

SPIROMICS Radiology MOP (Revised)

Date: 11/20/12

1 Purpose

Noninvasive measures (i.e. imaging) of airway structure and remodeling (e.g. thickened airway walls) as well as air trapping and other parameters of peripheral airway and parenchymal pathologies will allow us to longitudinally monitor the effects of various stimuli and treatments.

The University of Iowa (Eric Hoffman PI) will serve as the Radiology Center to provide standardization and harmonization of all CT imaging protocols performed in SPIROMICS. In addition, this center will provide initial quantitative CT analysis of all images following this protocol and provide this data to the SPIROMICS DCC. The Radiology Center will govern all imaging for SPIROMICS, review quality performance of imaging sites, and report to the Steering Committee its recommendations. The Chair of the Radiology Committee (Eric Hoffman) will report to the Steering Committee at regular scheduled meetings.

2 Introduction

Baseline and Follow-up scans: The CT scanning protocol for SPIROMICS consists of obtaining multi-detector CT (MDCT) images of the entire lung at full inspiration (TLC) and at Functional Residual Volume (RV). TLC & RV scans will be performed at baseline and follow up approximately 1 year later. At all visits subsequent to the baseline visit, participants will be scanned with the same CT parameters, such as the same dose and diameter field of view (DFOV) used during the baseline CT visit unless either 1) the original scan was at a higher than appropriate dose (e.g., small subject scanned as a medium) or 2) the participant's body mass index (BMI, in kg/m²) changes **more than three units on either side** of the BMI thresholds for the original dose category. In the case of conditions 1 or 2, the subject will be scanned at a dose appropriate to their present BMI. Follow-up visit should match the same DFOV used for the TLC scan at baseline (which should have matched the RV DFOV at baseline).

Unique breathing instructions are required to obtain appropriate images. Parameters such as dose have been adjusted to minimize exposure by using different independent mAs or mA settings for 1) each body size (large, medium, small and extra small subjects) and 2) scan type (TLC vs RV). The images from the MDCT chest will be stored locally and will be sent to the Imaging Core (University of Iowa) via DISPATCH software (University of Iowa) which anonymizes the scans in a consistent fashion for protocol compliance verification.

3 CT Scanning Parameters

Radiation Exposure Specification: Scanners of different makes and models deliver differing number of photons to the subjects for a given mAs setting because of differences in beam filtration, variances in tube potential, etc. Therefore using a fixed milli-ampere (mA) across scanners will result in dissimilar exposures, leading to noise differences and possible inconsistencies in the reported CT number (HU) ... and radiation exposures. The SPIROMICS imaging protocol recommends documentation of the scanner reported CTDIvol located on the scanner console to determine a standard exposure across scanners, recognizing that the reported CTDIvol is an average across a given make and model and not exact for the particular

scanner. International standards regulation IEC 60601-2-44 require that the CTDIvol to be reported within 15% across CT scanners.

Dose modulation is not recommended for quantitative CT studies since each manufacturer modulates differently, causing an increased likelihood of system differences across scanners.

BMI and scan type will determine the CTDIvol and subsequently the effective mAs or mA setting. Five levels of CTDIvol are recommended as a function of 1) large, medium, or small BMI and 2) scan type (i.e. TLC or RV). This mechanism allows for optimal doses to the various size subjects. The BMI values will be provided by the study coordinator. The CT Technologist will use these guidelines to choose the effective mAs (Siemens) or mA (GE) setting for a given BMI. Appendix (A) Table I demonstrates the the CTDIvol number for a given BMI size.

Scout scans will be obtained to minimize the subject's exposure to radiation and must be performed at the lung volume for which anatomical boundaries are being evaluated. Each study site should perform scouts as deemed locally appropriate to specify a TLC and RV scan such that when spirally scanned, the full extent of the lung is acquired at the respective lung volumes and over-scanning is kept to a minimum (no more than 2 cm cephalad to the apical or 5 cm caudal to the basal lung borders). Inadequate scout scans may be repeated as per site-specific determination. (Spiral scans, however, may not be repeated.) The exposure factors (kV and mA) for the topogram should be set to the lowest available on the CT scanner that provides an acceptable image. For GE scanners 80 kv and 20 mA is sufficient to achieve satisfactory scout image quality.

