0	<2	1.0 - 3.5	>1
C	>80%	8.0 - 12.0	0.5 - 1.0	<3	<4.0	>1
D	>80%	8.0 - 12.0	Outside range	>3	<4.0	>1
F	-	-	-	-	-	-

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:
 - VI (inspiratory volume of DLco test) as a percentage of SVC target
 - BHT: Breath-hold time in seconds
 - DLco variability in absolute values
 - Inspiratory time in seconds
 - 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)

12j.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.

12j.3. Export Patient Data from DLco device to Flash Drive

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, 8005 (EasyOne Pro[®]) This password is case sensitive and should be entered in all capital letters.
- d. Select *Login*
- e. Choose the “Export Data” button; do not use the “Export EasyWare” button.



- 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.

12j.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.sqlite file (see Figure 12-5)
- c. File->Copy
- d. File->Paste
- e. Select the Copy
- f. File-> Rename
- g. Rename this file to: *Centercode_COPDGene_DLco_MM_DD_YYYY.sqlite*
- 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 (KnowlesR@NJHealth.org) at the DCC.
- j. On the left panel, click on “PFT Files.”
- k. Log into the website again.
- l. Click on the **files** 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 sqlite file you just 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.

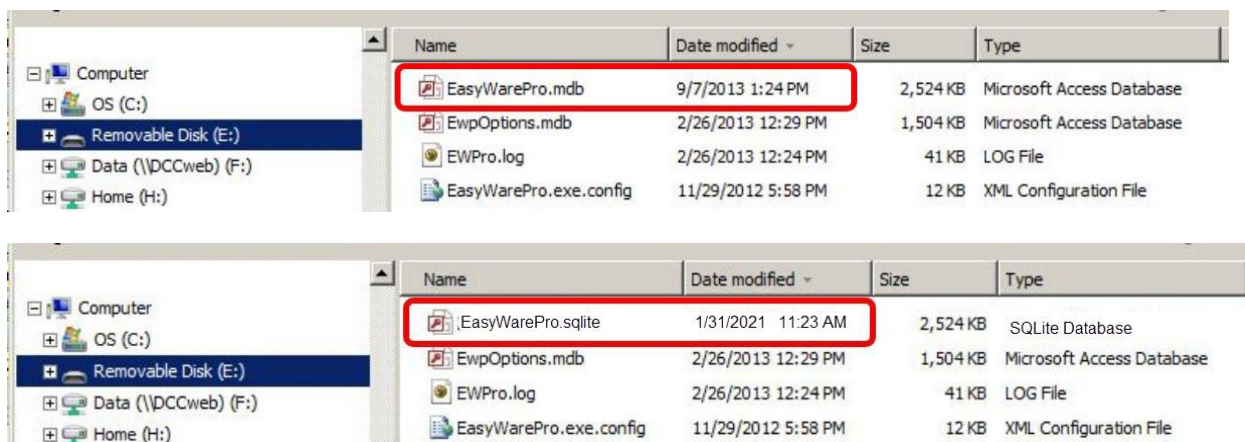


Figure 12-5. Removable Flash Drive with DLco EasyWarePro.sqlite master file

12k. 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.

12l. 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[®] Administrative Center will create local prediction equations based on healthy never smokers at that site.

12m. 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.

12m.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 from 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.

12n. 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.

12o. Trouble Shooting

Refer to the section 9 of the EasyOne Pro[®] Operator Manual for troubleshooting tips.

12p. Add 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 ProTM 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.

12q. DLco Checklist

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

Subject Identification Number: _____ Test Date: _____

Action		Comments
Safety Assessment Form administered	<input type="checkbox"/>	
Prepare to conduct DLco	<input type="checkbox"/>	
Confirm race/ethnicity of participant	<input type="checkbox"/>	
Explain purpose of test	<input type="checkbox"/>	
Demonstrate maneuver	<input type="checkbox"/>	
Perform 2 to 5 additional DLco tests and wait 4 minutes between each test	<input type="checkbox"/>	
Print results	<input type="checkbox"/>	

12r. 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:

1. American Association for Respiratory Care Clinical Practice Guideline: Static lung volumes. Respir Care 1994; 41:629-636.
2. Clausen JL, Coates A, Quanjer PH. Measurement of lung volumes in humans: reviews and recommendations from an ATS/ERS workshop. Eur Respir J 1997; 10:1205-1206.
3. Coates AL, Reslin R, Rodenstein D, Stocks J. Measurement of lung volumes by plethysmography. Eur Respir J 1997; 10:1415-1427.

4. Newth CJ, Enright P, Johnson RL Jr. Multiple-breath nitrogen washout techniques: including measurements with patients on ventilators. *Eur Respir J* 1997; 10:2174-2185.
5. American Thoracic Society: Lung function testing: selection of reference values and interpretive strategies. *Am Rev Respir Dis* 1991; 144:1202-1218.
6. Stoller JK, Basheda S, Laskowski D, Goormastic M, McCarthy K. Trial of standard versus modified expiration to achieve end-of-test spirometry criteria. *Am Rev Respir Dis* 1993; 148:275-280.
7. Enright P. Can we relax during spirometry? *Am Rev Respir Dis* 1993; 148:274.
8. MacIntyre N, Crapo RO, Viegi G, Johnson DC for the ATS/ERS Standardization of Lung Function Task Force. Standardization of the single breath determination of carbon monoxide uptake in the lung. *Eur Resp J* 2005; 26:720-725.

13. 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.

13a. 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 > 170 mmHg or resting diastolic blood pressure > 100 mmHg)
- Resting bradycardia (< 50 beats/min), history of complex ventricular arrhythmia or sustained SVT
- Use of > 6 L/min oxygen flow with activity

13b. 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

13c. 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 previous COPDGene® visits. 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.

13d. 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 Six-Minute Walk walk test.

13e. 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.

13f. 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?”

13g. 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.

13h. 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 Six-Minute Walk 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, you must still complete the 6MW Test form in REDCap. There is an option on the REDCap form to select “No, safety concern noted on safety form” for the question “Did the subject attempt the Six-Minute walk?” Under that same question, there are also options to indicate instances when the subject refuses the test without a safety concern, or the subject is non-ambulatory.

Did the subject attempt the 6-minute walk?
* must provide value

Yes
 No, safety concern noted on Safety form
 No, non-ambulatory
 No, subject refused, no safety concern

reset

Figure 13-1: This question is found in the Six-Minute Walk walk form and allows the coordinator to indicate whether or not the subject completed the test, and if not for what reason.

13i. 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

14. Phase 3 Hierarchy Preference

In line with the study goal of maximizing the total number of return subjects, options have been added to the protocol to get subjects seen for Phase 3 even if the subject cannot return to the Clinical Center where he/she was seen for Phase 1 or Phase 2. Despite the addition of these options, it is ultimately preferred to have a subject return to the Clinical Center where he/she was previously seen. Other options should be exercised only in cases where the subject is unwilling or unable to come to the Clinical Center. 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. IRB approval must be granted to utilize these other options (this was included in Phase 2 IRB documents). 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 3. A full Phase 3 visit at the Clinical Center a subject was seen previously 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. These options are not applicable for enrollment of new nonsmoker control subjects.



Figure 14-1 illustrates the order of preference of procedures in the event that a subject cannot return to the Clinical Center for their Phase 3 visit. As a general principle, a full Phase 3 visit at the Clinical Center is preferred.

14a. Subject has moved and is closer to a different Clinical Center for Phase 3

In the event that a 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 Phase 3 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.

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



Figure 14-2. Map of COPDGene® Centers in United States

14a.1. Procedure

The Clinical Center where subject was seen for their previous visit will ask the subject for verbal approval to send their name and contact information to the new Clinical Center. Once the subject’s verbal approval is obtained, the Clinical Center from the previous visit should complete the web-based COPDGene® Subject Referral Form. The form includes the Subject ID, Interviewer, date, previous Clinical center where subject was seen, this phase 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.

14a.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 then they were previously seen, 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 original 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.)

If the new Clinical Center does not confirm the transfer, the subject will remain a subject of the originating center.

14b. Subject Travel Reimbursement

There may be times when a subject is unable to travel to a clinical center. For instance, in times of financial hardship, having moved further from the clinical center, or loss of transportation means. In these cases, when IRB approved the Clinical Center may offer reimbursement for travel expenses incurred. Each case over \$100 must receive prior approval from the COPDGene® Administrative Core.

There are two ways to handle this reimbursement:

1) The subject pays for the expense and COPDGene will reimburse the subject directly. The subject will need to fill out the Travel Reimbursement Form (https://dccweb.njhealth.org/sec/COPDgene/Forms/eForms/COPDGene_ExpenseForm_Subject_Travel_Reimbursement.doc) and sign it and provide a W9. We reimburse at the end of each quarter, so best practice is to subjects at the end of a quarter (but also allow enough time to send all receipts with accompanying form and W9 to the Admin Core before the end of the quarter).

2) The clinical center pays for the expense and COPDGene reimburses the clinical center. This is the preferred method. We only require the receipts and travel form (https://dccweb.njhealth.org/sec/COPDgene/Forms/eForms/COPDGene_ExpenseForm_Subject_Travel_Reimbursement.doc) but it does not have to be signed by the center or subject.

The center should make efforts to reimburse the subject from their funds (#2 above), and the Administrative Core will later reimburse the center.

All reimbursements will be made on a quarterly basis.

The guidelines for reimbursement follow in the table below. These are approximations and may be modified with approval from the COPDGene® Administrative Core and the center IRB.

Subjects who must travel a substantial distance to return to the Clinical Center	
Car Travel to the Clinical Center (at IRS yearly rate)	Up to \$200 round trip
Plane Fare	Up to \$500 round trip
Tolls	With receipts
Hotel Lodging	Up to \$150 per night (maximum of 2 nights)
Meals	Up to \$50 per day (maximum of 2 days)

14c. Home Visit

The home visit should be considered an option to get the subject seen for the Phase 3 Visit. 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
- Sit-to-Stand
- Hand grip strength
- Please see Appendix A, Part 1 – Home Visit Preparation Checklist and Appendix A, Part 2 – Home Visit Procedures Checklist for further details.

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.

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 14-3).

The screenshot shows a web form with two sections. The first section is titled "Phase 3 Screener status" and has a red asterisk with the text "must provide value". It contains two radio button options: "Preliminary" (unselected) and "Final" (selected). The second section is titled "Final: What type of visit is the subject doing for Phase 3?" and also has a red asterisk with "must provide value". It contains three radio button options: "On-site" (unselected), "Home" (selected), and "Phone" (unselected). Both sections have a "reset" link in the bottom right corner.

Figure 14-3. Screen shot from final screening form.

Clinical centers should have site Standard Operating Procedures to follow when conducting home visits.

14c. Completing Questionnaires with subject over the phone

If the subject cannot do a phase 3 clinical center visit, a home visit is preferred prior to completing all Questionnaires over the phone. If that is not possible the coordinator should proceed with asking the subject the questionnaires over the phone.

When you have the subject on the phone, be sure to review and update their contact information.

In Phase 2, IRB approval was requested (around April 2014) 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. Clinical centers should also have made a submission to their IRB to compensate each subject that completes the questionnaires over the phone \$25 for their time.

Clinical centers will be compensated \$200 for completing all questionnaires over the phone per subject.

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, so data is not lost. Later the forms will be entered into REDCap under the correct subject ID. 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 subject's personal information.

- 1) Final Screener (ensure to select 'phone' for Question 9)

The screenshot shows two sections of a form. The first section is titled "Phase 3 Screener status" and has a red asterisk indicating it is a required field. It contains two radio button options: "Preliminary" (unselected) and "Final" (selected). The second section is titled "Final: What type of visit is the subject doing for Phase 3?" and also has a red asterisk. It contains three radio button options: "On-site" (unselected), "Home" (unselected), and "Phone" (selected). Both sections have a "reset" link on the right side.

Figure 14-4. Screen shot from final screening form.

- 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) CAPTURE
- 10) PROactive
- 11) DASIS
- 12) Residential and Occupational History
- 13) Optimism Questions

14d. 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 3 visit, to have a home visit, to answer the questionnaires over the phone, or to participate in additional follow up. Subjects who request withdrawal should also be asked if they are willing to complete this questionnaire prior to discontinuation. The purpose of the Limited Follow-Up Questionnaire is to gather longitudinal information on the subject related to respiratory symptoms, exacerbations, and comorbidities.

14e. Waiver of Informed Consent

In later October 2018, a waiver of consent summary was sent to each Clinical Center. The Phase 1 consent allowed subjects to be contacted for *up to 10 years*. If subjects were not brought back in Phase 2, then this 10 year Phase 1 anniversary date is about to occur. All clinical centers are asked to submit this waiver so that these subjects can continue to be contacted regarding future phases of COPDGene.

