Clinical Center Manual of Procedures

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Administrative Core
National Jewish Health

Data Coordinating Center
National Jewish Health

Genotyping and Analysis Core
University of Colorado Health Sciences Center
Brigham and Women's Hospital/Harvard School of Public Health
Johns Hopkins School of Medicine

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

Pulmonary Function Core
LDS Hospital

Clinical Centers
Brigham and Women's Hospital and Fallon Clinic
Baylor College of Medicine and Veterans Administration Medical Center Houston
Columbia University Medical Center
Duke University Medical Center
Johns Hopkins School of Medicine and Bloomberg School of Public Health
Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center
Morehouse School of Medicine
National Jewish Health
Temple University
University of Alabama, Birmingham
University of California, San Diego
University of Iowa
University of Michigan and Ann Arbor Veterans Administration Medical Center
University of Minnesota and Health Partners Research Foundation
Minnesota Veterans Administration Medical Center
University of Pittsburgh
University of Texas Health Science Center at San Antonio

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1. COPDGene® Overview

1a. Rationale

COPD is the fourth 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 thus is one of the most devastating disease epidemics in the United States. The determinants of the development of COPD and the factors that influence its progression remain poorly understood. Although the most common cause of COPD is cigarette smoking, a minority of people who smoke develop COPD. Thus, there are individuals who are prone to develop lung disease and other individuals who are protected from the effects of cigarette smoke. This study will investigate the genetic determinants associated with the development of COPD.

This study will create a large cohort of subjects who 1) have COPD (GOLD Stages 1 - 4), 2) do not have COPD but have smoked cigarettes (GOLD 0), 3) Do not have COPD or airway limitation by FEV_1/FVC ratio ≥ 0.70 but present with low FEV_1 (<80%) (Unclassified group), and 4) Do not have COPD and do not smoke with no airflow limitation (non-smoking controls). This cohort will be phenotyped physiologically (spirometry, 6-minute walk), clinically (health status, dyspnea, BODE score), and radiographically (chest CT scan). Genome-wide association analysis will be performed using a staged approach to identify and replicate COPD susceptibility genes. The cohort will be balanced for gender and age. The size of the cohort has been chosen to provide sufficient statistical power to identify genetic risk factors in both non-Hispanic White and non-Hispanic African-American subjects. All results will be validated in the entire cohort and in two external family-based association cohorts.

The goal of this project is to identify and correlate the genetic risk factors and phenotypic features that underlie COPD. The cohort will initially be used in a cross-sectional design but is also designed for future longitudinal follow-up. A series of case-control analyses will be conducted to identify genes controlling risk for COPD and confirm their effects. The first phase of this study is a genome-wide screen using a conventional case-control design (stratified by racial groups). Subsequent confirmation of SNPs (single gene polymorphisms) yielding statistical signals will be carried out in a second phase of independent case-control analysis. Finally, we will conduct detailed analysis of genes/regions around these confirmed SNPs that appear to influence risk of COPD. We will also validate the effects of genes identified here in two external family-based populations and a large group of mild COPD cases (GOLD Stage 1). Over time, the phenotypic, pathophysiologic and genetic data collected here can be used to identify factors that control progression of COPD as these subjects are followed prospectively.

1b. Subjects

The total number of subjects in COPDGene® is 12,000

1. Subjects with COPD – Up to 6,000 total subjects
    - Mild COPD, GOLD Stage 1 – 1,500 subjects
    - Moderate to very severe COPD, GOLD Stages 2-4 – Up to 4,500 subjects

2. Subjects without COPD (history of cigarette smoking and spirometry without airflow limitation) – Up to 4,500 subjects

3. Subjects without COPD but with airway restriction – Up to 1000 subjects (history of cigarette smoking and abnormal spirometry FEV_1/FVC ratio ≥ 0.70 but present with low $FEV_1 < 80\%$. (Please note that these 1000 subjects will be extracted from the COPD smoking Gold 1-4 groups).

4. Subjects with no smoking history and no COPD or airway restriction (normal spirometry and $FEV_1 > 80\%$) – Up to 1500 total subjects with 1000 white subjects and 500 African American subjects.

1c. Hypotheses and Specific Aims

Hypotheses:

1) Phenotypic characterization of COPD subjects using computed tomography, as well as clinical and physiological measures, will enable the broad COPD syndrome to be decomposed into clinically significant subtypes.
2) Genome-wide association studies will identify genetic determinants for COPD susceptibility that will provide insight into clinically relevant COPD subtypes.
3) Distinct genetic determinants influence the development of emphysema and airway disease.

To test these hypotheses, we will carry out genome-wide studies for genetic determinants of COPD that include precise characterization of COPD subjects using computed tomography, as well as clinical and physiological measures. This high level of detailed phenotypic characterization will enable the broad COPD syndrome to be decomposed into clinically significant subtypes and thereby enable more informative searches for genetic associations. To address our underlying hypotheses, we will complete the following Specific Aims.

Specific Aim 1: Cohort Building

Recruit a large population stratified by severity of COPD, airway restriction, and including controls (smoking controls - history of cigarette smoking with normal spirometry, non-smoking controls – no smoking history with normal spirometry) to conduct cross-sectional case-control studies. We will identify and phenotype COPD cases and control subjects from two racial groups (non-Hispanic whites and non-Hispanic African Americans) for genetic, epidemiologic, and natural history studies.

Specific Aim 2: Genome-Wide Association Study

a. Phase 1. A genome-wide panel of single nucleotide polymorphisms (SNPs) will be tested for associations with COPD in case-control samples of non-Hispanic whites and non-Hispanic African Americans.
b. Phase 2. Confirmation of SNPs yielding evidence of association in a second case-control population from these same racial groups to identify genomic regions for intensive investigation.

c. Phase 3. Mapping of 50 genomic regions yielding strong, confirmed association signals within each racial group in a third case-control population to identify susceptibility genes for COPD.
d. Phase 4. Fine mapping of candidate genes to identify susceptibility alleles and/or high risk haplotypes using
   - the entire set of case-control samples from both racial groups collected in Specific Aim 1.
   - external validation using family-based association analysis in the Boston Early-Onset COPD Study and the International COPD Genetics Network.

Specific Aim 3: Characterization of Subtypes of COPD

a. Characterize unique airway and parenchymal phenotypes among COPD cases and determine specific clinical, physiologic and functional profiles.
b. Identify susceptibility genes for COPD subtypes, including CT-defined emphysema and CT-defined airway disease.

Specific Aim 4: Natural history of COPD and Risk Factors for Progression. The cohort will be established for longitudinal follow-up with regular contact made to determine mortality, co morbid disease events and disease status based on clinical and/or chest CT evidence of progression.

1d. Future Program Goals:

1. Follow-up this large COPD cohort longitudinally to:
   - Determine risk factors that influence which GOLD 1 subjects progress to more severe stages of COPD
   - Assess risk factors for COPD progression, morbidity, and mortality.
2. Characterize functional variants in the susceptibility genes identified.
3. Additional external validation in other population cohorts to assess the generalizability of our findings about genetic determinants of COPD.

Subjects are being enrolled at twenty-one Clinical Centers in the United States:

National Jewish Health, Denver, CO
Brigham and Women's Hospital, Boston, MA
Baylor College of Medicine, Houston, TX
Columbia University Medical Center, New York, NY
Duke University Medical Center, Durham, NC
Houston Veterans Administration Medical Center, Houston, TX
John Hopkins School of Medicine and Bloomberg School of Public Health, Baltimore, MD
Los Angeles Biomedical Research Institute, Los Angeles, CA
University of Minnesota, Minneapolis, MN
Minnesota Veterans Administration Medical Center, Minneapolis, MN
Health Partners Research Foundation, St. Paul, MN
Morehouse School of Medicine, Atlanta, GA
Temple University School of Medicine, Philadelphia, PA

University of Alabama, Birmingham, AL
University of California, San Diego, CA
University of Iowa, Iowa City, IA
University of Michigan, Ann Arbor, MI
Ann Arbor Veterans Administration Medical Center, Ann Arbor, MI
University of Pittsburgh, Pittsburgh, PA
University of Texas Health Science Center at San Antonio, TX
Fallon Clinic, Worcester, MA

Please note: The name COPDGene® has been registered. When using this name in printed material, it should include the registered symbol (®) as a superscript following the name.

2. Human Subject Protection

Each site will submit an application to their local governing Institutional Review Board for Human Subjects (IRB) prior to enrolling any subjects in the study. The most current version of the study protocol is available on the COPDGene® website (https://biosweb.njc.org/sec/COPDGene/MainPage.cfm). 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.

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 the study. Any changes to the consent form or study protocol made and IRB-approved at the Clinical Center must be sent to the COPDGene® Administrative Core in a tracked changes format as well as in final clean form. A brief summary of what changes were made 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 Administrative Core. Each site should also transmit updated, stamped informed consent forms and IRB approval letters to the Administrative Core yearly and whenever the protocol is modified.

2a. Informed Consent Form

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

2b. Informed Consent Process

No procedures can be performed on any subject prior to the subject providing informed consent and receiving a unique Study Identification Number.

Informed consent is a dynamic interactive process requiring that the subject first fully understand the protocol and all procedures and only then provide consent for participation. Although the informed consent process may be delegated to a research coordinator, the local site Principal Investigator has ultimate responsibility for informed consent.

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, review subject understanding of the project, and then co-sign the consent statement acknowledging subject understanding and consent to participate.

2c. General Comments on Subject Enrollment

Making people who volunteer for this research project feel good about their experience is extremely important for 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 of us involved in the project.

If subjects feel good about their involvement in the project they will be more likely to encourage their friends and acquaintances to consider participating. Conversely, if they have a negative experience they are likely to discourage others from participating. Word of mouth is an excellent method of recruiting study subjects – especially controls who should be similar to enrolled COPD subjects in age and socioeconomic status. We suggest that each enrollee identify several other individuals including spouse and friends who have a history of cigarette smoking. We would further suggest that enrolled subjects contact such individuals and ask that they contact the Clinical Center to participate in the study. Informative brochures to assist in recruitment will be provided by the Administrative Core to each Clinical Center. These recruitment procedures may require local IRB approval prior to use at the Clinical Centers.

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

The importance of establishing rapport with each subject is of paramount importance to maintain long-term contact with subjects. This investigation is designed for longitudinal follow-up that will be the subject of future grant applications. In addition, with subject consent and IRB approval, these subjects may also be contacted for other future investigations including but not limited to the NHLBI SPIROMICS initiative.

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
- Get some idea of family supports and relationships as you gather information about 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, scheduling, company or solitude
- Be aware of cultural preferences and barriers

Be honest without setting negative expectations

- 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

- 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)
- Offer all subjects informational COPDGene® IRB-approved brochures about the study to give to spouse and friends
- 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

3. Data Coordinating Center

The Data Coordinating Center is located at the National Jewish Medical and Research Center within the Biostatistics Department headed by James Murphy, PhD. The DCC is under the direction of Douglas Everett, PhD, Assistant Head of the National Jewish Division of Biostatistics and Bioinformatics. 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.

Questions about the process of enrollment, use of the website and collection of study-related data including questionnaires and procedures should be directed to Sandi Uno, DCC Administrative Assistant at unos@njhealth.org, 303-398-1861. Contact information for other Data Coordinating Center personnel are on the study website. Questions about the protocol and manual of operations should be addressed to the COPDGene® Administrative Core Program Manager at 303-270-2399 or Barry Make, MD, Clinical Center Director at makeb@njhealth.org, 303-398-1720.

Study Website

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

https://biosweb.njc.org/sec/COPDGene/MainPage.cfm

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

Each COPDGene® investigator and coordinator is required to have a unique login identity and password to use the website. Clinical coordinators and investigators should be registered through the COPDGene® Administrative Core before they request a logon. In order to obtain your logon identity and password, please contact Ruthie Knowles (KnowlesR@njhealth.org, 303-270-2133) at the Data Coordinating Center.

