



AUDIT, RESEARCH AND GUIDELINE UPDATE

## Design of the Subpopulations and Intermediate Outcomes in COPD Study (SPIROMICS)

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► Additional material is published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/thoraxjnl-2013-203897>).

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Received 21 May 2013

Revised 22 August 2013

Accepted 28 August 2013

### ABSTRACT

Subpopulations and Intermediate Outcomes in COPD Study (SPIROMICS) is a multicentre observational study of chronic obstructive pulmonary disease (COPD) designed to guide future development of therapies for COPD by providing robust criteria for subclassifying COPD participants into groups most likely to benefit from a given therapy during a clinical trial, and identifying biomarkers/phenotypes that can be used as intermediate outcomes to reliably predict clinical benefit during therapeutic trials. The goal is to enrol 3200 participants in four strata. Participants undergo a baseline visit and three annual follow-up examinations, with quarterly telephone calls. Adjudication of exacerbations and mortality will be undertaken.

### INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a chronic, usually progressive, lung disease characterised by incompletely reversible airflow obstruction. Both the airways (obstructive bronchiolitis/small airways disease) and the parenchyma (emphysema/parenchymal destruction) contribute to the airflow obstruction and ultimately dyspnoea. Additional processes such as mucous hypersecretion (chronic bronchitis) and exacerbations contribute to the overall impact of the disease. COPD is the third leading cause of death in the USA.<sup>1</sup>

There are no proven medical therapies for COPD, other than supplemental oxygen and smoking cessation, which significantly reduce mortality.<sup>2</sup> No pharmacological treatments have been shown to modify meaningfully the long-term decline in lung function. Complicating the therapeutic scenario is the fact that the disease is highly heterogeneous. Obstructive bronchiolitis and emphysema are clinically distinct histological entities, but individual patients with COPD may have either or both. Moreover, each can occur in the absence of spirometrically defined COPD and likely result from a number of mechanistic pathways. The recognition of COPD as a systemic disease that affects extra-pulmonary systems, including cardiovascular, sleep and muscle function, further complicates disease classification. Because of clinical and pathological heterogeneity, individual patient subtypes may benefit from unique therapeutic regimens. Identifying meaningful subpopulations of COPD patients is a key goal of the Subpopulations and Intermediate Outcomes

### Key messages

#### What is the key question?

- What is the design of the Subpopulations and Intermediate Outcomes in COPD Study (SPIROMICS) and what are its aims?

#### What is the bottom line?

- SPIROMICS aims to identify homogeneous subgroups of patients with chronic obstructive pulmonary disease (COPD) for targeted enrolment in future therapeutic clinical trials and to discover and validate intermediate endpoints.

#### Why read on?

- To understand how SPIROMICS aims to move the field of COPD research forward.

in COPD Study (SPIROMICS). Additionally, the efficiency and cost of clinical trials could be improved considerably by validated intermediate endpoints.

### OBJECTIVES OF SPIROMICS

SPIROMICS has two primary aims. Primary aim 1 is to identify homogeneous subgroups of patients with COPD for targeted enrolment in future therapeutic clinical trials. Primary aim 2 is intermediate endpoint discovery and validation. SPIROMICS will endeavour to identify intermediate outcome measures that predict long-term clinical endpoints of morbidity. There are also three secondary aims, involving cohort building, developing a COPD controlled vocabulary, and supporting ancillary studies.

Further details of the aims and other aspects of the study are provided in the online supplement.

### STUDY DESIGN AND METHODS

SPIROMICS is a prospective cohort study that will enrol 3200 participants into four strata (non-smokers, smokers without airflow obstruction, mild/moderate COPD, and severe COPD) as shown in table 1.

Participants may be enrolled in concurrent observational studies, excluding the COPDGene Study,<sup>3</sup> which will facilitate combined analyses between SPIROMICS and COPDGene. Subjects enrolled in

**To cite:** Couper D, LaVange LM, Han ML, *et al*. Thorax Published Online First: [please include Day Month Year] doi:10.1136/thoraxjnl-2013-203897

**Table 1** SPIROMICS enrolment 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         |
| FEV <sub>1</sub> /FVC ratio criteria              | FEV <sub>1</sub> /FVC>0.7 | FEV <sub>1</sub> /FVC>0.7 | FEV <sub>1</sub> /FVC<0.7      | FEV <sub>1</sub> /FVC<0.7   |
| Other lung function criteria                      | FVC>LLN                   | FVC>LLN                   | FEV <sub>1</sub> >50% pred.    | FEV <sub>1</sub> <50% pred. |
| Sample size                                       | N=200 (6.25%)             | N=900 (28.1%)             | N=1500 (46.9%)                 | N=600 (18.75%)              |

COPD, chronic obstructive pulmonary disease; FEV<sub>1</sub>, forced expiratory volume in 1 s; FVC, forced vital capacity; LLN, lower limit of normal; SPIROMICS, Subpopulations and Intermediate Outcomes in COPD Study.

therapeutic clinical trials may enrol in SPIROMICS after the treatment is unmasked; those in SPIROMICS may be recruited into other interventional studies after SPIROMICS baseline values are obtained.

