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To:	Geoffrey Chupp, M.D.
From:	Maurice Mahoney, M.D., J.D., Chair
Date:	02/23/2015
HIC Protocol #:	0102012268
Study Title:	Mechanisms and Mediators of Asthma and Chronic Obstructive Pulmonary Disease (COPD)
Committee Action:	**Approval**
Committee Action Date:	02/18/2015
Expiration Date:	02/28/2016
Submission Type:	Continuing Review/Continuation

This protocol was reapproved by the full Human Investigation Committee at its meeting held on the Committee Action Date noted above. This review meets approval criteria set forth in 45 CFR 46.111. Please be advised that the protocol is due to be reapproved by the expiration date noted above.

Please note the Review Comments listed below that were raised by the Committee during its review of this study.

Review Comments:

- As part of the protocol review process, the HIC now checks to see that all responsible protocol personnel have a current financial disclosure form on file with the University's Conflict of Interest Office. The record indicates that the Jack Elias' disclosure has expired. He should follow this link to the COI Office Website to update the form: http://www.yale.edu/coi/ To enter the disclosure system, click on the link to the External Interests Disclosure form. Once the disclosure is updated, the HIC can commence with the approval of this protocol. Please note that investigators and study personnel who have not completed the COI requirement cannot engage in human subjects research activities on this study and all other human research studies they are listed on until the COI is completed. Failing to adhere to training requirements could be considered non-compliance and may be referred to the Research Quality Assurance & Compliance division within the Human Research Protection Program. J. Elias will be removed from this study if the COI requirements are not met by the time of this protocol's approval.

- The protocol continues to have benefits which outweigh the risks, deemed greater than minimal by the Committee, and attempts to minimize risks to subjects.

- The Committee found this study to meet the requirements of 45 CFR Part 46.406. The Committee finds that: 1. This study presents more than minimal risk to the minor subjects with no prospective direct benefit to individual subjects. 2. This study is likely to produce generalizable knowledge about the subjects disorder or condition which is vitally important for the understanding or amelioration of the subjects disorder or condition. 3. That the risk is only a minor increase over minimal risk. 4. The research intervention presents experiences to subjects that are reasonably

commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations. 5. That the study may be carried out with the assent of the minor AND the permission of BOTH parents, unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child. For the subset of essential adolescent particpants, the HIC found this study to meet the requirements of 45 CFR § 46.404 in that it presents no more than minimal risk to the minor subjects. Permission of one parent or guardian is sufficient to carry out the study.

- The HIC acknowledges receipt and review of the form 5R.

- Documents approved and uploaded in COEUS: HIC application, parental permission (2), consent forms(3) assent forms (2)

It is the investigator's responsibility to apply for reapproval of ongoing research prior to one year from the date this protocol was reviewed by the full Committee or earlier if required by previous HIC approval. Therefore this protocol must be reapproved before the above-referenced expiration date. Please allow two months for re-approval.

Adverse Reactions: Serious, unanticipated and possibly, probably, or definitely related adverse events, and unanticipated problems involving risk to subjects or others must be reported within 48 hours to the HIC, using Form 6A.

2. **Minimizing Risks:** Describe the manner in which the above-mentioned risks will be minimized.

Risks will be minimized by appropriate subject exclusions, close medical supervision throughout the protocol, and adaptation of testing to identify patients who might be at higher risk. Subjects experiencing adverse events will have access to full in-patient medical facilities of the Yale-New Haven Hospital, should more intensive treatment be necessary to reverse an asthma attack or complication during the study. All patients will be under full-time nursing supervision throughout every phase of these procedures. The knowledge gained from this study will lead to enhanced information about the pathogenesis of severe asthma, an invaluable factor for improving diagnosis, treatment and prevention of asthma in the future. All patients and control subjects will be compensated for their participation.

Risks will be minimized by appropriate subject exclusions, close medical supervision throughout the protocol, and adaptation of testing to identify subjects who might be at higher risk. Subjects will have the opportunity to be more conscious of their respiratory health through education, and seeking medical consultation and instruction when necessary. The results of this study will lead to many indirect benefits to patients with lung disease. Identifying novel genes and molecules that contribute to the development and severity of these diseases will hopefully lead to new diagnostic tests, prevention strategies, and treatments. In addition, as there are currently no serological tests available to diagnose or study these diseases, this research may lead to clinically useful biomarkers.

3. **Data and Safety Monitoring Plan:** Include an appropriate Data and Safety Monitoring Plan (DSMP) based on the investigator's risk assessment stated below. (Note: the HIC will make the final determination of the risk to subjects.) For more information, see the Instructions, page 24.

The Principal Investigator will be responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews on a case by case evaluation or every six months, with an annual review by the Human Investigation Committee. The Data Safety Monitoring Plan for this protocol will follow the guidelines set by our HRU and the Human Investigation Committee (HIC). Any serious adverse events occurring during this trial will be reported to the Human Investigation Committee and a full report will be submitted within 24 hours of knowledge of the event. During the review process, the HIC and/or DSMC will evaluate whether the study should continue unchanged, require modification/amendment, continue or close to enrollment. Either the principal investigator, the HIC or the YCCI RSA, have the authority to stop or suspend the study or require modifications.

a. What is the investigator's assessment of the overall risk level for subjects participating in this study? Greater than minimal risk for all subjects (affected and nonaffected with lung disease $\geq$ 18 years of age).

b. If children are involved, what is the investigator's assessment of the overall risk level for the children participating in this study? For those affected subjects (with lung disease) $\geq$ 12 years of age, the overall risk assessment is as follows "Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition. [45 CFR 46.406] Within that overall assessment,

the risk for certain procedures currently requested for adolescents (the essential testing procedures), e.g. spirometry, blood drawing, urine testing, and exhaled breath condensate are considered minimal risk. The sputum induction is considered greater than minimal risk.

c. Data and Safety Monitoring Plan:

This protocol does not involve the use of any new drugs and all procedures are well established and are routinely performed at the Yale-New Haven Hospital (with the exception of the mini-BAL). Because all these procedures are standard clinical tests, (with the exception of the mini-BAL), and are used routinely in this population of patients, we expect the incidence of adverse reactions to be extremely low.