4. Subject Enrollment

4a. Before Enrolling Subjects in COPDGene®

The following information is provided to assist study personnel who are enrolling subjects in COPDGene®. It is strongly suggested 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
- Proximity to six-minute walk test course
- Proximity to CT scan
- Proximity to oxygen supply if needed for COPD subjects using oxygen

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 (consider a variety of cuff sizes for larger subjects)
- Scale (preferably measuring weight in kilograms, kg)

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 and Assignment forms that assure immediate access to whether subjects meet inclusion and exclusion criteria
- Internet access is necessary to download and transmit forms, and to download spirometry results
- A full version of Adobe Acrobat needs to be installed on the study computer. Appropriate versions include Adobe Acrobat Standard or Professional
- EasyWare™ software for the spirometer should be installed on the computer. It is highly recommended that spirometry be performed while the spirometer is connected to the computer. *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.
- Microsoft Excel™ is the suggested program to locally maintain contact information about each study subject using a form available on the study website. Alternate forms using other programs that can capture and store similar information for use only at the Clinical Center may be used.

- A laser printer, or access to a laser printer, is necessary to print barcode labels and study questionnaires and forms. Laser printers are preferable to ink jet printers

Order Materials and Supplies:

- Paper, pens, clipboard, printer supplies
- NDD EasyOne™ Spirometer Spirettes™ (mouthpieces)
- Nose clips for spirometry
- Albuterol MDI and Aerochamber® spacer
- Stop watch for six-minute walk test

Blood Processing and Shipping Supplies:

- Avery Labels #5267 for printing barcode labels
- Blood drawing supplies: tourniquet, needle, alcohol wipe, band-aid, gloves
- Blood tubes, plastic – 10 ml purple (EDTA) and 10 ml SST
- Centrifuge
- Blood shipping supplies (provided by Johns Hopkins Biorepository Core)
    - Blood sample packing boxes and packing materials
    - Blood sample shipping boxes
    - Cold pack
    - Federal Express labels for blood shipment
- Urine Pregnancy Test collection and testing supplies or order forms

Chest CT Scans:

- Have Radiology Department complete and send the CT Scan Site Survey Form to the Imaging Core prior to scanning any subjects
- Send a CT scan of a custom phantom to the Imaging Core and approval by the Imaging Core prior to scanning any subjects
- Ensure Radiology Technologists have completed PowerPoint slide training prior to scanning any subjects. Fax log signed by radiology technologists to Imaging Core to document completion of training prior to scanning any subjects
- 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 a procedure for providing the CT scan forms, DVDs and mailing cases to the Radiology Department and for retrieving the forms and DVDs following the scan
- Identify a secure location where the back-up CT scan DVD will be stored at your site
- Purchase recommended DVDs
- Obtain Federal Express labels and DVD shipping packages for CT scan shipment from Imaging Core

Spirometry

- Obtain spirometry certification for each coordinator performing spirometry in COPDGene®
    - Perform spirometry on 3 naïve subjects who have not previously performed spirometry
    - Subject IDs for test subjects as part of the spirometry certification process should be "Cert 1," "Cert 2," and "Cert 3"
    - Upload certification spirometry to the COPDGene® website
    - Obtain confirmation from the Administrative Core that the Pulmonary Function Core has certified each technician prior to performing spirometry on any COPDGene® subjects

COPDGene® Study Website

- Become familiar with website use for obtaining study forms, completing Eligibility and Assessment Forms and downloading subject questionnaires and forms
- Locate contact information for COPDGene® Administrative Core and Data Coordinating Center personnel and other study personnel

COPDGene® Forms

- Download all current study forms required for a subject visit and store one copy of each on your computer
- Read and become familiar with all study forms and questionnaires
- Know how to complete all study forms including Eligibility and Assessment Forms
- Know how to transmit study forms and questionnaires to the COPDGene® Data Coordinating Center

COPDGene® Protocol

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

Manual of Operations

- Print and read the Manual of Operations and maintain a copy that is readily available during Study Visits
- Contact the Administrative Core with questions (COPDGene@njhealth.org)

Practice Subject

- Consider using a colleague as a practice subject to become familiar with study procedures prior to enrolling any subjects in COPDGene®

Locked File Cabinet for Subject Forms and Source Documents

4b. Materials Needed for a Study Visit

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

- Subject Identification Number – this is a unique number for each study subject; this is obtained from the COPDGene® website prior to the Study Visit
- Printed barcode labels
- Your local IRB-approved consent form (2 copies)
- Questionnaires and Forms – either printed or on computer except as noted
    - Informed Consent and Permissions Form
    - Eligibility Form – the Final Eligibility Form must be completed on the computer and will require an internet connection
    - Assessment Form – this form must be completed on the computer and will require an internet connection
    - Safety Assessment Form
    - Demographics – Physical Exam Form
    - Spirometry Form
    - Respiratory Disease History Questionnaire
    - Medication History Questionnaire
    - Medical History Questionnaire
    - St. Georges Respiratory Questionnaire
    - SF-36 Form
    - 6-Minute Walk Test Form
    - Blood Collection Form
    - CT Assessment Form with barcode label
    - CT Acquisition Form with barcode label
    - Subject Contact Information Form (for local use only)
    - If previous CT is used for this subject - CT Parameters Form with barcode label
    - Discontinuation Form
    - Adverse Event Form

- Computer with software: EasyWare™ spirometry software, Adobe Acrobat
- EasyOne™ Spirometer
    - Spirettes™
    - Nose clip
    - Albuterol HFA
    - Spacer for albuterol administration, such as Aerochamber®
    - Connecting cable from EasyOne™ spirometer to computer
- DVDs (two) for chest CT scan
- Plastic sleeves (two) for chest CT scan DVD
- Stopwatch for walk test
- Oxygen – for subjects using oxygen
- Pens
- Extra paper for notes
- Folder for forms

- Blood drawing supplies
  - Barcode labels
  - Blood tubes, plastic – 10 ml EDTA and 10 ml SST (make sure you have extra tubes readily available)
  - 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)
  - Barcode labels
  - Permanent marking pen to label DVDs
  - 2 DVDs (one is kept at the site as a back-up)
  - 2 plastic DVD sleeves
  - Chest CT Federal Express™ Shipment Form

4c. Subject Identification Number

As the required first step, a Subject Identification Number should be obtained. This MUST be done before a subject is seen for an in-person Study Visit and should be obtained at the time a preliminary Eligibility Form is completed if used.

Assignment of a Subject Identification Number does not necessarily indicate that the subject has signed informed consent nor whether the subject has been enrolled in COPDGene®. By requiring a Subject Identification Number in all potential subjects that are screened, we will be able to assess the number of subjects that are excluded from enrolling in the study and the reason for exclusion.

Each subject who participates in screening either in person or over the phone should be given a unique Subject Identification Number. The following process describes how to obtain a Subject Identification Number.

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

   https://biosweb.njc.org/sec/COPDGene/register.cfm

   [Alternately, you may log in to the study site home page and then choose “Get an ID” on the left-hand side of the page. Use the login name and password provided to you by the Data Coordinating Center (DCC).]

Access to the site is password-protected. The DCC is responsible for issuing individual login names and passwords to COPDGene® personnel. If you forget this information you may contact Ruthie Knowles (KnowlesR@njhealth.org, 303-270-2133) at the DCC.

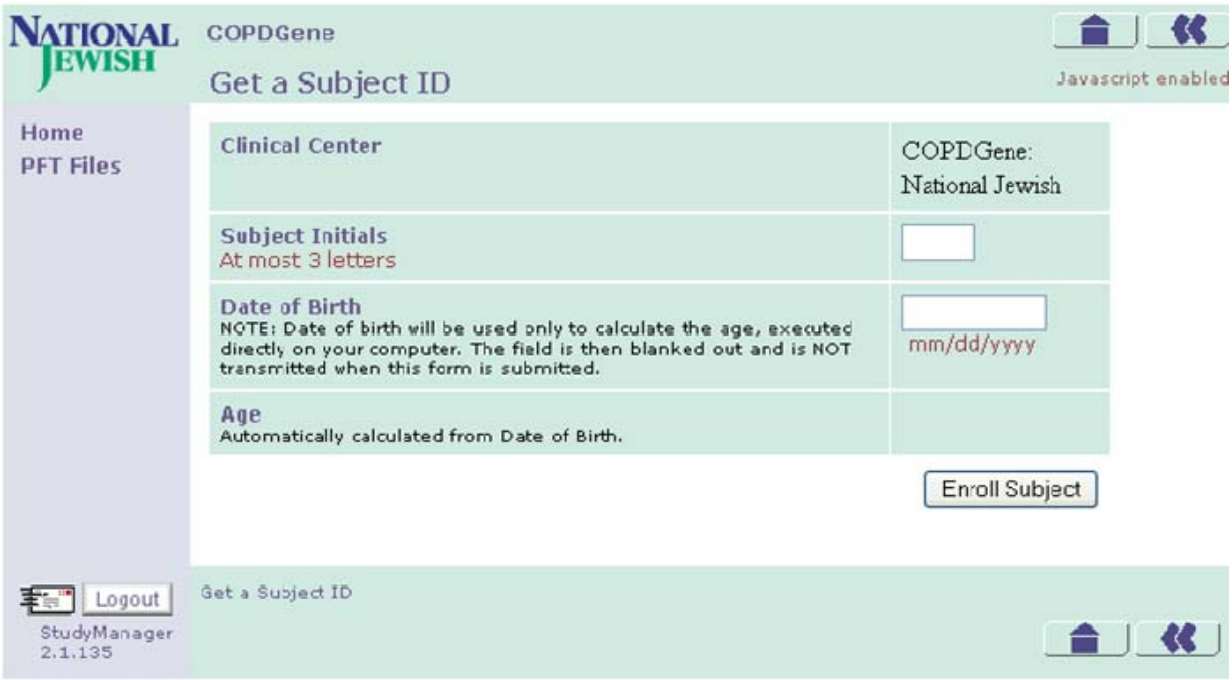
The subject ID consists of a 5-digit number followed by a character. The character is a check-digit that catches transposition of numbers in the numeric portion of the ID. In order to facilitate identification of the Center at which a subject is enrolled, a 3-character Clinical Center prefix is attached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

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

3. When an ID number is assigned, print the page with the ID number and keep this information with the source documents at your site for future reference. A sample subject identification form is available on the COPDGene® website.

4. Calculation of Age

This section clarifies the calculation of age for a COPDGene® subject. This calculation is done when a coordinator gets a subject ID at the following secure web site that is password protected: https://biosweb.njc.org/sec/COPDGene/sm/register.cfm.



This page is reached by clicking "Get an ID" under the Subjects heading of the left-hand menu of the COPDGene® web site. The highlighted text (see above) is certification by the COPDGene® Data Coordinating Center that date of birth is used only to calculate age. Depending upon the Clinical Center and their local IRB approval, age is rounded to the nearest

0.10 year or to 0.25 year (the latter for Veterans Administration Centers) on the computer of the user.

When a user goes to the web page
https://biosweb.njc.org/sec/COPDGene/sm/register.cfm
to get a subject ID, the web page itself, the coding that generates the web page, and the coding that calculates age are loaded within the browser (e.g., Internet Explorer, Firefox, Safari) that is running on the computer of the user. When date of birth is entered on this web page, that information goes no farther than the browser that resides on the computer of the user. Once the date of birth is calculated (rounded to the appropriate age per local IRB approval), the date of birth is cleared from the screen and no longer resides on the computer.

In summary, date of birth is only entered at the COPDGene® Center that is obtaining a subject ID and once the age is calculated the date of birth is not retained on the local computer.

Date of birth is also entered on the Demographics and Physical Characteristics Form. Date of birth is only entered on this form as allowed by the Clinical Center IRB approval and HIPPA restrictions. The date of birth entered on this form is only used as a check of the age calculated on the Get a Subject ID form.

4d. Barcode Labels

Once a subject receives a Subject Identification Number, barcode labels will be emailed to the coordinator. Barcode labels should be printed at the Clinical Center prior to the actual study visit since they will be needed during the study visit.

These labels will have a preprinted COPDGene® ID number that looks like this:

The labels are formatted for Avery 5267 label sheets. When printing the labels, make sure in the Page Handling section of the Print screen that Page Scaling is set to "None" before you print the labels. If you have questions about or problems with the labels, contact Ruthie Knowles (KnowlesR@njhealth.org, 303-270-2133) at the DCC.