Appendix A, Part 1: Home Visit Preparation Checklist

<input type="checkbox"/>	Complete preliminary screening online in REDCap at time of scheduling and also 24 hours before the visit to re-confirm eligibility
<input type="checkbox"/>	Prepare a folder with ICF (2 copies), all forms and questionnaires
<input type="checkbox"/>	Laptop and charger (for conducting spirometry)
<input type="checkbox"/>	Measuring tapes (steel and sewing)
<input type="checkbox"/>	Portable scale for collecting weight
<input type="checkbox"/>	Blood pressure equipment with extra cuff sizes
<input type="checkbox"/>	Pulse oximeter
<input type="checkbox"/>	Blue tape for measuring arm span and height
<input type="checkbox"/>	Pens, extra paper for notes
<input type="checkbox"/>	Clipboard
<input type="checkbox"/>	Dynamometer
<input type="checkbox"/>	Spirometer and screen connector (extra batteries)
<input type="checkbox"/>	Spirettes
<input type="checkbox"/>	Nose clips
<input type="checkbox"/>	Albuterol and Aerochamber
<input type="checkbox"/>	Blood draw supplies: Gloves, tourniquet, needle, alcohol wipe, gauze, band-aid
<input type="checkbox"/>	Blood draw collection kit from Channing Lab
<input type="checkbox"/>	Blood tube rack
<input type="checkbox"/>	Cooler and ice pack for blood transport
<input type="checkbox"/>	Transportable sharps container

Appendix A, Part 2: Home Visit Procedures Checklist

<input type="checkbox"/>	Informed Consent/HIPAA completion
<input type="checkbox"/>	Complete final screening form when present with subject
<input type="checkbox"/>	ICF/Permissions Granted Form
<input type="checkbox"/>	Demographics/Physical Characteristics Form
<input type="checkbox"/>	Subject Personal Information Form
<input type="checkbox"/>	Safety Assessment Form
<input type="checkbox"/>	Spirometry Form
<input type="checkbox"/>	Pre-BD Spirometry
<input type="checkbox"/>	Administer Albuterol, wait 15-20 minutes (but not more than 40)- can administer some of the quesitonnaires below now
<input type="checkbox"/>	Post-BD Spirometry
<input type="checkbox"/>	Hand grip strength
<input type="checkbox"/>	Medication History
<input type="checkbox"/>	Medical History
<input type="checkbox"/>	Respiratory Disease
<input type="checkbox"/>	Capture
<input type="checkbox"/>	COPD Assessment Test (CAT)
<input type="checkbox"/>	SF-36
<input type="checkbox"/>	SGRQ
<input type="checkbox"/>	HADS
<input type="checkbox"/>	Socioeconomic
<input type="checkbox"/>	eCigarette and Cannabis Use
<input type="checkbox"/>	PROactive
<input type="checkbox"/>	DASI
<input type="checkbox"/>	Cognitive Screening Items
<input type="checkbox"/>	Sit-to-Stand
<input type="checkbox"/>	Residential and Occupational History
<input type="checkbox"/>	Blood Sample Collection (The PAXgene tubes are both suitable for home visits (DNA and RNA), but it would not be optimal for plasma or serum (unless there were a portable centrifuge).
Post Visit	
<input type="checkbox"/>	Deliver CBC to local lab
<input type="checkbox"/>	Process Blood
<input type="checkbox"/>	Enter Quesitonnaires in REDCap
<input type="checkbox"/>	Upload Spirometry Data
<input type="checkbox"/>	Clinically Significant Findings Form
<input type="checkbox"/>	If applicable, mail subject/physician copies of records
Notes	

15. Traveling Research Team

The COPDGene® Administrative Core has assembled a traveling research team to help Clinical Centers complete study related work. Research Coordinators will be hired and paid by the Administrative Core. These coordinators will be trained on the study protocol and can travel to centers to help out with any aspect of the study. The coordinators can also help each center remotely as IRB regulations allow. Centers should work with the COPDGene® Project Manager to obtain information on getting help from a traveling coordinator. In the beginning of Phase 3, traveling coordinators will be traveling to each site to review site facilities (including but not limited to the exam rooms, radiology, lab, source document location, Six-Minute Walk course, etc.) The sites will be sent an agenda prior to the visit.

16. Mail Consent

All Clinical Centers should have obtained 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) in Phase 2.

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 3 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.

17. How to Talk to A Subject about a CT Scan

17a. Purpose

Provide instructions on how to speak with subjects who are unsure or hesitant of getting a CT scan due to fear, lack of understanding, and a previous scan close to the time of their visit.

If the subject still refuses a scan after their concerns have been addressed, contact the site PI.

17b. Prepare for the upcoming scan

To decrease the likelihood of a subject withdrawing from a CT scan, blood test or other procedure at the time of their visit, study visit procedures should be discussed with the subjects on the phone during their pre-screen.

Below are frequently asked questions or concerns about the chest CT scan. If a question/concern arises, coordinators should be ready to help the subject understand the procedure and minimize any fear or anxiety. If the subject refuses any study procedure, ask your physician investigator to speak to the subject.

17c. Subject had a recent CT scan prior to the visit

If a subject had a recent clinical CT scan, and is concerned with the short time between the two scans:

- Explain to the subject that there is no known increased risk of having 2 or more CT scans performed within a short period of time. The time between the scans does not increase that person's risk of exposure to radiation, above the known risk associated with a CT scan.
- Risk of radiation is calculated by lifetime cumulative exposure. So having one scan performed 2 days in a row has a similar risk as having 2 scans one year apart. It is the total number of scans over a lifetime that influences the risk of exposure to radiation.
- If a subject would prefer to postpone the entire visit for a later time, set a follow-up date as soon as convenient with this subject and complete the visit at a later date.

17d. Concern with the amount of radiation

If a subject is concerned with the exposure to radiation, it may be helpful to remind this subject that:

- Your local review board, and 19 others around the country, reviewed and approved the CT scan as part of the COPDGene[®] Study. This means that the potential risk of participating in this study is balanced against the gain of valuable information for the study. In addition, for many of our subjects with a heavy smoking exposure, they are at an increased risk of developing lung cancer. By having the scan they may have an early finding identified that can be treated.

18. Imaging

18a. 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 approximately 5 years later for Phase 2. For phase 3, the scans will be performed using a reduced dose protocol. Whenever possible, subjects who return for a follow-up visit will be scanned on the same CT scanner used for the phase 2 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.

18b. 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 3. This was distributed via a REDCap survey prior to the Phase 3 start.
- 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 3, 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 Acquisition 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 3.

STEP 3: DICOM Send Software

- 1) The DICOM send software de-identifies subject CT scans and transfers CT images from the clinical centers to the Imaging Core.
- 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 (3.0 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 and transfer to the Imaging Core using the DICOM Send software. In the rare event a scan needs to be burned to DVD and shipped to the Imaging Core, please use the following address.

Quantitative Imaging Laboratory – COPDGene[®] Study National Jewish Health
1400 Jackson St., K012H Denver, CO 80206


Fed Ex account number: 0802-2670-5

- 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 and will be sent to the Imaging Core using the DICOM Send software.

18c. CT Scan Parameters for Visit 3

- 1) The CT Acquisition form is accessed through the COPDGene® website.
- 2) The report may be printed from the Data Management section. Enter the subject id into the box under Review Data Records and click on the “CT Acquisition” link to generate the CT Acquisition form, customized for each subject (Figure 17-1).

Review Data Records



The screenshot shows a light green header bar. On the left, the word "Subject" is written in red and underlined. To its right, the text "Review Phase1/Phase2 data on subject:" is displayed in a dark red font. Next to this text is a white input box containing the subject ID "99999N". To the right of the input box, the text "CT Acquisition" is written in red and underlined, serving as a link.

Figure 18-1

- 3) For subjects who participated in Phase 1 or Phase 2 of the study, the report identifies the CT scanner to be used for each subject’s Phase 3 scan (Figures 17-2 and 17-2). The report provides the CT protocol settings to use and recommended DFOV and reconstruction kernel instructions based on the previous visit CT scan settings. The DFOV 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. DFOV is the same for inspiratory and expiratory scans and for each reconstruction.
- 4) CT acquisition date, CTDIvol for inspiratory and expiratory scans, and the CT technologist name should be recorded on the form at the time of CT acquisition.

COPDGene Phase 3 CT Acquisition Form

Subject ID [REDACTED]						
Scanner to be used:						
Scanner ID	Scanner			Scanner Location		
NJC02	Siemens SOMATOM Definition			A344		
Acquisition Parameters:						
Effort	Pitch	kVp	Exposure	Slice Thickness	Interval	Protocol Details
1. Insp Low-dose	1.0	120	Modulated Ref 35 mAs	0.75	0.5	Care Dose ON Rotation rate: 0.33 s
2. Expiratory	1.0	120	50 mAs	0.75	0.5	Care Dose OFF
Reconstruction Parameters:						
Effort	Recon	Kernel	Target DFOV* (cm)	Notes		
1. Insp Low	Low1	B31f	31.6 cm			
1. Insp Low	Low2	B45f	31.6 cm			
2. Exp	Recon 1	B31f	31.6 cm			
2. Exp	Recon 2	B45f	31.6 cm			

*Lung at maximum width plus 1 cm on each side.

Phase 3 Scan - Information below to be filled out by CT Technologist			
COPDGene Subject Id	[REDACTED]		
CT Acquisition Date	[REDACTED]		mm/dd/yyyy
CT Dose Index (CTDI) (mGy)	Insp Low	[REDACTED]	Exp [REDACTED]
Imaging Technologist	[REDACTED]		

Baseline Scan:	[REDACTED]/2008
Phase 2 Scan:	[REDACTED]/2013
Site Coordinator: Please record on CT Assessment form before delivering to radiologist.	

Figure 18-2. COPDGene® Phase 3 CT Acquisition Form – No Iterative Reconstructions

COPDGene Phase 3 CT Acquisition Form

Subject ID [REDACTED]						
Scanner to be used:						
Scanner ID	Scanner			Scanner Location		
NJC04	Siemens SOMATOM Definition AS+			A342 Smith		
Acquisition Parameters:						
Effort	Pitch	kVp	Exposure	Slice Thickness	Interval	Protocol Details
1. Insp Low-dose	1.0	120	Modulated Ref 35 mAs	0.75	0.5	Care Dose ON Rotation rate: 0.3 s
2. Expiratory	1.0	120	50 mAs	0.75	0.5	Care Dose OFF
Reconstruction Parameters:						
Effort	Recon	Kernel	Target DFOV* (cm)	Notes		
1. Insp Low	Low1	B31f	31.6 cm			
1. Insp Low	Low2	B45f	31.6 cm			
1. Insp Low	Low3i	I31f SAFIRE-2	31.6 cm	Iterative Recon: SAFIRE setting: 2		
1. Insp Low	Low4i	I31f SAFIRE-5	31.6 cm	Iterative Recon: SAFIRE setting: 5		
2. Exp	Recon 1	B31f	31.6 cm			
2. Exp	Recon 2	B45f	31.6 cm			

*Lung at maximum width plus 1 cm on each side.

Phase 3 Scan - Information below to be filled out by CT Technologist			
COPDGene Subject Id	[REDACTED]		
CT Acquisition Date	[REDACTED]	mm/dd/yyyy	
CT Dose Index (CTDI) (mGy)	Insp Low	[REDACTED]	Exp [REDACTED]
Imaging Technologist	[REDACTED]		

Baseline Scan:	[REDACTED]/2008
Phase 2 Scan:	[REDACTED]/2013
Site Coordinator: Please record on CT Assessment form before delivering to radiologist.	

Figure 18-3. COPDGene® Phase 3 CT Acquisition Form – Iterative Reconstructions

18d. 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:

General Electric		Philips		Siemens
Expiration Standard		Expiration B		Expiration B31f
Expiration Bone		Expiration D		Expiration B45f
Insp Lowdose STD		Insp Lowdose B		Insp Lowdose B31f
Insp Lowdose BONE		Insp Lowdose D		Insp Lowdose B45f
Insp Lowdose STD ASIR 40		Insp Lowdose B i3		Insp Lowdose i31f2
Insp Lowdose STD ASIR 100		Insp Lowdose B i6		Insp Lowdose i31f5

18e. 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.

18f. 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 R's.

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 3 as a reference guide during scanning.
3. **Right Scan Protocol:** Check that the correct CT scan parameters are selected for COPDGene[®] Phase 3.

18g. CT Breathing instructions

These are the instructions to be given by the Technologists at the time of scanning. Appendix D has been provided as a quick print guide for CT scanning instructions.

* 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 INSPIRATION:

Instruct the patient to breathe as follows:

“For the second part of this 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 third 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!”