The specific CT scanning parameters are listed in Appendix (B) & (C) Table II & III for the different scanner models in the SPIROMICS grant. The scanner settings utilized in SPIROMICS should be maintained consistent throughout the duration of the grant. The image data will be reconstructed with the reconstruction algorithms as outlined in Table II & III. The data shall be displayed using a display field of view (DFOV) that includes the lungs and approximately 2 cm or less chest wall in the right/left dimension so that resolution of the lung is maximum. The Standard reconstruction algorithm (B35, Standard, B) data is all that will be used for further computer analysis. The Lung reconstruction algorithm (B30, B31, YB, or Detail) depending on vendor data, is necessary for the supervising radiologist to interpret the image dataset in standard fashion. Further manufacturer and type-specific CT scan parameter data for each of the centers is summarized in Table II & III.

4 Breath Hold Technique for Scanning Procedure

In order to obtain appropriate image data, unique breathing instructions are required. These instructions are found on the *CT Technologist Reference Sheet*. Before the scans are acquired, the coordinator (or trained CT technologist) will review the breathing instructions with the participant and emphasize the importance of following them as closely as possible during the actual imaging of the lungs. In summary, the participant will be instructed to inhale deeply and exhale 3 times and then hold their breath two different ways: with the lungs full of air (TLC scan) and at the end of a normal breath of air (RV scan).

In order to extract the desired information from the CT images, it is very important that the breathing instructions are followed closely to ensure the subject is not arching back, to ensure the subject is breathing all the way in and out, and to make sure the subject reaches peak breath hold (TLC or RV) before imaging. An example of the breathing instructions can be found in

appendix G .

5 Proper Identification of the Scan Reconstructions

Scan reconstruction identifiers (this is information the techs can add to each reconstruction) should specify the lung volume (Inspiration (TLC) /Expiration (RV)), slice thickness, and recon kernel.

Here is an example of the labeling scheme for each of the four SPIROMICS reconstructions:

- Inspiration 0.75 slice thickness B35 kernel
- Inspiration 0.75 slice thickness B30 kernel
- Expiration 0.75 slice thickness B35 kernel
- Expiration 0.75 slice thickness B30 kernel

6 Imaging Forms

A *CT Acquisition Form* is completed by the technologist before and after each subject is scanned. When the CT technologist completes and signs the form legibly with their full name and no abbreviations, the technologist is taking responsibility for carrying out the scanning as specified by the this form, as approved by the IRB, and as agreed upon in the consent form. The *CT Acquisition Form* is sent to the University of Iowa for evaluation. Forms will be provided via the SPIROMICS website.

The *CT Technologist Reference Sheet* will help ensure the CT technologists have the proper information to complete the CT scans in accordance with the protocol. Each Center will maintain a copy of this reference sheet and give it to the CT Technologist each time a scan is to be done. The reference sheet details proper breathing instructions and scan parameters for GE and Siemens scanners. Forms will be provided via the SPIROMICS website

7 Data Analysis

The CT image data and the CT Acquisition Form for the given scan will be transmitted to the Radiology Center within 5 working days of performance of the CT via the provided DISPATCH software. (*note: if a site's Radiology Department keeps raw data on the scanner for shorter periods of time, the 5 day window should be narrowed so that there is time to correct reconstruction-based deviations should they be detected*) At the Radiology Center (University of Iowa), CT scans will be analyzed using automated, quantitative airway evaluation software designed to reconstruct 3-D lungs, lobes and airway trees from MDCT images (Apollo, VIDA Diagnostics). Analysis will provide airway and parenchymal-based metrics which will be transmitted from the Radiology Core to the data center.

Using existing techniques, the lungs will be segmented to identify left and right lungs along with their associated lobes. Air and tissue volumes will be reported for the whole lung, right and left lungs, and for each individual lobe. Local statistical measures of lung parenchymal attenuation values will be computed for each lobe and sublobar region. Parenchymal measures from the TLC scans will include voxels below -950, -910 and -856, density histogram-based means, modes, skewness, kurtosis as well as measures of air and non-air volumes for the whole lung, left and right lung, and lobes. The airway tree will be segmented to include 6 primary paths (RB1, RB4, RB10, LB1, LB4, LB10). The Apollo software automatically labels airway segments

according to standard bronchoscopic terminology. Airway segment maximum and minimum diameters will be reported for the middle third of each segment (avoiding the branch point saddles); segment lengths will be included which permit the calculation of segment luminal volumes. Airway wall thickness will be reported for the middle third of each segment. Airway wall thickness will be normalized to the lumen plus wall area to provide a wall area percent measure for each found segment, and a Pi10 measure will be reported for each of the above named 6 paths. This measure is derived from a plot of the inner perimeter (x-axis) vs Square Root of the airway wall area (y-axis), identifying a regression line and identifying the modeled airway wall area associated with an inner perimeter of 10mm using the relationship defined by the regression. Air trapping on the RV scans will be defined as the percent voxels (on a whole lung, left and right lung, and lobar basis) falling below -856HU. Airways will not be assessed on the RV scans.