Although we have assessed this study, as overall one of greater than minimal risk, the potential exists for anticipated and/or unanticipated adverse events, serious or otherwise, to occur, since it is not possible to predict with certainty, the absolute risk in any given individual or in advance of first-hand experience with the proposed study methods. Therefore, we provide a plan for monitoring the data and safety of the proposed study as follows:

Attribution of Adverse Events:

Adverse events will be monitored for each subject participating in the study and attributed to the study procedures/design, by the Data Safety Monitoring Committee(DSMC) consisting of Drs. Hilary Cain, MD, Frédéric F. Little, MD, Stuart Seropian, MD, according to the following categories:

a) Definite: Adverse event is clearly related to investigational procedures
b) Probable: Adverse event is likely related to investigational procedures
c) Possible: Adverse event may be related to investigational procedures
d) Unlikely: Adverse event is likely not to be related to the investigational procedures
e) Unrelated: Adverse event is clearly not related to investigational procedures

Plan for Grading Adverse Events:

The following scale will be used in grading the severity of adverse events noted during the study:

1) Mild adverse event
2) Moderate adverse event
3) Severe

Plan for Determining Seriousness of Adverse Events:

An adverse event is considered serious if it:

1-is life-threatening
2-results in in-patient hospitalization or prolongation of existing hospitalization
3-results in persistent or significant disability or incapacity
4-results in a congenital anomaly or birth defect OR
5-results in death

6-based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition, or

7-adversely affects the risk/benefit ratio of the study

An adverse event may be graded as severe but still not meet the criteria for a Serious Adverse Event. Similarly, an adverse event may be graded as moderate but still meet the criteria for an SAE. It is important for the PI to consider the grade of the event as well as its "seriousness" when determining whether reporting to the HIC is necessary.

Plan for Reporting Adverse Events:

For the current study, the following individuals, funding, and/or regulatory agencies will be notified:

1-all co-investigators listed on protocol
2-Data and Safety Monitoring Committee(DSMC)
3-Yale Center for Clinical Investigation Research Subject Advocates (RSAs)
4-National Institutes of Health

The DSMC, will conduct a review of all adverse events upon completion of every study subject. The DSMC will evaluate the frequency and severity of the adverse events and determine if modifications to the protocol or consent form are required.

Assessment of risks: There are a total of 12 tests that subjects will have an opportunity to participate in, most, routinely used in clinical medicine. The risks associated with this study are the following:

Minimal risk: 1) venipuncture, 2) disclosure of genetic information, 3) endotracheal sputum collection, 4) exhaled breath condensate collection, 5) MRI 6) pulmonary function testing (spirometry)

Procedures for affected adolescents ≥ 12 years of age ONLY: pulmonary function testing (spirometry), blood drawing, exhaled breath condensate, urine testing, and sputum induction . No adverse events have been seen in any of the 500 adults recruited for these procedures in this study, to date.

Greater than minimal risk for adult subjects ≥ 18 years of age: 1) methacholine challenge testing,2) HRCT scan of the chest; 3) allergy testing, 4)mini-BAL (for selected ICU subjects)

High risk: 1) bronchoscopy

1) Minimal risks of venipuncture (all subjects):

1-The procedure involved in obtaining blood specimens for laboratory analysis is conducted through the use of standard phlebotomy methods. The personnel obtaining these samples are highly trained nurses or technicians, well versed in this collection method, thereby, imposing minimal risk.

2-Occasionally, a subject will experience "light-headedness" during the phlebotomy procedure. To minimize the risk of this occurrence, all subjects will be placed in a supine position on a hospital bed, attended by trained personnel and monitored following the procedure.

3-Should a bruise or swelling occur following the phlebotomy procedure, ice will be applied to the site and the site will be monitored by trained personnel. This bruising/swelling is associated with minimal risk.

2) Minimal Risk of disclosure of genetic information (all subjects):

1-All samples will be stored by de-identifying the sample to a code number.

2-Genetic analysis results will not be placed in the subject's medical record nor shared with the subjects' primary physician.

3-Access to study records will be limited to investigators on the study and the Human Investigation Committee.

3) Minimal risk of endotracheal sputum collection (not done in adolescents—only in adult subjects ≥ 18 years of age):

1- Endotracheal suction specimens are routinely acquired from patients on mechanical ventilation. No specific intervention occurs outside of usual care.

4) Minimal risk of EBC testing (all subjects):

1- Subjects will breathe normally through their mouth into this device. There is no resistance to breathing with the device; hence, no risk

5) Minimal risk of MRI scan (not done in adolescents—only in adult subjects)

1-MRI produces detailed images of the human body without the use of X-rays. Images are created using a powerful magnet, radio waves and a computer system to process data. This is a painless procedure and involves no ionizing radiation, and the contrast used in not radioactive and doesn't contain iodine.