18h. CT Scanning Protocol

3.0 CT Scanning Protocol	Inspiratory Lowdose	Expiratory	Inspiratory Lowdose	Expiratory	Inspiratory Lowdose	Expiratory
Scanner Make	GE	GE	GE	GE	GE	GE
Scanner Model	VCT 64	VCT 64	Discovery CT 750 HD 64	Discovery 750 HD 64	Revolution 256	Revolution 256
Scan Type	Helical	Helical	Helical	Helical	Helical	Helical
Scan FOV	Large	Large	Large	Large	Large	Large
Rotation Time (s)	0.5	0.5	0.5	0.5	0.5	0.5
Det. Configuration	64 x 0.625	64 x 0.625	64 x 0.625	64 x 0.625	64 x 0.625	64 x 0.625
Pitch	0.984	0.984	0.984	0.984	0.992	0.992
kVp	120	120	120	120	120	120
mA Setting		100		100		100
Dose Modulation	Auto-mA, Smart-mA ON	Auto-mA OFF	Auto-mA, Smart-mA ON	Auto-mA OFF	Auto-mA, Smart-mA ON	Auto-mA OFF
HD Mode	OFF	OFF	OFF	OFF	OFF	OFF
Target noise index	NI=66.5		NI=66.5		NI=50.6	
Max mA limit	100		100		100	
Scan Time(s) 30cm Length	<10	<10	<10	<10	<10	<10
Additional Image Filters	No Selection	No Selection	No Selection	No Selection	No Selection	No Selection
Thickness (mm)	0.625	0.625	0.625	0.625	0.625	0.625
Interval (mm)	0.5	0.5	0.5	0.5	0.5	0.5
Iterative Reconstruction (Noise Reduction)	per recon	ASIR OFF	per recon	ASIR OFF	per recon	ASIR OFF
Recon Mode	plus		plus		plus	
Reconstructions						
Insp Low 1	Standard		Standard		Standard	
Insp Low 2	Bone		Bone		Bone	
Insp Low 3i	Standard ASIR 40%		Standard ASIR 40%		Standard ASIR 40%	
Insp Low 4i	Standard ASIR 100%		Standard ASIR 100%		Standard ASIR 100%	
Exp Recon 1		Standard		Standard		Standard
Exp Recon 2		Bone		Bone		Bone
DFOV	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. DFOV is the same for all inspiratory and expiratory reconstructions. Guidance may be provided on the CT acquisition form.					

3.0 CT Scanning Protocol	Inspiratory Lowdose	Expiratory	Inspiratory Lowdose	Expiratory	Inspiratory Lowdose	Expiratory
Scanner Make	GE	GE	GE	GE	GE	GE
Scanner Model	VCT 64	VCT 64	Discovery CT 750 HD 64	Discovery 750 HD 64	Revolution 256	Revolution 256
Scan Type	Helical	Helical	Helical	Helical	Helical	Helical
Scan FOV	Large	Large	Large	Large	Large	Large
Rotation Time (s)	0.5	0.5	0.5	0.5	0.5	0.5
Det. Configuration	64 x 0.625	64 x 0.625	64 x 0.625	64 x 0.625	64 x 0.625	64 x 0.625
Pitch	0.984	0.984	0.984	0.984	0.992	0.992
kVp	120	120	120	120	120	120
mA Setting		100		100		100
Dose Modulation	Auto-mA, Smart-mA ON	Auto-mA OFF	Auto-mA, Smart-mA ON	Auto-mA OFF	Auto-mA, Smart-mA ON	Auto-mA OFF
HD Mode	OFF	OFF	OFF	OFF	OFF	OFF
Target noise index	NI=66.5		NI=66.5		NI=50.6	
Max mA limit	100		100		100	
Scan Time(s) 30cm Length	<10	<10	<10	<10	<10	<10
Additional Image Filters	No Selection	No Selection	No Selection	No Selection	No Selection	No Selection
Thickness (mm)	0.625	0.625	0.625	0.625	0.625	0.625
Interval (mm)	0.5	0.5	0.5	0.5	0.5	0.5
Iterative Reconstruction (Noise Reduction)	per recon	ASIR OFF	per recon	ASIR OFF	per recon	ASIR OFF
Recon Mode	plus		plus		plus	
Reconstructions						
Insp Low 1	Standard		Standard		Standard	
Insp Low 2	Bone		Bone		Bone	
Insp Low 3i	Standard ASIR 40%		Standard ASIR 40%		Standard ASIR 40%	
Insp Low 4i	Standard ASIR 100%		Standard ASIR 100%		Standard ASIR 100%	
Exp Recon 1		Standard		Standard		Standard
Exp Recon 2		Bone		Bone		Bone
DFOV	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. DFOV is the same for all inspiratory and expiratory reconstructions. Guidance may be provided on the CT acquisition form.					

3.0 CT Scanning Protocol	Inspiratory Lowdose	Expiratory
Scanner Make	Philips	Philips
Scanner Model	iCT/Brilliance 64/256	iCT/Brilliance 64/256
Scan Type	Spiral Helix	Spiral Helix
Scan FOV	No Selection	No Selection
Rotation Time (s)	0.5	0.5
Det. Configuration	64 x 0.625	64 x 0.625
Pitch	0.923	0.923
kVp	120	120
mAs		mAs 50
Reference mAs	46 mAs (128mA)	
Dose Modulation	Z-DOM or DoseRight ON	Dose Right (ACS) OFF
HD Mode	n/a	n/a
Scan Time(s) 30cm Length	<10	<10
Additional Image Filters	Adaptive Filtering OFF	Adaptive Filtering OFF
Thickness (mm)	0.67	0.67
Interval (mm)	0.5	0.5
Iterative Reconstruction (Noise Reduction)	per recon	iDose OFF
Reconstructions		
Insp Low 1	B	
Insp Low 2	D	
Insp Low 3i	B iDose L3	
Insp Low 4i	B iDose L6	
Exp Recon 1		B
Exp Recon 2		D
DFOV	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. DFOV is the same for all inspiratory and expiratory reconstructions. Guidance may be provided on the CT acquisition form.	

3.0 CT Scanning Protocol	Inspiratory Lowdose	Expiratory	Inspiratory Lowdose	Expiratory	Inspiratory Lowdose	Expiratory
Scanner Make	Siemens	Siemens	Siemens	Siemens	Siemens	Siemens
Scanner Model	Biograph 40 slice	Biograph 40 slice	Sensation 64 slice	Sensation 64 slice	Definition DS/AS 64 slice	Definition DS/AS 64 slice
Scan Type	Spiral	Spiral	Spiral	Spiral	Spiral Single Source	Spiral Single Source
Scan FOV	No Selection	No Selection	No Selection	No Selection	No Selection	No Selection
Rotation Time (s)	0.5	0.5	0.5	0.5	0.5	0.5
Det. Configuration	40 x 0.6	40 x 0.6	(64) 32 x 0.6	(64) 32 x 0.6	(64) 32 x 0.6	(64) 32 x 0.6
Pitch	1.1	1.1	1	1	1	1
kVp	120	120	120	120	120	120
Eff. mAs		Effective mAs 50		Effective mAs 50		Effective mAs 50
Reference mAs	Reference 35mAs		Reference 35mAs		Reference 35mAs	
Dose Modulation	Care Dose ON	Care Dose OFF	Care Dose ON	Care Dose OFF	Care Dose ON	Care Dose OFF
HD Mode	n/a	n/a	n/a	n/a	n/a	n/a
Scan Time(s) 30cm Length	<10	<10	<10	<10	<10	<10
Additional Image Filters	No Selection	No Selection	No Selection	No Selection	No Selection	No Selection
Thickness (mm)	0.75	0.75	0.75	0.75	0.75	0.75
Interval (mm)	0.5	0.5	0.5	0.5	0.5	0.5
Iterative Reconstruction (Noise Reduction)	per recon	SAFIRE OFF	per recon	SAFIRE OFF	per recon	SAFIRE OFF
Reconstructions						
Insp Low 1	B31f		B31f		B31f	
Insp Low 2	B45f		B45f		B45f	
Insp Low 3i	I31f SAFIRE 2		I31f SAFIRE 2		I31f SAFIRE 2	
Insp Low 4i	I31f SAFIRE 5		I31f SAFIRE 5		I31f SAFIRE 5	
Exp Recon 1		B31f		B31f		B31f
Exp Recon 2		B45f		B45f		B45f
DFOV			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. DFOV is the same for all inspiratory and expiratory reconstructions. Guidance may be provided on the CT acquisition form.			

3.0 CT Scanning Protocol	Inspiratory Lowdose	Expiratory	Inspiratory Lowdose	Expiratory	Inspiratory Lowdose	Expiratory
Scanner Make	Siemens	Siemens	Siemens	Siemens	Siemens	Siemens
Scanner Model	Definition (AS+) 128 slice	Definition (AS+) 128 slice	Definition Flash 128 slice	Definition Flash 128 slice	Somatom Force	Somatom Force
Scan Type	Spiral	Spiral	Spiral Single Source	Spiral Single Source	Spiral Single Source	Spiral Single Source
Scan FOV	No Selection	No Selection	No Selection	No Selection	No Selection	No Selection
Rotation Time (s)	0.5	0.5	0.5	0.5	0.5	0.5
Det. Configuration	(128) 64 x 0.6	(128) 64 x 0.6	(128) 64 x 0.6	(128) 64 x 0.6	(128) 64 x 0.6	(128) 64 x 0.6
Pitch	1	1	1	1	1	1
kVp	120	120	120	120	120	120
Eff. mAs		Effective mAs 50		Effective mAs 50		Effective mAs 50
Reference mAs	Reference 35mAs		Reference 35mAs		Reference 35mAs	
Dose Modulation	Care Dose ON	Care Dose OFF	Care Dose ON	Care Dose OFF	Care Dose ON	Care Dose OFF
HD Mode	n/a	n/a	n/a	n/a	n/a	n/a
Scan Time(s) 30cm Length	<10	<10	<10	<10	<10	<10
Additional Image Filters	No Selection	No Selection	No Selection	No Selection	No Selection	No Selection
Thickness (mm)	0.75	0.75	0.75	0.75	0.75	0.75
Interval (mm)	0.5	0.5	0.5	0.5	0.5	0.5
Iterative Reconstruction (Noise Reduction)	per recon	SAFIRE OFF	per recon	SAFIRE OFF	per recon	ADMIRE OFF
Reconstructions						
Insp Low 1	B31f		B31f		Bf40d	
Insp Low 2	B45f		B46f		Qr44d	
Insp Low 3i	I31f SAFIRE 2		I31f SAFIRE 2		Bf40d ADMIRE 2	
Insp Low 4i	I31f SAFIRE 5		I31f SAFIRE 5		Bf40d ADMIRE 5	
Exp Recon 1		B31f		B31f		Bf40d
Exp Recon 2		B45f		B46f		Qr44d
DFOV			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. DFOV is the same for all inspiratory and expiratory reconstructions. Guidance may be provided on the CT acquisition form.			

18i. 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 must 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.

CT Scans should not be repeated for COPDGene.

18j. Examples of Image Quality Issues



Figure 18-4. Poor DFOV

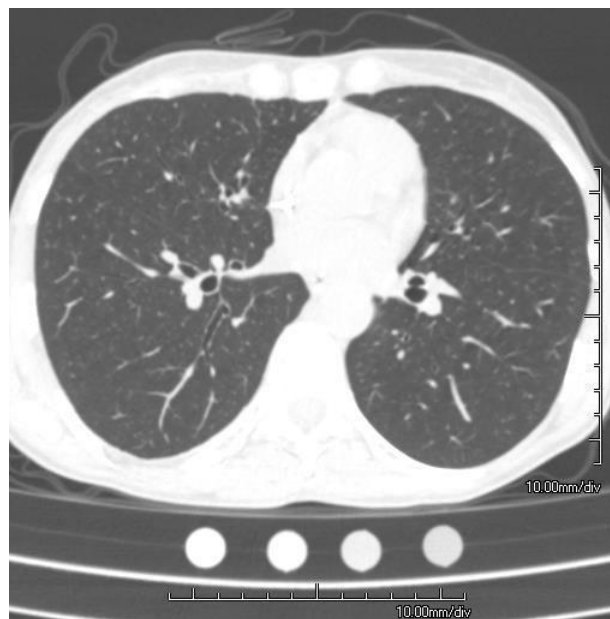


Figure 18-5. Appropriate DFOV

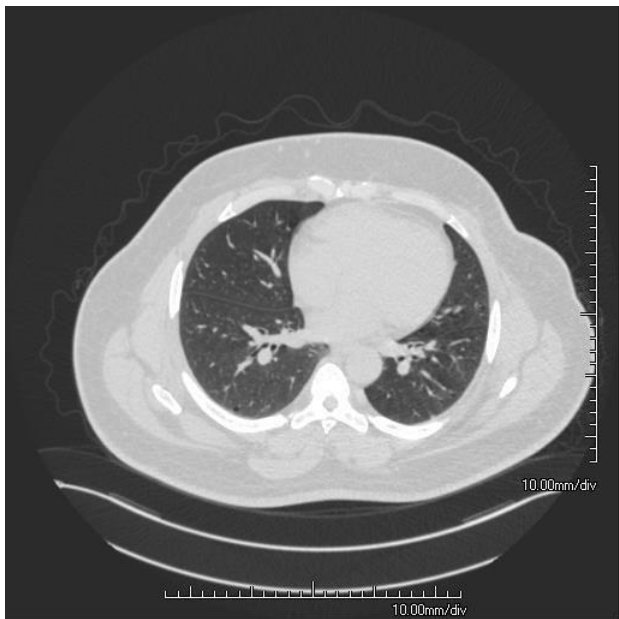


Figure 18-6. Inappropriate scan length includes head



Figure 18-7. Scan does not include entire lungs

18k. 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, i.e. 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.