The Institutional Review Boards/Ethics Committees of all the cooperating institutions have approved the study protocols.

### Inclusion and exclusion criteria

Participants must be 40–80 years of age at baseline, have a smoking history of  $\leq 1$  pack-year (stratum 1) or  $\geq 20$  pack-years (strata 2–4) and meet lung function criteria as specified in table 1. Major exclusion criteria are non-COPD obstructive lung disease or a history of diseases or treatments likely to interfere with interpretation of study tests, body mass index  $>40$  kg/m<sup>2</sup> at baseline, hypersensitivity to or intolerance of the bronchodilators used in study assessments and diagnosis of unstable cardiovascular disease. Lung surgery and metal in the chest that may affect the chest CT interpretation is also exclusionary. Online supplementary table S1 contains the complete list of exclusion criteria.

### Baseline and follow-up assessments

There are baseline (visit 1) and three annual in-person follow-up visits (visits 2–4). Participants also receive quarterly follow-up calls to assess health status and determine if an exacerbation has occurred. Visits 1, 2 and 4 include anthropometry, seated blood pressure, spirometry, 6 min walk test, biological specimen collection, and a series of questionnaires (see online supplementary table S2). Information is collected on medical history, respiratory exposures and current medications. Visit 3 omits specimen collection. Visits 1 and 2 include a thoracic CT scan at maximum inspiration and expiration.

Clinical outcomes, including hospitalisations and deaths, will be adjudicated centrally.

### Imaging

Acquisition of state-of-the-art CT images is a key component in SPIROMICS for detailed phenotype identification (see online supplementary table S3). Two CT scans are performed, one at total lung capacity (TLC), and one at residual volume. The CT protocol for the TLC scan is identical to that used in other National Heart, Lung, and Blood Institute (NHLBI)-sponsored studies, including the Multi-ethnic Study of Atherosclerosis (MESA) Lung Study and the Severe Asthma Research Program (SARP), which will facilitate comparative papers across studies.

### Biospecimen collection

Fasting blood and urine specimens are collected at visits 1, 2 and 4. Approximately 70 mL of blood is collected per visit, including plasma and serum. DNA will be extracted from blood collected at visit 1 and RNA from PAX-Gene tubes collected at

visits 1 and 2. Urine is collected into aliquots with and without preservative. One ethylenediaminetetraacetic acid plasma specimen is assessed locally for complete blood, differential and platelet count. All other samples are sent to the SPIROMICS biospecimen repository. Additional blood and urine samples are collected from participants in the substudies. Induced sputum samples are collected at the baseline visit. Sputum is being processed using the ‘whole sputum’ method.

### SUBSTUDIES AND ANCILLARY STUDIES

A substudy is a component of the protocol funded by the SPIROMICS contract and performed on a subset or the entire cohort. An ancillary study is one that contributes new data to SPIROMICS but whose aims are distinct from the parent study. Ancillary studies are not funded as part of the parent study. However, they must be approved by SPIROMICS to assure that the use of SPIROMICS resources are scientifically and practically justified and that the study does not interfere with the primary goals of SPIROMICS.

Three key substudies are the Repeatability and Replicate Substudy, in which 100 participants will have the entire baseline clinic visit including the CT scanning repeated to quantify reliability and short-term within-person variability of study procedures and assay methods; (2) the Bronchoscopy Substudy, in which 300 participants will undergo bronchoscopy with bronchoalveolar lavage, epithelial brushings and bronchial biopsies; and (3) the Exacerbation Substudy, in which up to 400 participants will be followed prospectively and biological samples and clinical information will be collected at the time of an acute exacerbation.