1) Minimal risk of pulmonary function testing (done in adolescents with lung disease and adults (≥ 18 years of age) with and without lung disease):

1-Pulmonary function testing is performed in the PFT lab at YNHH or the Research Room LMP 5046, by a trained technician.

2-Occasionally, a subject will experience dizziness while performing the test. This is usually temporary and the subjects are seated throughout the procedure.

3-Very rarely, people with airway disease may wheeze or cough following these tests. A bronchodilator is available for these subjects.

2) Moderate risk of Methacholine challenge testing (only done in adults ≥ 18 years of age):

1- Methacholine challenge testing is a test of non-specific airway reactivity (bronchial hyper-responsiveness) and is used in the diagnosis of asthma. Subjects with asthma are more susceptible to the bronchoconstricting effects of methacholine. This procedure is performed by highly trained personnel.

2-The procedure for MCT involves subjects inhaling an aerosolized solution of methacholine (0.01mg/ml-25mg/ml) via a nebulizer. The study is terminated when the subject's FEV1 decreases 20%, regardless of the dose. (The dose of methacholine that results in a 20% decrease is a patients forced expiratory flow in 1 second (FEV1) is recorded as the PC20).

3-MCT is performed in the PFT lab at YNHH by experienced PFT technicians. It is possible that subjects could experience wheezing and shortness of breath during the procedure. Emergency measures are available which include a bronchodilator and an emergency cart in the room for pulmonary testing.

4-Subjects with asthma with baseline FEV1 less than 50% predicted, will be excluded from methacholine challenge testing. Subjects with COPD generally have less hyper-responsiveness and safely undergo PFT.

3) Greater than minimal risk of sputum induction (12): Done in adolescents with lung disease and adults with and without lung disease

1-Sputum induction is performed in a sitting position by a nurse in the Yale Asthma Center in YNHH or the Research Room LMP 5046. This test is routinely performed in the evaluation of many pulmonary disorders.

2-the subject breathes aerosolized saline solution which causes the subject to cough and produce a sputum sample for testing.

3-Individuals with airway disease may continue to cough which may cause some shortness of breath. This test will be monitored closely and the procedure will be stopped if a subject's FEV1 or peak expiratory flow decreases by >20%. Sputum induction has been safely performed in subjects with moderate lung disease, as well as subjects with severe airflow limitation. Bronchodilators and emergency procedures are available in the Yale Asthma Center if subjects have difficulty with this testing. Sputum induction in adolescents was approved by the NHLBI (granting agency for this study) as a low risk procedure. The investigative team performing these procedures has experience with these procedures, should events arise during sample acquisition. Inclusion of children is important in this study so as to define these biomarkers in young subjects over time. Further, sputum induction was performed in a European study in 185 healthy control subjects. These authors (Grootendorst, et al., 2002) stated that in general, sputum induction in children is a safe procedure. Reported side effects include cough, airway obstruction, vomiting and anxiety, which all might occur when a child has an upper respiratory infection. As recommended by these authors, these procedures will be conducted by trained staff who are experienced in lung function and sputum induction measurements in children and the identification and management of adverse effects in children.

4) Moderate risk of HRCT scan (not done in adolescents—only in adults)::

1-HRCT scans are performed by trained technicians in Diagnostic Imaging at YNHH.

2-HRCT scans of the chest involve exposure to radiation. This risk of harm from the amount of radiation in this study is unknown but is minimal. The whole body radiation exposure from a CT scan is about 85 mrem. This is less than one-third of the average annual exposure a person in the United States receives from natural background radiation.

5) Moderate risk of allergy testing (only in adults):

1-Standard allergy testing is used to determine the subject's allergy status and is part of routine asthma evaluation.

2-The procedure for allergy testing involves placing a panel of 14 allergens on the arm or back. This consists of pricking the skin with a needle and is performed by a trained physician.

3-Allergy testing causes skin redness, swelling and itching if the test is positive. This improves within 24 hours and can be relieved with the application of a steroid cream (which is provided to the subjects).

6) Moderate risk of mini-BAL(not done in adolescents-only in adults):

1-Procedure that can be associated with discomfort, arterial hypoxemia, increases in heart rate, and increases in blood pressure

2-To prevent discomfort, subjects who are not already sedated or have symptoms that suggest their level of sedation is not enough to prevent discomfort from the procedure (often patients

requiring mechanical ventilation for acute lung injury are sedated), will be given (additional) sedatives prior to the procedure. To prevent hypoxemia, the level of oxygen will be increased to 100% 5 minutes before the procedure. Oxygen saturation and vital signs will be monitored continuously during the procedure. One of the study investigators will always be present during this 5 minute procedure

3-Risk of obtaining lung fluid sample is some slight discomfort. Additional sedation may be given prior to the procedure to help subject relax. Investigations have shown that this procedure is as safe as routine suctioning of patients. Oxygen saturation and vital signs are constantly monitored.

1) High risk of bronchoscopy(14,15,16) (not done in adolescents—only in adults): Bronchoscopy is safe, commonly used in clinical medicine in the evaluation of lung disease with a low incidence of complications. (Incidence of serious complications <0.05% or 5 in 10,000 in over 23,000 bronchoscopies). Bronchoscopy has been performed safely in subjects with mild to severe lung disease(14). This procedure is performed by a pulmonologist (study PI or Co-investigator) in the Bronchoscopy Suite in Diagnostic Imaging at YNHH. The physician performing the procedure will be present throughout the procedure, ensure subject safety and manage any adverse events. The procedure will be performed in accordance with published guidelines (see inclusion/exclusion criteria). Subjects will be monitored pre and post bronchoscopy in the HRU at YNHH. To minimize risk and maximize safety subjects are monitored at all times during and after the procedure by study personnel and diagnostic imaging nursing staff.