18l. COPDGene® Lung Phantom (* CTP674 Lung Phantom™)

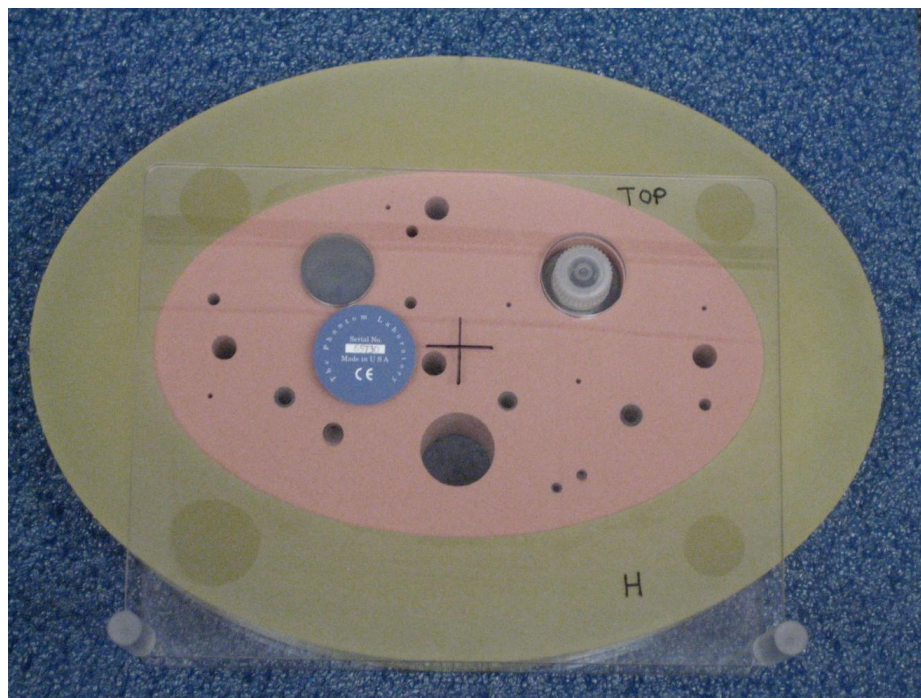


Figure 18-8. COPDGene® Lung Phantom

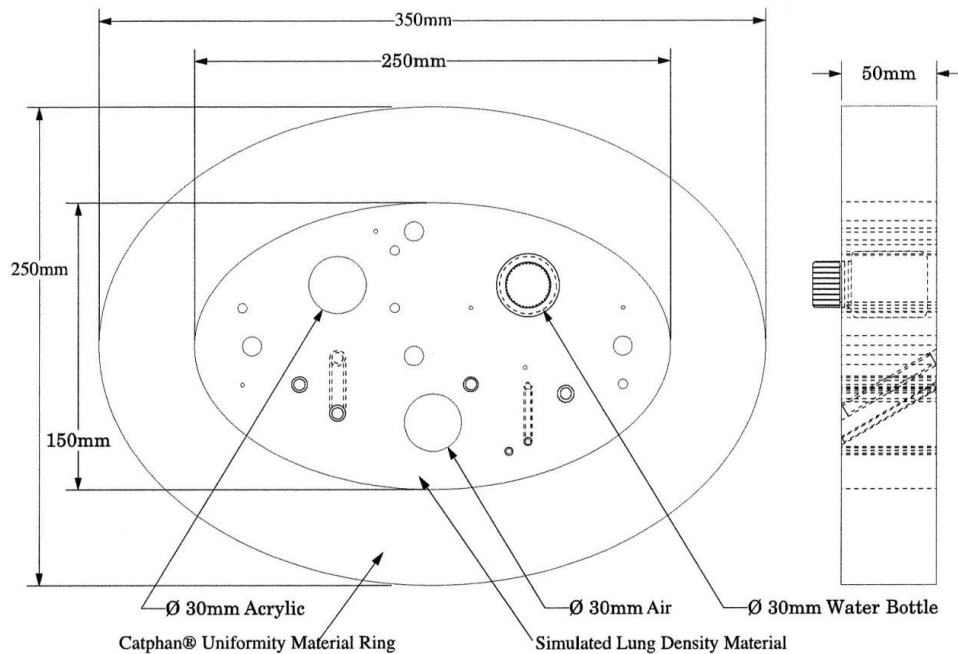


Figure 17-9. Schematic Drawing

18m. 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 17-10.

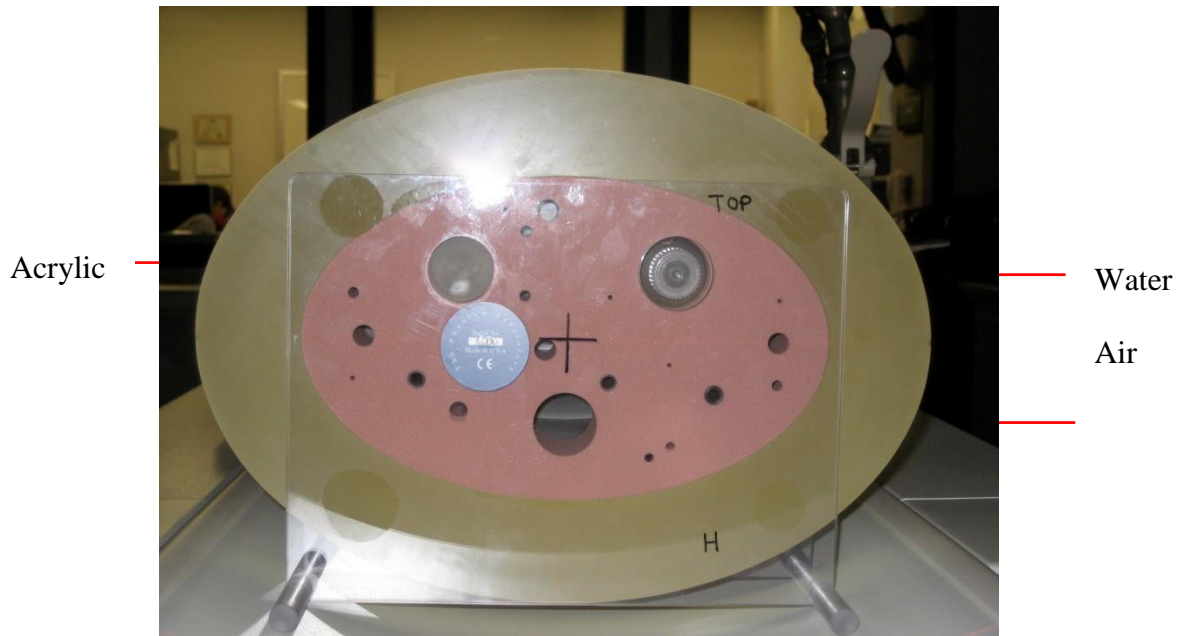


Figure 18-10.

18n. 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 17-11.

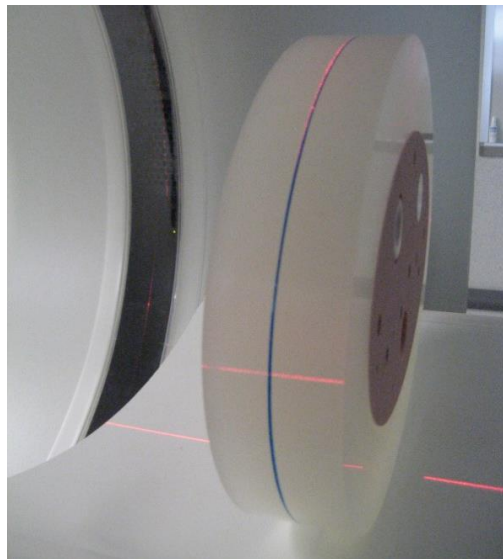


Figure 18-11.

Step 1: The phantom will arrive to you without the legs of the base attached. Screw the legs into the acrylic plates. Figure 18-12.

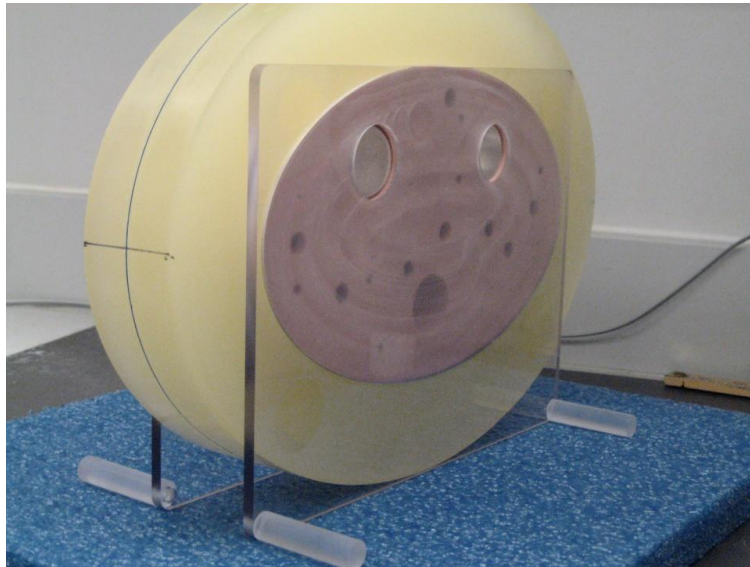



Figure 18-12

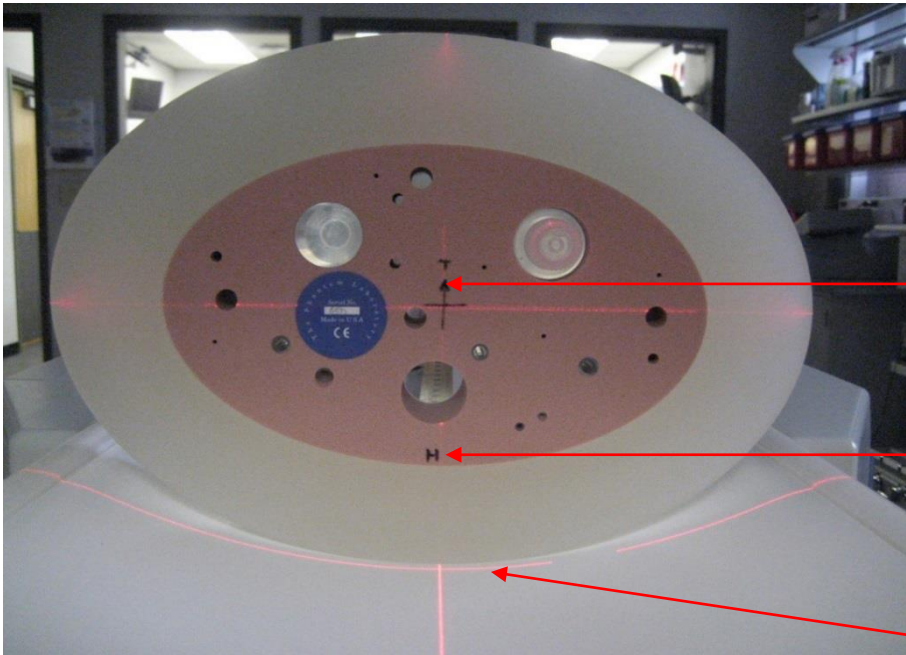
Step 2: Prior to placing the phantom on the scanner table you must first ensure the water bottle top is sufficiently level with the back edge of the phantom. The bottle must be level with the phantom foam material not the protective plate.

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.

Step 6: Align the scanner crosshairs with the  on the front of the phantom. Figure 17-13.



**Align with
Crosshairs**

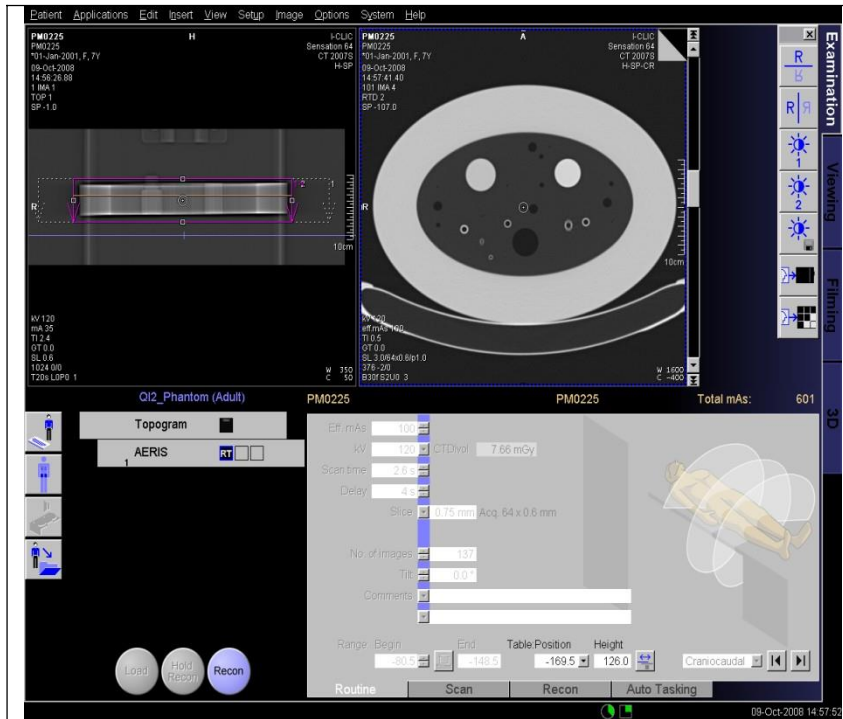
**“H” marking
Head
Position**

**Detector
Center
Line**

Figure 18-13

Step 7: Move the scanner table. Do not allow the phantom to go past the detector center line.