### STUDY ORGANISATION

SPIROMICS has six core clinical centres, with subsites and satellite clinics, and several central agencies. These are the NHLBI Project Office, a Genomics and Informatics Center (which functions as the data and statistical coordinating centre and includes the biospecimen core), a Radiology Center, a Pulmonary Function Test Reading Center, and a Sputum Reading Center. An Observational Studies Monitoring Board provides annual and ad hoc evaluations of the study with recommendations to the NHLBI. An External Scientific Board that is composed of representatives from the pharmaceutical industry and the US Food and Drug Administration serves in an advisory role.

### DISCUSSION

The marked clinical and mechanistic heterogeneity that characterises COPD confounds development of novel treatments. It is likely that mechanistically based therapy will be effective only in selected subsets of the COPD population. SPIROMICS is designed to identify meaningful subsets of the COPD population appropriate for future mechanistically based therapeutic

interventions. Furthermore, the identification and validation of meaningful intermediate outcomes would facilitate development and testing of new treatments by enabling the design of more efficient clinical trials.<sup>4</sup> Although a number of such measures have been suggested, the validation of these measures is limited by the lack of data in a well characterised, longitudinal COPD cohort.

Several other studies will complement SPIROMICS to help address these questions. Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE)<sup>5</sup> used a 3-year observation period similar to SPIROMICS and shares similar goals. COPDGene<sup>3</sup> was originally designed to explore the genetics of COPD in a large cohort of subjects. Longitudinal data and collection of blood biomarkers are now in progress.

While the goals for SPIROMICS are ambitious, there are limitations. Even combined with other large studies like COPDGene and ECLIPSE, SPIROMICS will not be able to fully characterise COPD heterogeneity, its natural history or to fully validate biomarkers and other intermediate outcomes. These goals will undoubtedly require additional studies. SPIROMICS is committed to sharing protocols, instruments and data with other investigators. The availability of standardised methods and datasets will facilitate the development of other large cohorts and expedite their comparison with SPIROMICS and other studies.

Strengths of SPIROMICS include the large cohort with two types of controls, detailed characterisation at baseline and longitudinally, and extensive follow-up, with central adjudication of clinical outcomes.

In summary, SPIROMICS is a prospective observational study of COPD subjects and controls. It will characterise individuals with clinical, physiological, imaging, biochemical, cellular and histological parameters. Samples will be collected by a variety of methods. A subset of participants will be assessed at the time of an exacerbation. The rich characterisation of subjects with COPD will permit definition of meaningful subsets of patients with COPD. By assessing the relationship of clinical measures with longitudinal outcomes, SPIROMICS will advance validation of intermediate measures to be used in COPD. Finally, the availability of a well characterised cohort of participants that can be used in specific ancillary studies should prove to be a long-term resource for furthering understanding of COPD.

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**Contributors** DC takes responsibility for the overall content as guarantor. The manuscript was written primarily by DC, SR and MH. It is based on the (unpublished) SPIROMICS protocol. LML, as PI of the Genomics and Informatics Center at the time, and SR as Chair of the Steering Committee, led development of the study protocol. All authors were involved in planning various aspects of the study and all authors reviewed the manuscript and provided feedback. This work was performed while LML was at the University of North Carolina. She is now at the US Food and Drug Administration (FDA).

**Funding** Provided by the National Heart, Lung, and Blood Institute (NHLBI) of the NIH, contract and grant numbers: NHLBI contracts HHSN268200900013C, HHSN268200900014C, HHSN268200900015C, HHSN268200900016C, HHSN268200900017C, HHSN268200900018C, HHSN268200900019C, and HHSN268200900020C; NHLBI grant R01HL110906. The funder proposed the study and continues to be involved in its management.

