MOP 1

CLINICAL CENTER PROCEDURES

Version 5
October 3, 2014

1.0 Objectives and Background

1.1 Inclusion/Exclusion

1) Identify homogeneous subgroups of COPD patients for targeted enrollment in future therapeutic clinical trials.

2) Identify and conduct preliminary validation of intermediate biological or clinical outcomes for use as clinical trial endpoints.

1.2 Background

COPD is a chronic, progressive disease characterized by airflow obstruction that reflects defects in airway function and/or abnormalities in the alveolar parenchyma. COPD is the fourth leading cause of death in the US, currently affecting between 12,000,000 and 24,000,000 people. Most (~90%) COPD is associated with cigarette smoking, although only ~20% of the smoking population exhibits this phenotype (Gerald and Bailey, 2002). COPD typically manifests in the mid-thirties to mid-forties with changes in spirometry (lung function), but clinically apparent symptoms are often not apparent until patients are in their mid-fifties (Pauwels, et al., 2001). There are few, if any, specific therapies for this disease. For all patients, smoking cessation is important. For patients with mild disease (GOLD Stage I) inhaled short-acting bronchodilators (e.g., β_2-agonists and/or anticholinergics) are used on an as needed basis. Maintenance long-acting bronchodilator treatment is recommended in patients with moderate disease (GOLD Stage II). Addition of inhaled corticosteroids is added to GOLD Stage II and IV treatment to improve health status, primarily by reducing the frequency of exacerbations. Long-term oxygen therapy may be needed in GOLD State IV patients. Importantly, none of the presently used pharmacological treatments for COPD are documented to prospectively modify the long-term decline in lung function; rather they are used primarily for symptom relief and to reduce the frequency of serious exacerbations (Gross, 2008; Cazzola, 2009).

Complicating the therapeutic scenario is the fact that the disease is highly heterogeneous, with cigarette smoke-induced chronic bronchitis (CB) and emphysema subsumed within the COPD definition, even though CB and emphysema likely reflect histologically and clinically distinct entities. Recent literature suggests that dividing patients into these two phenotypes is insufficient to characterize patients suffering from lung disease attributable to cigarette smoking, and other classifications have been proposed. The recognition of COPD as a systemic disease, affecting extra-pulmonary systems, including cardiovascular and muscle functions, further complicates the disease phenotype. Friedlander and Lynch (2007) suggest as many as seven clinical phenotypes and nine physiologic phenotypes are needed to fully characterize the disease spectrum. This complex phenotypic picture suggests the need for phenotype-specific treatments, which would require careful evaluation and classification of individual patients in order to be applied appropriately. Indeed, it has recently been proposed that COPD be classified as

an "orphan disease," despite the large numbers of individuals afflicted with the disorder, partially because the disease itself is so heterogeneous and each individual subtype of the disease would likely benefit from its own unique therapeutic regimen (Rennard and Vestbo, 2008).

2.0 Study Design

2.1 Study Methodology

SPIROMICS is a prospective cohort study that will enroll approximately 3,200 subjects at six clinical centers and associated sub-sites over three years. Subjects will be distributed across four enrollment strata (i.e., Non-smokers, Smokers without COPD, Mild/Moderate COPD, and Severe COPD) as shown in Table 1.

Table 1. SPIROMICS Enrollment Strata

	Non-Smokers (Stratum 1)	**Smokers (Stratum 2)**	**Mild/Moderate COPD (Stratum 3)**	**Severe COPD (Stratum 4)**
Smoking Status	**< 1 pack-year**	**> 20 pack-years**	**> 20 pack-years**	**> 20 pack-years**
Bronchodilator Status for Assessing Lung Function	**Pre-bronchodilator**	**Post-bronchodilator**	**Post-bronchodilator**	**Post-bronchodilator**
FEV1/FVC ratio criteria	**FEV1/FVC > .7**	**FEV1/FVC > .7**	**FEV1/FVC < .7**	**FEV1/FVC < .7**
Other Lung Function Criteria	**FVC>LLN**	**FVC>LLN**	**FEV1 > 50% pred.**	**FEV1 < 50% pred.**
Sample Size	**N = 200 (6.25%)**	**N = 600 (18.75%)**	**N = 1800 (56.25%)**	**N = 600 (18.72%)**

Spirometry Value Definitions
FEV1—Forced expiratory volume in first second
FVC—Forced vital capacity
LLN—Lower Limit of Normal

3.0 Sampling and Recruitment

3.1 Recruitment and Examination Goals by Center

Each clinical center will recruit approximately 533 individuals evenly divided between men and women. Efforts will be made to obtain an appropriate representation of minorities.

4.0 Contacting Participants/ Making the Clinic Appointment

Subjects can be recruited from both internal and external sources, including from the patient population at each clinical center. Patients may be referred by their physician to study personnel, or study personnel may, after obtaining permission from a patient's physician, approach patients directly regarding interest in the study. Study personnel may use the SPIROMICS Introductory Letter and/or SPIROMICS study pamphlet (both available on study website: www2.cscc.unc.edu/spiromics) when contacting potential participants.

Study coordinators may also recruit from existing databases of participants for both healthy controls and participants with COPD. Coordinators should not actively recruit from databases of asthmatics, although asthma is not an exclusionary criteria.

Clinical centers may solicit participants using posters or flyers that comply with the official study template (available on study website: www2.cscc.unc.edu/spiromics). Any communication to potential participants must be approved by the clinical center's IRB and comply with any institutional requirements. Flyers can only be placed in locations where they will be seen by individuals seeking medical care (e.g., doctor's office, pulmonary rehabilitation clinic). Flyers should not be placed in public locations, such as elevators or cafeterias.

Potential subjects may self-refer via the SPIROMICS study website (www.spiromics.com). In the event that the GIC receives questions regarding participation in the study, the individual will be referred to the appropriate clinical center.

4.1 Participant Eligibility

The study coordinator should review participant eligibility prior to scheduling the participant for a baseline study visit. This can be done either via a telephone interview or by records review, depending on site preference and policy. Prior to scheduling the post-baseline visits (V2, V3 and V4) the study coordinator should review the exclusionary criteria to assess if the participant has had any change(s) in eligibility.

Temporary exclusion criteria:

Temporary exclusion criteria are events, diseases, or treatments that require a waiting period to elapse before a participant can be screened for SPIROMICS. **These criteria should be applied when scheduling all primary study visits: Baseline, Years 1, 2, and 3 visits.**

- Participants who present with a pulmonary exacerbation, either solely participant-identified or that has been clinically treated, in the last six weeks can be rescreened for the study once the six-week window has passed.

- Participants who present with an upper respiratory infection, either solely participant-identified or that has been clinically treated, in the last six weeks can be rescreened for the study once the six-week window has passed.

- Participants who present with current use of acute antibiotics or steroids can be rescreened for the study ≥30 days after discontinuing acute antibiotics/steroids. This does not apply to participants who are on chronic prednisone therapy of <10 mg per day or <20 mg every other day or participants who are currently on chronic, prophylactic, or suppressive antibiotic therapy.

- Participants who are currently on chronic, prophylactic, or suppressive antibiotic therapy must have started this therapy at least 6 weeks prior to the baseline visit.

- Participants who present with a myocardial infarction or eye, chest or abdominal surgery within six weeks can be rescreened after the six week window has passed. Study coordinators should consult with the site principal investigator prior to rescreening these participants.

- Female participants who present <3 months after giving birth will be asked to reschedule their visit until three months have passed since the birth.

Regarding participation in other studies:

1. Participants may participate in concurrent observational studies excluding the COPDGene Study (COPDGene Investigators, 2010)
2. Participants in therapeutic clinical trials can be included after the treatment is unmasked.
3. Participants in ongoing, open-label clinical trials can be enrolled if the participant is in the control group of such a study.
4. Participants recruited into SPIROMICS can be recruited into other interventional studies after SPIROMICS baseline values are obtained. Clinic staff will maintain records documenting activity in interventional studies.

4.2 Preparing the Participant for the Clinic Visit

In order to obtain accurate results on the Pulmonary Function Tests (PFTs) and to reduce variability in the Biospecimen Collection, subjects should be asked during the scheduling phone call to withhold/refrain from the following activities for the duration indicated prior to the study visit (consult section 5.4 for recommendations for split-date study visits):

Vigorous exercise (0.5 hours)
Smoking (1 hour)
Inhaled albuterol (6 hours)
Inhaled ipratropium (8 hours)
Other bronchodilators (”withhold dosing for twice the recommended duration”).