18o. 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).

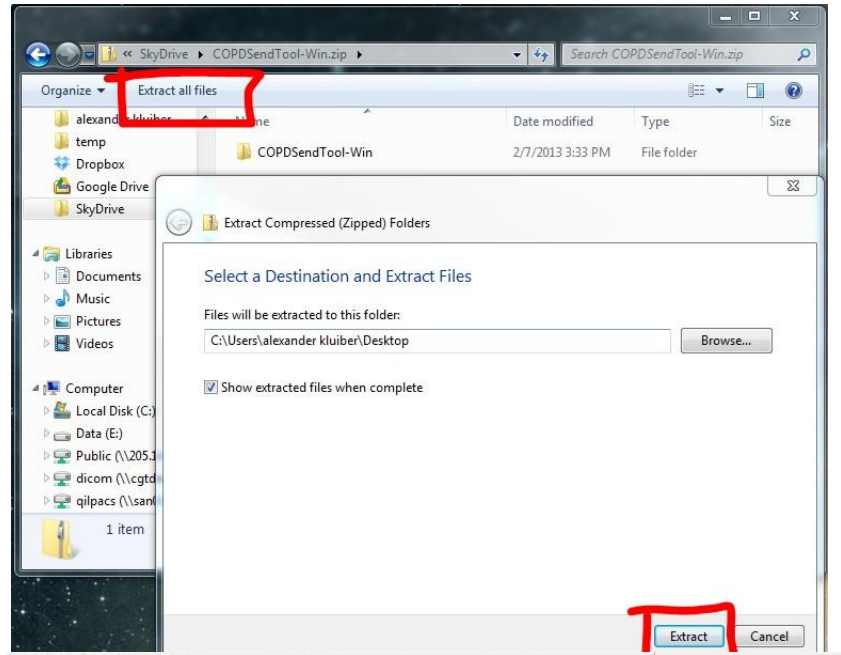
Figure 18-14

- 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 DICOM send software zip file and technical manual is located at: <http://copdsendtool.njh-imaging.org/>

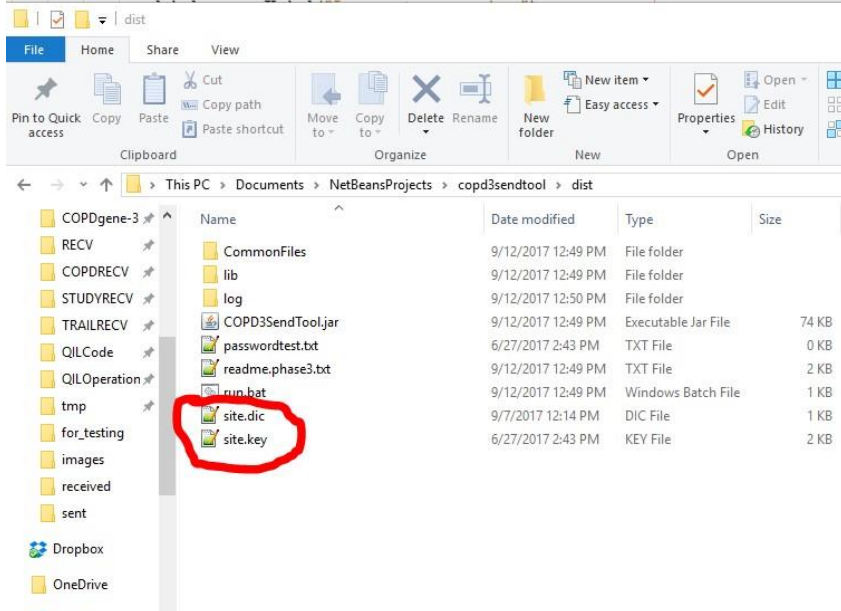
- 2) Open the zip file, extract the contents to your desktop and open the folder.



- 3) site.dic specifies the three letter designated site ID for use by the COPDSendTool.

site.key is a password protected key file required for secure network access.

Without a valid key file, access to the program is denied. This key file will be provided to sites by the Quantitative Imaging Lab at National Jewish Health.



- To run the COPDSendTool:

Windows:
double-click run.bat

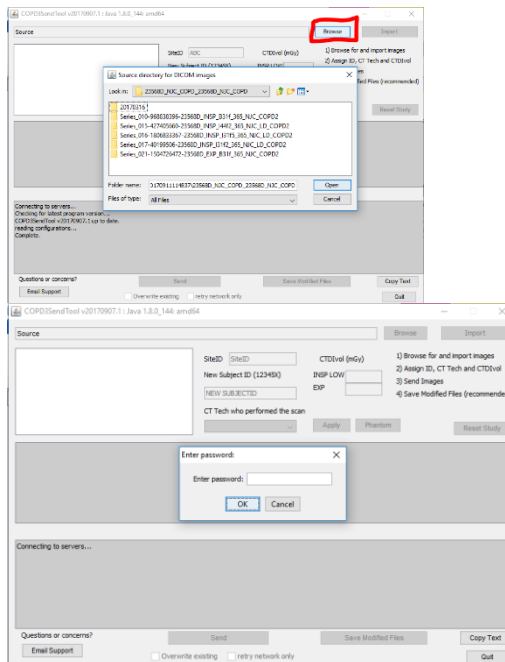
OSX:
double-click run.command

Linux:
double-click run.sh

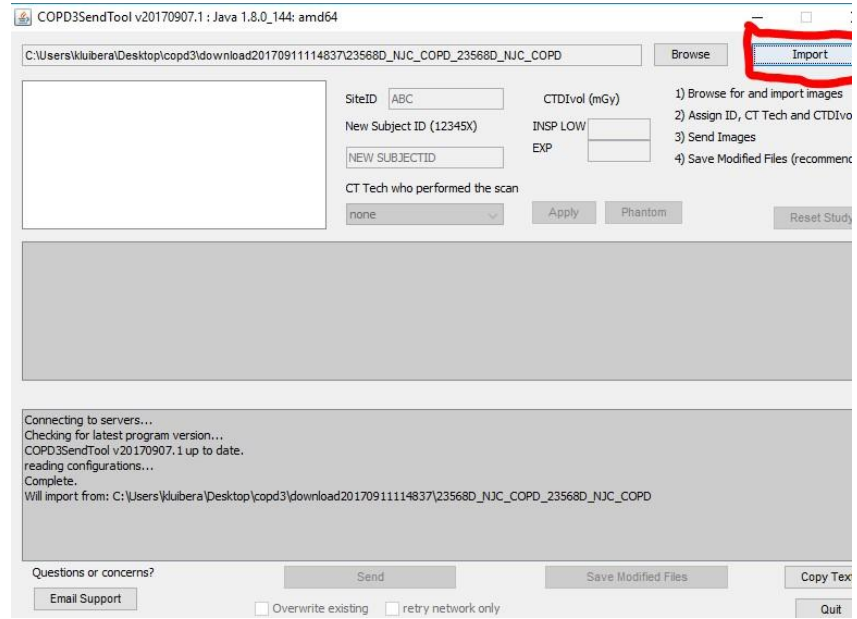
Name	Date modified	Type	Size
CommonFiles	9/12/2017 12:49 PM	File folder	
lib	9/12/2017 12:49 PM	File folder	
log	9/12/2017 12:50 PM	File folder	
COPD3SendTool.jar	9/12/2017 12:49 PM	Executable Jar File	74 KB
passwordtest.txt	6/27/2017 2:43 PM	TXT File	0 KB
readme-phase3.txt	9/12/2017 12:49 PM	TXT File	2 KB
run.bat	9/12/2017 12:49 PM	Windows Batch File	1 KB
site.doc	9/7/2017 12:14 PM	DIC File	1 KB
site.key	6/27/2017 2:43 PM	KEY File	2 KB

- Upon opening the tool will ask for a password, provided to sites by NJH, in order to connect to the QIL servers and download configuration parameters per site ID.

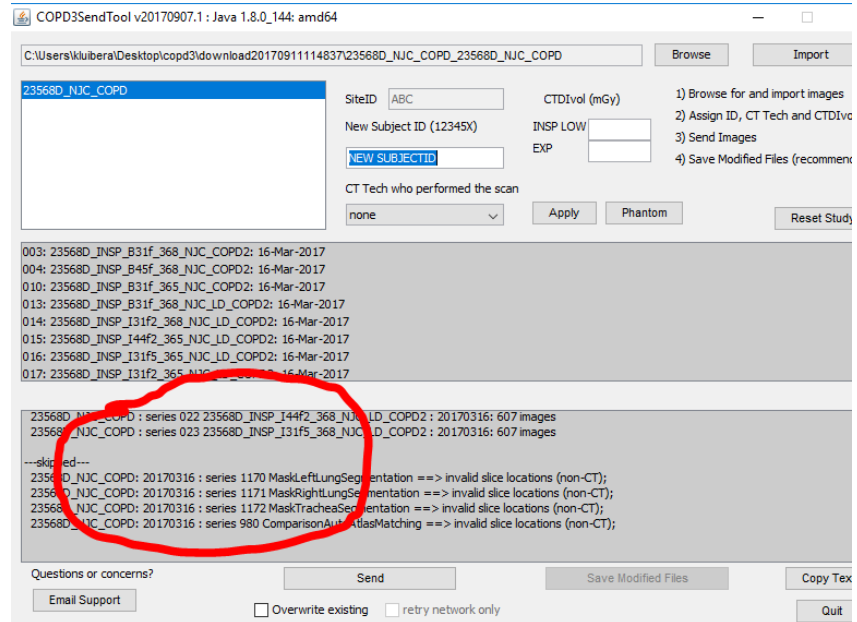
- When that is finished, click 'Browse' to locate your images.



- 7) Click 'Import' to scan for and import the images into the COPDSendTool.

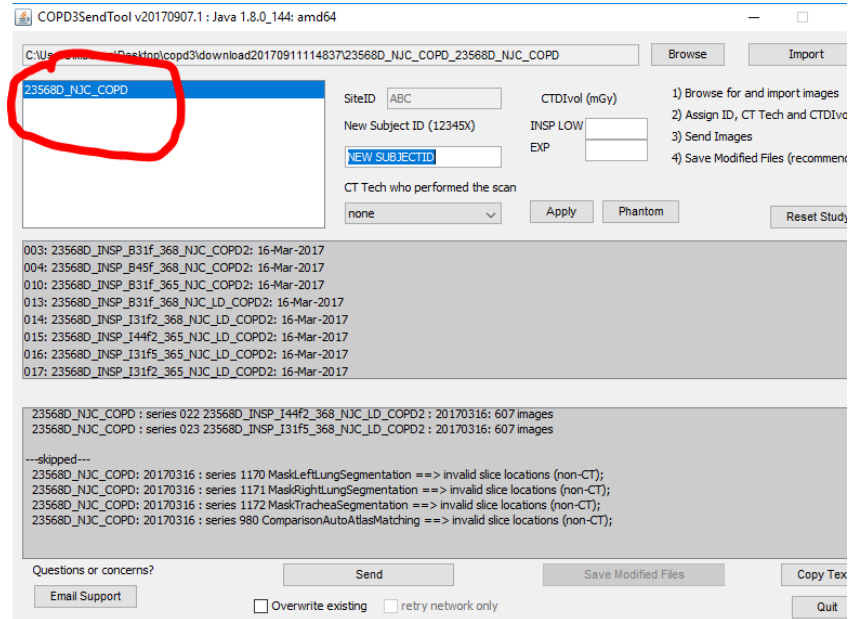


- 8) A log will be maintained of the session actions.

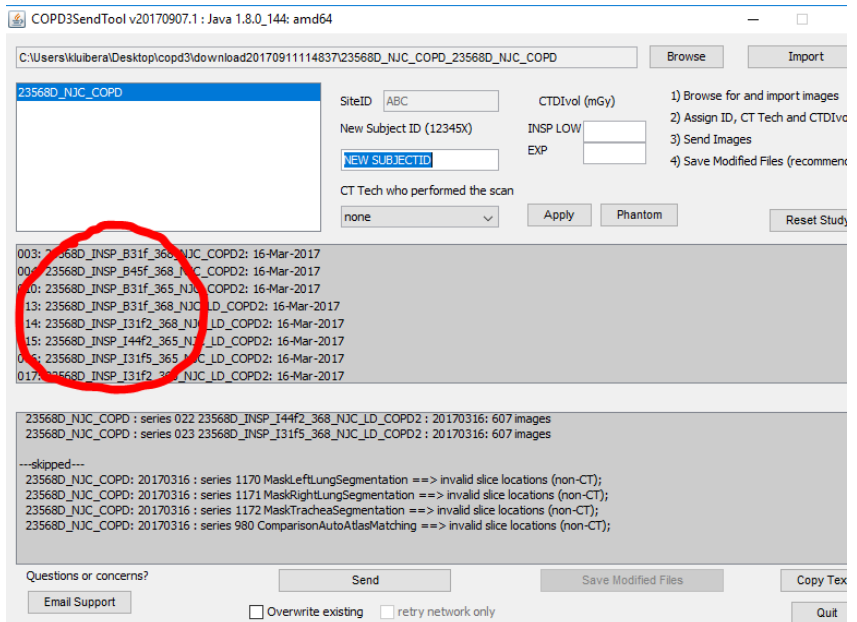


- 9) Notice any invalid images/series will be listed with explanations in the log.

