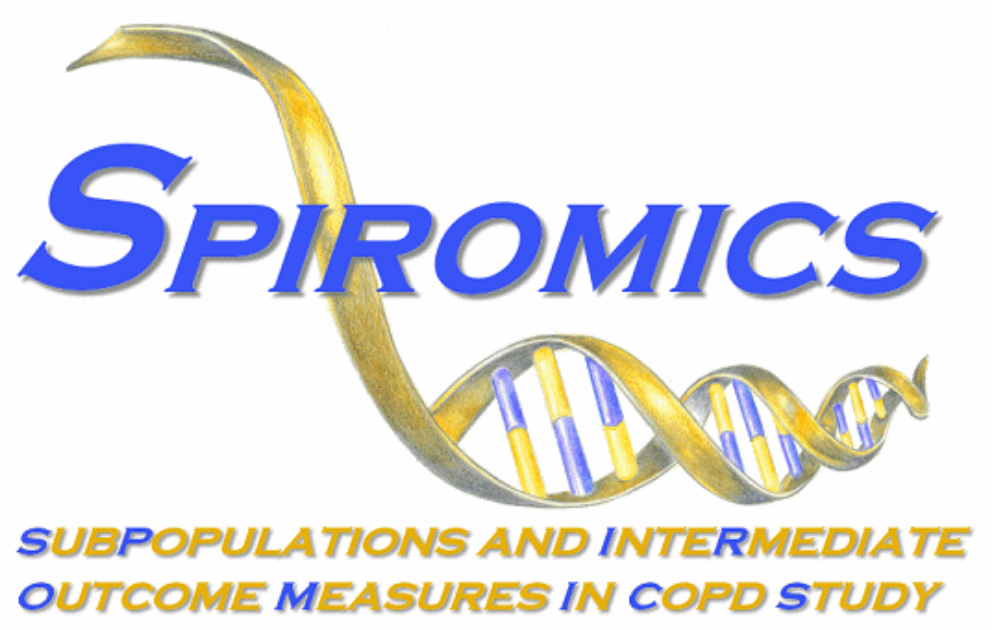

Protocol Synopsis

SPIROMICS Protocol Synopsis

1. Study Objectives

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

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

2. Study Design

SPIROMICS is a prospective cohort study with an enrollment target of approximately 3,200 subjects recruited at six clinical center networks. Subjects were distributed across four enrollment strata (i.e., Never-smokers, Smokers without airflow obstruction, Mild/Moderate COPD, and Severe COPD) as shown in Table 1.

Table 1. SPIROMICS Enrollment Strata

	Never-Smokers (Stratum 1)	**Smokers w/o Airflow Obstruction (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	$FEV_1/FVC > 0.7$	$FEV_1/FVC > 0.7$	$FEV_1/FVC < 0.7$	$FEV_1/FVC < 0.7$
Other Lung Function Criteria	FVC>LLN	FVC>LLN	$FEV_1 > 50\%$ pred.	$FEV_1 < 50\%$ pred.
Sample Size	N = 200 (6.25%)	N = 900 (28.13%)	N = 1500 (46.88%)	N = 600 (18.72%)

3. Study Visits

All subjects had up to four in-person, study-related visits (Baseline and Annual Clinic Visits at Years 1, 2, 3 after Baseline). During the Baseline, Year 1, and Year 3 study visits, clinic staff conducted physical examinations and tests, collected biological specimens (e.g., blood, urine), and administered a series of questionnaires to study subjects. During Year 2 study coordinators primarily collected pulmonary function data. In addition, the Baseline study visit included a sputum induction and a CT scan. The CT scan was repeated in Year 1. Subjects also received quarterly follow-up calls to assess health status and determine if an exacerbation occurred. A detailed schedule of study measurements is available in Section 6.2 of the SPIROMICS protocol.

4. Endpoints Processing

As part of the SPIROMICS protocol, participant hospitalizations and deaths are investigated to allow classification of events, particularly to ascertain whether an event is related to pulmonary exacerbation. During the quarterly phone calls and in-person study visits, coordinators collect data on hospitalizations since the last contact. These hospitalizations, as well as any deaths identified during follow-up, are investigated by obtaining medical records and death certificates. These records are blinded and transferred to the GIC where they are abstracted by a nurse abstractor. All deaths and a subset of events are then reviewed by investigators so that they can be classified.

5. Substudies

a. Bronchoscopy and Immunophenotyping Substudy

The Bronchoscopy Substudy enrolled up to 50 subjects per site, for an enrollment target of 300 participants. These participants were recruited across all four study strata.