**Competing interests** R Graham Barr reports royalties from UpToDate, reimbursement for travel to the TransAtlantic Airways Conference (Boehringer Ingelheim). Richard C Boucher reports board membership, consultancy, patents, royalties and stock/stock options, all from Parion Sciences. Elizabeth Carretta reports money paid to her institution, towards her employment on studies other than SPIROMICS, from the NIH and the COPD Foundation. Jeff Curtis reports grants (other than for SPIROMICS) from the NIH and the Department of Veterans Affairs, and travel/accommodation/meeting expenses (other than for SPIROMICS) from the American Thoracic Society. Meilan Han reports consulting fees or honoraria from GSK, Pfizer, Boehringer Ingelheim, Forest, Grifols, Novartis, Medimmune and Ikaria, fees for participation in review activities from GSK, royalties from UpToDate, payment for development of educational presentations from the Office of Research on Women's Health (ORWH) at the National Institutes of Health (NIH) and the Office of Women's Health (OWH) at the Food and Drug Administration, from WebMD, and from the National Association for Continuing Education. Nadia Hansel reports a consultancy with Boehringer-Ingelheim. Eric A Hoffman is a founder and shareholder of VIDA Diagnostics, a company commercialising lung image analysis software developed, in part, at the University of Iowa. Eric Kleerup reports a 1-day consultancy with Ikaria, grants from Boehringer Ingelheim, Forest, GlaxoSmithKline, Novartis, Osiris, Pearl Therapeutics, Schering Plough and Sunovion. GlaxoSmithKline donated Ventolin HFA for spirometric testing in this study to the Foundation for the NIH. Boehringer Ingelheim donated Atrovent HFA for spirometric testing in this study to the Foundation for the NIH. (EK heads the Spirometry Reading Center for SPIROMICS.) Fernando J Martinez reports board memberships of Actelion, Almirall/Forest, Nycomed/Takeda, Bayer, Ikaria, Merck, Pearl, Pfizer, Janssen and Vertex, consultancies with Actelion, Forest, American Institute for Research, AstraZeneca, GSK, Gilead, HCRC, Merion, Sudler and Hennessey, Carden Jennings and Grey Healthcare, grants other than for SPIROMICS from the NIH, payment for lectures

including service on speakers bureaus from Forest, Nycomed/Takeda, AstraZeneca, Bayer, William Beaumont Hospital, Boehringer Ingelheim, GSK, Lovelace, University of Illinois—Chicago, University of Texas—Southwestern, Wayne State University and Spectrum Health, royalties from Informa, payment for development of educational presentations from the American College of Chest Physicians, the Center for Healthcare Education, CME Incite, France Foundation, MedEd, NACE, St Luke's Hospital, UpToDate, University of Virginia, American Thoracic Society, NCME, Projects in Knowledge, and MedScape/WebMD, service on a DSMB for Novartis. Wanda O'Neal reports salary support (other than for SPIROMICS) paid to her institution by the NIH. Robert Paine reports research grants (other than for SPIROMICS) from NHLBI and the Department of Veterans Affairs. Stephen P Peters reports service on advisory boards for AstraZeneca, Aerocrine, Airsonett AB, GlaxoSmithKline, Merck, Targacept and TEVA, payment for lectures from Merck, and Integrity Continuing Education, royalties from UpToDate. Stephen Rennard reports grants to his institution from AstraZeneca, Biomarck, Centocor, Mpex, Nabi, Novartis and Otsuka, consulting fees or honoraria from AstraZeneca, Novartis and Otsuka, board memberships for Almirall, Novartis, Nycomed and Pfizer, consultancies with Able Associates, Adelphi Research, APT Pharma/Britnall, Aradigm, AstraZeneca, Chiesi, CommonHealth, Consult Complete, COPDForum, Data Monitor, Decision Resource, Defined Health, Dey, Dunn Group, Easton Associates, Equinox, Gerson, GlaxoSmithKline, Infomed, KOL Connection, M. Pankove, MedaCorp, MDRx Financial, Mpex, Oriol Therapeutics, Otsuka, Pennside, ParmaVentures, Pharmaxis, Price Waterhouse, Propagate, Pulmatrix, Reckner Associates, Recruiting Resources, Roche, Schlesinger Medical, Scimed, Sudler and Hennessey, TargeGen, Theravance, UBC, Uptake Medical, VantagePoint Management, Forest, Nycomed, Pearl, Sankyo and Novartis, grants from AstraZeneca, Biomarck, Centocor, Mpex, Nabi, Novartis, Otsuka, Boehringer Ingelheim and Nycomed, payment for lectures including service on speakers bureaus from AAAAI, American College of Osteopathic Physicians, Asan Medical Center, American Thoracic Society, AstraZeneca, California Society of Allergy, Convergent Health Solutions for Reviews and Trends in COPD, COPDFoundation, Creative Educational Concepts, Dey, Duke University, France Foundation, Information TV, University of Southern California—Los Angeles, Network for Continuing Education (CHARM), Novartis (Horsham), Nycomed, Otsuka, Pfizer, Sarasota Memorial Hospital, Spanish Thoracic Society, University of Washington, University of Alabama—Birmingham, University of Pittsburgh, University of British Columbia, University of California—Davis, and Sioux Falls VA,