Eating or drinking anything, including alcohol and caffeine, after midnight the day before the exam.

Practicality may require some long-acting bronchodilators to simply be noted rather than withheld. Instructions given to participants while scheduling the study visit for withholding bronchodilator medications prior to testing will stress the continued use of rescue medication if needed. Failing to withhold/refrain from the above activities will not exclude a participant from continuing with PFTs.

The study participant should also be told to fast starting at midnight the night before the exam. A snack is provided about two hours after the start of the examination. Fasting means no consumption of food or drinks (including alcohol), with the exception of water. The study coordinator should confirm that there are no medical reasons why the subject should not fast for this length of time, and alternate arrangements should be made, if necessary, after consulting with the clinical center PI. The study coordinator should also ask whether the patient has any dietary needs or restrictions, in order to ensure that an appropriate snack is available.

During the scheduling phone call, it is important that study staff remember to:

- explain where the clinic is located
- relay the appointment time
- ask about any special medical conditions (including temporary exclusion criteria and dietary restrictions for the study-provided snack)
- provide brief but complete instructions
- answer questions

Optional: If the study site has chosen to distribute confirmation letters with instructions and informed consent in advance, the coordinator should mention this information will be mailed to the participant. Also, staff can mention that a reminder call will be made, if the site has chosen to implement these.

4.3 Appointment Reminders and Instruction for the Clinical Examinations

1. Appointment Date and Time
2. Preparations:
    a) Instructions on how to complete the fast;
    b) Instructions on proper hydration while maintaining the fast;
    c) Instructions concerning restrictions on the use of tobacco and vigorous physical activity the morning prior to the visit;
    d) Instructions on refraining from use of bronchodilators;
    e) Instructions on appropriate clothing to wear for the examinations.
3. Items to bring to the clinical center:
    a) Eyeglasses for reading;

b) Name and address of primary care physician and/or clinic;
c) Name, address, and phone number of contact persons;
d) Medication Instruction Sheet: Instructions to bring all prescription and over-the-counter medications, including vitamins and mineral supplements, taken within one month prior to the examination. This includes pills, liquid medications, skin patches, inhalers, and injections.

4. Overview of Clinic Operations:
   a) A listing of the interviews and procedures for the examination (optional);
   b) A reminder that a snack is provided during the exam;
   c) Clinic hours and phone number for questions or rescheduling appointment.
5. Directions to the clinic (e.g., a map) and to parking facilities:
   a) A reminder of the arrangements for parking and/or reimbursement.
6. Transportation, if applicable (some centers provide transportation and arrange for participant pick-up).

4.4 Split Baseline Examinations

The clinic exam can be split over multiple days as long as all study visits are completed within 42 days of the initial visit. Fasting should only occur the night before clinic exams where the participant will have blood and/or urine collected. Withholding bronchodilators should only occur prior to the clinic exam involving PFTs.

If the sputum induction is conducted prior to the CT scan the participant must be scheduled for a second visit at least 24 hours after the sputum induction to allow the lungs to return to their pre-induction state.

5.0 Informed Consent

Informed consent (see study website) is the first data collection form administered during the clinic exam. A signed informed consent means the patient fully understands the requirements of the procedures and assessments included in the study as well as the risks of those procedures/assessments. It is important that the patient fully comprehends the time commitment required for participation, as well as the potential implications of specimen storage and dissemination of study findings.

The informed consent is tailored at each clinical center to assure compliance with local regulations and IRB requirements. While the consent form may vary from site to site, all are in full compliance with NHLBI guidelines.

Depending on local requirements, participants may have previously consented via telephone screening or pre-screening for SPIROMICS. While the pre-screening/telephone screening consent form may have described the study, it is necessary to complete the informed consent before beginning the baseline examination to ensure that participants fully understand their rights, particularly to withdraw from the study, and the risks of clinic procedures and specimen storage.

5.1 Reception

Prior to the patient's arrival the coordinator should review the prescreening form to determine if there are any known special needs for this patient. Upon arrival at the clinical center the study coordinator should greet the patient and confirm patient's identity. No data can be collected until the full informed consent has been obtained.

5.2 Administration

The study coordinator should take the patient to a quiet, private area to review the informed consent. The coordinator should provide a copy of the consent to the participant, and ask the participant whether he or she would like to read the consent form or have it read to them by the staff person. If the participant is visually handicapped, the coordinator should read the form to him or her. If the participant chooses to read the form, the coordinator should still review, although not read, the consent form with the participant to ensure he or she is fully informed. This should be handled sensitively, so as not to imply poor comprehension on the part of the patient. The coordinator should encourage the participant to ask for clarification or any questions he or she may have. The original signed copy of the informed consent should be kept with the participant's study information. A copy of the signed consent form should be provided to the participant if he or she requests it or if the local IRB requires it.

5.3 Training and Certification

All study coordinators and personnel interacting with SPIROMICS participants must have receive appropriate training and certification in confidentiality, privacy, and informed consent prior to having any contact with participants.

5.4 Data and Collection

Informed consents are collected on paper. Depending on local regulations, some clinical centers may need to use two separate forms, one for participation, and one for specimen storage. In addition, local regulations will guide what documentation of informed consent is to be given to the participant as well as what needs to be saved with the participant records by the study coordinator.

5.5 Ability to Comprehend the Informed Consent

The ability to provide informed consent is a requirement for participation in SPIROMICS. In order to remain in compliance with ethical and regulatory standards, study coordinators should make every effort to ensure the patients understand their rights and risks when participating in this study.
It can be difficult to determine whether a participant understands the informed consent. SPIROMICS has no procedures for assessing this, although coordinators should check with their local IRBs. Behaviors and patterns to look for that might indicate poor comprehension include repetitive behaviors and speech patterns and looking to spouses

and companions for assistance answering questions. If the coordinator doubts the patient's comprehension, he or she can ask the patient to explain the rights and risks detailed in the consent form in his or her own words. If the coordinator continues to question the ability of the patient to consent, he or she should speak with his or her supervisor.

5.6 Informed Consent Tracking (ICT)

The Informed Consent Tracking (ICT) form is completed solely by the study coordinators. It is an internal form to track a participant's initial consent, subsequent consents, and any changes to consent over the course of the study. The consent form indicates whether a participant agrees to: 1) participate in the study overall, 2) the sharing of relevant results with a clinical care provider, 3) storage of biological specimens, and 4) storage of DNA. Depending on local IRB requirements, the primary consent form may also include an option to consent for SPIROMICS substudies (e.g., the exercise substudy). Some IRBs may also require participants specifically consent to be contacted for additional studies, such as ancillary or substudies.

6.0 Tracking and Follow-Up Information

6.1 Quarterly Follow-Up

Follow-Up Reports
For each participant a Follow-up Report should be generated at the conclusion of the Baseline Clinic Visit. This report lists the target date for each follow-up call and clinic visit, along with the dates the contact window opens and closes.

To generate a follow-up report login to the DMS. From the menu on the left select data extraction→reports. Select the Spiromics Follow-up from the Report listing by clicking on the first icon to the right. A parameter screen will appear asking for the date ranges of interest. All quarterly follow-up calls and study visits due within the parameters will be listed.

A 28 day window before and after the 'target' date for the quarterly calls will be displayed. Coordinators should make every possible attempt to reach participants by phone for the quarterly calls within the window. If unable to administer the Follow-up Questionnaire within the window, the coordinator should continue to attempt contact with the participant. If the next quarterly call window opens before a previous call has been completed; the previous quarterly Follow-up Questionnaire should be set to permanently missing in the DMS.

Participants in SPIROMICS will be contacted quarterly (every three months) by phone for follow-up. During these calls, the study coordinator will complete the Follow-up Questionnaire (FUQ) to collect information about exacerbation events, including hospitalizations, emergency department visits, and antibiotic use. These calls also serve

to ensure contact information for participants is up-to-date, and engages the participant in order to improve retention in the study.

In the event that the participant has died since the last contact, the study coordinator will complete the Informant Interview (IFI).

A detailed description of the follow-up procedures is available in MOP 8.