2-The subject receives a mild sedative (fentanyl and midazolam, via I.V.) and atropine, IM (to dry the subject's nose and mouth) for the procedure. Lidocaine is used to numb the nose and throat, vocal cords, and trachea to prevent pain and cough. The bronchoscope is passed through the nose into the trachea. Bronchoalveolar lavage (BAL) is performed through a channel in the bronchoscope with successive instillation and then withdrawl of 4-5 50ml syringes of saline. There is usually a 30-50% return of fluid that is rich in cells and proteins for analysis. In addition, bronchial biopsies from the second or third order airways are recovered using small forceps.

3-During or following the procedure, the subject may experience temporary coughing, gagging, or a sore nose and throat. Post-bronchoscopy fevers can occur which are transient and easily treated with Tylenol. Subjects occasionally cough up of small flecks of blood for 24 hours following the procedure which spontaneously resolves. Hypoxemia may occur during the procedure, but is usually transient and responds to supplemental oxygen**.**

4-More serious complications include: lung infection, major bleeding, pneumothorax**,** irregular heartbeat or in rare cases, death. We have not seen any serious side effects in over 500 bronchoscopy subjects at our institution.

5-Subjects will be continually monitored throughout the procedure by study personnel to ensure subject safety and identify and manage adverse events early and rapidly. If a subject develops an adverse reaction during the procedure, the bronchoscopy will be terminated immediately and the adverse event treated. The bronchoscopy suite is located in YHH and fully equipped with all the emergency equipment to handle mild to severe adverse reactions. These include an intubation kit (for respiratory failure, refractory hypoxemia or massive bleeding), code cart (with a complete set of medications for cardiac chemical cardioversion, anti-seizure medications, and vasopressor agents), a cardiac defibrillator. If a major adverse event occurs the physician performing the bronchoscopy will have immediate access to anesthesia, respiratory therapy, and the medical intensive care unit physicians to help manage the event.

4. **Confidentiality & Security of Data:**

Confidentiality**:** This is a single center trial. All data will be entered into databases that are protected with appropriate passwords and routine backups of all data will be carried out. All data collected on the subjects will be coded with numbers to maintain confidentiality. Access to the files will be restricted to the investigators and study personnel on this protocol. It is possible that the Human Investigation Committee, YCCI , or the NIH, may review study results during auditing procedures but these individuals are required to keep all information confidential.

Source of Research Materials: Clinical data will be stored with specific patient identifiers, (de-identification of samples), and maintained in a locked file, separate from any other clinical records with limited access, to assure patient confidentiality. All research specimens, including blood, BAL fluid, sputum, and biopsy specimens will be identified by a patient code for correlation purposes. Results will be assembled with confidential clinical research records, but will be unidentifiable without these files, to assure confidentiality. The only data that will be used in this study is the information directly obtained from the subjects and assays of the material taken (blood, sputum, BAL, lung biopsies) during the clinical testing procedures. No existing material or record will be used.

a. What protected health information about subjects will be collected and used for the research?

The entire medical record will be reviewed to distinguish what disease category subjects will be assigned.

b. How will the research data be collected, recorded and stored? We will have shadow files on each subject, and pertinent data to the study will be entered into a secure database.

c. How will the digital data be stored? ☐ CD ☐ DVD ☐ Flash Drive ☐ Portable Hard Drive X ☐ Secured Server ☐ Laptop Computer ☐ Desktop Computer ☐ Other

d. What methods and procedures will be used to safeguard the confidentiality and security of the identifiable study data and the storage media indicated above during the subject participation in the study?

Subjects receive a “de-identifying” number assigned at entry to the study. All specimens, collected from this study, use this number to identify subjects, and the database is maintained by the PI and Study Coordinator.

e. What mechanisms are in place to ensure the proper use and continued protection of these data after the subject participation in the study has ceased?

When all measurements and analyses are completed on this population, all datasets and hard copy files will be destroyed.

f. What will be done with the data when the research is completed? Are there plans to destroy the identifiable data? If yes, describe how, by whom and when identifiers will be destroyed. If no, describe how the data and/or identifiers will be secured.

Since this is an ongoing protocol and we continue to pursue new and exciting approaches to analyzing our population, we do not anticipate destroying any data in the near future. In the

interim, we will continue to ensure that all participants' health and privacy are maximally protected.

g. Who will have access to the protected health information? (such as the research sponsor, the investigator, the research staff, all research monitors, NIH, FDA, QUACS, SSC, etc.)

All members of the research team will have access to the PHI, but are required to keep all information confidential.

h. Which external or internal individuals or agencies (such as the study sponsor, FDA, QUACS, SSC, etc.) will have access to the study data?

The HIC, NIH, YCCI will have access to this data

i. If appropriate, has a Certificate of Confidentiality been obtained? N/A

j Are there any mandatory reporting requirements? (Incidents of child abuse, elderly abuse, communicable diseases, etc.) Incidences of child abuse or neglect will be reported to the proper authorities.

5. **Potential Benefits:** Identify any benefits that may be reasonably expected to result from the research, either to the subject(s) or to society at large. (Payment of subjects is not considered a benefit in this context of the risk benefit assessment.)

