AUDIT, RESEARCH AND GUIDELINE UPDATE

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

David Couper,[1] Lisa M LaVange,[1] MeiLan Han,[2] R Graham Barr,[3] Eugene Bleecker,[4] Eric A Hoffman,[5] Richard Kanner,[6] Eric Kleerup,[7] Fernando J Martinez,[8] Prescott G Woodruff,[9] Stephen Rennard[10] for the SPIROMICS Research Group

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.[1]

There are no proven medical therapies for COPD, other than supplemental oxygen and smoking cessation, which significantly reduce mortality.[2] 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,[3] which will facilitate combined analyses between SPIROMICS and COPDGene. Subjects enrolled in

	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_1/FVC ratio criteria	$FEV_1/FVC>0.7$	$FEV_1/FVC>0.7$	$FEV_1/FVC<0.7$	$FEV_1/FVC<0.7$
Other lung function criteria	FVC>LLN	FVC>LLN	$FEV_1>50\%$ pred.	$FEV_1<50\%$ pred.
Sample size	N=200 (6.25%)	N=900 (28.1%)	N=1500 (46.9%)	N=600 (18.75%)

Table 1 SPIROMICS enrolment strata

COPD, chronic obstructive pulmonary disease; FEV_1, 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 ≤1 pack-year (stratum 1) or ≥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^2 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.[4] 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)[5] used a 3-year observation period similar to SPIROMICS and shares similar goals. COPDGene[3] 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.

Author affiliations
[1]Department of Biostatistics, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA
[2]Division of Pulmonary & Critical Care, University of Michigan, Ann Arbor, Michigan, USA
[3]Department of Medicine, Columbia University, New York, New York, USA
[4]Center for Genomics and Personalized Medicine Research, Wake Forest University, Winston-Salem, New York, USA
[5]Department of Radiology, University of Iowa, Iowa City, Iowa, USA
[6]Department of Internal Medicine/Pulmonary and Critical Care Medicine, University of Utah, Salt Lake City, Utah, USA
[7]Department of Medicine, University of California at Los Angeles, Los Angeles, California, USA
[8]Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan, USA
[9]Division of Pulmonary, Critical Care, Sleep and Allergy, Department of Medicine, University of California at San Francisco, San Francisco, California, USA
[10]Division of Pulmonary, Critical Care, Sleep & Allergy, Department of Internal Medicine, University of Nebraska, Omaha, Nebraska, USA

Collaborators Neil Alexis, Department of Pediatrics, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA. Wayne Anderson, Department of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA. Safwan Badr, Division of Pulmonary Critical Care and Sleep Medicine, Department of Internal Medicine, Wayne State University School of Medicine, Detroit, Michigan, USA. Patricia Basta, Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA. Richard C Boucher, Department of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA. Elizabeth Carretta, Department of Biostatistics, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA. Christopher B Cooper, Department of Medicine, University of California at Los Angeles, Los Angeles, California, USA. Jeff Curtis, Department of Internal Medicine, University of Michigan Health System, Ann Arbor, Michigan, USA. Claire Doerschuk, Departments of Medicine and Pathology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA. Jane Greenberg, School of Information and Library Science, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA. Nadia Hansel, Department of Medicine, Johns Hopkins University, Baltimore, Maryland, USA. Robert Kaner, Institute of Genetic Medicine, Weill Cornell Medical College, New York, New York, USA. Mehmet Kesimer, Department of Pathology and Laboratory Medicine; and Cystic Fibrosis/Pulmonary Research and Treatment Center, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA. Stephen C Lazarus, Department of Medicine, University of California at San Francisco, San Francisco, California, USA. Deborah Meyers, Center for Genomics and Personalized Medicine Research, Wake Forest University, Winston-Salem, North Carolina, USA. Wanda O'Neal, Department of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA. Robert Paine, III, Department of Internal Medicine/Pulmonary and Critical Care Medicine, University of Utah, Salt Lake City, Utah, USA. Stephen P Peters, Department of Internal Medicine, Wake Forest School of Medicine, Winston-Salem, North Carolina, USA. Sanjeev Raman, Department of Internal Medicine/Pulmonary and Critical Care Medicine, University of Utah, Salt Lake City, Utah, USA. Mary Beth Scholand, Department of Internal Medicine/Pulmonary and Critical Care Medicine, University of Utah, Salt Lake City, Utah, USA. Krishna Sundar, Department of Internal Medicine/Pulmonary and Critical Care Medicine, University of Utah, Salt Lake City, Utah, USA. Donald P Tashkin, Department of Medicine, David Geffen School of Medicine, University of California at Los Angeles, Los Angeles, California, USA. Robert A Wise, Division of Pulmonary and Critical Care Medicine, Johns Hopkins University, Baltimore, Maryland, USA. Fred A Wright, Department of Biostatistics, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA.

REFERENCES

1 Minino A, Xu J, Kochanek M. Deaths: preliminary data for 2008. *Natl Vital Stat Rep* 2010;59:1–71.
2 Global Strategy for Diagnosis, Management and Prevention of COPD (updated 2013). 2013. http://www.goldcopd.org/uploads/users/files/GOLD_Report_2013_Feb20.pdf (accessed 4 September 2013).
3 Regan EA, Hokanson JE, Murphy JR, *et al*. Genetic epidemiology of COPD (COPDGene) study design. *COPD* 2010;7:32–43.
4 Vestbo J, Rennard S. Chronic obstructive pulmonary disease biomarker(s) for disease activity needed—urgently. *Am J Respir Crit Care Med* 2010;182:863–4.
5 Vestbo J, Anderson W, Coxson HO, *et al*. Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE). *Eur Respir J* 2008;31:869–73.