travel, accommodation and meeting expenses, other than for SPIROMICS, from Amirall, AstraZeneca, Boehringer Ingelheim, California Allergy Society, Creative Educational Concept, France Foundation, GlaxoSmithKline, Information TV, Network for Continuing Education, Novartis, Nycomed and Pfizer. Krishna Sundar reports payment for lectures including service on speakers bureaus from Forest, and Boehringer Ingelheim, travel, accommodations and meeting expenses other than for SPIROMICS from Spiriva and Forest, serving as an investigator for Gilead. Donald P Tashkin reports board memberships with Sunovion, AstraZeneca, Novartis and Mylan, consultancies with Sunovion, AstraZeneca, Novartis and Mylan, grants from Boehringer-Ingelheim, Pearl Therapeutics, Sunovion, GlaxoSmithKline, Forest and Pfizer, payment for lectures including service on speakers bureaus from Boehringer-Ingelheim, AstraZeneca, Forest, Novartis, Pfizer. Robert A Wise reports consultancies with BIPI, GSK, Merck, Mylan, Sunovion, Spiration, Pulmonx and Intermune, grants from BIPI, GSK and Merck. Prescott G Woodruff reports consultancies with Boehringer-Ingelheim, Merck, Kalobios and Medimmune. All other authors report only contracts/grants from NHLBI to their institution for SPIROMICS and for travel to SPIROMICS meetings.

**Ethics approval** The Institutional Research Board at each of the participating institutions.

**Provenance and peer review** Not commissioned; internally peer reviewed.

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## Supplementary Tables

**Supplementary Table 1. Inclusion/Exclusion Criteria**

|  | Non-smokers | Smokers | Mild/Mod COPD | Severe COPD |
|--|-------------|---------|---------------|-------------|
| <b>Inclusion Criteria</b>  |             |         |               |             |
| Between age 40 and 80 (inclusive) at Baseline Visit  | X           | X       | X             | X           |
| Able to tolerate and willing to undergo study procedures   | X           | X       | X             | X           |
| <1 pack-year history of smoking  | X           |         |               |             |
| >20 pack-year history of smoking   |             | X       | X             | X           |
| Pre-bronchodilator: FEV <sub>1</sub> /FVC $\geq$ .7 and FVC>LLN  | X           |         |               |             |
| Post-bronchodilator: FEV <sub>1</sub> /FVC $\geq$ .7 and FVC>LLN   |             | X       |               |             |
| Post bronchodilator: FEV <sub>1</sub> /FVC < .7 and FEV <sub>1</sub> > 50% pred  |             |         | X             |             |
| Post bronchodilator: FEV <sub>1</sub> /FVC < .7 and FEV <sub>1</sub> < 50% pred  |             |         |               | X           |
| Able to understand English and/or Spanish  | X           | X       | X             | X           |
| <b>Exclusion Criteria</b>  |             |         |               |             |
| Women only: Cannot be pregnant at baseline or plan to become pregnant during the course of the study   | X           | X       | X             | X           |
| Dementia or other cognitive dysfunction which in the opinion of the investigator would prevent the participant from consenting to the study or completing study procedures   | X           | X       | X             | X           |
| Has plans to leave the area in the next 3 years  | X           | X       | X             | X           |
| Smoking history of > 1 pack-year but <21 pack-years  | X           | X       | X             | X           |
| Has a BMI > 40 kg/m <sup>2</sup> at baseline exam  | X           | X       | X             | X           |
| Prior significant difficulties with pulmonary function testing   | X           | X       | X             | X           |
| Hypersensitivity to or intolerance of albuterol sulfate or ipratropium bromide or propellants or excipients of the inhalers  | X           | X       | X             | X           |
| Non-COPD obstructive lung disease (various bronchiolitis, sarcoid, LAM, histiocytosis X) or parenchymal lung disease, pulmonary vascular disease, pleural disease, severe kyphoscoliosis, neuromuscular weakness, or other conditions, including clinically significant cardiovascular and pulmonary disease, that, in the opinion of the investigator, limit the interpretability of the pulmonary function measures. | X           | X       | X             | X           |
| History of Interstitial lung disease   | X           | X       | X             | X           |
| Current diagnosis of asthma  | X           |         |               |             |
| History of Lung volume reduction surgery or lung resection   | X           | X       | X             | X           |
| History of lung or other organ transplant  | X           | X       | X             | X           |
| History of endobronchial valve therapy   | X           | X       | X             | X           |
| History of large thoracic metal implants (e.g., AICD and/or pacemaker) that in the opinion of the investigator limit the interpretability of CT scans  | X           | X       | X             | X           |