Table 2. SPIROMICS Bronchoscopy/Immunophenotyping Enrollment Strata

	Never-Smokers (Stratum 1)	Smokers without airflow obstruction(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 > 0.7	FEV1/FVC < 0.7	FEV1/FVC < 0.7
Other Lung Function Criteria	FVC>LLN	FVC>LLN	FEV1 > 50% pred.	FEV1 < 50% pred.
Sample Size	N = 60 (20%)	N = 100 (33%)	N = 120 (40%)	N = 20 (7%)

b. Repeatability and Replicate Substudy

The entire clinic was to be repeated on 100 (3%) volunteers to determine reliability of measurement procedures. All baseline study-related procedures and questionnaires, including the CT scan, were re-administered and new samples of blood, urine, saliva, and sputum were collected. Field center staff processed these biospecimen samples according to protocol.

Table 3. Distribution of Participants in Repeatability Substudy Across Sites

	Total	**Stratum 1**	**Stratum 2**	**Stratum 3**	**Stratum 4**
Columbia	9	1	2	3	3
JHU	8	1	1	3	3
WFU	17	2	3	6	6
UCLA	17	2	3	6	6
UCSF	17	2	3	6	6
MI	16	2	3	5	6
Utah	16	2	3	6	5
Total	100	12	18	35	35

Sites recruited participants through March 2015, and completed a total of 98 of the 100 planned visits.

In addition, sites collected replicate samples at the Baseline, Year 1, and Year 3 visits. These were obtained by either drawing one to two additional tubes of blood or by dividing a urine sample into separate containers. The replicate samples were then processed using the same method as for the original samples. The replicate samples are blinded such that investigators and laboratory staff analyzing and processing the samples are unable to distinguish the replicates from the main study samples. Over the entire study, replicate samples were obtained on 5% of each specimen type (n = 160 at baseline, n=151 at year 1, and n=134 at year 3 for each

specimen). Nine participants were needed to provide a complete set of 9 QC replicate specimens (8 tubes of blood and 1 urine specimen), unless urine was collected from a participant providing a blood specimen replicate.

Table 4. Number of replicates per specimen for Baseline, Year 1, and Year 3 Across All Sites

	Red Top 1	Red Top 2	EDTA 1	EDTA 2	ACD	PaxGene	P100	Urine
Baseline	160	160	160	160	160	160	160	160
Year 1	151	151	151	151	151	151	151	151
Year 3	134	134	134	134	134	0	134	134

c. Exacerbations Substudy

The Exacerbations Substudy had a target enrollment of approximately 67 participants per site, for a total of 400 participants. The study enrolled into two strata: frequent exacerbators (those with 1 or more exacerbations reported in the last 12 months) and infrequent exacerbators (those with no reported exacerbations in the past 12 months). The study was divided into two waves. In both waves participants were asked to complete an electronic diary with the EXACT each night before bed and participants were contacted monthly to determine vital status.

Wave 1 had a target enrollment of 300 participants. These participants were instructed to contact the clinical center if they experienced an exacerbation that triggered a healthcare utilization (HCU event). The coordinator then queried the study subject using a simple case report form and algorithm. If the event was likely an acute exacerbation the subject was asked to come to the SPIROMICS center within 72 hours. The participant was then assessed by a study physician to determine if the event was an acute exacerbation. If the event was ruled an acute exacerbation, a complete study assessment was performed and the electronic diary was re-programmed to detect an acute, sustained symptomatic worsening, using pre-defined change thresholds in EXACT scores (12-point increase for 2 days or 9-point increase for 3 days). The subject was instructed to notify the SPIROMICS center to arrange a visit and assessment if such an EXACT triggered event occurs. The projected number of HCU and EXACT events is included in Table 5a below:

Table 5a. Expected Number of Exacerbations and Study Visits over 12 Months - Wave 1

Overall	N	HCU Events	HCU Visits*	EXACT Events	EXACT Visits*	TOTAL VISITS
Frequent exacerbators	200	120	79	32	21	100
Infrequent exacerbators	100	22	15	6	4	19
Total	300	142	94	38	25	119

*Number of projected visits is fewer than the number of events because the investigators project only 60% of participants will be seen during the 72-hour window.

Wave 2 had an enrollment target of 100 participants and would be initiated at a site only if the number of HCU events was fewer than anticipated. The number of subject-initiated HCU and symptom-defined events at each site was monitored monthly during Wave 1. If the number of events at any given site was fewer than anticipated, Wave 2 would be initiated at that site. In Wave 2 the subject was instructed to come to the clinical center for either a symptom-defined (EXACT) or subjected-initiated HCU event.

Table 5b. Expected Number of Exacerbations and Study Visits over 12 Months - Wave 2

	N	Event 1	Visits 1*	Events 2	Visits 2*	TOTAL VISITS
Frequent exacerbators	75	45	30	9	6	36
Infrequent exacerbators	25	8	5	1	1	6
Total	100	53	35	10	7	42

*Number of projected visits is fewer than the number of events because the investigators project only 60% of participants will be seen during the 72-hour window.