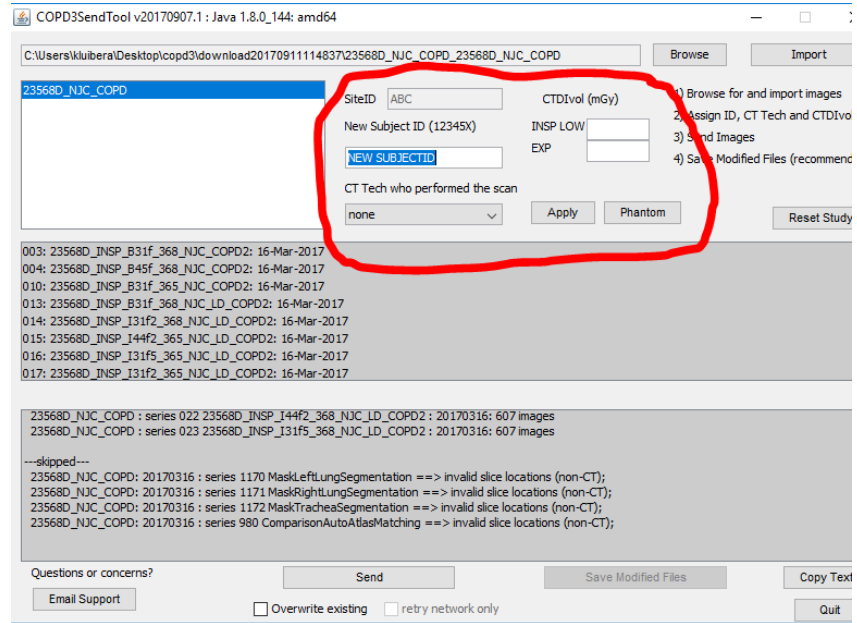
10) Studies found are listed in the upper left.



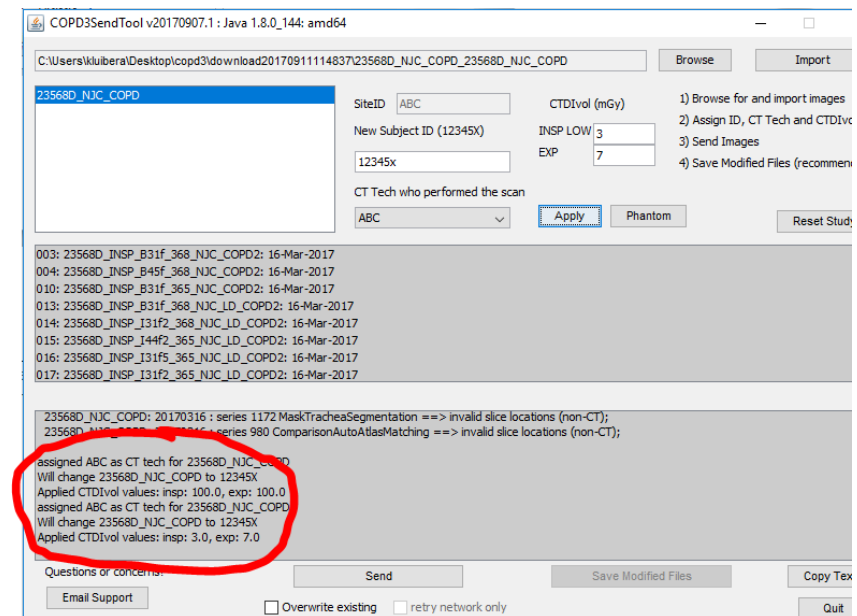
11) Series for the selected study are list in the middle.



- 12) Assign the subject ID, CT tech and CTDI values for the selected study.
- 13) Click 'Apply' to submit these assignments.
- 14) Click 'Phantom' if the selected study is a Phantom study.

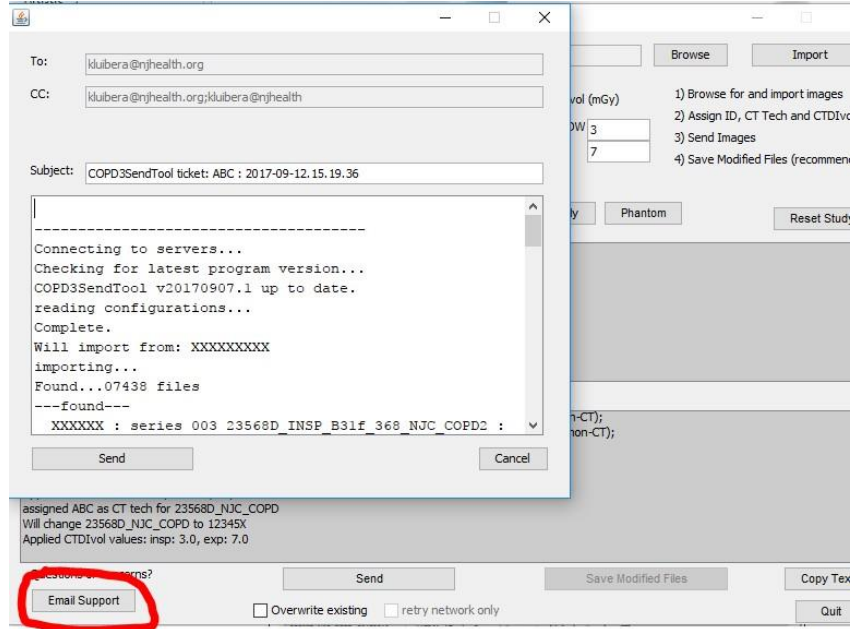


- 15) All subjects must have all values assigned before processing.
- 16) Phantom scans do not require CTDI values.
- 17) The log will list relevant errors when they occur.
- 18) Correct the mistakes until verification of the submission.



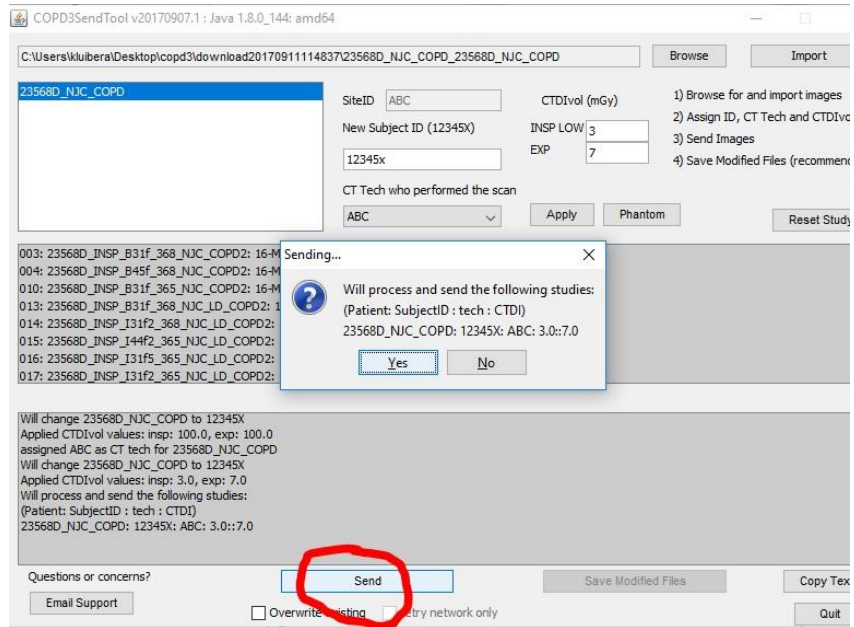
19) If you do not understand the error messages or you are not able to resolve errors, click 'Email Support.'

The software will email a detailed description of the problem to Technical Support

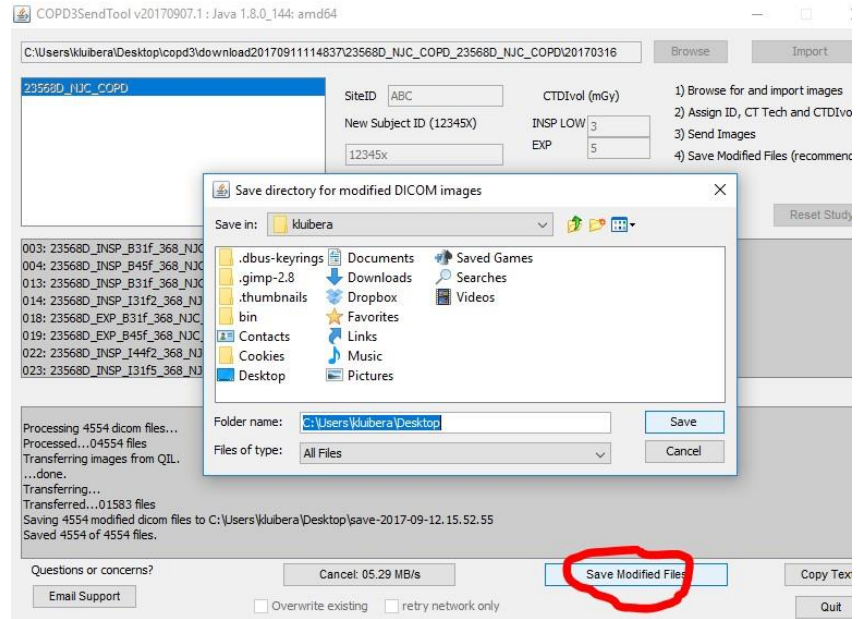


20) After all studies have had their values assigned, click 'Send' to process and transfer the images.

Review the assignments summary dialog to make sure information has been entered correctly.



21) As soon as image processing is finished, you may save the modified files locally.



22) After successful transfer, a notification email will be sent to the lab and site coordinators.

COPDgene image transfer notice: ABC: 2017-09-12.15.56.03

qil@njh-imaging.org

Sent: Tue 9/12/2017 3:58 PM

To: Kluiber, Alexander

Cc: Kluiber, Alexander; kluibera@njhealth

Site: ABC

Subjects and Series:

12345X ==> series 003: 23568D_INSP_B31f_368_NJC_COPD2: 16-Mar-2017
 12345X ==> series 004: 23568D_INSP_B45f_368_NJC_COPD2: 16-Mar-2017
 12345X ==> series 013: 23568D_INSP_B31f_368_NJC_LD_COPD2: 16-Mar-2017
 12345X ==> series 014: 23568D_INSP_I31f2_368_NJC_LD_COPD2: 16-Mar-2017
 12345X ==> series 018: 23568D_EXP_B31f_368_NJC_COPD2: 16-Mar-2017
 12345X ==> series 019: 23568D_EXP_B45f_368_NJC_COPD2: 16-Mar-2017
 12345X ==> series 022: 23568D_INSP_I44f2_368_NJC_LD_COPD2: 16-Mar-2017
 12345X ==> series 023: 23568D_INSP_I31f5_368_NJC_LD_COPD2: 16-Mar-2017

Sent: 4554 of 4554 images.

Time: 0 hours, 3 mins, 26 secs.

Average rate: 12.03 MBps

End of transmission report.

COPD3SendTool v20170907.1

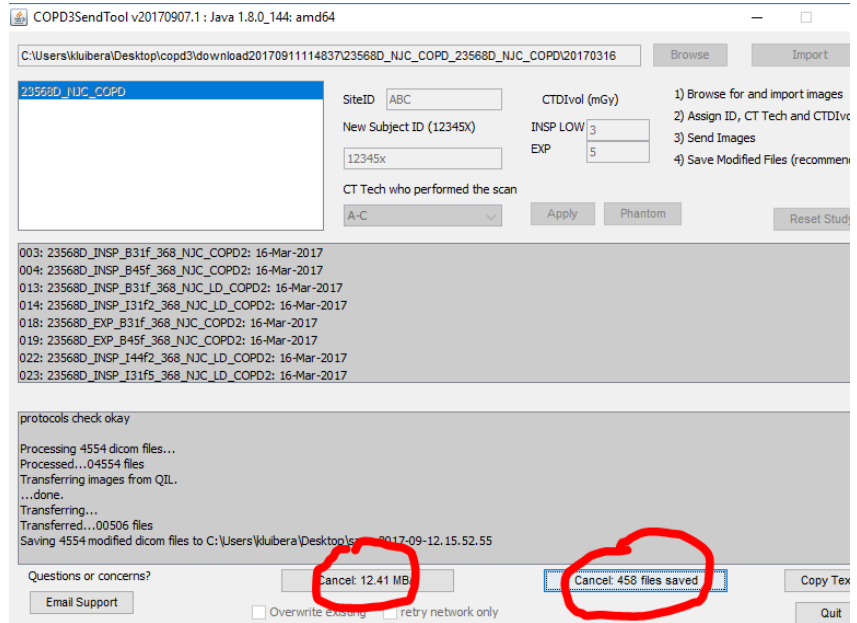
For questions or comments contact:

Alex Kluiber

303-270-2595

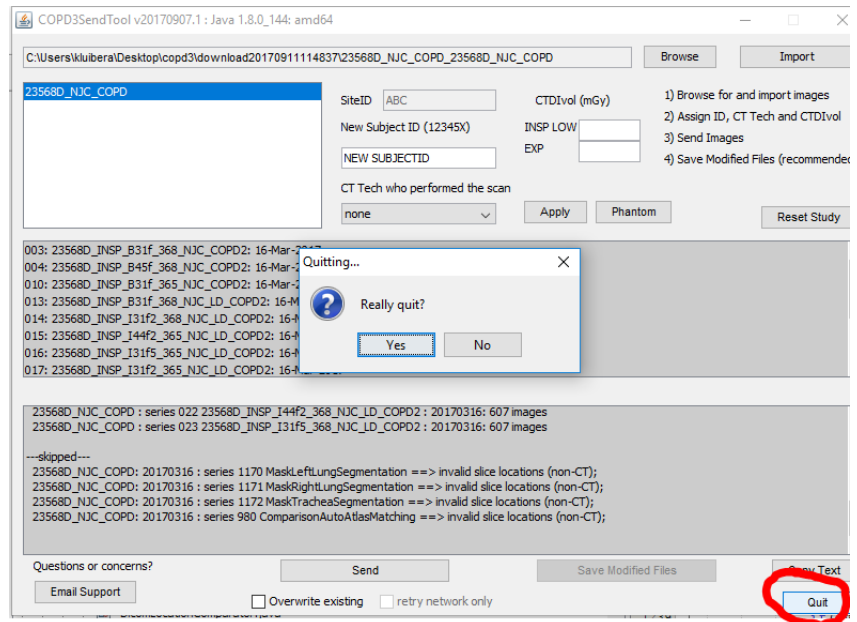
kluibera@njhealth.org

23) If necessary, you may cancel/stop the import, send and save processes as needed.