Barcode labels should be attached to the following:

- All blood tubes
- Blood Collection Form
- CT Acquisition Form
- Chest CT scan DVD holder
- CT Shipment Form
- Chest CT Assessment Form
- Subject's Study Folder

4e. Informed Consent Administration

The study should be explained to potential subjects who pass the Preliminary Eligibility Assessment (if IRB approved at the Clinical Center to permit use of this form before informed consent is obtained). Subjects should be allowed to ask questions and may request additional time to review the informed consent and study 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 and informed consent.

4f. Eligibility Assessment

Prior to the Study Visit: Make sure you have obtained a Subject Identification Number. A *Preliminary* Eligibility Assessment may be completed prior to the Study Visit, if approved by the 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 help assure that potential subjects are not unnecessarily scheduled for a Study Visit. Check on the "Preliminary" button on the Form only when entering information for screening prior to an in-person Study Visit. This information may be saved for later review and should also be printed as a source document. To save the preliminary information, check the box to confirm all responses, and click on "Save Preliminary".
If preliminary data is entered, this information can be retrieved at a later time for that subject, as long as it has been saved. To retrieve the Preliminary Eligibility Assessment, re-enter the subject ID, select "Preliminary screening", and click on "Edit Preliminary". The data entered previously for this subject will be shown on the screen.

At the In-Person Study Visit: A *Final* Eligibility Assessment must be performed to assure the subject is still eligible and that information has not changed since the time of the Preliminary Eligibility Assessment.

When completing a Final Eligibility Assessment on the website, the study coordinator should perform this assessment based on information obtained during the face-to-face Study Visit from the potential study subject. This step is required before any questionnaires are administered, before spirometry, and prior to any testing. This form incorporates the inclusion criteria and exclusion criteria for the study and assures subjects meet these criteria prior to any evaluations. Subjects who do not pass the Eligibility Assessment are considered to have failed screening.

Even if a *Preliminary* Eligibility Assessment was completed prior to the in-person Study Visit, a *Final* Eligibility Assessment MUST be completed with the patient after the informed consent is obtained to assure it is accurate and correct. For example, a subject may have had a COPD exacerbation between the time of the Preliminary Eligibility Assessment and the in-person visit – this would exclude the subject from study procedures. (Note: Subjects who have had a recent exacerbation may be enrolled at a later date after the exacerbation is resolved – one month or more after completing antibiotics or steroids prescribed for the exacerbation.) **Do NOT click the FINAL button until you are ready to reenter all of the eligibility information. Clicking on FINAL will clear all data.**

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

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

INCLUSION/EXCLUSION CRITERIA

The inclusion/exclusion criteria for the two groups of subjects (COPD and non-COPD) are available in the study protocol and are also listed here for convenience.

General Inclusion and Exclusion criteria for all study subjects

The following criteria will be required on ALL smoking and non-smoking study subjects:

Inclusion criteria

Age 45 - 80 years
Non-Hispanic Whites and African Americans

Exclusion criteria

Smoking , ten pack years of more than 100 cigarettes in a lifetime
Physician diagnosed respiratory disease other than COPD or asthma (based on subject report)
Other concomitant respiratory disorder(such as, but not limited to, diffuse bronchiectasis, cystic fibrosis, or interstitial lung disease)
Lung surgery with removal of a lobe or more (including lung volume reduction and lung transplantation)
Lung cancer, known or suspected
Bronchoscopic lung volume reduction
Pregnancy or suspected pregnancy
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)
Use of antibiotics and/or systemic steroids (new prescription or increased dose) for a COPD exacerbation within the last month
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
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
Subjects unable to perform spirometry due to:

- 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

Participation in the ECLIPSE study
Inability to provide two telephone contact numbers
Place of permanent residence of three months or more

- **COPD Subjects:**

Additional Inclusion criteria

Smoking history of ≥ 10 pack-years
Diagnosis of COPD (post-bronchodilator $FEV_1/FVC < 0.70$) Stages 1, 2, 3 and 4 by GOLD criteria (7)

Additional Exclusion criteria

Smoking history of < ten pack years

Notes (These notes generally apply to both subjects with and without COPD):

Age: Exclusions to allow enrollment of subjects who do not meet age criteria will not be given. Subjects must be 45 years of age or older at the time of the Study Visit and must be 80 years of age or younger at the time of the Study Visit.

COPD Diagnosis: The diagnosis of COPD includes airflow limitation on spirometry and a history of risk factors (most commonly cigarette smoking) known to cause COPD. We will use NHANES (Hankinson) predicted spirometry values obtained in the United States. Subjects will be placed in a COPD Stage after post-bronchodilator spirometry that demonstrates airflow limitation ($FEV_1/FVC < 0.70$) obtained during the Study Visit. Subjects in the COPD Group do not need to have a prior physician's diagnosis of COPD. Subjects who have been given a diagnosis of COPD but who have normal spirometry will be enrolled as control subjects.

Cigarette Smoking: There are no uniform criteria for the amount of cigarette smoking required for the diagnosis of COPD. We have chosen a threshold for cigarette consumption (10 pack-years) to ensure that all subjects have a substantial environmental stress to differentiate those who have an abnormal pulmonary response to cigarette smoke and those who do not have such a response. Non-smoking controls will be defined as having smoked less than 100 cigarettes, 52 cigars or 12 oz. of pipe tobacco in a lifetime.

Other Diagnoses: Subjects will be included in the COPD group if they have evidence of airflow limitation "that is not fully reversible" using the GOLD (Global Initiative on Obstructive Lung Disease) criteria with a post-bronchodilator $FEV_1/FVC < 0.70$. The distinction between asthma and COPD is often difficult. Review of medical records of patients with COPD frequently demonstrates a physician-listed diagnosis of asthma. Elimination of asthma patients with fixed airflow limitation would inappropriately bias the findings of this study. Thus, if a subject meets

the smoking history and spirometry criteria for the study, they should NOT be excluded if they have a concomitant diagnosis of asthma.

We will employ the FVC as the primary measure of lung volume since this will allow us to compare the study results to previous large-scale epidemiologic investigations. Normal values have been published, and this maneuver is widely used. Subjects who are known to have interstitial lung disease are excluded.

COPDGene® is not targeting patients with known alpha-1 antitrypsin deficiency. Coordinators should NOT recruit patients with known alpha-1 antitrypsin deficiency. However, if patients are enrolled in the study and later found to have alpha-1 antitrypsin deficiency they will not be excluded. Alpha-1 antitrypsin deficiency is a known genetic risk factor for COPD and enrollment of large numbers of such patients will weaken our ability to find new genetic determinants of COPD.

Prior Lung Surgery or Lung Volume Reduction: Subjects are excluded if they have had a lobe or more of one lung removed, lung volume reduction surgery, bronchoscopic lung volume reduction, or lung transplant. Such surgery will impact lung function such that it will be impossible to determine the Stage of COPD.

Lung Cancer: If there is an excess number of subjects with lung cancer among COPD cases in this study, then we may detect genes associated with lung cancer rather than genes associated with COPD. Subjects with known or suspected lung cancer will be excluded. Subjects with a prior history of lung cancer, even if successfully resected and cured will be excluded. Subjects who may in the near future have a resection of a lesion suspected to be lung cancer will be excluded; these subjects may be included at a later time if the lesion proves not to be cancer and the resection removes less than one lobe of the lung. Subjects with small, indeterminate pulmonary nodules are eligible to participate.

Uncontrolled Cancer: Subjects with uncontrolled cancer of any type will be excluded because the cancer or cancer treatment may alter lung function and thus misclassify the respiratory status of the subject. In addition, we expect to conduct long-term follow-up the cohort of subjects enrolled in this study; subjects with uncontrolled cancers may expire within 5 years and prior to future planned reassessment and follow-up. These principles and the details noted above in these exclusion criteria should be used to determine which subjects should be excluded. The following examples may be used as a guide. A potential subject with a history of prostate cancer that has not been treated may be included in COPDGene®. A potential subject with a history of breast cancer without known metastases who had surgery two years ago may be included in COPDGene®.

Radiation Therapy: Subjects who have had radiation therapy to the chest or mediastinum should be excluded. Radiation therapy may alter lung function making it difficult to assess the presence and Stage of COPD. Subjects who have had radiation therapy for breast cancer may be included in COPDGene® since modern radiation techniques do not usually cause radiation changes in the lungs.

Recent Antibiotic or Steroid Use: A recent COPD exacerbation may temporarily alter lung function thus misclassifying the presence of COPD and the COPD Stage of such subjects. In addition, a recent COPD exacerbation may have an ongoing inflammatory pulmonary process or an infection that will impair the ability to diagnose, characterize and phenotype subjects in their usual stable state. Subjects who have had antibiotics or systemic steroids for a COPD exacerbation can be re-screened 30 days after cessation of antibiotics or corticosteroids. Subjects who have used an antibiotic for an infection other than a respiratory infection may be enrolled at any time they are clinically stable and do not have to wait 30 days. An example would be outpatient antibiotic treatment for a urinary tract infection.

Inability to Use Albuterol: Albuterol administration is required to obtain post-bronchodilator spirometry to assess the presence and severity (Stage) of COPD. Subjects who refuse to have albuterol administered should be excluded. Based on the Safety Assessment, subjects who have had or have the potential to develop adverse effects of albuterol should be assessed by a physician investigator to determine if it is safe for the subject to receive albuterol and continue in the study.

Relative of a COPDGene® Subject: Subjects who are related to another subject already enrolled **by marriage** are allowed to participate. For example, a sister-in-law of a COPDGene® participant may be enrolled. A spouse of a COPDGene® subject may be enrolled.

More than one racial category: Subjects are excluded if they self-designate that they are in more than one racial category.

Metal Objects in the Chest: Metal objects in the chest or chest wall will interfere with the chest CT scan. This may make assessment of the amount of emphysema and airways impossible. Metal objects in the chest include defibrillators, pacemakers, metal shoulder prosthesis and prosthetic *metal* heart valves, metal projectile or metal weapon fragment (bullet, shrapnel, shotgun shot). If there is a question about other metal objects, contact your local PI, COPDGene® radiologist, or the COPDGene® Imaging Core.

- **Smokers without COPD**

  Additional Inclusion criteria

  History of cigarette smoking $\geq$ 10 pack-years

  Post-bronchodilator $FEV_1/FVC \geq 0.70$ and $FEV_1 > 80\%$ predicted(9).

  Additional Exclusion criteria

  Smoking history of < ten pack years

Notes:

Lung Disease: The primary criterion for determination of COPD cases vs. non-smokers without COPD is spirometry, not physician diagnosis. However, subjects with pulmonary diseases including, but not limited to, interstitial lung disease, diffuse bronchiectasis, or cystic fibrosis, are not eligible for COPDGene®. Physician-diagnosed lung disease other than COPD is an exclusion for non-COPD subjects.

Note: In order to avoid potential biases involved in allowing asthmatic subjects to be part of the COPD case group but not the control group, asthmatic subjects are eligible to be either cases or controls. However, an excess of asthmatic subjects in the control group could interfere with the genetic association results. Therefore, Clinical Centers are encouraged not to enroll control subjects from sources that are enriched for asthmatics (e.g. Asthma Clinics).

Subjects may have been previously told by a physician or other health-care practitioner that they have COPD, emphysema or chronic bronchitis. Such subjects who have normal spirometry do not meet spirometric criteria for COPD and will be included in COPDGene®. In such cases where COPD is suspected, the Final Eligibility Form may have been submitted with a positive response to the question about physician-diagnosed lung disease. If this form needs to be changed based on normal spirometry results and the subject needs to thus be re-classified as *not* having COPD, coordinators should first obtain confirmation from their Clinical Center Investigator. Then the coordinator should contact Maura Robinson at the Data Coordinating Center to inform her of the need to change the Final Eligibility Form.

Spirometry: Sources of subjects will vary from center to center, but will likely include inpatient and outpatients at the centers, spouses and friends of subjects with COPD, patients in primary care practices, local patient support and educational groups, and local and national COPD voluntary organizations (such as COPD Foundation and American Lung Association).