Individual subjects may not benefit directly from this study. The standard clinical tests performed (blood work, pulmonary function tests, etc…) may contain medical information that will be useful for the patient's health care. The results of these tests will be communicated to the patient. We will also send a copy of lab results to the subjects to suggest they follow up with their primary care doctor, if applicable. Information acquired from this study may help identify mediators of lung disease progression and lead to improved and novel therapies. None of the procedures or testing done in this study will be charged to the patient or the patient's insurance company. Another example is that in subjects with COPD, bronchoscopy may lead to early diagnosis of lung cancer and a better chance of cure.

SECTION X: RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

1. **Alternatives:** What other alternatives are available to the study subjects outside of the research?

The alternative is to decline participation in the study.

2. **Payments for Participation (Economic Considerations):** Describe any payments that will be made to subjects and the conditions for receiving this compensation.

Subjects will be compensated for their participation with testing done for the study and depending on the number of tests undertaken. None of the procedures done specifically for this study will result in cost to the subject. Below is the adult subject compensation schedule:

PFT	$20
Blood draw (up to 20ml per visit)	$20 (may have up to 160ml/year)
Sputum Induction	$20
Exhaled Breath Condensate	$20

HRCT	$25
MRI	$25
MCT	$25
Allergy Testing	$10
Bronchoscopy	$500

Adolescents will be paid for the following:

PFT	$20
Blood draw (up to 20ml per visit)	$20 (may have up to 160ml/year)
Sputum Induction	$20

Since the number of blood draws will vary depending on the number of clinic visits and exacerbation visits, the precise maximal amount will vary. Clinical information relevant to the patient's health status, such as pulmonary function test results, CT scan and blood work results will be communicated to the patient by either visit to clinic during regular clinic visit or in a letter by one of the study investigators. Subjects may withdraw from the study at any point in time and will be compensated for any studies completed up to that point in time.

3. **Costs for Participation (Economic Considerations):** Clearly describe the subject's costs associated with participation in the research, and the interventions or procedures of the study that will be provided at no cost to subjects.

   There will be no cost to subjects for participation in the study, and no interventions or procedures outside the suggested testing procedures.

4. **In Case of Injury:** This section is required for any research involving more than minimal risk.
   a. Will medical treatment be available if research-related injury occurs?
   b. Where and from whom may treatment be obtained?
   c. Are there any limits to the treatment being provided?
   d. Who will pay for this treatment?
   e. How will the medical treatment be accessed by subjects?

   Medical treatment will be provided for research-related injury by physicians at Yale-New Haven Hospital facilitated by the Principal Investigator. The subject's insurance carrier will be expected to pay the costs of this treatment.

YALE CENTER FOR ASTHMA AND AIRWAY DISEASE SPUTUM INDUCTION PROTOCOL

Author: Naiqian Niu, MD

Purpose:
To establish a protocol to be followed during the collection of induced sputum samples for clinical and research purposes at the Yale Center for Asthma and Airway Diseases.

Objective:
To obtain at least 200 mg of sputum.

Time required to performed procedure:
Around 45 minutes.

Materials and location:

- Portable Spirometer with computer.
- Ultrasonic nebulizer with disposable mouth piece UNIVERSAL III (FLAEM NUOVA, BRESCIA, ITALY)
- Albuterol 90mcg inhaler
- Aerochamber or spacer
- Normal (0.9%) and hypertonic saline at different concentrations (3%, 4% and 5%)
- N-95 protective mask (OPTIONAL)
- The sputum should be induced in the sputum collection room located in LMP-5046, using negative pressure (OPTIONAL).
- The induction should be done while the patient is sitting down.
- Sterile Petri dish sputum collection or sterile specimen collection cup.
- Drinking water and cups for mouth rinsing.
- Tissues.
- Alcohol swabs.
- Stop watch/timer.
- Cleaning supplies to clean nebulizer (10% Clorox).
- Calculator and record sheet.
- Pen or pencil.

Warnings:

- **Induced sputum should be obtained after clinician evaluation and with informed consent from the patient.**
- **Induced sputum can cause bronchospasm and should be avoided in patients with FEV1 <0.8 liters. Albuterol should be used before sputum induction to decrease risk of bronchospasm.**
- **Induced sputum should be performed during office hours when clinical stuff is present and available in the Winchester clinic.**

- **If patient has uncontrollable coughing spell or changes in dyspnea the procedure should be discontinue.**

Sputum Induction Protocol (Hunter 5)

1. Store saline at room temperature as recommended by the manufacturer.
2. Check the expiratory date on saline bottles before initiation of induction.
3. Please read the ***Instructions to patient section*** (page 4) aloud to inform the patient of the purpose of the test, how it will be conducted, how to obtain sputum from the lungs and how to avoid the contamination of sputum with postnasal secretions.
4. Measure the baseline FEV1 and FVC as per ATS guidelines using portable spirometer.
5. If the patient has not had any Albuterol in the prior 2 hours then give 2 puffs of Albuterol, wait 10 minutes and measure FEV1 and FVC following the ATS guidelines.
    a. Use the following formula to calculate the % change in FEV1 after nebulization:

$$(\text{Best Post Albuterol FEV1} - \text{Post} - \text{Nebulization FEV1})/(\text{Best Post Albuterol FEV1}) * 100$$