24) 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.

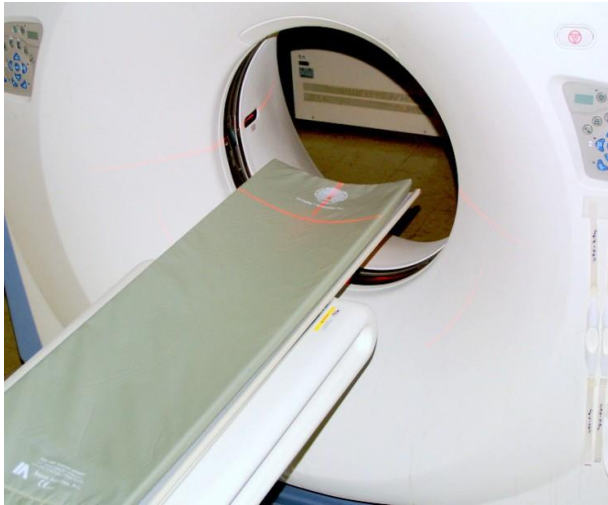
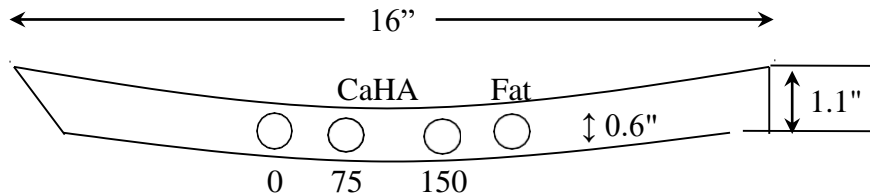


Image Analysis, Inc.

www.image-analysis.com



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:

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:

Melissa Saylor, RT (R)(CT)
Research Associate
(319) 384-7946
melissa-saylor@uiowa.edu

Shipping Address:

University of Iowa Hospitals and Clinics
200 Hawkins Drive, 54 MRF
Department of Radiology, Division of Imaging
Iowa City, IA 52242

Appendix D: CT Tech Instructions



CT TECHNOLOGIST INSTRUCTION FORM

Effective Date: 10/16/2017 Rev. 6.0 Pg. 1 of 2

It is important that the subject fully understands the breath hold and scanning procedure and that all concerns are addressed prior to performing the CT scan. Participants must be scanned with the same CT acquisition and reconstructions parameters used during the previous study CT visit. The CT Acquisition Form will provide the target DFOV setting to use for the current visit. All other scan parameters are provided in study CT Imaging MOP and CT Acquisition Form. Participants who did not have a Phase 1 or Phase 2 CT should be scanned according to protocol. If you do not have the appropriate baseline information, do not perform the CT scans.

Subject Preparation

- Remove jewelry and items from pockets that could appear in the CT scan images.

Patient Position

- Place subject in a supine position, arms position comfortable above the head with biceps next to ears.
- No items that could affect the body alignment, such as pillows, should be placed under the subjects during scanning.
- Using the laser position lights, line up the subject so the chest is iso-center (in the middle: left-right; up-down) of the CT gantry.
- Move the table so the subject is in the correct position for a chest CT scan.

Scan Coverage

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. CT scan must include the lungs, but ONLY the lungs. Start the scan using the scout as a reference at the apex of the lungs and stop it once the scan is through the base of the lungs as shown in Figures 1 and 2.

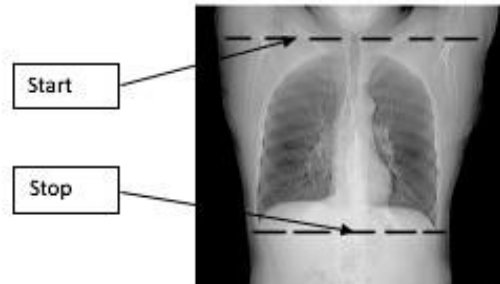


Figure 1

The DFOV should tightly fit the TLC lung as shown in Figure 3, then use the TLC DFOV for the FRC scan so that all the scan reconstructions have the same DFOV. If this is a subsequent to the baseline visit, participants must have the same Diameter Field of view (DFOV) used during the baseline CT visit. Again, refer to the study coordinator for this information.

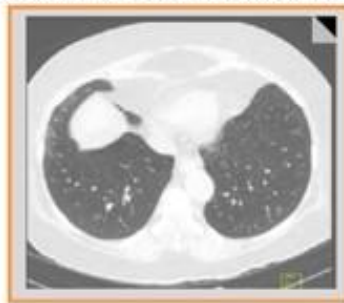


Figure 3

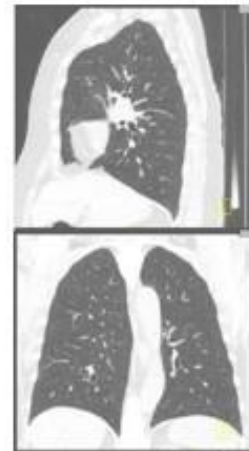
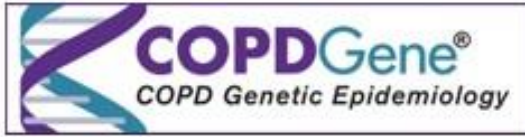


Figure 2



CT TECHNOLOGIST INSTRUCTION FORM

Effective Date: 10/16/2017 Rev. 6.0 Pg. 2 of 2

The following breathing instructions must be given to the subject:

- * **Bold instructions are what must be said to the subject during CT.**
- ** (*italic*) information represents reminders directed towards the CT technologist.

SCANNING:

Use the breathing instructions to perform:

- A practice breathing session
- Scouts - as needed - to position the FOV to cover the entire lung and as little soft tissue as possible
- The Inspiration CT scan (TLC)

Inspiratory CT (TLC)

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!"

SCANNING

Use the breathing instructions to perform:

- A practice breathing session
- Scouts - as needed - to position the FOV to cover the entire lung and as little soft tissue as possible
 - The Expiration CT scan (FRC)

Expiratory CT (FRC)

Instruct the patient to breathe as follows:

"For the third 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!"

19. Collection of Blood Samples

19a. Purpose of COPDGene® Study Center Phase 3 Laboratory Manual

This manual serves to identify those involved with the COPDGene® Phase 3 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. There is also a PowerPoint presentation and YouTube video describing these procedures on the COPDGene® website.




19b. Biological Specimen Handling



19b.1. Labeling and Identification

Purpose: Ensure all collected samples are labeled accurately and adequately. Also review the tube expiration dates prior to the draw and be sure that they are not expired prior to collection.

By Whom: COPDGene® Site Coordinator/phlebotomist

Procedure:

1	<p>The COPDGene® site will use pre-barcoded labels, as provided by the Channing Lab Biorepository, to label all specimen collection containers and documents. The labels include the laboratory barcode number, the COPDGene® ID number, and the sample or blood tube type. The labels will be used for all blood tubes and specimen transmittal documents for the lab. The extra labels can also be used for other COPDGene® study documentation. An example of the label designed by the Biorepository is below:</p> 
2	<p>One sample collection kit per subject will be provided containing blood tubes, pre-printed blood tube labels, and labeled matrix aliquot tubes. Extra labels will be provided with the COPDGene® subject ID only.</p>  

<p>3</p>	<p>Place each blood tube label on the correct blood tube. Be sure to position the label from top to bottom, so the barcode can be scanned by the Biorepository. Be sure to label all tubes <i>prior to the blood draw</i>.</p> 
<p>4</p>	<p>Organize the matrix aliquot tubes by plasma and serum and position the tubes in one of the provided matrix racks. Be sure to organize all matrix aliquot tubes prior to the blood draw.</p> 
<p>5</p>	<p>Note: When drawing blood from more than one subject on the same day, keep tubes from each subject separate and only label tubes for one subject at one time.</p>

COPDGene® Phase 3b Short-Term Follow-Up Collection Kits

This document describes the blood collection kits intended for COPDGene® Phase 3b Short-Term Follow-Up sample collections. These sample collection kits are intentionally different, so they may be easily distinguished from the regular COPDGene® Phase 3 sample collection kits.

- 1 Candidate subjects for the Phase 3b Short-Term Follow-up visit are pre-determined. One Phase 3b sample collection kit per candidate will be provided, containing blood tubes, pre-printed blood tube labels, and labeled matrix aliquot tubes. The outside of the collection kit will have a green dot to indicate that it is a Phase 3b kit, and all matrix tubes will have green caps. Please note, nutrition questionnaires will not be included in this collection kit.

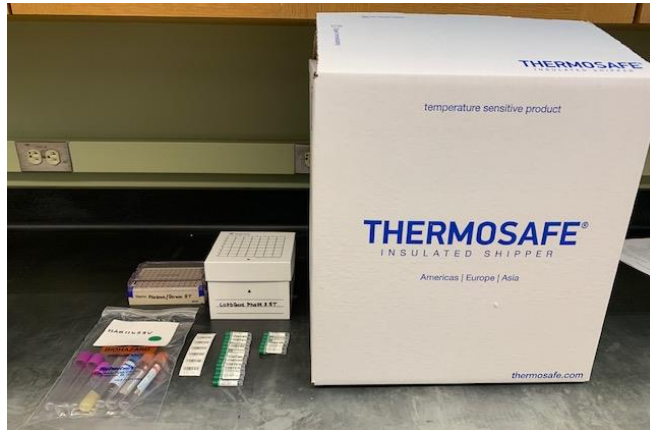


- 2 The Phase 3b Short-Term Follow-Up sample collection kits contain pre-barcoded labels, to label all specimen collection containers and documents. The labels include the laboratory barcode number, the COPDGene® ID number, and the sample or blood tube type with “ST,” indicating “short-term.” An example of the new label is below:



- 3 Phase 3b Short-Term Follow-Up supply shipments will contain sample collection kits, one matrix rack, one cardboard blood storage box, 3mL pipettes, 1mL pipettes, one dry ice label, and a return shipping label contained in an insulated shipping container. Please note that Phase 3b Short-Term Follow-Up supply shipments will contain fewer supplies

while the total number of patients returning for the visit is assessed. If additional supplies are needed for these visits, please contact the Channing Lab.



4 For sample collection, refer to the COPDGene[®] Manual of Operations and proceed accordingly. Following sample collection, keep the serum and plasma aliquots separate from the regular Phase 3 samples and place the aliquots in the matrix rack labeled “Serum/Plasma ST.” Keep the blood tubes separate from the regular Phase 3 samples and place the tubes in the blood storage box labeled “COPDGene Phase 3 ST.”

5 Specimens should be shipped to the Channing Lab either quarterly or when samples from 24 subjects have been accumulated, whichever comes first. For shipping instructions, please refer to the COPDGene[®] Manual of Operations. Please ship Phase 3b Short-Term Follow-Up samples separately from regular Phase 3 samples; do not combine samples from both visits in the same shipment. The Shipment Tracking system will be modified to give you an option for Short-Term samples.