Subjects should not primarily be recruited from sources that include a high prevalence of asthmatics such as asthma clinics or asthma patient groups. While subjects with asthma are not excluded in either control or COPD subjects in order to assure similar inclusion/exclusion criteria in both populations, the study is not designed as a study of the genetics of asthma. Thus subjects who have asthma as their primary respiratory disease should not be targeted for recruitment.

Although the primary focus of this project is COPD and COPD-related phenotypes, subjects will also be informed that this cohort may be used to study the genetic and environmental determinants of other smoking-related illnesses such as lung cancer and coronary artery disease and, with their permission on the consent form, other disorders that are not smoking-related.

- **GOLD Unclassified Subjects:**
  Inclusion criteria
    Smoking history of $\geq$ 10 pack-years
    Spirometry (Post-bronchodilator $FEV_1/FVC \geq 0.70$ FEV_1 <80% predicted)
  Exclusion criteria
    Smoking history of < ten pack years

Subjects that meet the required smoking history parameter but do not fall into either COPD or smoking control categories will be included as Smoking Unclassified subjects. These subjects will be grouped based on the occurrence of a normal spirometry accompanied by a presence of reduced air flow (post-bronchodilator $FEV_1/FVC \geq 0.70$, lowFEV_1 <80%). To date, we have found approximately 10 - 12% of our smoking subjects fall into this category. The inclusion of

the Unclassified smoking group will provide additional and possibly novel information regarding the categorization, clinical presentation, and progression of COPD in smoking populations. Since this group is already present within the current subject pool, these subjects will be clarified as a distinct subject group.

- **Non-smoking Controls**

  Additional Inclusion criteria

  No smoking history as defined by less than 100 cigarettes, 52 cigars or 12 oz. of pipe tobacco smoked in a lifetime

  No airflow limitation (Post-bronchodilator $FEV_1/FVC \geq 0.70$ $FEV_1 > 80\%$ predicted)

  Additional Exclusion criteria

  Smoking history of more than 100 cigarettes, 52 cigars or 12 oz. of pipe tobacco smoked in a lifetime

  No physician diagnosed history of respiratory disease

Subjects with no smoking history and no airflow limitation will be included as a reference population for comparison with those affected by smoking exposure. These subjects will also offer information on the processes involved in normal lung aging. Non-smoking control subjects are critical for supporting genetic and pathological findings within smoking and diseased subject groups by acting as a baseline for normal pulmonary physiology within a genetically mixed population.

Race/Ethnicity

This information is required as part of the eligibility assessment. Subjects will be asked to provide their ethnicity and race according to National Institutes of Health (NIH) categories. Subjects should be shown the following table and

- first asked to identify one ethnic category and then
- indicate one or more racial categories that they believe most accurately describes themselves.

Subjects will only be enrolled if they indicate a racial category of Black/African American or White. Potential subjects who indicate more than one race may *not* be enrolled in COPDGene®.

Only subjects who self-indicate they are non-Hispanic should be enrolled.

ETHNIC CATEGORY (indicate only one)
Hispanic or Latino
Not Hispanic or Latino
RACIAL CATEGORY
Black or African American
White
American Indian / Alaska Native
Asian
Native Hawaiian or Other Pacific Islander

Subjects should be shown the chart above and asked to self-identify race and ethnicity. Subjects may choose as many responses as they feel are appropriate. This should be completed by the subject without coaching from the coordinator or investigator.

5. Collection of Other Medical Information

Every reasonable effort should be made to collect other relevant medical information from the subject's primary care provider or physician specialists. The patient should sign a consent for release of medical information to obtain protected medical information. The following information should be obtained if available:

- High resolution CT scan within the last year if an appropriate CT protocol was used and if the required computerized archive is available for computer analysis,
- Pulmonary function tests including lung volumes and diffusing capacity within the last year,
- Arterial blood gas within the last year.

6. Subject Enrollment and Evaluation Sequence

IMPORTANT NOTE:
In order to enroll a subject and perform a chest CT scan in COPDGene®, steps 1 through 14 below MUST be followed precisely in the order specified here.

The order of Steps 1 through 14 is to assure that subjects meet inclusion and exclusion criteria as soon as possible and as efficiently as possible. Subjects may screen fail at any point during these initial steps. All data must be collected within six months of initial patient visit. Chest CT scans will be done on *all* subjects.

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

1. Prior to the study visit, obtain a unique Subject Identification Number
2. Prior to the study visit, print barcode labels that are emailed from the COPDGene® Data Coordinating Center to the principle coordinator
3. Perform *Preliminary* Eligibility Assessment over the phone or in-person, if IRB approved at the Clinical Center
4. Obtain informed consent from the subject
5. Complete Informed Consent and Permissions Form
6. Perform *FINAL* Eligibility Assessment to determine if subject is eligible to continue
7. If a pregnancy test is required, you should do it at this point prior to spirometry and albuterol.
8. Complete Demographics-Physical Exam Form including resting heart rate, oxygen saturation, blood pressure, height and weight
9. Complete Safety Assessment Form
10. Perform spirometry before bronchodilator
11. Administer 2 puffs of albuterol HFA with an appropriate spacer such as an Aerochamber
12. Wait 15 - 20 minutes after albuterol. It is suggested the wait be as short as possible to most efficiently determine if the subject will meet entry criteria. While you are waiting, you may collect contact information during this period and/or administer brief questionnaires.
13. Perform spirometry after bronchodilator and complete Spirometry Form
14. Complete Assignment Form to determine if the subject meets inclusion/exclusion criteria. This form must be completed on a computer with an internet connection. This form is necessary to determine if the subject should continue in the study for the rest of the visit including the Chest CT scan.

If a subject fails to meet study entry criteria at any time during the procedures above a Discontinuation Form must be completed. This form is also used if the subject withdraws permission to participate at any time.

The target for post-bronchodilator spirometry is 15 - 20 minutes post albuterol administration. The window for post-bronchodilator spirometry is 15 - 40 minutes post albuterol.

After the initial Steps 1-14 are completed, the remaining Questionnaires, Forms, Walk Test, CT scan and blood draw must be performed. 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 might 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.
- Ability of subjects to walk for long distances to other procedures like spirometry (pre/post bronchodilator testing), the chest CT scanner and six-minute walk course
- Potential subject fatigue after the Walk Test
- Potential subject fatigue after spirometry
- Scheduling of Chest CT scanner

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 may 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 spirometry before and after albuterol be performed with a questionnaire administration during the time between albuterol administration and post-bronchodilator spirometry. Spirometry should not be performed immediately following blood sampling. The Walk Test should be done at least 20 minutes after the albuterol administration and after the post-bronchodilator spirometry.

As an example, after the initial Steps 1-14 above, one test sequence of the remaining questionnaires and procedures that may maximize efficiency is:

15. St. George's Respiratory Questionnaire, SGRQ (to allow a rest after spirometry)
16. Respiratory History Questionnaire
17. MOS SF-36 Questionnaire
18. Blood Sampling
19. Medical History Questionnaire
20. Medication Questionnaire
21. 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.)
22. Chest CT Scan

7. Questionnaires

Questionnaires can be completed on a computer copy of the questionnaire or on a printed copy of the questionnaire.

- If you are completing Forms and questionnaires using a printed copy, you should 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 a computer copy of the Form and transmitted to the Data Coordinating Center. 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. Maintain a computer copy of each form as well on the study computer at your site.
- If you are completing Forms and questionnaires on the computer, create a folder on the computer with the Subject Identification Number. Place a copy of each Form in the folder and label each Form with name of the Form and the Subject Identification Number. Use a name for the Forms in a consistent manner that is most convenient for you and allows you to identify the Subject and the Form in the future; for example you might re-name the COPDGene® Spirometry Form as "NJ_99999Z Spirometry."

Materials for Administering Questionnaires:

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

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

Questionnaires are downloaded from the study website: https://biosweb.njc.org/sec/COPDGene/MainPage.cfm.

A new questionnaire should be used for each subject and completed on a computer. The coordinator must administer each questionnaire and fill in the subject's responses on the computer form. The coordinator MUST review all completed questionnaires with the subject to assure that all questions are answered by the subject.

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."

7a. Demographic Data and Contact Information

A Microsoft Excel spreadsheet is provided on the study website to facilitate collection of demographic information at the Clinical Center. This information should be kept at the Clinical Center and is NOT transmitted to the DCC. This information will be used by the site to contact the subject for future studies twice a year. This contact may be in the form of a phone call, a newsletter with a reply card, and/or an email with a required response.

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

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

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

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

7b. Safety Assessment Form

Prior to administration of albuterol and prior to the walk test, the Safety Assessment questionnaire should be administered. This Form provides guidelines for when an investigator should be contacted prior to performance of spirometry, administration of albuterol and performance of the Walk Test. Coordinators may ask additional questions not on this form in order to assist the local physician investigator 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 collect this information and transmit such information to the physician investigator who will make a final determination of whether the subject may proceed with COPDGene® testing. Based upon the Clinical Center Physician Investigator 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.

7c. 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.

7d. Medications Questionnaire

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.

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

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

CLASS OF MEDICATION	EXAMPLES
Short-acting beta-2 agonist	albuterol, salbutamol, pirbuterol (Maxair™), terbutaline
Anticholinergic inhaler	Atrovent™, ipratropium
Oral beta-2 agonist	Albuterol
Oral theophylline	Theodur™
Long-acting beta-2 agonist (including combination preparations that contain a long-acting beta agonist bronchodilator)	Salmeterol (Serevent™), Advair™, formoterol (Foradil™, Performomist™), Symbicort™
Long-acting anticholinergic	Spiriva™, tiotropium

7e. Respiratory History Questionnaire

These questions have been taken from the ATS Adult Respiratory Questionnaire and are used to gather a respiratory history on all subjects. Some of the questions are from the new version of the ATS questionnaire. If interviewer administration is used (which is preferred), 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 they do 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 questionnaire 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 might 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.

Question 15 – Unable to walk because of another condition. In addition to asking this question, you may OBSERVE if the subject is disabled from walking (e.g., in wheelchair, amputated leg, etc.). If subject is disabled from walking by any condition other than heart or lung disease, then fill in the reason at this item and skip to next section on COPD Exacerbations in the Last Year.

Question 16 – No attempt is to be made to separate out breathlessness from cardiac conditions.

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

Question 5 through 7 – Chronic Bronchitis, Emphysema, COPD. We are interested if they have been labeled 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 – 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 non-smoking 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 them to give you a general idea of their smoking habits. Asses 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).

Educational and Occupational History

Questions 4 and 9 - Do not include "housewife" or "house-husband" as affirmative occupation response and do not write them in the occupation field.

Family History

Question 1 - Ask all questions about father first, then all questions about mother.

7f. St. George's Respiratory Questionnaire

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

7g. MOS 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 non-smoking 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 non-smoking 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.

8. Physical Characteristics

8a. Height

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

Measure the subject's height either in centimeters (cm) to the nearest cm, or in inches (in) to nearest 1/2 inch 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.

If the subject is unable to stand, or has marked spinal deformity (e.g., severe kyphoscoliosis), an arm span measurement may be used to estimate standing height. Have the subject stretch the arms in opposite directions and attain the maximal distance between the tips of the middle fingers. For white men, height = arm span/1.03, for African-American men height = arm span/1.06, and for women, height = arm span/1.01. Be sure to denote the correct units of measurement on the Physical Characteristics Form.

8b. Weight

The subject's weight should be measured using an accurate scale with the subject barefooted or in stocking feet. 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 may be recorded in kilograms (kg) to nearest 0.5 kg, or in pounds (lb) to the nearest pound. Be sure to denote the correct units of measurement on the Demographics and Physical Characteristics Form.

8c. Pulse Oximetry and Heart Rate

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

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

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

9. Spirometry

9a. 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 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. The subject's effort is called the *forced expiratory maneuver* and most commonly only measures the amount and speed of air that is exhaled.

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

9b. 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 (FEV_1)** 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 limitations such as COPD and asthma. The FEV_1 may also be reduced in patients with restrictive disorders.