6. If the best post Albuterol FEV1 is less than 1.0 L proceed cautiously. If the FEV1 is 0.8 or less **do not proceed with induction but try to obtain a spontaneous sample.**
   Starting concentrations:
    - If FEV1 >70% (regardless of reversibility) start with3% hypertonic saline.
    - If the FEV1 <70% start with normal (0.9%) saline.
7. Place 9 cc of the starting concentration into the well of the nebulizer. Place the mouthpiece onto nebulizer. Adjust the regulating valve to “max” and depress the activator button to begin nebulization.
    a. Do not use nose plugs
    b. The clock/stop watch should be started at the beginning of each inhalation period and stopped as needed. (i.e., if the patient needs to stop due to cough, dyspnea, talk, etc.)
8. Instruct the patient to breathe normally (tidal volumes) while inhaling the saline mist for **7 minutes**.
    a. Some side effects, which may occur with hypertonic saline are gagging, sore or burning throat but these rarely interfere with the test. These are usually not bothersome. Sometimes the patient hyperventilates. Also a runny nose has been noticed and it is crucial for the patient to blow his/her nose before obtaining the sputum sample in order to decrease contamination by squamous cells.
9. After 7 minutes, stop the nebulizer and the timer.

10. Ask the patient to first blow their nose, and then rinse their mouth with water and swallow the water. Ask the patient to try to cough sputum from the chest into a sputum container.
11. Measure FEV1 once, record it on your worksheet and calculate any % fall.
12. If there has been <10% fall in FEV1 (from the best post Albuterol FEV1 measurement), you can continue with your second nebulization using the next higher saline concentration inhalation for 7 minutes.
    a. (If the FEV1 has fallen >10%, see item #13 or #14)
13. Repeat steps 8-12 until:
    a. 3 nebulizations or a total of 21 minutes has been completed or
    b. The FEV1 has dropped >20% from the best post Albuterol value (#15).
14. If the FEV1 fell between 10-20% form the (baseline) post Albuterol value after any nebulization, the concentration of saline must be kept the same for any further nebulization. Carefully monitor the patient and repeat all induction steps until the three 7-minute inhalations (total 21 minutes) have been completed, or until the FEV1 falls >20%.
15. If the FEV1 fell >20% from the (baseline) post Albuterol FEV1 measurement at any time **OR** if bothersome symptoms happen, discontinue all inhalations of saline and treat with 2 puffs of Albuterol.
    a. Sputum induction **should NOT be resumed**.
    b. Check the FEV1 10 minutes after Albuterol and monitor this until the FEV1 has returned to within 5% of the (baseline) initial post Albuterol FEV1.
    c. If the patient has not produced any sputum, have them rest with no coughing for another 10 minutes, and then ask them to try again to produce a sample.
16. You should have now completed your sputum induction.
    a. If no sputum is obtained, have the patient try to coughing again after 10 minutes.
17. Label the sputum cup or Petri dish with the patient's name, physician, date and time of collection. Place the Petri dish or sterile sputum container with the sputum in a biohazard container and deliver for processing to the lab as soon as possible. If there is any delay, keep the specimen in the refrigerator and process it within 2 hours. For clinical purposes cell counts are unchanged for up to 8 hours if kept in the refrigerator.

Instructions to patient about sputum induction:

1. You will inhale a salty mist to try to loosen some secretions from the chest so that you can cough them up into a jar.
2. You will inhale the mist for up to 7 minutes each time for a total of 3 times (21 minutes total).
3. Place your lips around the mouth piece and breathe normally through your mouth.
4. If you experience any chest discomfort during the test please let me know and we will stop and check your breathing.
5. You will be given a bronchodilator before starting the nebulization of saline to check your baseline pulmonary function tests and also to avoid possible complication of the sputum induction ie: bronchoconstriction.
6. If at any time you can cough up some phlegm from your chest, just come off the nebulizer and spit into the jar (Petri dish).
7. Be careful not to sniff back from your nose – you must cough from your chest.
8. At the end of each 7 minute period, I'll ask you to blow your nose, take a sip of water and try to cough from your chest and spit into the jar.

Other Considerations

- If the FEV1 is less than 1.0 L from the baseline best post Albuterol FEV1, caution must be exercised with the inhalations. Monitor the patient's FEV1 at the 3.5 minute interval during the initial 0.9% saline nebulization.
- If the patient wishes to cough during any of the inhalation periods, turn off the nebulizer and clock and obtain the specimen. Then continue the same nebulization and restart the clock.
- If the patient states he does not have any secretions and sounds very dry at early inhalations, encourage a deep breath and cough but only one or two times and continue the next inhalation so as not to tire the patient or cause throat soreness. If the patient does not cough spontaneously, you can let the patient sit for 1-2 minutes and then try to cough.
- Remind the patient to clear secretions from the throat forward by using the muscles at the side of the throat. It is important to instruct them to deliberately not swallow the sputum.
- Listen to the patient to ensure that the sample is truly from the lungs and not postnasal secretions.

Spontaneous sputum – obtaining a good sample:

- Blow nose and avoid contamination of sputum with nasal secretions.
- Rinse the mouth with water and swallow it.
- Cough deeply to ensure that the sputum is coming from the chest.
- Cough up the sputum into a sterile container.

- Label the container with the patient's name, doctor, date and time of collection.
- If the specimen may be adequate, deliver for examination as for induced sputum.

Equipment cleaning:
Careful cleaning and thorough drying are essential for good hygienic maintenance of this equipment. Do not immerse the nebulizer unit in any solution. After each use, remove the hard plastic mouthpiece and place it in dirty core container for cleaning for sterilization in autoclave later.
Rinse the well of the nebulizer and pour a small amount of isopropyl alcohol into the well. Allow the alcohol to sit a few minutes, empty, air dry and then rinse with water and allow to air dry (according to manufacturer's directions)

Personal safety:
When patient is coughing, maintain a minimal one-meter distance according to infection control protocol. Have the patient face straight ahead and not towards you. Clean the workspace after each patient.