19b.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:

1	The following table summarizes draw order and volume for the collection of blood samples into <i>plastic</i> vacutainer tubes:																													
	<table border="1"><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>EDTA purple top*</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>7</td><td>Paxgene RNA tube</td><td>2.5 ml</td></tr><tr><td colspan="2">Total</td><td>48.5 ml</td></tr></tbody></table>			Draw Order	Tube Type	Tube Amount	1	EDTA purple top	10 ml	2	EDTA purple top	10 ml	3	EDTA purple top*	4 ml or 5 ml	4	SST red-grey top	10 ml	5	Paxgene DNA tube	8.5 ml	6	Paxgene RNA tube	2.5 ml	7	Paxgene RNA tube	2.5 ml	Total		48.5 ml
	Draw Order	Tube Type	Tube Amount																											
	1	EDTA purple top	10 ml																											
	2	EDTA purple top	10 ml																											
	3	EDTA purple top*	4 ml or 5 ml																											
	4	SST red-grey top	10 ml																											
	5	Paxgene DNA tube	8.5 ml																											
6	Paxgene RNA tube	2.5 ml																												
7	Paxgene RNA tube	2.5 ml																												
Total		48.5 ml																												
*The 4mL or 5mL EDTA purple top tube is drawn for CBC (complete blood count) analysis, to be processed by a local CLIA- approved clinical laboratory.																														
2	Blood should be drawn using standard phlebotomy technique with tourniquet applied to identify the vein and released after adequate blood flow is obtained.																													
3	The needle or catheter should preferably be no smaller than 21 gauge to minimize risk of hemolysis.																													
4	Be sure to wear appropriate PPE (Personal Protective Equipment) when handling blood and throughout blood processing. To safely handle blood, latex or nitrile gloves, a laboratory coat, and a face shield should be worn.																													

19b.3. Sample Processing

Immediately after collecting the blood samples, double check that the barcode labels have been placed and adhered on each tube and that they 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.

PAXgene DNA and PAXgene RNA Tubes

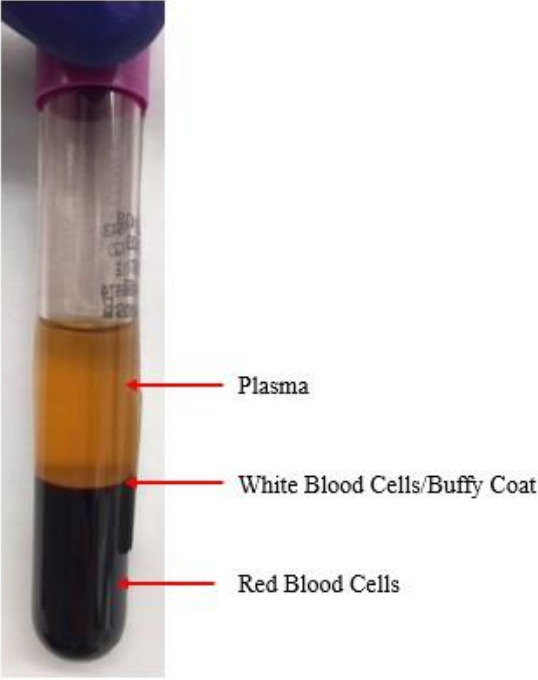
Procedure:

1	After obtaining the PAXgene RNA and PAXgene DNA blood tubes, mix each tube thoroughly by inverting 10 times.
2	The PAXgene DNA and PAXgene RNA tubes can go right into the -80C freezer, they do not need to sit at room temperature for 1-2 hours.
3	Note: PAXgene RNA and DNA tubes do not need to be centrifuged or aliquoted. Let the tubes incubate at room temperature in an upright position while preparing the plasma and serum aliquots.
4	Place the PAXgene RNA and PAXgene DNA blood tubes in the blood storage box. Store samples at -80 degrees Celsius.

EDTA Purple Top Tubes

Procedure:

1	After obtaining the EDTA purple top blood samples, mix each tube thoroughly by inverting 5 times.
2	Send the 5mL EDTA purple top tube to the local clinical laboratory for a Complete Blood Count with machine cellular differential. The CBC must include automated differential.
3	Follow manual instructions for use of the local centrifuge. Ensure the tubes are balanced within the centrifuge.
4	Centrifuge tubes at 2500 RPM (1000-3000 x g) for 10 minutes at room temperature.
5	Remove tubes from the centrifuge. Note that the blood has separated into 3 layers: <ul style="list-style-type: none">• Top Layer: Plasma (yellow or transparent)• Middle Layer: White blood cells/buffy coat (thin, white membrane layer)• Bottom Layer: Red blood cells (dark red)

	
6	Carefully remove the rubber stopper. Remove the caps from the matrix aliquot plasma tubes.
7	Note: During aliquoting, be careful not to disturb the white blood cell/buffy coat layer. Leave a small volume of plasma in the tube to ensure that no white blood cells are removed.
8	Using the smaller 0.3mL transfer pipet, aliquot the following samples from each EDTA tube. Reference the markings on the transfer pipet to measure the correct volume. With the 0.3mL transfer pipet, pipette up to the second marking to achieve 250uL. <ul style="list-style-type: none"> • 2 x 0.25mL (250uL) plasma
9	Using a 3mL transfer pipet, aliquot the following samples from each EDTA tube. Reference the markings on the transfer pipet to measure the correct volume. <ul style="list-style-type: none"> • 5 x 0.5mL (500uL) plasma
10	Note: If there is insufficient volume to create all of the specified aliquots, create as many aliquots as possible at the appropriate specified volume and return empty matrix aliquot tubes to the Biorepository.
11	Note: If there is <u>extra</u> volume after all aliquots have been created, leave the remaining plasma in the blood tube.
12	Re-cap the EDTA purple top blood tubes and re-cap the matrix aliquot tubes.
13	Place the EDTA blood tubes in the blood storage box. Store samples at -80 degrees Celsius.
14	Place the matrix aliquot tubes in the matrix rack “Plasma.” Store samples at -80 degrees Celsius within 2 hours after collection.

SST Red-Grey Top Tube

Procedure:

1	After obtaining the SST blood sample, allow the blood to clot for 30 minutes (but not longer than 60 minutes) in a vertical position at room temperature.
2	Follow manual instructions for use of the local centrifuge. Ensure the tubes are balanced within the centrifuge.
3	Centrifuge tube at 2500 PTM (1000-3000 x g) for 10 minutes at room temperature.
4	Carefully remove the rubber stopper. Remove the caps from the matrix aliquot serum tubes.
5	Using a 3 mL transfer pipet, aliquot the following samples from the SST tube. Reference the markings on the transfer pipet to measure the correct volume. <ul style="list-style-type: none">• 6 x 0.5mL (500uL) serum
6	Note: If there is insufficient volume to create all of the specified aliquots, create as many aliquots as possible at the appropriate specified volume and return empty matrix aliquot tubes to the Biorepository.
7	Note: If there is <u>extra</u> volume after all aliquots have been created, leave the remaining serum in the blood tube.
8	Once all serum aliquots have been prepared, dispose of the SST blood tube.
9	Re-cap the matrix aliquot tubes. Place the tubes in the matrix rack labeled “Serum.” Store samples at -80 degrees Celcius within 2 hours after collection.

19c. Sample Distribution/Shipping

19c.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, which may include trans-shipment between transport units and warehouses, as well as 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:

1. *Primary Receptacle:* Blood vacutainer tubes (EDTA, PAXgene RNA, PAXgene DNA, and matrix aliquot tubes)
2. *Secondary Packaging:* Specimen freezer storage boxes or matrix racks packed inside Saf- T-Pak envelopes.
3. *Rigid Outer Packaging:* 19 ¾ x 16 ¾ x 15 ⅜ Thermosafe Styrofoam shippers with outer cardboard box

Primary receptacles (blood tubes and matrix tubes) must be packed in secondary packaging (blood storage boxes or matrix racks) 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 the outer packaging.

Procedure:

A PowerPoint presentation outlining specific packing information for the blood and matrix tube shipment has been developed and is available on the COPDGene® website. All coordinators are expected to be familiar with this presentation.

1	Insert the Styrofoam container into the cardboard box.
2	No more than 15 minutes prior to packaging the shipment, remove blood storage boxes and matrix tubes from the -80 degrees Celcius freezer.
3	Individually pack the blood storage boxes into the large Saf-T-Pak envelopes.
4	Individually pack the matrix racks containing the plasma and serum aliquots into the small Saf-T-Pak envelopes.
5	Place the blood storage boxes and the matrix racks into the shipping container.
6	Place enough dry ice into the Styrofoam container until it is approximately ¾ full. Be sure that all samples are covered with dry ice, while still allowing some room to securely close the Styrofoam container lid. Place the lid on the Styrofoam container.
7	Place the specimen transmittal forms on top of the Styrofoam lid and seal the cardboard box with packing tape.
8	Note: DO NOT seal the Styrofoam container. DO NOT seal the cardboard box completely. Sealing the box airtight can cause the package to explode, as dry ice produces carbon dioxide over time and requires adequate ventilation.

19c.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

Procedure:

1	Specimens should be shipped to the Channing Lab when samples from 24 subjects have been accumulated.
2	Note: Specimens may only be shipped Monday-Wednesday to ensure arrival at the Channing Lab on a weekday. Notices will be sent to coordinators via email prior to holidays to indicate any changes to this shipping schedule. Holidays observed at the Channing Lab are as follows:

	New Year's Day Martin Luther King Jr. Day Presidents' Day Memorial Day Independence Day Labor Day Columbus Day Thanksgiving Christmas
3	Ship To: Brigham and Women's Hospital Channing System Genetics and Genomics Laboratory 221 Longwood Avenue, EBRC Room 610 Boston, MA 02115 617-732-5560
4	Refer to the previous section for detailed instructions on assembling the shipment.
5	Place the pre-printed FedEx airway bill on top of the box, inside a clear plastic sleeve. Call FedEx for pick-up. Please contact the Channing Lab if a pre-printed label is needed
6	Enter the tracking number of the COPDGene® website. A shipping notification will be generated and sent to the Channing Lab.
7	Once the shipment has been received by the Channing Lab, the received date will be entered on the COPDGene® website. This will confirm and resolve the shipment. Problems or delays with a shipment will be handled on a case-by-case basis and may be noted on the COPDGene® website.

19d. Supplies and Ordering

By Whom: Channing Lab and Clinical Center site technicians

Sample Collection Supplies				
Item Name	Supplier	Catalog Number	Cost/Unit (prices are approximate)	To be supplied by
Purple top plastic EDTA tubes 10 ml	VWR	BD366643	Case of 10x100 \$345	Channing Lab
Red-Gray plastic SST tubes 10 ml	VWR	BD367985	Case of 10x100 \$755	Channing Lab
Purple top plastic EDTA tubes 4 ml	VWR	BD367862	Case of 10x100 \$387	Channing Lab
Paxgene DNA plastic tubes 8.5ml	Qiagen	761115	Case of 100 \$37	Channing Lab
Paxgene RNA plastic tubes 2.5ml	Qiagen	762165	Case of 100 \$1,133	Channing Lab
Butterfly needles 21 G (Preferred)	VWR	BD367281	Case of 4x50 \$250	Site

Butterfly needles 23 G	VWR	BD367283	Case of 4x50 \$250	Site
Tourniquets (reusable)	VWR	VT367203	Case of 20x25 \$187	Site
Tube adapters	VWR	VT367290	Case of 10x100 \$317.86	Site
Gauze	VWR	82004-740	Case of 5000 \$127	Site
Bandage	VWR	56612-996	Case of 12x100 \$62	Site
Alcohol pads	VWR	15648-981	Case of 15x200 \$92	Site
Hamilton Bell™ Vanguard Centrifuge*	MarketLab	JL9576	\$359	Site
Tube/Document Labels	Brady	THT-125-499-3	3000 per roll, \$127	Channing Lab
3mL sterile transfer pipets (20/pack)	VWR	10754-266		Channing Lab
1mL sterile transfer pipets (5/pack)	VWR	414004-025		Channing Lab

***Note: An alternate centrifuge can be used if available.**

19e. 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:

Shipper's Declaration not Required.
Dry ice amount must be in kilograms.
Note: 2 lbs. = 1 kg.

Airwaybills / airbills must have the following:
1. Dry Ice: UN 1845
2. 1 x 15 kg (weight) (net)

Dry Ice
15 kg.

UN 1845

Shipper's Name and Address
DANIEL CASSETTE
221 WINGWOOD AVE
BOSTON, MA 02115
(Contact Tel. No.)

Consignee Name and Address

9

- 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).**

20. Summary of Changes

Version/Date	Changes
Version 9.0a, 05 Oct 2017	Initial Release for Phase 3
Version 9.0b, 05 Dec 2017	Updated to include Biorepository section (section 18)
Version 9.0c, 20 Dec 2017	Updated to include some modifications to the Biorepository section (section 18)
Version 11.0 , 04 April 2020	Updated contact information
	Clarified order of procedures
	Added Short-term follow-up visit information (section 7)
	Updated with new questionnaires
	Updated medication examples
	Clarified Pulse Oximetry and Heart Rate instructions (section 9d)
	Updated Home Visit procedures.
	Included information about Short-Term Follow-up visit collection kits
	Added COVID-19 modified visit information
Version 12.0, March 01, 2021	Updated to include information that pertains to amendment 9.4
	Updated software information for PFTs
Version 13.0 March 31, 2022	Updated to include information that pertains to amendment 9.5
Version 13.0a, June 06, 2022	Updated hand-grip-strength information
Version 14 March 6, 2023	Updated Redaction Methods, removed Shandi Watts and added Sara Cummings for study contacts