C. **The ratio of FEV_1 to the FVC (FEV_1/FVC)** is the most sensitive and specific index of airflow limitation measured by a spirometer. It is obtained by dividing the FEV_1 by the FVC, and is expressed as a percent (i.e., 100 x FEV_1/FVC). *Note that the FEV_1/FVC ratio is the ratio of the absolute FEV_1 and absolute FVC in liters and is not usually expressed as a percent of predicted.*

D. **Forced Expiratory Volume at Six Seconds (FEV_6)** 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 FEV_6, and more particularly in the FEV_1/FEV_6 ratio, as an alternative to the FEV_1/FVC ratio. Use of the FEV_6 may be easier to obtain, particularly for patients with severe airflow limitation with long forced exhalation times.

E. The ratio of FEV_1 to the FEV_6 (FEV_1/FEV_6) is an alternative to the FEV_1/FVC ratio. A secondary objective of COPDGene® is to evaluate the utility of the FEV_1/FEV_6 ratio, particularly with respect to the assessment of COPD.

9c. 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, preferably with a window, 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 and document them in their local Manual of Procedures.

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

The ndd EasyOne™ Spirometer does not need calibration. However, a calibration check should be carried out daily to ensure that the spirometer is reading accurately. Instructions for performing the calibration check are in the ndd EasyGuide™ technical manual and appear in section 9n. The calibration syringe and adapter should always be stored next to the spirometer so that the temperature between 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.

9d. Setting up the ndd EasyOne™ Spirometer

Prior to conducting the spirometry measurement, the technician should assure that the configurations of the EasyOne™ are set according to the specifications outlined under the "ndd Configuration Settings for Use in COPDGene®" below in sections 9j and 9p. 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.

9e. Setting up the Computer to be Used with the Spirometer

Install the EasyWare™ software from the CD included with the ndd spirometer on all PC computers that will be used for spirometry the study. Note that a Macintosh computer can NOT 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™.

After installing the EasyWare™ software on your computer, follow the directions below to change the default settings:

1. Open the EasyWare™ program on your computer.
2. Open the "File" pull-down menu.
3. Select "Preferences"
4. Mark the "Screen Connector" button (***NOT*** USB Cradle or Serial Cradle)
5. Click "OK."

9f. Medication Use Prior to Testing

The subject's recent bronchodilator use needs to be recorded on the COPDGene® Spirometry Form. Some commonly used currently available bronchodilators and their classes are listed in the table in section 7d 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 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 it is the post-bronchodilator measurements that are used to define and assess the Stage of COPD.

9g. Bronchodilator Administration

In order to provide an assessment of bronchial hyper-responsiveness and to establish a diagnosis of COPD and the 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™.

9h. Contraindications

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

- chest or abdominal surgery in the past three months
- a heart attack in the last three months
- detached retina or eye surgery in the past three months

- hospitalization for any other heart problem in the past month
- a resting pulse rate more than 120 beats/minute (participant should be sitting for at least 5 minutes prior to pulse rate determination)

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

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

9i. 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.

9i.1. Safety checks

Complete the Demographic Physical Exam Form and Safety 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, check 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 bottom of the Safety Assessment Form.

9i.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.

9i.3. Enter the participant data into the spirometer

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

- ID field: Enter the participant's COPDGene® ID number. This must be done in order to link the participant's questionnaire data with their spirometry data.
- Name field: Leave blank. Please do NOT enter the participant's name into the ndd.
- Tech ID: Enter the 3-letter initials of the coordinator performing the test.
- Other fields: Enter the subject's age, height, weight, ethnic category, gender.

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

9i.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.

9i.5. Demonstrate the maneuver

Explain that the participant should:

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

A vigorous demonstration of the maneuver by the technician will help to prevent wasted time and effort caused by the participant's lack of understanding. Demonstrate the correct placement of the mouthpiece. The technician should take a deep breath and emphasize the maximal depth of inhalation. He/she should then demonstrate the proper positioning of a demonstration Spirette™ mouthpiece and dramatically blast the air out as fast as possible.

9i.6. Pre-bronchodilator test

After instructing the participant about the procedure for spirometry testing, proceed with the actual testing, following the procedures outlined in sections 5.2 to 5.4 of the ndd EasyGuide™ Users' Manual and the detailed steps beginning on page 44.

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 FEV_1s and the two best FVCs from these maneuvers both within 150 milliliters of each other.

9i.7. 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 to do the post-BD spirometry.

9i.8. Post-bronchodilator maneuver

The post-bronchodilator (post-BD) maneuver can start anytime after the 15-minute wait. 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.

9i.9. Print results

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

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

9i.10. 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. 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.

9j. Step by Step Spirometry Instructions

9j.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."

9j.2. Conduct the Pre-bronchodilator Spirometry

Note: The subject must have already completed and passed the Safety Assessment and if necessary been approved for albuterol use by one of the site's Investigators prior to spirometry.

a. Connect the EasyOne™ USB cable to the computer's USB port.
b. Launch the EasyWare™ software via the desktop icon.
c. First time only: Choose "File", then choose "Preferences," and ensure that "Screen Connector" is selected.
d. Power on the EasyOne™ and connect it to the cable. ("Device Connected" will display at the bottom of the EasyWare™ window.)
e. From the **Edit** menu, choose **New Patient**, and enter the subject identification numbers, three-letter Tech ID, date of birth, height, weight, gender, asthma status, ethnicity, and smoking status. Confirm with **OK**.
f. Insert a new Spirette™ into the EasyOne™, matching the arrows on the front of both.

g. From the **View** menu, choose **Test On-Line**.

h. To perform the Forced Vital Capacity maneuver, do the following on the EasyOne™ device keypad:
   i. Use (>) to highlight 'Recall' and press ENTER to choose it
   ii. Use ENTER to choose "Last Test"
   iii. Verify the subject ID number and press ENTER.
   iv. Press ENTER to choose FVC (Expiratory)
   v. **It is extremely important that 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
   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 (best two FEV_1 and FVC volumes within 150 mL of one another), or until 8 efforts have been made. **Note: The EasyOne™ software may consider a session complete before these criteria have been met. If that is the case, choose ADD to continue the session**.
   x. If the "Acceptable" message appears, use (>) to highlight 'Post' and press ENTER to choose it, preparing 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 a copy of all data at your site.

9j.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.

9j.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
    ix. When prompted, with "Blast Out," assist participant in applying nose clips and instruct them to execute a forced expiratory maneuver.
    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.

Complete the Assignment Form from the COPDGene® on the computer. Enter the post-bronchodilator values for FVC and FEV1. Also enter the predicted values for FVC and FEV1 (the values are obtained from the pre-bronchodilator tests)—the percent predicted will be calculated from these values.

9j.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.

9j.6. Upload the Database File to the Website

The file that should be uploaded to the website is the Access database itself. If for some reason you need to open the database and examine the tables, the password is "LungHealth", but this

should not be necessary. Further, if you open it, Access might try to "convert" the version. **Never** choose to convert to a newer version – this will make the database malfunction with the EasyWare™ software. Simply choose to open the database.

If you cannot find the location of this file on your computer, follow these steps:

1. Open the EasyWare™ software on your computer.
2. Click on "File".
3. Click on "Preferences".
4. In the box below "Database Path and Name", is the place where your mdb file is located.
5. The default location for your database file is: C:\Program Files\ndd Medizintechnik\EasyWare\EasyWare.mdb. You should find your file in this location, unless you or someone else has changed the settings for the software.

All data that the PFT Core needs is in the "Easyware.mdb" file. Make a copy of this and upload it to the COPDGene® website (see steps below). It would be helpful if you rename it when you up load it. Please use the following format:

SITENAME_COPDGene_MM_DD_YYYY.mdb

For example: Uploading a file from Iowa on Feb 14, 2008, you would name the file the following:

"IOWA_COPDGene_Feb_14_2008.mdb"

This will provide a unique name for every site on every day that they upload.

To upload the database to the website:

1. Open your internet web browser and go to the COPDGene® website (https://biosweb.njc.org/sec/COPDGene/MainPage.cfm).
2. Log into the website. If you have lost your log-in information, contact Maura at the DCC.
3. On the left panel, click on "PFT Files."
4. Log into the website again.
5. Click on the 

button across from the group called "COPDGene: Your Site."
6. Click on the "Browse" button and locate your database (see the directions above if you cannot find it).
7. Click on the .dmb file and choose to open it.
8. You may use the comments section to indicate if the new tests are for certification or subjects.
9. Click "Add File Now." You should now see your file in the table.
10. Once you add a file to a group, everyone in the group will be emailed that you have uploaded a file to their group (you will not receive the email). These emails are sent from the DCC hourly.

9k. 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 FEV_1 taken from acceptable forced expiratory maneuvers must show minimal variability (preferably within 150 milliliters of the second highest FVC and FEV_1). 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 FEV_1 and FVC as the best measurements from acceptable and reproducible maneuvers. **It is not necessary that they all come from the same maneuver**. The FEV_1/FVC and FEV_1/FEV_6 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.

9l. 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 FEV_1 and FVC are considered to be in the normal range. Individuals whose test results are below this level may have an abnormality.

The ndd EasyOne™ spirometer offers a number of published predicted values, most of which were derived from studies of largely white participants. Four ethnic correction settings are available that allow you to customize the amount of adjustment that is made for selected racial

groupings. Consult the EasyGuide™ users' manual, sections 8 and 12, for more information regarding the use of prediction equations. For COPDGene®, we will use the reference values that were derived from the 3rd National Health And Nutrition Examination Survey (NHANES III) in the United States (Hankinson et al., AJRCCM 1999; 159:179-187). This study used a large, randomly selected subset of the entire U.S. population, which included a variety of ethnic groups and strict attention to quality control according to current American Thoracic Society guidelines.

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

9m. 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.

9m.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 also will prevent 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 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 FEV_1 and FVC results used in the study.

9n. 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 test, 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.

9o. Trouble Shooting

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

9p. ndd EasyOne™ Configuration Settings for Use in COPDGene®

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

Test Settings:

1) Predicted = "NHANES III"
2) Add Ped = "Blank"
3) Value Sel = "Best Value"
4) Interpretation = "- - - -"
5) Lung Age = "OFF"
6) Automatic QC = "ON"

7) FVC Selection = “FVC”
8) PEF unit = “L/sec”
9) African ethnic = 88%
10) Asian = 100%
11) Hispanic = 100%
12) Other ethnic = 100%
13) Curve Storage = “3 Best Curves” **<Very Important!!! >**

General Settings:

1) Time Form = 24 hr(
   Date Format = “DD/MM/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 Humidity = 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

9q. 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	□	
Safety Assessment Form administered	□	
Prepare to conduct spirometry	□	
Confirm race/ethnicity of participant	□	
Explain purpose of test	□	
Demonstrate maneuver	□	
Complete pre-bronchodilator test	□	
Administer bronchodilator	□	
Wait 15-40	□	
Complete post-bronchodilator test	□	
Print results	□	

9r. Common Questions and Answers for the ndd Spirometer

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

1. CALIBRATION CHECK ERRORS

Problem: Unable to obtain an acceptable calibration check.

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

a. The calibration syringe may be defective.

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

b. Faulty ndd device.

Solution: We are aware of at least one instance where the ultrasound transducer was not mounted correctly in the factory and therefore resulted in excessive variability (up to 10%)

during calibration tests. If you suspect you may have a faulty device, notify the Operations Center, which will in turn notify ndd. If the unit is indeed defective, ndd will replace it.

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

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

d. The room is very 'windy' because the windows and the doors are open to supply cooling.

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.

FEV_1 values will be different since in human tests the FEV_1 calculation needs to follow ATS algorithms. If there is slow flow before the actual start of the blow, this would cause a lower FEV_1. To correct for this, the t-zero point is calculated by back extrapolation from the maximum volume increase in the Volume Time Curve. FEV_1 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 FEV_1 values will be.

The flow parameters (PEF) can usually vary more than the Volume parameters. In the ATS waveform test a variation of +/- 12% is allowed for PEF. This is because gas can be compressed and resistance between syringe and sensor can influence the result.