6.2 SPIROMICS Annual Visits as a Phone Follow-up

The ideal for the study is to have all participants return to the clinic to complete in-person visits for Years 1-3. However, if a participant refuses to return to the clinic then he or she can complete a phone follow-up for the yearly visit to collect as much data as possible. Ideally, the participant would complete a visit within +/- 30 days of the target date. It is always preferable to complete an in-person visit, even if that visit will be very out-of-window.

A full phone visit with a participant that covers both the Tier 1 and 2 forms below should take approximately 90 minutes. NHLBI will be offering reimbursement for these visits that complete **at least the Tier 1 forms**, but they require **PRIOR APPROVAL**. Once you have identified patient(s) that will receive a phone follow-up in lieu of an in-person annual visit, you must submit a list to the Contracts Office of participant IDs along with the specific visit number for each ID.

Phone visits should not be completed until the Contracts Office has notified you that the phone visits have been approved. Note each approval will be based on a specific follow-up visit so if you have a participant who is unable to come in for their Year 1 visit and also has a problem at Year 3, you will need to submit a separate request at the time of the visit.

The following forms should be collected while on the phone with the participant. Please note the order of importance, if the participant has limited time available then the coordinator should collect the Tier 1 forms first, then work on the Tier 2 as time allows. As with an in-person visit the forms can be collected over multiple contacts within 42 days of the initial phone contact. The self-report questionnaires should be conducted as interview questions for the purpose of the phone visit.

<u>Tier 1 Forms: (approximately 25-30minutes for completion)</u>

1) CIF – Contact Information Form
2) DEM – Demographic Information Form – *(Add a notelog to Q1 that says "Phone Visit")*
3) HEF – Hospitalizations and Exacerbations
4) MHF – Medical History Form for Follow-up
5) MRC- Modified Medical Research Council Dyspnea Scale

6) RDF - Respiratory Disease and Smoke Exposure Questionnaire for Follow-Up

Tier 2 Forms: (approximately 60 minutes for completion)

7) BSQ - Berlin Sleep Questionnaire
8) CAT – COPD Assessment Test
9) FCT – FACIT-F
10) HDS – Hospital Anxiety and Depression Scale
11) MCQ - Questionnaire for ease of cough /sputum clearance
12) PSQ - Pittsburgh Sleep Quality Index
13) RMU - Respiratory Medication Use Questionnaire
14) SFH – SF12v2 Health Survey
15) SGR – St. George's Respiratory Questionnaire
16) VSA – Veterans Specific Activity Questionnaire *(for all participants regardless of military status)*
17) EHA – Employment History Form

For the DEM form, the site should add a notelog (by clicking on the >> by the answer box of the first question) that says "Phone Visit" to alert the GIC to the type of visit completed. For more information about the specific forms and questionnaires please see MOP 8 and 17.2.
Once the phone follow-up visit is completed, the following forms should be marked permanently missing (if present at that visit) to avoid data queries for the site.

1) ANT – Anthropometry Form
2) BIO – Biospecimen Collection Form
3) BPF – Blood Pressure Form
4) CBC – CBC Results Form
5) PFT – Pulmonary Function Eligibility Form
6) SDF – Spirometry Data Form
7) SMW – Six Minute Walk Test
8) SPW – Sputum Processing Worksheet

6.3 Procedures to Remove a Participant from the Study

A study subject can be withdrawn from the study at the subjects request or at the PIs discretion, including a situation where the clinical center PI determines that it is unsafe or

unethical for the subject to continue in the study. Situations that might result in this kind of withdrawal include:

- bodily impairment such that the subject cannot complete the study protocol (meets one or more exclusionary criteria)
- institutionalization (e.g., long-term care facility, prison)
- aggressive or antagonistic behavior towards clinical center staff

Subjects may withdraw at any time for any reason. At the time of withdrawal, subjects can either 1) decline to provide any more data or specimens to the study but allow use of previously collected data and/or specimens, 2) withdraw all their data from study databases and request that any stored samples be destroyed, or 3) withdraw some portion of the data collected (i.e., subjects may withdraw specimens but not exam data or vice versa).

If a subject chooses to withdraw from the SPIROMICS study, the study coordinator will conduct an exit interview to determine the disposition of the subjects' study data. This information should be recorded on the RSW – Reason for Study Withdrawal. The coordinator will also provide the subject with any clinically relevant study results or establish how the participant would like to be contacted if relevant results become available in the future. The subject may decline to participate in the exit interview, in which case the consent in place at the time of study withdrawal will be used to determine the status of the subject's data.

6.4 Participants Lost to Follow-Up

Participants that are lost to follow-up for the quarterly phone interviews and the yearly clinic visits are still considered enrolled participants and attempts at follow-up should still be made, unless the contact information is no longer valid and new contact information is unobtainable.

7.0 Participant Flow and Itinerary

The SPIROMICS study exam flow is provided in the table below. Procedures and assessments are broken into blocks, some fixed and some flexible, to accommodate hospital scheduling needs. If necessary the exam may be split over two days, which can take place within 42 days of each other. Before beginning data collection, a participant must be complete an informed consent.

Participants begin the baseline study visit by completing the Inclusion/Exclusion Criteria form (IEC). Upon completion of the IEC the study coordinator should determine if the participant meets all the eligibility requirements by running the Eligibility Report. If the participant is eligible, the study coordinator should collect blood and urine. In order to make the specimens as comparable across participants as possible, it is strongly encouraged that collection of blood and urine occur in a fasting state. For this reason,

and to further reduce differences between biospecimens, it is recommended that, as much as possible, urine collection and phlebotomy occur in the morning, after obtaining informed consent. If the participant is uncomfortable in his or her fasting state, you may provide them with the snack immediately following blood and urine collection. If the study visit is split over two days, these biospecimens should be collected on the day when the participant arrives in a fasting state.

If the participant's self-reported BMI is greater than 35 but less than 40, it is recommended that, if the participant passes the rest of the eligibility criteria, the coordinator collect the Anthropometry Data collection (ANT) immediately to obtain a BMI based on measured height and weight. A participant whose measured BMI is greater than 40 does not qualify for the study, even if their self-reported BMI was less.

Study coordinators should proceed with collecting anthropometry, demographic information, and spirometry. Please note that the demographic information and anthropometry can be collected during the 30 minute waiting period after bronchodilators have been administered.

Once the study coordinator has completed and entered into the DMS (data management system) the Inclusion/Exclusion Criteria form (IEC), Demographic Information (DEM), Anthropometry (ANT), and Spirometry Data Form (SDF), he or she should run the Stratification Report to determine if the participant meets the requirements for the study strata and/or that the qualifying strata is not full.

Once a participant has been stratified, coordinators should complete the Enrollment Form (ENF). The ENF confirms that for a given participant the Eligibility and Stratification Reports have been checked. It also captures which stratum a participant is eligible for.

Once the ENF is complete, the coordinator should continue with the study visit. Please note that it is very important that in situations where sputum induction is scheduled for the same day as PFTs and/or multidetector row computed tomography (MDCT or CT), the induction should occur **after** either, or both of these procedures are completed.

Table 2

Exam Procedure	Estimated Time (min)
Check in and informed consent, and Inclusion/Exclusion	30
Assess Eligibility	
Phlebotomy	15
Urine	05
Snack	15
Anthropometry and Demographics	10
Spirometry	135
Assess Stratification	

Flexible Block A	
Six Minute Walk	15
Flexible Block B	
Medical and Medication Histories	30
FACIT-F Questionnaire	15
Seated Blood Pressure	10
Lunch	30
Flexible Block C	
MDCT	60
Flexible Block D	
Smoking History	5
Modified MRC Dyspnea Scale	1
St George's Respiratory Questionnaire	20
Flexible Block E (must be after PFT and MDCT)	
Sputum Induction	60
Questionnaire for Ease of Cough and Sputum Clearance	5
Flexible Block F	
COPD Assessment Test	7
MOT Short Form -12	5
Veterans Specific Activity Questionnaire	1
Flexible Block G	
Berlin Sleep Questionnaire	5
Pittsburgh Sleep Quality Index	5
Hospital Anxiety and Depression Scale	8
Length of Study Visit Day	492 (~8.5 hours)

8.0 Interviews

Interviews play a crucial role in SPIROMICS, providing important participant medical history as well as measures of participant health and well-bring. The SPIROMICS questionnaires are both interviewer-administered via the web-based data entry system and self-administered for later entry into the web-based system. All interviewer administered responses are to be directly entered into the data management system. Direct data entry provides the highest quality data entry, allowing for immediate range checks and assisting with skip patterns. Questionnaires that are self-administered should be reviewed by the coordinator while the participant is still present. If at all possible, the coordinator should attempt to enter the questionnaires during the course of the study visit in order to confirm all questions are answered and all skip patterns are followed. Coordinators must key any self-administered questionnaires within two weeks of the participant visit.