8 Certification of Imaging Technologists

It is a strong recommendation that the technologist be a CT certified radiologic technologist; and they must have specific training and certification detailed to the SPIROMICS MOP. This certification regarding SPIROMICS can come from the SPIROMICS Radiology Center or from a SPIROMICS site-certified technologist who will report new certifications to the SPIROMICS Radiology Center. A training video will be provided by the Radiology Center as well as an on-line Power Point-based tutorial. A test will be administered at the end of the on-line tutorial. Technologist privileges with respect to SPIROMICS CT scanning can be revoked as deemed necessary by a consensus opinion of the Radiology Coordinating Center, site Radiologist and site SPIROMICS PI.

9 Quality Control

The site study coordinator will take responsibility to provide the radiology technologist with subject specific SPIROMICS protocol upon delivery of the subject to the CT suite and will remain in the CT control room during scanning to assure that appropriate breath hold instructions are being given. Because of the reliance of the study coordinator to the on-site “eyes and ears” for SPIROMICS at the time of subject scanning, the study coordinator should be familiar with the radiology protocol requirements.

The CT scanner needs to be operated according to the recommendations of the manufacturer; this includes the use of weekly water phantoms and daily air calibrations. The SPIROMICS CT protocol needs to be pre-loaded into the protocol list of the designated CT scanner with each study acquired using this preset protocol.

All CT scanners used in SPIROMICS must be certified with a phantom (COPDGene Phantom) scan. This phantom scan will provide checks for protocol adherence and proper calibration of the CT scanner. The initial phantom scan from any new CT scanner must be sent to the University of Iowa via DISPATCH for scanner approval prior to scanning human subjects. Phantom scans not meeting the scanning protocol defined by this MOP will be automatically rejected by DISPATCH with an explanation. The explanation will provide feedback regarding the nature of the failure and how to correct for it. If it is a post processing issue such as the wrong DFOV, slice thickness or slice spacing, DISPATCH will inform what parameter failed and the Radiology Reading Center will include how to fix it without a rescan. If the problem is related to scan acquisition, i.e. wrong mAs/mAs, kV, pitch, or exposure time, the phantom must be re-scanned and DISPATCH will

explain the parameter that failed as well as provide the correct parameter to use. Scanners may also be rejected if the scanner does not meet calibration criteria. Once the scanner is approved, monthly scans must be completed for quality assurance purposes and transmitted via DISPATCH. These ongoing phantom scans should be continued through the course of the studies. If phantom scans show a scanner to deviate from the approved baseline measures, decisions regarding continuation of scanning will be made through a consultation between the Radiology Center, site Radiologist and Site PI. Questions or concerns regarding scanning of the phantom may be referred to the University of Iowa.

10 Data and Safety Monitoring Plan

All SPIROMICS sites agree to perform research CT imaging on participants using the approved SPIROMICS Imaging Manual of Procedures. All sites will input the radiation dose information for each CT into the PVS software.

All SPIROMICS datasets from participants and phantoms will be transferred to University of Iowa Radiology Center within 5 working days of its performance to ensure protocol compliance. A monthly report will be generated and sent to the DCC and each site's PI, lead coordinator and radiologist.

Protocol issues will be classified as "deviations" if they are related to radiation dosing. These deviations are those resulting in radiation exposure greater or less than approved limits. Examples of deviations are excessive current or voltage setting, repeating the TLC or FRC scans. Once the scan is received, the Radiology Center will confirm that the radiation dose utilized was consistent with the radiation risk language in the site's Informed Consent and with the SPIROMICS Imaging Manual of Procedures.