2. SETTING ZERO FLOW BASELINE

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

Explanation: Prior to every FVC test or calibration check, the zero flow baseline needs to be set. You should see the message "setting baseline. Block Spirette™ to avoid flow" on the screen. The technician should make sure that there is absolutely no flow through the Spirette™ while the baseline is set. Hold the instrument still and block the Spirette™ or hold the instrument close to the body to make sure there is no flow. If the baseline is not set correctly, there is an offset in the flow measurement. This causes an inaccuracy in the FVC value. The longer the measurement takes, the bigger the error in the result. If there is a 20 ml offset, the error after 8 seconds in the FVC value is 160 ml. In the FEV_1 value the error is only 20 ml.

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

3. SMALL CURVES

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

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

This problem can be easily avoided if the patient holds the instrument himself. 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™ recognizes when the actual test starts. EasyOne™ will recognize the incorrect trial and give a coaching message.

4. "ERROR 6" MESSAGE

Problem: Some instruments have occasionally displayed an "error 6" message on the screen. The message prevents further test maneuvers from being performed on the patient.

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

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

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

6. "KEEP GOING..." MESSAGE

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

Explanation: In most cases this happens due to incorrect baseline setting (see #2 above). At the beginning of a new test session make sure the user blocks the Spirette™ to avoid

flow. If this is not done carefully, a wrong flow offset can be set which leads to the described behavior.

7. POWER DOES NOT TURN ON/OFF CORRECTLY

Problem: the device cannot be switched on or off.

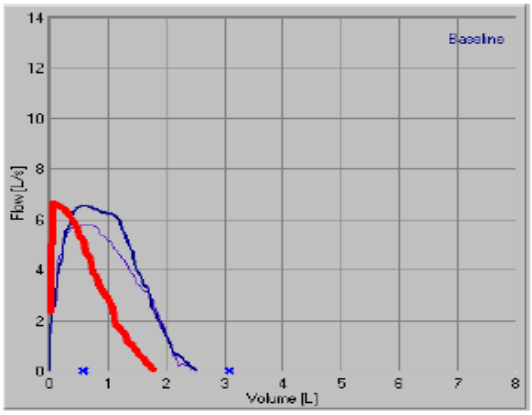
Explanation: ndd has not been able to reproduce this problem, and would appreciate more information in order to properly investigate the issue. If the problem occurs, please supply the following information: does the issue always happen with the same device, how often does it happen, and under what circumstances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

8. FLOW-VOLUME CURVES HAVE STRANGE SHAPE

Problem: Some of the flow-volume curves have a strange shape and the FEV_1 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 interviewer would hold the device while the patient inhaled through it prior to the exhalation. At the end of the inhalation the interviewer would press the ENTER key to start a new trial.

The ndd 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 and the patient when they do not get acceptable results. The interviewer should make sure that the instrument is started early enough, at least one second prior to the forced exhalation. (see also #3 above)

9. QUALITY GRADE GETS WORSE

Problem: It can happen that the quality grade changes from A or B to C (i.e., 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 C or D. (see also #5 and #11)

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

10. EASYONE™ WON'T ACCEPT POST TEST DATA

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

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

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

11. EASYONE™ ACCEPTS BAD TESTS

Problem: Occasionally the EasyOne™ accepts bad curves, which can result either in inappropriate values for FEV_1 and FVC or in inappropriate QC grades.

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

a. A double inspiration due to cough or hesitation in starting
b. Variable effort or cough during a trial

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

during the test and on the report. Other than this, the test procedures and messages are the same as when the QC grade function is turned on.

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

12. STAFF DISAGREE WITH GOOD QC RATING

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

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.

10. 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.

10a. Contraindications

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

10b. Facilities/Equipment

- Stopwatch
- Course pre-marked with distances
- Portable oxygen delivery system if the patient is on oxygen (nasal cannula)
- Subject instructions below

10c. 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 for all subjects. 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.

10d. Procedure

Oxygen saturation, heart rate, and blood pressure will NOT be monitored during the walk. A staff member will carry a portable oxygen supply if supplemental oxygen is used by the patient.

10e. 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.

10f. 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?"

10g. Instructions during Walking

At the end of each minute the patient will be given the time elapsed, the time remaining, and a standard phrase of encouragement as follows:

Minute 1 – "Do your best."
Minute 2 – "Try your hardest."
Minute 3 – "Keep going."
Minute 4 – "Give it your all."
Minute 5 – "Walk faster if you can."

For example, at the end of minute 4, the technician would say: "4 minutes, you have 2 to go, give it your all."

10h. Research Coordinator Responsibilities

Carry supplemental oxygen, if oxygen is routinely used by the subject during activity. 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 meter or foot. Rest periods are not recorded; a test lasts 6 minutes if the patient is on the course for 6 minutes; the patient need not walk continuously for 6 minutes for the walk to be considered to have a normal termination.

If the test terminates abnormally (i.e., patient leaves the course before 6 minutes have elapsed), record the distance walked, time on the course, and reason why the test was terminated before 6 minutes had elapsed.

10i. Abnormal Test Termination Criteria

- Chest pain suspicious for angina.
- Evolving mental confusion or lack of coordination.
- Evolving lightheadedness.
- Otherwise warranted based on clinical condition.

11. Imaging

11a. CT Acquisition at Study Sites

11a.1. Site Survey

Clinical Centers must complete an initial Imaging Site Survey Form (Appendix) to identify responsible personnel and CT scanner models prior to obtaining scans for the study.

Each scanner will be assigned a specific ID number by the Imaging Core; this information will be recorded on the Image Collection Form when each scan is performed.

Survey should be faxed to the Imaging Center at 303-270-2538. This survey should also be kept on file at each clinical site.

11a.2. Technologist Training

A PowerPoint training set, "CT Imaging in COPDGene®" has been implemented for technologists at the Clinical Centers to assure understanding of the outline of the study, and compliance with the radiology protocols. Each technologist involved in the acquisition of scans must be certified as having reviewed the training set prior to performing CT scans for the study.

After the technologist reviews the PowerPoint slides, they must sign the Technologist Training Log to attest that they have reviewed and understand the study protocol. Before the start of enrollment, the clinical center must ensure that each involved technologist reviews the slides and signs the Log. After all technologists have reviewed the slides, the clinical center should fax this form to the Imaging Core at 303-270-2538. The original copy of this form should be kept at the clinical sites.

When additional radiologic technologists become involved in the study, the additional technologist should review the slides and sign the log. At this point, the clinical center should again fax the form to the Imaging Core so that the core has record of every new technologist.

The Imaging Core will keep a record of the study-affiliated technologists at every clinical center. An email will be sent from the Imaging Core to the study coordinator notifying them regarding the receipt of a signed Technologist Training Log.

11a.3. Scanner Quality Assurance

At each study site, each CT scanner used in the study will scan a phantom at the initiation of subject enrollment, on an ongoing monthly basis, and after any hardware or software change. The site will use a customized COPDGene® phantom.

The phantom will be scanned using the study protocol parameters for each scanner. The phantom scans will be transferred on DVD to the Imaging Core for analysis. Scan information will be recorded on the Image Collection Form (see appendix).

The DVD with the Phantom Scan information and the Image Collection Form should be sent to the Iowa Imaging Core.

11a.4. Subject Preparation for CT Scan

1. Prior to the study, the subject's identity will be confirmed according to institutional policy.
2. The subject will remove all metallic devices from the chest area.
3. The subject will be informed of the importance of compliance with the breathing instructions (in Section 11c below). Ability to comply with instructions should be assessed, and conditions that might impair compliance such as deafness, breathlessness, or mental impairment should be noted.
4. At least one rehearsal of the end-inspiratory breathhold should be performed.

11a.5. CT Acquisition

All CT scans will be obtained using the protocol and breathing instructions as indicated (see Protocol in Section 11c). Scans must be reconstructed using two algorithms, edge enhancing and smooth. Contiguous end-expiratory CT images will also be obtained where possible. Additional reconstructions may be performed as required at study site, but only the contiguous thin section images, reconstructed in two formats, should be sent to the Core Laboratory.

The responsible CT technologist should complete the Image Acquisition Form, and sign to confirm that the study protocol was followed and the scan meets the expectations of the study. The protocol for CT acquisition will be printed on the reverse of the Image Collection Form.

11a.6. Non-study Scans

Scans on eligible patients performed outside the COPDGene® study may be accepted for purposes of the analysis if they meet the non-study scan criteria (see appendix). Final decisions on acceptability of these scans will be at the discretion of the Imaging Core, based on their adequacy for quantitative image analysis. The study coordinator should ensure that the CT Assessment Scoresheet and the Non- COPDGene® Scan CT Acquisition Parameters forms are completed for these subjects (see instructions in the CT Assessment Scoresheet section).

11a.7. CT Assessment Scoresheet

The radiologist will complete the CT Assessment Scoresheet on each subject for both study and non-study scans, and will sign off on the quality of the scan. This scoresheet will be both submitted electronically and the original, signed copy will be sent with the Image DVD to the Imaging Core.

How to Submit the CT Assessment Scoresheet Electronically:

1. Sign in to the COPDGene® website at https://biosweb.njc.org/sec/COPDGene/MainPage.cfm
2. Click on the "Forms" heading.

3. Download the scoresheet as a PDF by clicking on the "CT Assessment Scoresheet" link.
4. Complete the required information on the form.
5. Print and save a copy of this form at the Clinical Center.
6. Submit the scoresheet information by clicking on the "Send the data to the DCC" link at the bottom of the last page.
7. A copy signed by the radiologist must be shipped to the Imaging Core with the Image DVD.

Note: The electronic submittal of the CT Assessment Scoresheet is performed by either the radiologist or the study coordinator. The process will be determined and coordinated individually by each clinical center.

11a.8. Image Acquisition Form

There are a number of Image Acquisition Forms provided on the COPDGene® website. The purpose of the different versions is to provide the technologist with the form and the appropriate protocol for the scanner that will be used. The proper version of the Image Acquisition Form will help to ensure that the proper COPDGene® protocol is accurately followed.

The Image Collection Form should be printed from the website by the coordinator and a bar code applied to the top portion. The form with the appropriate protocol should then be submitted to the radiologist technologist before the scan is performed. The technologist will fill out this form. When the Images are shipped to the Imaging Core, this form should be included in the shipment.

If the CT was not performed according to the COPDGene® protocol, the "Non- COPDGene® Scan CT Acquisition Parameters" form must be completed by doing the following (to be performed by the coordinator):

1. Sign in to the COPDGene® website at https://biosweb.njc.org/sec/COPDGene/MainPage.cfm
2. Click on the "Forms" heading.
3. Download the form as a PDF by clicking on the "CT Acquisition Parameters" link.
4. Complete the required information on the form.
5. Print and save a copy of this form at the Clinical Center.
6. Submit the scoresheet information by clicking on the "Send the data to the DCC" link at the bottom of the last page.

11a.9. Scan Shipment

CT Scans on DVD

All protected health information (PHI) should be removed from the DICOM header, and replaced with the participant's study ID. Specific DICOM fields to be removed include the patient name, accession number, medical record number, date of birth, date of examination, and comment field.

The anonymized scan data should be written to DVD, and sent to the Imaging Core in a polypropylene protective case.

Ideal Items to Be Used:

Item	Manufacturer	Provided By
DVD-R (Gold Archival Grade)	Verbatim Ultralife Gold Archival Grade 4.7 GB 8X	Clinical Center
Polypropylene DVD Case	TRIMPak II	Imaging Core
Padded Pak	FedEx	Imaging Core
Preprinted Airbill	FedEx	Imaging Core

Imaging Shipment Form

The Imaging Shipment Form should be included with each shipment sent to the Imaging Core. This Form will be used to document the materials included in each shipment as a quality control measure. Be sure to add the barcode of each subject to this form.

Keep a copy of this form at the Clinical Center.

Labeling Imaging Materials

The DVD should be labeled using a black permanent marking pen. The following information should be printed clearly on the DVD:

- Subject ID including Clinical Center, such as NJC
- Date of scan
- COPDGene®

The DVD should then be placed in the Plastic Case provided. Only one DVD should be placed in each Plastic Case. A barcode label should be placed on the Plastic Case. Barcodes are generated by the DCC (these are the same barcodes that are used for Blood shipment). These barcodes will be emailed to the study coordinator as a PDF file after the subject is assigned an ID number by the DCC on the COPDGene® website. The PDF file will be printed on Avery 5267 8.5 x 11 paper labels, 4 across and 20 down, using a standard office printer. An example of the barcode is shown below.