The following questionnaires should be given to participants for self-administration:

1) FACIT
2) MMRC

3) SGRQ
4) Questionnaire for ease of cough /sputum clearance
5) Berlin Sleep Questionnaire
6) Pittsburgh Sleep Quality Index
7) HADS

Questionnaires can be administered in Spanish or English. The language used during the interview is determined by the participant. (**Note:** Spanish language interviews are not available at all sites).

8.1 Interview Style

Interviews should be conducted in a polite, professional, and non-judgmental tone. It is critical for the interviewer to establish rapport and confidence with the participant. Pacing of the interview should be adjusted to each participant. Interviewers should be careful not to interrupt, correct, or paraphrase participant's responses. Coordinators should conduct interviews in quiet, private settings.

8.2 Interviewer Presentation and Techniques

Interviewers should be familiar with the forms and questionnaires they are administering, including skip patterns and instructions. Familiarity allows the coordinator to maintain eye contact with the participant, which helps build rapport. The interviewer must be careful not to inadvertently change the wording of questions or instructions because he or she has partially memorized the interview.

Interviewers should reassure participants of the confidentiality of their answers. If the interviewer feels a particular question is sensitive or embarrassing, it is important that he or she ask the question in the same neutral, non-judgmental tone as all other questions, as the interviewer's discomfort can be non-verbally communicated to the participant.

If a participant appears to not understand the question or provides an incomplete answer, the interviewer may employ several techniques to improve participant response. In the case of misunderstood questions, the interviewer may re-read the question with a different emphasis, stressing the part of the question the subject appears to have misunderstood. The interviewer should not modify the question wording, unless alternate wording is provided in the Question-by-Question (QxQ) instructions for the form.

For incomplete answers, interviewers may use probing to further clarify a participant's answer. Interviewers may use probing unless the QxQs specifically state that probing is not allowed. The most commonly used probing technique is silence. In this situation the interviewer waits for the participant to provide an answer. Participants may require time to recall events or consider how to respond. If the participant seems uneasy with the length of time he or she is taking to answer a question, the coordinator may reassure the participant, i.e., "Take your time" or "There is no rush."

Other types of probing include repetition of the original question, channeling ("tell me more about ..."), clarification ("when did your doctor tell you that?"), elaboration/continuation ("what happened next?"), encouragement ("I see, um, uhuh") and completion ("anything else?"; "can you tell me anything more about that?").

The most effective, spoken probes are neutral, such as:

"How do you mean that?" instead of "Why?"

"Can you tell me more about this?"

"Can you give me an example?" or "Can you explain that in a little more detail?"

"How are you using that term?"

"If you had to choose, which would you say?"

"What else can you tell me about that?" instead of "Anything else?"

8.3 Quality Assurance of Interviews

A random sample of interviews may be recorded for quality control purposes.

9.0 Recording Medications and Supplements

Participants should be asked to bring their medications and supplements with them for the SPIROMICS exam. This allows the coordinator to determine drug names and doses, rather than relying on participant recall. Some participants may not bring their medications with them or may not bring everything they take. Regardless, coordinators should administer the Baseline Respiratory Medication Use Questionnaire (RMU). The RMU asks participants about a variety of medications commonly prescribed to COPD patients. Any medications or supplements that the participant takes that are not listed in the RMU are to be included via free text at the end of the questionnaire.

10.0 Initial Biospecimen Collection-Urine

A urine sample is collected from all participants. If at all possible, collect urine as soon as possible after the participant has completed the informed consent. Participants are asked to void in the provided specimen cup. Participants will need to provide at least 30mL of urine for study processing. Participants will be asked to collect their specimen using the clean catch method (see MOP 4 Biospecimen Collection), and will label their specimen with the date and time collected. Specimens will be transferred to storage at 4◦C as soon as possible after collection and no more than one-half hour after collection. For women of child bearing potential a pregnancy test must be conducted to determine eligibility. Women who are pregnant are ineligible. Local institutional policy will mandate whether a urine or serum pregnancy test is required. If a urine pregnancy test is

required, the test should be administered and the results recorded prior to the urine specimen transfer to 4°C storage. Testing will vary by site but is usually handled by the study coordinator or lab processing staff. Transfer to storage will vary by site but will either be handled by the study coordinator or lab processing staff. See MOP4 for complete details.

11.0 Seated Blood Pressure

11.1 The Blood Pressure (BPF) form

Blood pressure measurements are recorded on the Blood Pressure Form (BPF). The form records whether the measurement was taken in the right arm, and if not, why. For each of the three measurements the coordinator will record the time collected, the systolic pressure, the diastolic pressure, and the respiration rate per minute.

11.2 Selection of the Arm

To reduce variation coordinators should attempt to measure blood pressure on the right arm of all participants. The coordinator should not use the right arm in cases where the arm is amputated, atrophied (withered), or puffy. Also, for participants with tubes, rashes, small gauze/adhesive dressings, casts, compression sleeves, open sores, hematomas (bruises), wounds, and arteriovenous (AV) shunt or any other intravenous access device the left arm should be used. The right arm should not be used if the participant has had lymph node dissection or radiation therapy to the right axilla,

11.3 Cuff Size Selection

In order to ensure accurate measurement of blood pressure, the correct cuff size must be selected. The guideline for cuff size is that the bladder length is 80% of the arm circumference and the width is 40% of the circumference (National Guideline Clearinghouse, 2005). Recommended cuff sizes are:

- For arm circumference of 22 to 26 cm, the cuff should be "small adult" size: 12X22 cm
- For arm circumference of 27 to 34 cm, the cuff should be "adult" size: 16X30 cm
- For arm circumference of 35 to 44 cm, the cuff should be "large adult" size: 16X36 cm
- For arm circumference of 45 to 52 cm, the cuff should be "adult thigh" size: 16X42 cm

The above is a guideline only. Please see specifications for your local equipment.

11.4 Measurement of Arm Circumference

i. Have the participant remove his/her upper garment or clear the upper arm area so that an unencumbered measurement may be made.

ii. Have the participant stand, with the right arm hanging and bending the elbow so that the forearm is horizontal (parallel) to the floor.
iii. Measure arm length from the acromion (bony protuberance at the shoulder) to the olecranon (tip of the elbow), using the study provided measuring tape.
iv. Mark the midpoint on the dorsal surface of the arm.
v. Have the participant relax arm along side of the body.
vi. Draw the tape snugly around the arm at the midpoint mark. NOTE: Keep the tape horizontal. Tape should not indent the skin.

11.5 Heart and Respiration Rate

Respiration rate is the number of times a participant breathes in (inspiration) and out (expiration) in a full minute. Count each inspiration and expiration as one breath. It is best done without the participant's knowledge because breathing is controlled by both the voluntary and involuntary muscles. Usually it is counted as you take the participant's pulse. (If the pulse is only recorded from the digital BP monitor, pretend you are taking it anyway). Observe and count each rise and fall of the chest as one respiration. Count respirations for 30 seconds and multiply by 2. If the rise and fall of the chest is not easily perceptible, place your hand gently but firmly on the shoulder or back and count in this manner.

Heart rate is the number of times a participant's heart beats per minute (bpm). If using an automatic BP machine, the heart rate is automatically recorded.
If taking an analog BP measurement, the heart rate is measured by taking the participant's radial pulse in the same arm. Count the pulse beats for 30 seconds and multiply by 2.

11.6 Position the Participant and Placing the Cuff

Also crucial to accurate blood pressure readings is the position of the participant and the placement of the cuff. Participants are to sit with their feet flat on the ground (uncrossed). Participants should site quietly for five minutes before taking the first blood pressure measurement. Participants should not talk and should remain as still as possible while the blood pressure measurements are taken.

The right arm should be bared and unrestricted by clothing with the palm of the hand turned upward and the elbow slightly flexed. The midpoint of the upper arm should be level with the heart.