***In order to prepare hypertonic saline at 4% and 5% you will need the following supplies:

1. Sterile container
2. Permanent marker to label solutions
3. 5 cc syringes (2)
4. 10% hypertonic saline vial (15cc for respiratory therapy, DEY®)
5. Sterile water for injection 10cc vial (Abraxis ®)

To dilute 10% hypertonic saline to 4%, add 4 ml of 10% hypertonic saline to 6 ml of sterile water and you will have enough 4% hypertonic saline for 1 nebulization.
To dilute 10% hypertonic saline to 5%, add 5 ml of 10% hypertonic saline to 5 ml of sterile water and you will have enough 5% hypertonic saline for 1 nebulization.

PROTOCOL FOR SPUTUM CYTOSPIN PREPARATION, CELL COUNTS, SUPERNATAN MEASUREMENTS AND DNA/RNA EXTRACTION

PRINCIPLE:
Portions of sputum free of saliva are selected and mixed with l to disperse the cells and permit reliable measurement of total and differential cell counts, supernatant indices and both cell surface and intracellular markers.

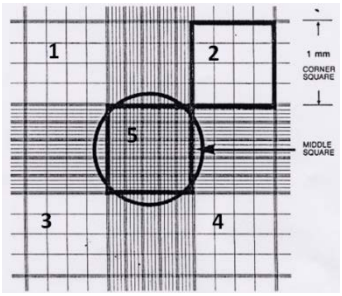
REAGENTS:
Sputolysin Reagent Dithiothreitol stock solution (DTT) (Caldon Biotech)
Dulbecco's phosphate buffered saline (D-PBS 1x)
Distilled water (D-H2O)
Trypan blue stain
Pre-weigh 15 ml tubes
Pre-weigh 50 ml tubes
40 micron cell strainer or 48 micron mesh

PROCEDURE:

1. Place entire sputum sample into a tissue culture dish, and record its macroscopic characteristics on the report form (page 8).
2. Record the weight of an empty 15cc polypropylene conical tube with a screw top.
3. With the use of forceps, select all portions of sputum (100-250mg) as free as possible of squamous cells (saliva). Verify under inverted microscope, minimal saliva contamination or obtain portions not evident otherwise and record the weight.
4. Zero the weight of the empty conical tube and weigh of the conical tube plus sputum to obtain the weight of sputum portion to be processed. ("I")
5. Prepare DDT working solution y adding 9 parts of D-H20 to one part of the sputalysin reagent stock solution. Vortex 15 sec. Example: 0.5 cc of DTT + 4.5cc of D-H2O.
6. Add a volume of DTT working solution equal to four times the processable sputum weight. Example: 200mg of sputum add, 0.8 ml of DTT.
7. Vortex for 30 sec.
8. Aspirate gently with a Pasteur pipette to ensure adequate homogeneity.
9. Place conical tube on a vortex and vortex at 800/min for 15 min or mix for 15 minutes.
10. Add a volume of D-PBS equal to four times that of the selected sputum weight. Example 200 mg then add another 0.8 ml of DPBS.
11. Vortex 15 sec.
12. Filter through a 3x32 piece of 48 µm nylon mesh (or 40 µm cell strainer soaked with PBS) into another pre-weighed conical tube.
13. Record the weight and subtract the weight of the empty tube to obtain the weight of the filtered cell suspension. ("II").

14. Mix 10 µl of Trypan blue® with the same volume of the filtrate produce during step 13.
15. Flood a heamocytometer with 10 µl of the above mixture

- Count non squamous cells in 4
- quadrants, recording viable and no viable cells (blue cells).
- Multiply total cell count (viable + blue stained cells) by 2 and divided 4,record under hematocytometer count (cell/ml) in the sputum processing form (page 8)



16. Calculate the total cell count (TCC) (II*III=IV).
17. Calculate the absolute number of non squamous cells retrieved and record. ["IV/(I*1000)"]
18. Determine non-squamous cell viability, express in percent and record {[blue cells/(viable+blue cells)]*100}.
19. Vortex the cellular suspension for 15 sec.
20. Prepare cytospins by adding 60-70 microL of 0.5-1x10^6 cell suspension (dilute in PBS as needed) into Shandon III Cytocentrifuge cups and spinning at 450 rpm for 6 min.
21. Airdry slide 10-15 min.
22. Stain with Wright's and perform a 400 cell differential.
23. Record the percentage of each cell type on the worksheet.
24. Place the remaining cell suspension into Eppendorf(s) and centrifuge at 6000 rpm (around 600g) for 4 min.
25. Aspirate supernatant and aliquot the aqueous phase into Eppendorfs as required and store at -70°F.
26. Resuspend cell pellets as needed with 1 ml PBS in order to concentrate them into 1 Eppendorf tube.
27. Once a final cell pellet is obtained then add 350 microL of previously prepared lysis solution (1 ml of lysis solution with 1 microliter of beta mercatoethanol from All-in-one kit, Norgen) and store at -70°F for DNA and RNA extraction.