Barcodes should be placed on:

- CT Scan Plastic Case
- CT Scan Assessment Scoresheet

- CT Acquisition Form or Non-Study Image Acquisition Form
- Image Shipment Form

A backup DVD, labeled in the same manner as the primary DVD sent to the Imaging Center, should be stored at the clinical site with the subject's study records and all source documents.

Shipping CT Scans to Imaging Core

Upon initiation of enrollment at the clinical center, the Imaging Core will arrange a shipment of 25 plastic DVD cases, 25 FedEx Padded Paks and 25 preprinted airbills to the site for shipment of CT scans.

Shipping Instructions:

1. Write information on DVD as noted above.
2. Place DVD in plastic case.
3. Place barcode labels on materials as noted above
4. Complete the Image Shipment Form.
5. Place scan DVD in the case, CT Acquisition Form, Image Shipment Form, and CT Assessment Scoresheet in FedEx Padded Pak.
6. Complete the preprinted FedEx Airbill and place on sealed package.
7. Call FedEx for a pickup, or drop-off at local Fed-Ex location.
8. Enter the shipment tracking number, shipment date, and subject IDs on the COPDGene® Website by clicking on the "CT Data" under the Tracking heading. This must be done on the same day that the CT is shipped.
9. The first 10 CT scans from each site or subsite should be sent as soon as they are completed. After the first ten have been quality checked, subsequent scans can be sent in weekly batches with a maximum of ten DVDs in each package.
10. More shipping supplies will be sent to your site as needed. Contact the Imaging Core at 303-270-2529 when your supply runs low.

11a.10. Quality Assurance

Anonymized images will be submitted on DVDs to the Imaging Core in DICOM format, using a study ID as the only identifier. Upon arrival at the Imaging Core at National Jewish Medical and Research Center, CT media will be processed by the research staff to verify anonymization and appropriate identification of study information, protocol compliance, image quality, and image count.

The Imaging Core will verify that the forms match the ID on the DICOM header on the submitted DVD. If quality issues are identified, the staff will complete a quality form and will contact the site to attempt resolution. The site will be notified within 5 business days of quality problems. If the CT data are found to be unusable because of quality problems, the participant will not be enrolled in the study.

11b. Data Reporting

The following data will be reported to the DCC:

- Receipt of complete and technically adequate scan

- Patient dose and scan duration as recorded on the image acquisition form
- Quantitative parameters outlined above
- Quality assurance data

11c. Instructions for CT Scan Acquisition

GENERAL: This study consists of 2 scouts (topograms) and 2 scans. All scans use the same parameter grid.

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

SUPINE INSPIRATION: Start at **bottom** of lungs, end at **top** of lungs. **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!"

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: Same protocol as **SUPINE INSPIRATION**. Start at **bottom** of lungs, end at **top** of lungs. **Instruct the patient to breathe as follows:**

"For the second part of this study you will be asked to blow out your breath and hold it out for about 20 seconds. This is usually more difficult than holding your breath in, but do the best that you can. If you cannot hold your breath out that long, take a very slow shallow breath in if you need to."

"For now, take several easy, deep breaths and relax while we prepare to take the last CT scan of your lungs."

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

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

"Take in a deep breath….and let it out."

"Take in another deep breath….and let it out."

"Take in another deep breath, let it out and hold your breath out! Do not breathe!"

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!"

(b) Inspiratory CT

Scanner make	GE	GE	SIEMENS	SIEMENS	PHILIPS	PHILIPS	PHILIPS
Scanner model	LS 16	VCT-64	Sensation-16	Sensation-64	16 slice	40 slice	64 slice
Scan Type	Helical	VCT Helical	Spiral	Spiral	Axial Helix	Axial Helix	Axial Helix
Rotation Time (s)	See mA	See mA	0.5	0.5	0.5	0.5	0.5
Det. Configuration	16x0.625	64x0.625	16x0.75	64x0.6	16x0.75	40x0.625	64x0.625
Pitch	1.375	1.375 mm	1.1	1.1	1.188	0.923	0.923
Speed (mm/rot)	13.75	13.75	13.2	21.1	0.5	0.5	0.5
kVp	120	120	120	120	120	120	120
mA	400 @ 0.5s	400 @ 0.5s	*Effective mAs:* 200	*Effective mAs:* 200	mAs 200	mAs 200	mAs 200
Dose modulation	Auto-mA off	Off	CARE Dose 4D off	CARE Dose 4D off	Off	Off	Off
Reconstructions							
RECON1							
Algorithm	BONE	BONE	B46f	B46f	Detail (D)	Detail (D)	Detail (D)
Thickness (mm)	0.625	0.625	0.75	0.75	0.9	0.9	0.9
Interval (mm)	0.625	0.625	0.5	0.5	0.45	0.45	0.45
DFOV (cm)	Lungs*	Lungs*	Lungs*	Lungs*	Lungs*	Lungs*	Lungs*
RECON 2							
Algorithm	Standard	Standard	B31f	B31f	B	B	B
Thickness (mm)	0.625	0.625	0.75	0.75	0.9	0.9	0.9
Interval (mm)	0.625	0.625	0.5	0.5	0.45	0.45	0.45
DFOV (cm)	Lungs*	Lungs*	Lungs*	Lungs*	Lungs*	Lungs*	Lungs*

* reconstruction field of view should encompass the widest diameter of the lung.

(c) Expiratory CT

Scanner make	GE	GE	SIEMENS	SIEMENS	PHILIPS	PHILIPS	PHILIPS
Scanner model	LS 16	VCT-64	Sensation-16	Sensation-64	16 slice	40 slice	64 slice
Scan Type	Helical	VCT Helical	Spiral	Spiral	Axial Helix	Axial Helix	Axial Helix
Rotation Time (s)	See mA	See mA	0.5	0.5	0.5	0.5	0.5
Det. Configuration	16x0.625	64x0.625	16x0.75	64x0.6	16x0.75	40x0.625	64x0.625
Pitch	1.375	1.375 mm	1.1	1.1	1.188	0.923	0.923
Speed (mm/rot)	13.75	13.75	13.2	21.1	0.5	0.5	0.5
kVp	120	120	120	120	120	120	120
MA	100 @ 0.5s	100 @ 0.5s	*Effective mAs:* 50	*Effective mAs:* 50	50 mAs	50 mAs	50 mAs
Dose modulation	Auto-mA off	Off	CARE Dose 4D off	CARE Dose 4D off	Off	Off	Off
Reconstructions							
RECON1							
Algorithm	BONE	BONE	B46f	B46f	Detail (D)	Detail (D)	Detail (D)
Thickness (mm)	0.625	0.625	0.75	0.75	0.9	0.9	0.9
Interval (mm)	0.625	0.625	0.5	0.5	0.45	0.45	0.45
DFOV (cm)	Lungs*	Lungs*	Lungs*	Lungs*	Lungs*	Lungs*	Lungs*
RECON 2							
Algorithm	Standard	Standard	B31f	B31f	B	B	B
Thickness (mm)	0.625	0.625	0.625	0.75	0.9	0.9	0.9
Interval (mm)	0.625	0.625	0.5	0.5	0.45	0.45	0.45
DFOV (cm)	Lungs*	Lungs*	Lungs*	Lungs*	Lungs*	Lungs*	Lungs*

* reconstruction field of view should encompass the widest diameter of the lung.

12. Collection of Blood Samples

12a. Purpose of COPDGene® Study Center LAB Manual

This manual serves to identify those involved with the COPDGene® LAB 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.

12b. Biological Specimen Handling

12b.1. Labeling and Identification

Purpose: Ensure all collected samples are labeled accurately and adequately.

By Whom: COPDGene® Site Coordinator/phlebotomist

Procedure:

The COPDGene® site will use the COPDGene® information system, as provided by the Data Coordinating Center (DCC), to print bar code labels that will be used to label all specimen collection containers, documents, etc. Example of the label designed by the DCC is below.

The labels will be generated at the clinical site using the system developed by the DCC. These labels will be printed on Avery 5267 8.5 x 11 paper labels, 4 across and 20 down, using a standard office printer. The items labeled with this label will not require a cryogenic, thermal transfer label to be applied at the Clinical Center. It will be printed and applied at the JHBR Lab.

These labels will be used for all blood tubes and specimen transmittal documents for the lab. They can be used also for other documentation.

Place label on tube from top to bottom.

The bar code labels should be placed on both the blood tubes and on the "Blood Specimen Transmittal Form."

12b.2. Blood Draws/Phlebotomy

Purpose: To ensure that venipunctures are performed following standard safety guidelines, and to ensure that blood samples are collected in the correct order and in accordance with study protocols.

By Whom: COPDGene® Site/Phlebotomist/nurse

Procedure:

The following table summarizes draw order and volume for the collection of blood samples into *plastic* vacutainer tubes.

Draw Order	Tube Type	Tube Amount
1	EDTA purple top	10 ml
2	EDTA purple top	10 ml
3	EDTA purple top	10 ml
4	SST red-grey top	10 ml
	Total	40 ml

Technique:

Blood should be drawn using standard phlebotomy technique with tourniquet applied to identify vein and released after adequate blood flow is obtained.

Needle or catheter should preferably be no smaller than 21 gauge to minimize risk of hemolysis.

12b.3. Sample Processing

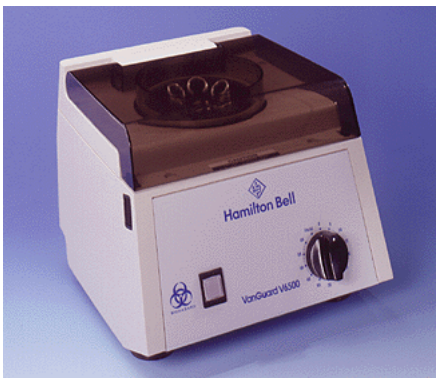
Immediately after collecting the blood samples, ensure the barcode labels are on each tube and correspond to the correct study subject

Samples should be refrigerated as soon as possible after they are drawn; samples MUST be refrigerated within 4 hours. All samples should be placed in a sample storage refrigerator. The refrigerator should be kept at +2 to +8 degrees C.

Cold Packs

Cold packs must be frozen at -20 degrees C for at least 12 hours prior to use in the shipping container. Cold packs should be placed flat on a shelf in the freezer.

All Tubes



Invert tubes to ensure specimen integrity.

Place tube in refrigerator after samples have been processed but prior to shipping to JHBR lab.

Purple Top Tubes

Purple top tube with EDTA should be inverted (not shaken) three times to mix EDTA Powder thoroughly.

SST Red-Grey Top Tube

Procedure*:

1) After obtaining the SST sample, allow sample to clot 30 minutes in a vertical position.
2) Follow manual instructions for use of local centrifuge, insuring balance of tubes within the centrifuge
3) Centrifuge it at 2500 RPM or 1000 to 1300 g for 15 minutes.
4) Do not create aliquots at the clinical center; ship the centrifuged SST sample to the COPDGene® Biorepository along with the EDTA tubes.

12c. Sample Distribution/Shipping

12c.1. Shipper Assembling and Packaging Instructions

Purpose: To ensure samples are correctly packaged and shipped according to specimen needs, study protocol, and IATA guidelines.

General Requirements

Technicians must be familiar with IATA guidelines outlined in the appendix. The packaging must be of good quality and strong enough to withstand the shocks and loadings normally encountered during transport – including trans-shipment between transport units and between transport units and warehouses as well as any removal from a pallet or over pack for subsequent manual or mechanical handling. Packaging must be constructed and closed so as to prevent any loss of contents that might be caused under normal conditions of transport, by vibration, or by changes in temperature, humidity or pressure.

The packaging must consist of three components:
a) A primary receptacle; (blood tubes – EDTA and SST)
b) A secondary packaging; (Plastic biohazard bag and Tyvek® bag – STP-710 along with the absorbent material – STP-152)
c) A rigid outer packaging. (Styrofoam and the cardboard box – STP-309)

Primary receptacles (blood tubes) must be packed in secondary packaging (plastic and the Tyvek® bag) in such a way that, under normal conditions of transport, they cannot break, be punctured or leak their contents into the secondary packaging. Secondary packaging must be secured in outer packaging (Styrofoam and cardboard box) with suitable cushioning material. Any leakage of the contents must not compromise the integrity of the cushioning material or of the outer packaging.