The arm should be positioned so that the midpoint of the upper arm is at the level of the heart. For SPIROMICS it is assumed that the heart is located on the lower left side of the sternum, at the top of the forth intercostal space (between the ribs). In order to achieve this with small or tall participants it may be necessary to adjust the sitting position, either by raising the body (for smaller participants) or by elevating the arm (tall participants). When making these adjustments be certain that the participant's feet remain flat on the floor.

11.7 Locating the Pulse Point

To locate the brachial artery, palpate the anterior elbow medial to the bicep tendon (i.e., at about the midpoint of the elbow near the bicep tendon). If unable to palpate the brachial artery, the pulse may be heard with the placement of a stethoscope to the same point.

11.8 Wrapping the Blood Pressure Cuff Around the Arm

Position the bottom of the blood pressure cuff over the brachial artery, wrapping the cuff around the arm so that it is snug but not tight. If the cuff that matches a participant's arm circumference is too loose on the arm, move to the next size smaller cuff.

11.9 Procedure for Automatic BP Machines

Automated oscillometric blood pressure devices are the method of choice for SPIROMICS. In addition to blood pressure the automated devices record heart rate as beats per minute (bpm). The midline of the bladder of the cuff (commonly marked on the cuff by the manufacturer) should be placed over the brachial artery. The device should be turned on. When the measurement has been completed the device will beep. Record the measurement, and then turn off the device. Please see the instruction manual for your local device for more specific instructions on how to use it.

The cuff should be deflated all the way prior to taking measurements 2 and 3.

Three consecutive measurements with 30 second intervals between each measurement will be taken.

11.10 Procedure for Analog BP Measurement

The ausculatory method includes the mercury sphygmomanometer and aneroid monitor.

It is recommended that the accuracy of the pressure registration mechanism be checked. In the case of mercury sphygmomanometers this involves checking that the upper curve of the meniscus of the mercury column is at 0mm Hg, that the column is free of dirt, and that it rises and falls freely during cuff inflation and deflation.

Aneroid devices or other nonmercury devices should be checked by connecting the manometer to a mercury column or an electronic testing device with a Y-tube. The needle should rest at the zero point before the cuff is inflated and should register a reading that is within 4 mm Hg of the mercury column when the cuff is inflated to pressures of 100 and 200 mm Hg. The needle should return to zero after deflation.

Successful inflation and deflation requires an airtight system, ongoing inspection and maintenance of the tubing for deterioration/cracking of the rubber and the release valve are required.

The midline of the bladder of the cuff (commonly marked on the cuff by the manufacturer) should be placed over the brachial artery with the lower end of the cuff 2 to 3 cm above the antecubital space to allow room for placement of the stethoscope. The cuff is then pulled snugly around the bare upper arm.

The bell or diaphragm of the stethoscope is placed over the brachial artery. Avoid contact with the cuff or any clothing which will create artifact noise. The participant's arm should be supported by the observer during the measurements to maintain proper positioning.

Close the valve on the rubber inflating bulb and squeeze the bulb rapidly to inflate the cuff until the dial or column of mercury reads 30 mmHg higher than the usual systolic pressure. If the usual systolic pressure is unknown, the cuff is inflated to about 210 mmHg.

Open the valve slightly, allowing the pressure to fall gradually (2 to 3 mmHg per second). As the pressure falls, the level on the dial or mercury tube at which the sound of blood pulsing is first heard is recorded as the systolic pressure.

As the air continues to be let out, the pulsing sounds will disappear. The point at which the sound disappears is recorded. This is the diastolic pressure.

The cuff should be deflated all the way (the dial or mercury tube should return to zero) prior to taking measurements 2 and 3.

Three consecutive measurements with 30 second intervals between each measurement will be taken.

11.11 Participant Safety

As a participant safety procedure, if the average blood pressure is equal to or greater than 200mmHg systolic or equal to or greater than 120 mmHg diastolic, or equal to or less than 100mmHg systolic or equal to or less than 60mmHg diastolic the coordinator should remove the BP cuff and reposition it per the above protocol. The coordinator will then remeasure the blood pressure.

If the average blood pressure is still equal to or greater than 200 mmHg systolic or equal to or greater than 120 mmHg diastolic, or equal to or less than 100mmHg systolic or equal to or less than 60mmHg diastolic the coordinator closes out the data entry screen per protocol, interrupts the examination, and notifies the supervisor of this immediately.

If the average heart rate is equal to or greater than 100bpm or equal to or less than 60bpm the coordinator should remove the BP cuff and reposition it per the above protocol if using a digital mechanism. If taking a radial pulse, the coordinator should take the pulse again counting the beats per minute for a full 60 seconds.

If the average heart rate is still equal to or greater than 100bpm or equal to or less than 60bpm the coordinator closes out the data entry screen, interrupts the examination and notifies the supervisor immediately.
With input from the supervisor, clinic manager, or site PI, clinic staff will then assist the participant in scheduling a visit to his/her provider of care or arrange transportation to the nearest emergency room for a medical evaluation of the participant's blood pressure and/or heart rate during the same day. Once the participant is attended to, the clinic staff should complete the Adverse Event form.

11.12 References

1. National Guideline Clearinghouse. Recommendations for blood pressure measurement in humans and experimental animals: Part 1: blood pressure measurement in humans: a statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research.. Released January 2005. Available at: http://www.guideline.gov/summary/summary.aspx?ss=15&doc_id=6527&nbr=4093. Last accessed on: March 5, 2010.
2. U.S. National Library of Medicine NIH National Institutes of Healthhttp://www.nlm.nih.gov/medlineplus/ency/article/003399.htm: Normal Results for Resting Heart Rate.

12.0 Biospecimen Collection and Processing

Blood and urine specimens are collected on all SPIROMICS participants at the baseline, Year 1, and Year 3 exams. Collection and processing procedures are outlined in detail in MOP 4 – Biospecimen Collection. Data related to collection and processing should be entered on the Biospecimen Collection Form (BIO). Only SPIROMICS certified personnel should collect and processes these samples. All samples are batch shipped to the GIC to be allocated for future testing or stored, except one EDTA tube which will be sent to sites' local laboratories for a CBC with differential. For female participants, it may be necessary to conduct pregnancy testing with urine or blood. If urine pregnancy testing is acceptable it may be tested on the collected sample. If serum pregnancy is required a serum tube will need to be drawn per institutional policy but this will be in addition to any samples collected as outlined in MOP 4 – Biospecimen Collection.

In order to reduce variability between subjects, coordinators are encouraged to collect these biospecimens as early in the day as possible. For this reason, blood and urine can

be collected prior to determining a subject's stratum. If the study visit will be conducted over two days, with PFTs occurring on the first day, then it is suggested that coordinators collect blood and urine on the second day.

13.0 Anthropometry

Anthropometric measures include height, weight, and arm span as well as waist, hip, and neck circumferences.

13.1 Equipment and Supplies

The equipment and supplies necessary for body measurements are as follows:
- Wall mounted stadiometer
- Gulick II 150 and 250 cm anthropometric tape
- Balanced weight scale

13.2 Staff

It is preferable to have an examiner and recorder for each procedure. Technicians are trained to perform both roles. If necessary, a technician may perform the measurements and enter the data into the data management system (DMS). If two staff members are not available, a full length, well-mounted mirror may be useful in assuring accurate measurements.

The examiner is responsible for positioning the participant, taking each measurement, and stating the measurement aloud to the recorder. The recorder keys the information into the data entry system and asks the examiner to confirm or re-measure any out-of-range measurements identified by the data entry system. Otherwise, the examiner proceeds to the next measurement in the sequence established by the protocol. The participant remains on the instrument / the measuring device remains on the participant, until the recorder enters the measurement on the data entry screen.

13.3 Anthropometry Form (ANT)

The ANT contains three sections for recording anthropometry measurements: (A) ability to stand, (B) height, weight, and arm span as well as neck, hip, and (C) waist circumference. As the technician progress through the examination procedures, they will directly enter results into the DMS.