Any apparent deviation of the proposed range of radiation exposure and from the site's Informed Consent, the University of Iowa, using PVS will send an electronic deviation report describing the issue to the DCC, site PI, coordinator, site radiologist and the Radiology Committee Chair. In addition, any two consecutive deviations or, over the previous 12 months, deviations of more than 5% (cumulative deviation) will generate an immediate report to the SPIROMICS DCC which will relay the report to the site PI, coordinator, radiologist, the Radiology Committee Chair, the SPIROMICS Steering Committee, NHLBI, and the DSMB. CT scanning will be suspended at that site until a report of the cause of the deviation and the SPIROMICS III Steering Committee and DSMB have approved the remediation plan. All deviations should be reported to their sites local IRB's.

Other types of protocol errors will be classified as "Quality Control Notifications" and are those protocol issues that do not result in non-approved radiation exposure. Examples of these quality control notifications are, whole lung not scanned, incorrect reconstruction kernel used, , TLC or FRC scan not performed (if allowed by protocol), CT data lost, CT tech not certified, and CT data not anonymized etc...

Quality control problems from the SPIROMICS Imaging Manual of Procedures detected by the University of Iowa will be reported to the Steering Committee if there are more than 10% occurrences at a particular site within the previous 12 months.

All SPIROMICS sites agree to report any protocol deviation or violation, consent violation, or adverse event that results in suspension of CT imaging to the SPIROMICS Steering Committee

and to the DCC. The DCC will relay the report to NHLBI and to the SPIROMICS DSMB. In addition, SPIROMICS sites will follow individual institutional IRB policies and procedures.

11 Data Transfer & Storage

DISPATCH (DICOM Selection Parser and Transfer Check), University of Iowa, is an automated system that imports medical image data that has been stored in a standardized file format known as DICOM (Digital Imaging and Communications in Medicine) and provides a mechanism of transmitting that data elsewhere via the internet in a secure manner. At the same time, it allows for the automated and customized interrogation of the header record of the image data to ensure the data has been gathered with the appropriate parameter ranges specified by the protocol.

DISPATCH runs on the transferring site's local machine and uses a web-based application to transfer imaging data. The input of study-specific criteria parses the data and restricts the upload of files which do not fit the protocol nor will it allow uploads of duplicate data; thus making the process more efficient on the part of the sender and the receiver. It is important that the DISPATCH user i.e. study coordinator only send the scan data needed for the study; otherwise the system will parse unnecessary data which will not pass the study-specific criteria previously determined. Study-specific scan reconstructions can be referenced above in section 5.

DISPATCH allows the user to ensure data was acquired according to a specific study protocol and check for errors prior to data transmission.

There are two training methods on the use of DISPATCH. The traditional method is a user manual which outlines the installation and set up as well as the process of using the tool. The second training tool is a video which describes DISPATCH how to use it and demonstrates its use. The Radiology Center will oversee the setup, training and maintenance of DISPATCH for the SPIROMICS imaging sites.

Medical Image File Archive and Retrieval (MIFAR), University of Iowa, is a web-based system that allows for secure storage of SPIROMICS data. MIFAR currently holds over 30,000 volumetric lung image data sets providing storage and retrieval of research records together with image data. MIFAR consists of a distributed set of software components that communicate with each other over a TCP/IP network. This system allows inter-site data exchange and enables security and quality control. MIFAR will be adapted to host a protocol platform to link MIFAR with DISPATCH to create a system network that monitors CT scanner changes during multi-center studies, allowing for detection of scanner changes and providing updates to the monitoring protocol, allowing for scanner evolution.

All SPIROMICS reconstructions must be archived and stored at the site.

Authorized Use Permission of DISPATCH

Use of the DISPATCH is allowed for SPIROMICS purposes only. Unauthorized usage of the system and making unauthorized copies of data, software, reports, and documents is strictly prohibited. If you wish to obtain waiver use or copy permissions, please contact the University

of Iowa, Division of Physiologic Imaging at 319-356-1381.

APPENDIX

A. Table I: CTDIvol setting based on BMI index

Body Size	BMI Range	CTDIvol (mGy)
Inspiration Large	>30	11.4
Inspiration Medium	20 to 30	7.6
Inspiration Small	>20	6.1
Expiration Large	>30	6.1
Expiration Small / Medium	<30	4.2