Step by step procedure:

A Power Point presentation outlining specific packing information for the blood tube shipment has been developed and is available on the COPDGene® web site. All coordinators are expected

to be familiar with this presentation. Shipping containers must be prepared in accordance with the steps shown in that presentation.

1) The Styrofoam container should be inserted inside the STP-309 cardboard box.
2) Place a frozen cold pack inside the Styrofoam container.
3) The blood tubes should be inserted into the bubble wrap sleeves and then rolled into a bundle. Secure the bundle with a rubber band.
4) Then place the bundle in the biohazard plastic bag along with the absorbent material. The absorbent material does not need to be wrapped around the bubble wrap sleeves.
5) Lay the plastic bag on a flat surface and press hard from the center working outward and gently seal the bag in order to remove as much air as possible.
6) Place the plastic bag into the Tyvek® bag and seal it.
7) Place the Tyvek® bag flat on the cold pack inside the Styrofoam box.
8) Place the second frozen cold pack on top of the Tyvek® bag. This will limit the space for movement of the secondary containers within the outer packaging.
9) Place the top on the Styrofoam container.
10) Place the appropriate, completed Blood Tracking Form on the top of the outside of the Styrofoam container.
11) Finally, securely seal the STP-309 box with packing tape.

12c.2. Shipping from COPDGene® Sites to JHBR LAB

Purpose: Ensure samples are correctly packaged and shipped according to specimen needs, study protocol, and IATA guidelines.

By Whom: COPDGene® Site/Study Coordinators

General Procedure:

Note: Samples should be shipped as soon as possible. For the most efficient use of resources, samples from three subjects should be placed in one shipping container whenever possible. **Samples should not be stored at the clinical site for more than four days prior to shipping**; to meet this requirement, samples from only a single subject may need to be packed in a single shipping container. Specimens may only be shipped Monday through Thursday to ensure arrival at the JHU LAB on a weekday. Avoid sending shipments that will be expected to arrive at JHU LAB on holidays.

SHIP TO:

Stacey Meyerer
Johns Hopkins University
Bloomberg School of Public Health
615 North Wolfe Street
Room W6618
Baltimore, MD 21205
410-955-7203

1) Refer to the previous section for detailed instructions on assembling and packaging the shippers.
2) Place the specimen transmittal forms for each subject on the top of foam on the inside of the shipping box and seal the box.
3) Complete the preprinted FedEx airway bill with DATE, PRIORITY OVERNIGHT, OTHER PACKAGING and list the number of boxes you will be shipping.
4) Place the airway bill on the box, inside the clear plastic sleeve and call for FedEx pick up.
5) Enter the shipment tracking number on the COPDGene® website, which will generate a shipment notification that will be sent to the lab.
6) Specimens should be shipped on Monday – Thursday only. Notices will be sent via email to coordinators one month prior to holidays to indicate any changes to lab and shipping schedules.
7) Specimens should be shipped when you accumulate 3 subjects. However, no sites should hold onto samples for more than 4 days; therefore, shippers may need to be sent with fewer than 3 samples in order to avoid storing samples for more than 4 days.
8) Once shipments are received in the lab, the received date will be entered on the COPDGene® website by the lab staff. This will confirm and resolve the shipment. Problems or delays with the shipments will be handled on a case by case basis with clinical sites as well as logged on the COPDGene® website.
9) The JHU LAB will return the empty boxes to each site so they can be used for future shipments.

Note: Specimens may only be shipped Monday through Thursday to ensure arrival at the JHU lab on a weekday. Samples collected on Friday, Saturday, or Sunday will be shipped during the following week. Exceptions will be dealt with on a case by case basis.

12d. Supplies and Ordering

By Whom: JHBR Lab and Clinical Center site technicians

Sample Collection Supplies				
Item Name	Supplier	Catalog Number	Cost/Unit	To be supplied by
Purple top plastic EDTA tubes 10 ml	VWR	BD366643	case of 10x100 $270.81	Site
Red-Gray plastic SST tubes 10 ml	VWR	BD367985	case of 10x100 $543.55	Site
Butterfly needles 21 G (Preferred)	VWR	BD367281	case of 4x50 $249.75	Site
Butterfly needles 23 G	VWR	BD367283	case of 4x50 $249.75	Site
Butterfly needles 25 G	VWR	BD367285	case of 4x50 $249.75	Site
Tourniquets (reusable)	VWR	VT367203	case of 20x25 $186.95	Site
Tube adapters	VWR	VT367290	case of 10x100 $317.86	Site
Gauze	VWR	82004-740	case of 5000 $126.54	Site
Bandage	VWR	56612-996	case of 12x100 $62.02	Site
Alcohol pads	VWR	15648-981	case of 15x200 $91.81	Site
Hamilton Bell™ Vanguard Centrifuge	MarketLab	JL9576	$359	Site
Tube/Document Labels	AVERY	5267	Local pricing	Site

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

12e. 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 Appendices:

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** (e.g., dry ice/carbon dioxide).

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.
- 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 STP-309 shipper

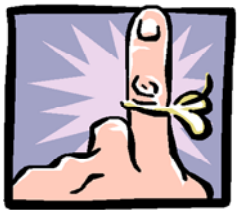
STEP 1.

- Items needed for blood shipment are (clockwise from upper left hand corner):
  - Styrofoam insulator box insert and top
  - COPDGene barcode labels
  - Saf-T-Pak Shipping Box STP-309
  - Absorbent Material
  - Blood Transmittal Form
  - 2 **FROZEN** Cold Packs
  - 3 EDTA and 1 SST 10 ml plastic blood tubes with COPDGene™ barcode labels
  - Bubble Wrap Sleeves for Blood Tubes
  - Tyvek Bag
  - Plastic Biohazard Bag

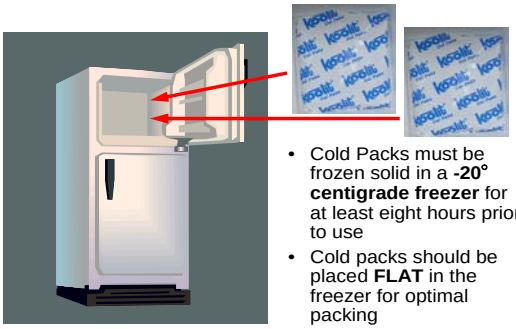
STEP 2.

Before Shipping Blood REMEMBER:

- All blood tubes must have the correct COPDGene™ barcode label
- The SST tube must be centrifuged before shipping



STEP 3.



- Cold Packs must be frozen solid in a **-20° centigrade freezer** for at least eight hours prior to use
- Cold packs should be placed **FLAT** in the freezer for optimal packing

STEP 4.

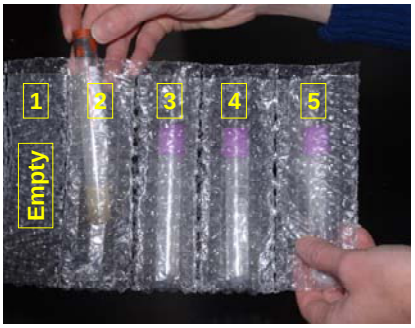
Prepare the Shipping Container:

1. Insert Styrofoam insulator into STP-309 box
2. Put one cold pack at the bottom of the Styrofoam

STEP 5.

Insert each blood tube into an individual sleeve in the bubble wrap

STEP 6.



Notice that one bubble wrap sleeve can hold 5 tubes. Each bubble wrap should hold one subject's blood tubes—there will be one empty sleeve.

STEP 7.

After placing tubes into the bubble wrap sleeves, roll up the bubble wrap and tubes.

STEP 8.

Secure the blood tubes in the bubble wrap with a rubber band

STEP 9.

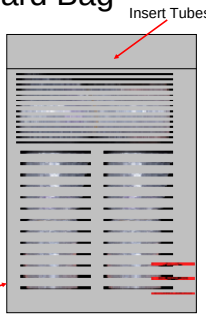
Insert the blood tubes in the bubble wrap into the Biohazard bag.

Also insert a loose piece of the absorbent material into the Biohazard bag. It does **not** need to the wrapped around the blood tubes.

STEP 10.

Putting Three Sets of Blood into One Biohazard Bag

- When you put three sets of blood into one shipment, space is very tight.
- To ensure that all materials fit, we suggest that you pack the biohazard bag as shown.



STEP11.

- Ensure that all air is removed from the biohazard bag before sealing
- Seal the biohazard bag

STEP 12.

Insert the Biohazard bag into the Tyvek bag

STEP 13.

- Ensure that all air is removed from the Tyvek bag
- Seal the Tyvek Bag

STEP 14.

- Put the sealed Tyvek bag on top of the first frozen cold pack inside the shipping container

STEP 15.

Place the second frozen cold pack on top of the sealed Tyvek bag

STEP 16.

Place the Styrofoam cover on the container

STEP 17.

Place the completed Blood Transmittal Form on top of the Styrofoam container

STEP 18.

Place the Styrofoam cover on the container

STEP 19.

Place the completed Blood Transmittal Form on top of the Styrofoam container

STEP 20.

Place the Styrofoam cover on the container

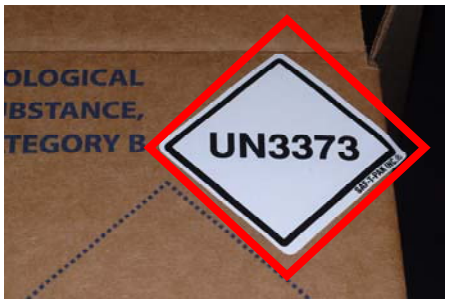
STEP 21.

Place the completed Blood Transmittal Form on top of the Styrofoam container

STEP 22.

Seal the box with packaging tape

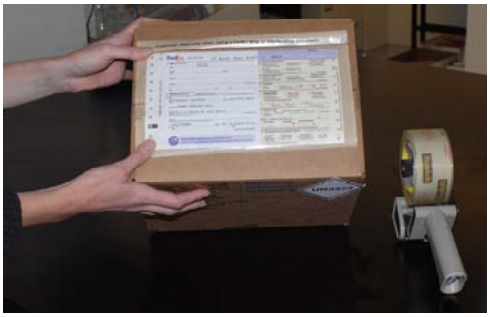
STEP 23.



Be sure that the box is compliant with label regulations.

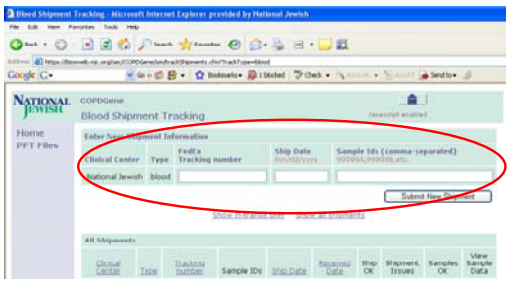
All boxes are required to have the Biological Substances B, UN3373 label.

STEP 24.



- Secure pre-filled FedEx label to the top of the box.
- Deposit at FedEx drop-off location

STEP 25.



- Record shipment immediately on COPDGene website: https://biosweb.njc.org/sec/COPDGene/sm/trackShipments.cfm?TrackType=blood

Holiday Calendar

2008	
New Year's Day	Tuesday, January 1 Do not ship on Dec 24 – Jan 2
Martin Luther King's Birthday	Monday, January 21
President's Day***	Monday, February 18
Memorial Day	Monday, May 26
Independence Day	Friday, July 4 Do not ship on July 3
Labor Day	Monday, September 1
Thanksgiving Day	Thursday, November 27 Do not ship on November 26
Day after Thanksgiving	Friday, November 28
Holiday Preparation	1/2 day during December Do not ship Dec 22 – Jan 2
1/2 Day, Christmas Eve	Wednesday, December 24
Christmas Day	Thursday, December 25
1/2 Day, New Year's Eve	Wednesday, December 31
2009	
New Year's Day	Thursday, January 1