13.4 Examination Procedures

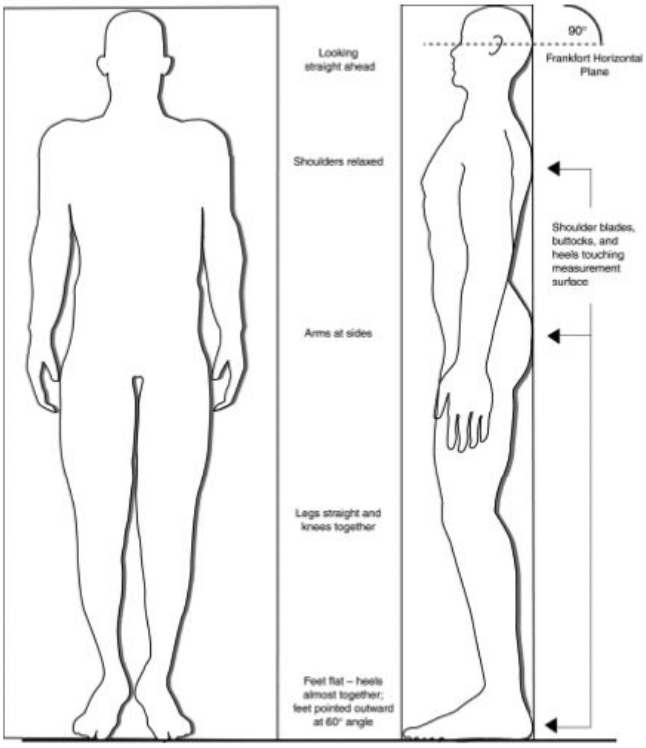
For all measurements, participants should wear light, non-constricting clothing and slippers or socks.

13.3.1 Standing Height

Standing height is an assessment of maximum vertical size. Standing height is measured with a fixed (wall mounted) stadiometer with a vertical backboard and a moveable headboard. Have the participant move or remove hair ornaments, jewelry, buns, braids,

and corn rolls from the top of the head in order to measure stature properly. Have the participant stand on the floor (see Figure 1) with the heels of both feet together and the toes pointed slightly outward at approximately a 60° angle. Make sure the body weight is evenly distributed and both feet are flat on the floor. Check the position of the heels, the buttocks, shoulder blades, and the back of the head for contact with the vertical backboard. Depending on the overall body conformation of the individual, all points may not touch. In such cases, make sure the participant's trunk is vertical above the waist, and the arms and shoulders are relaxed.

Figure 1



Align the head in the Frankfort horizontal plane. The head is in the Frankfort plane when the horizontal line from the ear canal to the lower border of the orbit of the eye is parallel to the floor and perpendicular to the vertical backboard. Many people assume this position naturally, but for some it may be necessary to make a minor adjustment. If required, gently tilt the head up or down until proper alignment is achieved with eyes looking straight ahead. Once correctly positioned, lower the headboard and instruct the participant to take a deep breath and stand as tall as possible. A deep breath allows the spine to straighten, yielding a more consistent and reproducible stature measurement.

Position the headboard firmly on top of the head with sufficient pressure to compress the hair. Then have the participant relax and step away from the stadiometer and record the participant's height on the computer system. The examiner should read the height at eye level to avoid parallax; a small stool may be required.

Some participants may have conditions that interfere with the specific procedure for measuring stature. One of the more common conditions is kyphosis. Kyphosis is a forward curvature of the spine that appears as a hump or crooked back condition. In these cases it is important to get the best measure possible according to the protocol.

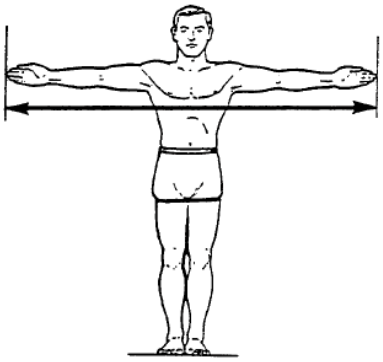
Please note that participants with mild kyphosis are allowed in the study but those with severe kyphosis or inability to stand should not be enrolled in SPIROMICS, as this interferes with the accuracy and reliability of pulmonary function testing. If a participant presents with kyphosis or any other physical condition that may interfere with the interpretability of the PFTs, CT scan, or biospecimens, the study coordinator should consult their local the GIC and their local Principal Investigator to determine whether the participant is eligible for SPIROMICS.

13.3.2 Weight

Participants' weight will be measured using a digital scale. Participants will be asked to remove their shoes, set down any purses or bags, and remove any overcoats before being weighed. Participants will be asked to stand with their weight evenly distributed across their feet. Study coordinators will record the digital weight readout.

13.3.3 Arm Span

Arm span will be measured using the study-provided measuring tape. Position the subject as you would to measure his or her height. Once positioned, ask the subject to raise his or her arms to be level with his or her shoulders. Subjects should stretch as widely as is comfortable with palms facing away from the wall and fingertips straightened. The study coordinator will measure the width from fingertip to fingertip. The measurement is taken at the maximum point of quiet respiration. It may be necessary for the coordinator to have assistance to take this measurement.



If the participants arm span is longer than the tape measure, measure to the end of the tape measure and place a mark on the participant's finger tip to identify the end. Record this *partial measurement* on paper, and then measure from the mark on the finger tip where the tape measure ended to the end of the finger tip. *Add the two measurements together for the complete arm span.*

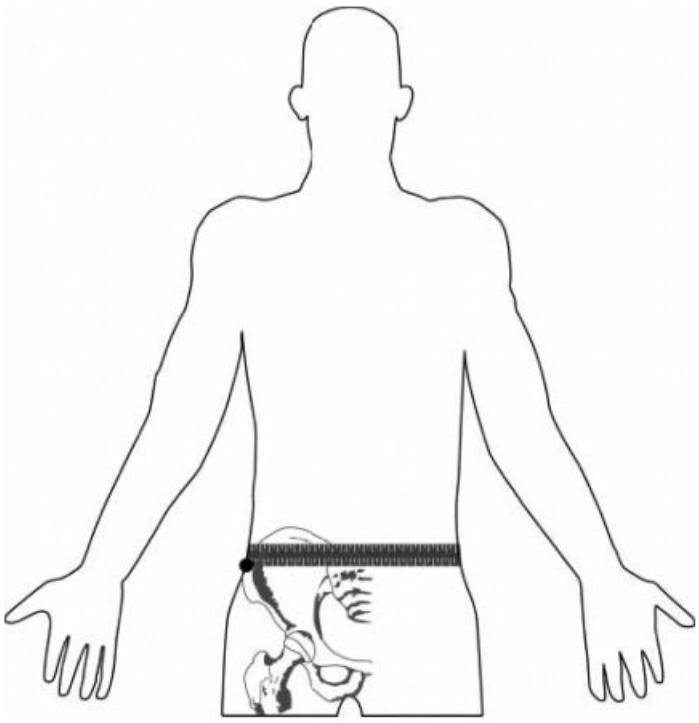
13.3.4 Waist Circumference

To define the level at which the waist of abdominal circumference is measured, you must first locate and mark a bony landmark, the lateral border of the ilium. Have the participant stand and hold their t-shirt above the waist. Lower the pants and underclothing of the participant slightly, and standing behind and to the right of the participant, palpate the hip area to locate the right ilium.

Draw a horizontal line just above the uppermost lateral border of the right ilium and then cross the line to indicate the mid-axillary line of the body. Standing on the participant's right side, place the measuring tape around the trunk in a horizontal plane at the level marked on the right side of the trunk. Hold the zero end below the measurement value.

If only one coordinator is available a mirror may be used to help ensure correct horizontal alignment of the measuring tape. This is especially useful when measuring overweight participants or women with hourglass-shaped torsos. The recorder (if available) makes sure that the tape is parallel to the floor and that the tape is snug, without compressing the skin. Measurements are made at the end of a normal expiration and reported to the recorder to the nearest centimeter.

Figure 2



13.3.5 Hip Circumference

Instruct the participant to stand erect but relaxed, with weight distributed equally over both feet. The hip girth is measured at the level of maximal protrusion of the gluteal muscles (hips). Verify this position by passing the tape above and below the observed maximum. Keep the anthropometric tape horizontal at this level and record the measurement to the nearest centimeter. The tape should be snug, but not tight enough to compress tissue. The measurement should be made from the participant's right side. Only one measurement is made.

The greatest source of error for this measurement is due to not having the tape horizontal. Before making the measurement the observer verifies the position of the tape from both the front and back to assure its correct position and that the tape is horizontal. In the absence of a recorder the technician uses the wall mirror to confirm that the tape is horizontal.

13.3.6 Neck Circumference

Neck measurements should be taken between the midcervical spine and midanterior neck using a study provided plastic tape. In participants with a laryngeal prominence (Adam's apple), measure just below the prominence. Take the measurements while the participant is standing with the shoulders relaxed.

