**PROTECTION OF HUMAN SUBJECTS**

There are two general sets of human subjects data that will be studied in this project. The first is the lung images and ancillary data that we will retrieve from the data archives at the University of Pennsylvania and the University of Virginia. These will be the data used in Aim 1 to generate the proposed multi-atlas libraries. Only previously collected data from human subjects will be used in this aim. No image acquisition or subject contact is included in this aim. We will be using datasets for processing and analysis from existing projects, for which Institutional Review Board approval is already in place. The source of the data is the archives of CT data stored in the Department of Radiology at the University of Pennsylvania and MRI data stored in the Department of Radiology and Medical Imaging at the University of Virginia. The data comply with all institutional, NIH, and HIPAA regulations on data protection, privacy, and confidentiality, in addition to being anonymized and stripped of all human identifiers. Thus, only existing data will be used, and solely for research purposes. All subjects who contributed data to the archived datasets were fully consented and consistent with the clinical or research guidelines of the relevant institution. Since we will only use existing, archived data, there will be no risks to nor need for potential medical intervention for those who contributed the data aside from breach of privacy. As stated above, all identifying information will be removed from the data, and only the anonymized data will be transferred from the archive.

The other set of human subjects data will be the lung images associated with each of the proposed evaluation studies in Aim 2. All partner investigators in Aim 2 have Institutional Review Board (or equivalent) approval for their projects. We will not engage in or involve partner projects involving human subjects without prior Institutional Review Board approval of those projects.

**A. Risks to Human Subjects**

The study will retrospectively identify 1) 30 human subjects who have performed both thoracic CT and pulmonary function testing as part of their standard of care at the University of Pennsylvania . The justification of the study is the lack of annotated lung imaging data with which to drive computational methods for quantitatively characterizing lung structure and function in health and disease, which significantly limits our ability to translate research innovations into the clinic.

The data will be anonymized prior to transfer for use in this study. There will be no interaction between subjects and researchers, as the data to be processed already exists and was obtained either as part of routine medical care or a previously IRB approved study. A waiver of written documentation of informed consent will be requested to the local institutional review board (IRB), since the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. It would be highly impractical (and probably prohibitive in terms of costs and time) to contact each and every patient to obtain consent. Since there is no intervention beyond the standard of care and due to the retrospective nature of the study, no other risks are anticipated.

**B. Adequacy of Protection Against Risks**

The raw data will be completely de-identified prior to transfer for use in this project. All imaging and non-imaging data will be anonymized prior to processing and analysis. Cases are coded by a number detached from the subject’s name. Only project investigators with direct involvement in data collection at the relevant institution will have access to a file containing patient identifiers such as age and medical record numbers. All other researchers will only have access to de-identified data. The file containing patient identifiers will be stored in a password-protected computer with an encrypted hard drive, which is stored in a room at the University of Pennsylvania with access limited to the investigators that is always locked, day and night.

**C. Potential Benefits of the Proposed Research to the Subjects and Others**

**Benefits to subjects.** There is no direct medical benefit to the subjects that participate in this project. Subjects will not be compensated.

**Benefits to others and risk/benefit ratio.** The overall risk to subjects in this protocol is assessed to be minimal, consisting solely of potential breach of confidentiality, and protections are in place to minimize this small risk. The benefits to the field of study and society at large are considerable, but there is no direct benefit to subjects.

**D. Importance of the Knowledge to be Gained**

One of the long-term goals of this project is to reduce the cost and duration of clinical trials in pulmonary disorders by developing and validating non-invasive biomarkers capable of more accurately detecting disease progression and treatment effects. Reducing the cost of clinical trials will enable more potential pharmaceutical treatments to be brought to clinical trials and thus, theoretically, increase the chance of finding a cure to lung disorders. The human subject studies in this project contribute to this goal by enabling the characterization of patterns of granular regional changes in lung structure and function that take place in the course of healthy aging or disease, thus making it possible to distinguish between these patterns.

In addition, general knowledge about the pathophysiology of the lung that is the collective goal of the research studies that from the basis of the evaluation component of this project may lead to a better understanding of the mechanisms of pulmonary disorders.

**E. Inclusion of Women and Minorities**

Both men and women will be studied. We expect an almost equal participation between males and females for the development of the CT library, reflecting the gender distribution of 48% male and 52% female population in Philadelphia. As the source of CT data is patients who have received care at the University of Pennsylvania, we do not necessarily exclude pregnant females or women of childbearing potential from this project. The greater Philadelphia area is very diverse racially, ethnically and socioeconomically. We expect that minorities will be represented in this project at ratios similar those in the surrounding community: Caucasian: 72%; African-American: 19%; Hispanic: 5%; Asian or Pacific Islander: 3%; Native American: <1%.

In keeping with NIH policy to allow women equal participation opportunities, we will make certain that recruitment announcements appear through women’s health sites. After initial screening of eligibility based on body size and lack of claustrophobia, and the other inclusion and exclusion criteria as described in the Protection of Human Subjects section, random callers will be assigned into recruitment. Based on the gender composition of the University of Virginia population area and our previous experience with recruitment for hyperpolarized-gas research studies, it is anticipated that approximately half of the study subjects will be women.

In keeping with NIH policy to provide equal participation opportunities for members of minority and ethnic groups, we will also make certain that recruitment announcements appear in Spanish. No specific racial or ethnic group will be excluded. After initial screening of eligibility based on body size and lack of claustrophobia, and the other inclusion and exclusion criteria as described in the Protection of Human Subjects section, random callers will be assigned into recruitment. Based on the racial and ethnic composition estimates for the UVa population area and our previous experience with recruitment for hyperpolarized-gas research studies, it is anticipated that roughly 10% of the study subjects will be from racial minorities and roughly 3% will be of Hispanic or Latino origin.

From the perspective of a scientifically sound design, the study population should provide a representative sampling of human lungs in the subject groups of interest. We are aware of no evidence to suggest that the outcome of our evaluations of these new imaging methods and treatment planning methods would be affected by the racial or ethnic composition of the study population and thus, while we will take steps to ensure equal participation opportunities as discussed above, there is no scientific basis for targeting the enrollment of a specific group in numbers higher than those represented in our underlying population (Caucasian: 78%; African-American: 10%; Hispanic: 6%; Asian or Pacific Islander: 5%; Native American: <1%)

**F. Inclusion of Children**

Children with asthma are included because manifestations and complications of severe asthma often begin in early childhood, and therapies targeted towards children may be developed that will ultimately change the clinical course of the disease.