B. Table II: CT Parameters: (TLC) Inspiration Protocol

Scanner make	SIEMENS	SIEMENS	SIEMENS	GE	GE	PHILIPS
Scanner model	Definition (AS Plus) 128 slice	Definition (DS) 64 slice	Sensation 64 slice	VCT 64 slice/ Discovery STE	Discovery CT 750HD 64 slice	Brilliance 64 slice
Scan Type	Spiral	Spiral Single Source	Spiral	Helical	Helical - Standard	Spiral Helix
Scan FOV	No selection	No Selection	No selection	Large	Large	No selection
Rotation Time (s)	0.5	0.5	0.5	0.5	0.5	0.5
Det. Configuration	128 x0.6	64 x0.6	64x0.6	64x0.625	64x0.625	64 x 0.625
Pitch	1.0	1.0	1.0	0.984	0.984	0.923
kVp	120	120	120	120	120	120
Siemens = Eff. mAs GE = mA setting Philips = mAs	<i>Effective mAs:</i> Ex S-60 S-90 M-110 L-165	<i>Effective mAs:</i> Ex S-55 S-85 M-105 L-150	<i>Effective mAs:</i> Ex S-50 S-80 M-100 L-145	<i>mA:</i> Ex S-100 S:145 M:180 L: 270	<i>mA:</i> Ex S-100 S:145 M:180 L: 270	<i>mAs:</i> Ex S-70 S-105 M-130 L-190
Dose modulation	Care Dose OFF	Care Dose OFF	Care Dose OFF	Auto mA OFF	Auto mA OFF	Dose Right (ACS) OFF
Standard Algorithm	B35	B35	B35	Standard	Standard	B
Lung Algorithm	B30	B31	None	Detail	Detail	YB
Additional Image filters	No Selection	No Selection	No Selection	No Selection	IQ Enhance Off	Adaptive Filtering off
Thickness (mm)	0.75	0.75	0.75	0.625	0.625	0.67
Interval (mm)	0.5	0.5	0.5	0.5	0.5	0.5
Iterative recon (noise reduction algorithm)	Do Not use IRIS	Do Not use IRIS	No Selection	Do not use ASIR	Do not use ASIR	Do not use iDOSE
Scan Time (Sec) 30cm length	<10	<10	<10	<10	<10	<10
Recon Mode	N/A	N/A	N/A	Plus	Plus	N/A
Smart mA	N/A	N/A	N/A	OFF	OFF	N/A

C. Table II: CT Parameters: (RV) Expiration Protocol

Scanner make	SIEMENS	SIEMENS	SIEMENS	GE	GE	PHILIPS
Scanner model	Definition (AS Plus) 128 slice	Definition (DS) 64 slice	Sensation 64 slice	VCT 64 slice/ Discovery STE	Discovery CT 750 HD 64 slice	Brilliance 64 slice
Scan Type	Spiral	Spiral Single Source	Spiral	Helical	Helical Standard	Spiral Helix
Scan FOV	No selection	No Selection	No selection	Large	Large	No selection
Rotation Time (s)	0.5	0.5	0.5	0.5	0.5	0.5
Det. Configuration	128 x0.6	64 x0.6	64x0.6	64x0.625	64x0.625	64 x 0.625
Pitch	1.0	1.0	1.0	0.984	0.984	0.923
kVp	120	120	120	120	120	120
Siemens = Eff. mAs GE = mA setting Philips = mAs	<i>Effective mAs:</i> Ex S-45 S/M-65 L-90	<i>Effective mAs:</i> Ex S-40 S/M-60 L-85	<i>Effective mAs:</i> Ex S-35 S/M-55 L-80	mA: Ex S-65 S/M:100 L:145	mA: Ex S-65 S/M:100 L:145	mAs: Ex S-50 S/M-70 L- 105
Dose modulation	Care Dose OFF	Care Dose OFF	Care Dose OFF	Auto mA OFF	Auto mA OFF	Dose Right (ACS) OFF
Standard Algorithm	B35	B35	B35	Standard	Standard	B
Lung Algorithm	B30	B31	None	Detail	Detail	YB
Additional Image filters	No Selection	No Selection	No Selection	No Selection	IQ Enhance Off	Adaptive Filtering off
Thickness (mm)	0.75	0.75	0.75	0.625	0.625	0.67
Interval (mm)	0.5	0.5	0.5	0.5	0.5	0.5
Iterative recon (noise reduction algorithm)	Do Not use IRIS	Do Not use IRIS	No Selection	Do not use ASIR	Do not use ASIR	Do not use iDOSE
Scan Time (Sec) 30cm length	<10	<10	<10	<10	<10	<10
Recon Mode	N/A	N/A	N/A	Plus	Plus	N/A
Smart mA	N/A	N/A	N/A	OFF	OFF	N/A