13.4 Training, Certification, and Quality Control

Technicians or examiners are centrally trained in all anthropometric measures. Technicians who cannot attend the central training can be trained and certified locally by the clinic coordinator. Each technician performs a minimum of 5 observed procedures to receive certification, with a level of agreement of measurements relative to the supervisor‘s measurements as specified in the QA/QC manual (MOP 7).

Technicians are observed by the clinic coordinator twice monthly for the first month and then quarterly, to ensure standardization. The Supervisor Checklist is used to document these observations, and deviations from the protocol are reviewed with the technicians. A minimum of 6 procedures every month is required in order to maintain certification.

13.5 References

1. National Heath and Nutrition Examination Survey. Body Measurements (Anthropometric) Manual. Available at cdc.gov/nchs/data/**nhanes**/**nhanes**3/cdrom/NCHS/.../ANTHRO.PDF. Access on March 5, 2010.

14.0 Lung Function Testing

Lung Function Testing, or Pulmonary Function Testing (PFT), is a critical component of SPIROMICS. Please see MOP 2 for a detailed description of PFT procedures. In brief, lung function will be assessed using spirometry and the six-minute walk test. Because these tests are sensitive to participant fatigue, as much as is possible, the coordinator should try to perform spirometry early in the study day. Spirometry results should be recorded on the SDF form, and results of the six minute walk are captured on the SMW form. Spirometry must be completed before sputum induction, as the induction process will affect the results of spirometry.

Spirometry results are essential for determining a subject’s strata. For this reason site’s are encouraged to collect this data as early in the visit process as possible.

15.0 Multidetector Row Computed Tomography

Multidetector Row computed tomography (MDCT), or CT scan, will be used to gather radiographic images of participants lungs. CT acquisition will be recorded on the CTA form. Coordinators will transfer CT image data to the Reading Center via the Dicom Parsar software (please see MOP 3 - Imaging for specific details regarding MDCT procedures). In summary, two different types of CT scans will be collected as part of SPIROMICS: inspiratory and expiratory. It will be very important for the study coordinator to work with CT technicians to ensure that the correct scanner settings are used and that the CT technicians are faithful to the SPIROMICS script for coaching participants. CT scans can be conducted at any point during the study day prior to

sputum induction. CT scans will only be conducted at the baseline and year 1 follow-up visits.

It will be very important for the coordinator and CT technician to assure that a pregnancy test be conducted prior to the CT scan for all women of childbearing potential.

16.0 Sputum Induction

Sputum Induction is a process during which participants inhale a saline solution, thereby increasing the production of mucus in the lungs. Mucus is then expectorated, collected, and processed for various analyses. Sputum induction is only included during the baseline visit. It is important that coordinators conduct sputum induction after PFTs and MDCT in order to not adversely affect the results of those studies. Details on the sputum induction and sputum processing can be found in MOP 5. Data for sputum induction are collected on the ISP or ISW (depending on FEV1 status), and processing data are collected on the SPW form.

17.0 Questionnaires

17.1 When to Complete Questionnaires and Forms

Eight forms should be completed during the fasting block (first portion of study exam). These forms are the Informed Consent Tracking (IEC), Personal Identifiers (PID), Baseline Medical history (BMH), Baseline Respiratory Medication Use (RMU), Baseline Exacerbation History (BEQ), Employment History (EHF), Pollution/Residential History (PRH), and Demographic Information (DEM). Study coordinators should administer these forms, recording participants' answers directly into the data management system (DMS). Please refer to the Question by Question instructions for more details on how to answer participant questions and probe for more information.
The study questionnaires can be administered in three blocks (see Table 2), with the exception of the FACIT questionnaire (administered during the first block) and the Ease of Cough and Sputum Clearance (administered during the sputum induction block).

17.2 How to Complete Questionnaires and Forms

Some questionnaires are interview administered and entered directly into the DMS and others are self-administered. It is important that only the participant is answering the questions. If a family member or friend is present, he or she should not assist in completing the instruments. When the participant is completing questionnaires, the study coordinator should remain available to answer any questions or assist with any computer-related issues.
Interviewer Administered Questionnaires, entered directly into the DMS:
Informed Consent Tracking (IEC), Personal Identifiers (PID), Baseline Medical history (BMH), Baseline Respiratory Medication Use (RMU), Baseline Exacerbation History (BEQ), Employment History (EHF), Pollution/Residential History (PRH), and Demographic Information (DEM), and SF12v2 Health Survey.

Self-Administered Questionnaires, entered into the DMS by Coordinators:
FACIT Fatigue Questionnaire (FCT), Modified Medical Research Council Dyspnea Scale (MRC), St. George's Respiratory Questionnaire (SGR), Questionnaire for ease of Cough/Sputum Clearance (MCQ)-*administered prior to the sputum induction*, Veteran's Specific Activity Questionnaire (VSA), Berlin Sleep Questionnaire (BSQ), Pittsburgh Sleep Quality Index (PSQ), and Hospital Anxiety and Depression Scale (HDS).

St. George's Respiratory Questionnaire for COPD Patients (SGRQ-C)

The St. George's Respiratory Questionnaire for COPD Patients (SGRQ-C) is the recently revised and shortened form of the well-established The St. George's Respiratory Questionnaire. The SGRQ-C has 40 items, and will take approximately 10 minutes to complete.

Modified Medical Research Council (mMRC) Dyspnea Scale

The Modified Medical Research Council Dyspnea Scale (mMRC) is a five-item instrument to assess a patient's degree of breathlessness in relation to physical activity. Participants read each brief description of an activity and then asked to select the statement that best describes their experience with dyspnea. This scale takes approximately one minute to complete (Mahler et al, 1988).

Berlin Questionnaire

The Berlin Questionnaire is a 14-item instrument used to predict a patient's risk of sleep apnea. The assessment takes approximately five minutes to complete.

Pittsburgh Sleep Quality Index

The Pittsburgh Sleep Quality Index (PSQI) is a 19-item questionnaire assessing sleep quality. The questionnaire takes approximately 5-10 minutes to complete.

Veterans Specific Activity Questionnaire

The Veterans Specific Activity Questionnaire (VSAQ) is a 13-item questionnaire. Participants select the level of activity that best describes their own. This questionnaire takes approximately five minutes to complete.

Hospital Anxiety and Depression Scale (HADS)

The Hospital Anxiety and Depression Scale (HADS) is a 14-item questionnaire, assessing anxiety and depression. The questionnaire takes approximately 2 to 5 minutes to complete.

COPD Assessment Test

The COPD Assessment Test (CAT) is an eight-item questionnaire that should only be administered to participants with COPD (Strata 3 and 4). These eight questions cover cough, phlegm, chest tightness, breathlessness going up hills/stairs, activity limitation at home, confidence leaving home, sleep, and energy. Each question is rated on a likert scale ranging from zero to five, with high scores indicating poorer COPD-related health status (Jones et al, 2009). The questionnaire takes two to five minutes to complete.

MOT Short Form – 12 (SF12v2 Health Survey)

The Medical Outcomes Study Short Form – 12 (SF-12) is a twelve-item questionnaire, assessing overall health status. This questionnaire takes approximately 10 minutes to complete.

Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F)

The Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) questionnaire is a 40-item scale used to assess fatigue in the setting of chronic illness. This questionnaire should only be administered to participants with COPD (Strata 3 and 4)

Questionnaire for Ease of Cough and Sputum Clearance (MCQ)

The Questionnaire for Ease of Cough and Sputum Clearance is an 8-item scale to assess participant perception of the severity and frequency of cough symptoms. This questionnaire will be administered prior to the sputum induction.

18.0 Ending the Visit and Data Inventory

NOTE: The Clinic Checklist (CCL) is no longer routinely collected as part of SPIROMICS. From time to time the GIC or Steering Committee may request sites collect the CCL in order to monitor visit length.

At the end of the study day the study coordinator should review the Clinic Check List (CCL) to check that all data points have been collected and entered. This is an opportunity for the participant to ask any questions or provide feedback on the visit day.

During this time the coordinator will review the expected follow-up with the participant. He or she will describe when the participant should expect to receive follow-up calls and what material will be covered. The coordinator should also tell the participant approximately when he or she can expect to return for a follow-up visit.