|  |   |   |   |   |
|--|---|---|---|---|
| Currently taking $\geq 10$ mg a day/20mg every other day of prednisone or equivalent systemic corticosteroid   | X | X | X | X |
| Currently taking any immunosuppressive agent   | X | X | X | X |
| Current illicit substance abuse, excluding marijuana   | X | X | X | X |
| History of or current use of IV Ritalin  | X | X | X | X |
| History of or current use of heroin  | X | X | X | X |
| History of illegal IV drug use within the last 10 years or more than 5 instances of illegal IV drug use ever   | X | X | X | X |
| Known HIV/AIDS infection   | X | X | X | X |
| History of lung cancer or any cancer that spread to multiple locations in the body   | X | X | X | X |
| History of or current exposure to chemotherapy or radiation treatments that, in the opinion of the investigator, limits the interpretability of the pulmonary function measures. | X | X | X | X |
| Diagnosis of unstable cardiovascular disease including myocardial infarction in the past 6 weeks, uncontrolled congestive heart failure, or uncontrolled arrhythmia              | X | X | X | X |

**Supplementary Table 2. Schedule of Study Measurements**

|   | <b>V1</b> | <b>V2</b> | <b>V3</b> | <b>V4</b> |
|---|-----------|-----------|-----------|-----------|
| <b>Physiological Measures</b>                         |           |           |           |           |
| <b>Pulmonary Function Testing</b>                     |           |           |           |           |
| Exhaled CO (eCO)                                      | X         | X         |           | X         |
| Forced Vital Capacity                                 | X         | X         | X         | X         |
| Slow vital capacity                                   | X         | X         | X         | X         |
| Bronchodilation                                       | X         | X         | X         | X         |
| Forced Vital Capacity                                 | X         | X         | X         | X         |
| Slow Vital Capacity                                   | X         | X         | X         | X         |
| Six minute walk test with continuous pulse oximetry   | X         | X         | X         | X         |
| <b>Anthropometric Measurements</b>                    |           |           |           |           |
| Height  | X         | X         | X         | X         |
| Weight  | X         | X         | X         | X         |
| Arm Span  | X         | X         | X         | X         |
| Waist   | X         | X         | X         | X         |
| Hip   | X         | X         | X         | X         |
| Neck  | X         | X         | X         | X         |
| Seated Blood Pressure                                 | X         | X         | X         | X         |
| <b>MDCT</b>   | X         | X         |           |           |
| <b>Biospecimen collection</b>                         |           |           |           |           |
| <b>Blood</b>  |           |           |           |           |
| Serum (Two – RT)                                      | X         | X         |           | X         |
| Plasma (One – P100)                                   | X         | X         |           | X         |
| Plasma (Three – Plasma/DNA w/EDTA; one – CBC w/EDTA)  | X         | X         |           | X         |
| Plasma (One – with citrate)                           | X         | X         |           | X         |
| RNA (One – PAX-Gene)                                  | X         | X         |           |           |
| Urine   | X         | X         |           | X         |
| Induced Sputum  | X         |           |           |           |
| <b>Questionnaires</b>                                 |           |           |           |           |
| Medical History                                       | X         | X         | X         | X         |
| St. George’s Respiratory Questionnaire                | X         | X         | X         | X         |
| MOT Short Form – 12                                   | X         | X         | X         | X         |
| COPD Assessment Test                                  | X         | X         | X         | X         |
| Modified Medical Research Council (MRC) Dyspnea Scale | X         | X         | X         | X         |
| <b>Sleep questionnaires</b>                           |           |           |           |           |
| Berlin Questionnaire                                  | X         | X         | X         | X         |
| Pittsburgh Sleep Quality Index                        | X         | X         | X         | X         |
| Veterans Specific Activity Questionnaire              | X         | X         | X         | X         |
| Hospital Anxiety and Depression Scale (HADS)          | X         | X         | X         | X         |
| FACIT   | X         | X         | X         | X         |
| Questionnaire for Ease of Cough and Sputum Clearance  | X         | X         | X         | X         |

**Supplementary Table 3. Imaging protocol in SPIROMICS**

|                         | BMI < 20  | BMI 20-30 | BMI > 30 |
|-------------------------|---|-----------|----------|
| kVp setting             | 120 kVp   | 120 kVp   | 120 kVp  |
| CTDIVol for inspiration | 6.1 mGy   | 7.6 mGy   | 11.4 mGy |
| CTDIVol for expiration  | 4.2 mGy   | 4.2 mGy   | 6.1 mGy  |
| mAs setting             | Depends on scanner type and whether inspiration or expiration |           |          |