Please note that if the study visit is split over two days, the coordinator should still review the data inventory at the end of both study days to ensure all data are collected.

19.0 Participant Safety

It is expected that some subjects will experience changes in disease severity, will develop comorbidities to COPD, and/or will expire during the course of participating in SPIROMICS. SPIROMICS staff will provide appropriate referrals for medical care if during study visits clinically relevant changes in disease status are found. SPIROMICS is not a treatment trial and as such will not report the above listed events as adverse or serious adverse events, as they are considered to be part of or consistent with the natural progression of COPD.

Adverse events that result directly from study procedures, including those risks outlined in each procedure section and those not listed in this document, will be reported to the Steering Committee and OSMB.

Procedures for Serious Adverse Events

The FDA (2009) defines a serious adverse event as an adverse event that:

- Results in the participant's death,
- Is life-threatening,
- Results in Hospitalization (initial or prolonged),
- Results in significant, persistent, or permanent change, impairment, damage, disruption, or disability in the participant's body function/structure, physical activities or quality of life,
- Results in a congenital anomaly, or
- Requires Intervention to Prevent Permanent Impairment or Damage.

If a serious adverse event (SAE) occurs during a study visit the study coordinator should first insure the participant receives any needed medical attention. If the study coordinator is notified by phone, the coordinator should confirm that the participant has received medical attention. The study coordinator should then notify the site Principal Investigator and complete the Adverse Event form. For serious adverse events, the study coordinator should submit the form to the GIC within 48 hours of learning of the event. Study coordinators should comply with local regulations and policies when notifying the institutional IRB.

The GIC will notify the Project Officer, Steering Committee, and Observational Studies Monitoring Board within 48 hours of receiving the initial event notification.

Procedures for Adverse Events

Adverse events are undesirable experiences resulting from participation in the SPIROMICS study (FDA, 2009). Common adverse events are listed in the risks section of each procedure.

If an adverse event (AE) occurs during a study visit the study coordinator should first insure the participant receives any needed medical attention. If the study coordinator is notified by phone, the coordinator should confirm that the participant has received medical attention. The study coordinator should then notify the site Principal Investigator and complete the Adverse Event form found on the study website (www2.cscc.unc.edu/spiromics) For adverse events the study coordinator should submit the form to the GIC within seven days of learning of the event. Study coordinators should comply with local regulations and policies when notifying the institutional IRB.

The GIC will notify the Project Officer, Steering Committee, and Observational Studies Monitoring Board within a week of receiving the initial event notification.

Measures to Protect the Participant

Some of the procedures performed during a SPIROMICS have known potential risks. A number of safety measures are in place to minimize these risks. At baseline and all protocol scheduled follow-up visits, subjects will be screened for conditions that might increase their risk while participating in study procedures, including history of heart disease, heart failure, or recent myocardial infarction. In addition, clinical center staff will discuss the risks associated with each of these procedures with subjects during the screening process and before each procedure begins.

If a subject experiences a condition requiring immediate medical attention, such as a cardiac event, angina, acute hypertension the research physician will be consulted immediately and the visit terminated.

Emergencies

In the event of a life-threatening emergency a subject will require immediate transport to an acute care facility however clinical center staff may need to implement some emergency measures prior to transport. Many minor emergencies will require only onsite treatment.

Major Emergencies

Each clinical center will establish procedures for handling major medical emergencies including plans for how to transport a subject to the nearest medical facility. These procedures will define:

1) Who is in charge during an emergency
2) Who is to administer treatments
3) Who is to be notified
4) What action clinic staff is to take
5) Which reports are to be filed

Clinical centers will have access to either a physician, physician's assistant, or a registered nurse any time a subject is being interviewed or participating in a procedure. Each center has, in additional to trained personnel and emergency equipment, the phone numbers for policy and fire stations, ambulance services, and specific phone numbers or codes to alert medical teams (if applicable) posted in conspicuous places. In each subject's record contain contact information for his or her primary care physician, home or work numbers, and one or more emergency contacts.

Minor Emergencies

Minor emergencies are those not requiring emergent medical care, and can be handled at the clinical center. Common minor emergencies include syncope and dyspnea and clinic staff is trained in the appropriate response. While a minor emergency may not require physician care, study staff is to alert the research physician present to the event.

Reporting

All emergencies, major or minor, are documented. Documentation includes completing institutionally approved forms identifying the emergency as well as reporting the event to the Project Office and GIC. This form is to be completed by the person in charge at the time of the emergency, and all reports are co-signed by the clinic physician.

20.0 Substudies

20.1 Bronchoscopy Substudy

Bronchoscopy with bronchoalveolar lavage, epithelial brushings and bronchial biopsies will be conducted on a subgroup of the overall SPIROMICS subjects, comprising 50 subjects per site (total n=300). The goal of the bronchoscopy sub-study is to bank samples for future analyses.

NOTE: The first five bronchoscopies completed at each site should be in subjects with a post-bronchodilator FEV1>50% predicted. The data from these first five bronchoscopies must be reviewed by the Bronchoscopy Subcommittee before the site is approved to proceed with subjects with lower FEV1.

Refer to The SPIROMICS Bronchoscopy Sub-study Study Design and MOP for the specific procedures including guidelines for strata enrolment, for scheduling subjects for the two separate visits: one for sputum induction and one for the bronchoscopy; requesting shipment of the pre-made antibody aliquots from the Immunophenotyping Core and shipping specimens.

20.2 Repeatability and Replicate Substudy

Repeatability Substudy
The **entire clinic visit will be repeated** on 100 volunteers to determine reliability and short-term variability of measurement procedures. For this substudy, all interviews will be re-administered, all procedures (including CT) will be repeated and new samples of blood, urine, and saliva will be collected. The repeatability visit will occur at least two but no more than six weeks from the first visit. Clinical center staff will process these biospecimen samples according to the already established protocol.

Replicate Substudy
To estimate the reliability of laboratory measures, a replicate substudy will be conducted. For the Replicate Substudy, some participants will provide **an additional sample of blood or urine repeated on the same visit** (this distinguishes the Replicate Substudy from the Repeatability Substudy).

Refer to MOP 10 - Repeatability and Replicate Procedures for the specific procedures including guidelines for scheduling subjects participating in both the Repeatability and the Bronchoscopy Substudy; and labeling visits and/or samples using “phantom IDs” and linking forms (RID for the Repeatability Substudy and PLI for the replicate samples).

20.3 Exacerbation Substudy

The Exacerbation Substudy is a prospective, observational study, which will allow the assessment participant exacerbations using two definitions: health care utilization and

symptom-defined. The symptom defined events will be measured by using the EXACT-Pro instrument, a daily symptom diary collected via PDA. In addition to collecting detailed symptom data, participants will be seen in the study clinic at the time of an acute exacerbation. Participants will be enrolled a minimum of 12 months to a maximum of 18 months in one of two study waves.

Refer to The SPIROMICS Exacerbation Substudy and MOP for the specific procedures including guidelines for wave enrollment, for contacting participants for the two types of exacerbation events (health care utilization and EXACT defined events), and scheduling visits.

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Appendix 1 - List of excluded Immunosuppressives

- Azathioprine
- Calcineurin inhibitors
- Tacrolimus (Advagraf, Prograf)
- Cyclosporine (Neoral, Sandimmune)
    - Sirolimus (Rapamune)
    - CD2 blocker
    - Alefacept (Amevive)
- CD3 blocker
    - Munomonab cd3
- CD11a blocker
    - Efalizumab (Raptiva)
- CD20 blocker
    - Rituximab (Rituxan, MabThera)
- CD28 blocker
    - Abatacept (Orencia)
- CD25 blocker
    - Daclizumab (Zenapax)
- Cyclophosphamide
- Gold (Auranofin)
- Hydroxychloroquine (Plaquenil)
- IL1 β blockers
    - Anakinra (Kineret)
    - Canakinumab (Llaris)
    - Rilonacept (Arcalyst)
- IL-2 receptor antagonist
    - Basiliximab (Simulect)
- IL 12/23 mab
    - Ustekinumab (Stelara)
- Leflunomide (Arava)
- Methotrexate
- Mycophenolate
    - CellCept
    - Myfortic
- TNF blockers
    - Adalimumab (Humira)
    - Certolizumab (Cimzia)
    - Etanercept (Enbrel)
    - Golimumab (Simponi)
    - Infliximab (Remicade)