RNA ,DNA and protein extraction and purification

Procedure for Total RNA extraction and purification
Reagents:
Norgen All in-one purification Kit
Qiagen RNeasy plus Micro kit
95% ethanol
8o% ethanol
70% ethanol

A. Add 200 ul 95% ethanol to 350 ul the lysate and Vortexing for 10 second to bind the large RNA to column.
B. Apply up to 600 ul of lysate with the ethanol onto an All-in-one spin column and 14,000rpm centrifuge for I minute(if the entire lysate volume has not passed, spin for an additional minutes),Save the flow-through for protein purification.
C. Apply 400 ul of RNA wash solution to the column and centrifuge for 1 minute .
D. Wash column a second time by adding another 400ul of RNA wash solution and centrifuge for 1 minute.
E. Discard the flow-through and reassemble the spin column with a collection tube, re-spin again for 2 minutes in order to dry the resin and discard the collection tube.
F. Place the column into a fresh elution tube and add 50 ul RNA Elution solution to the column. Centrifuge for 1 minute at 14,000 rpm to collect the RNA.(Retain the column for Genomic DNA isolation and Protein purification)
G. Using Qiagen RNeasy plus micro kit for RNA purification. Add 350 ul buffer RLT to 50 ul of collected RNA and mix well by pipetting.
H. Transfer the sample to a gDNA Eliminator spin column (blue) and centrifuge for I minute at 10,000rpm, save the flow-through.
I. Add 1 volume of 70% ethanol to the flow-through (400ul) and mix well by pipetting. Transfer the sample to an RNeasy MinElute spin column placed in a 2ml collection tube and centrifuge for30 seconds at 10,000rpm.discard the flow-through.
J. Add 700 buffer RW1 to the RNeasy MinElute spin column. And centrifuge for 30 seconds at 10,000 rpm to wash the spin column membrane. Discard the flow-through.
K. Add 500ul buffer RPE to the RNeasy MinElute spin column and centrifuge for 30 seconds. Discard the flow-through.
L. Add 500 ul 80% ethanol to the RNaesy MinElute spin Column and centrifuge for 2 minutes at 10,000rpm.Discard the flow-through.
M. place the MinElute spin column in a new collection tube and centrifuge at 14,000rpm for 5 minutes. Discard the collection tube.
N. Place the RNeasy MinElute spin column in a new 1.5ml collection tube and add 25 ul RNase-free water directly to the center of the spin column membrane. Centrifuge for 1 minute at full speed to elute the RNA.
O. Purified RNA will store in -80C for further study.

Procedure for DNA extraction and purification

A. Place the saved all-in-one spin column to a new collection tube and add 500 ul of gDNA wash solution to the column. Centrifuge 2 minutes at 14,000rpm.
B. Discard the flow-through and reassement the spin column with its collection tube. Spin the column for 2 minutes in order to thoroughly dry the resin. Discard the collection tube.

C. Place the column into a fresh 1.5 mi Elution tube and add 100 ul of gDNA Elution buffer to the column.
D. Centrifuge for 2 minutes at 14,000rpm to collect gDNA(Retain the spin column for protein purification).
E. Purified gDNA will store in -80C for further study.

Procedure for Total protein purification

A. Adjusting the saved flow-through from RNA extraction to 600ul with water and add 24 ul of protein PH Binding Buffer. Mix contents well.
B. Apply up to 650 ul of the pH-adjusted protein sample onto the spin column and centrifuge for 2 minutes at 800rpm.Discard the flow-through.
C. Apply 500 ul of protein wash buffer to the column and centrifuge for 2 minutes at 8,000rpm.if necessary, spin 1 more minute to dry.
D. Add 9.3 ul Neutralizer to a fresh 1.5ml Elution tube. Transfer the spin column from the column wash procedure into the Elution tube.
E. Apply 100ul of the protein elution buffer to the column and centrifuge for 2 minutes at 8,000rpm to elute bound protein.
F. The eluted protein will store in -80c for further study.

July 2015 **[SPUTUM INDUCTION PROTOCOL]**

PATIENT NAME:_____ **ID#**_____

DATE:_____/_____/20_____ **Gender: (M) or (F)**

BP_____/_____ **Pulse**_____**RR:**_____ **Wgt** _____lbs **Hgt**_____feet and _____inches

Spirometry Data: **Predicted FEV1:**_____ **Predicted FVC:**_____

Patient FEV1 (before Albuterol):_____ **FVC:**_____ **FEV1/FVC Ratio:**_____

Baseline FEV1 (post Albuterol)_____ **FVC:**_____ **FEV1/FVC Ratio:**_____

After 0.9 saline FEV1:_____

After _____ **saline FEV1:**_____

After _____ **saline FEV1:**_____

After _____ **saline FEV1:**_____ **STOP FEV1:**_____ **10% FEV1:**_____

SPUTUM SAMPLE: Spontaneous **( )** Induced **( )** Unsuccessful **( )**

Appearance:

Mucoid **( )** Purulent **( )** Mucopurulent **( )** Bloody **( )**

Color:

Colorless **( )** White **( )** Grey **( )** Yellow **( )** Green **( )** Brown **( )** Red **( )**

Sputum Sample Processing

Used Microscope: Y ( ) N ( )

Wgt of sample to be processed:_____ **mg (I)** **Wgt of suspension after filtration:**_____**mg(II)**

Hematocytometer count: _____ **(III)** **Total Cell Count :** _____ ***10⁶ cell/mL (II*III=IV)**

Absolute number cells retrieved: _____ ***10⁶ cells/g (IV/I*1000)**

Viability:_____**% (40-100%)**

Total processing time:_____ **Processed by:**_____

Differential:

Neutrophils _____**%**							**<64.4%**
Eosinophils_____**%**	**Granules:**		**Few**	**Mod**	**Many**	**None**	**<2.0%**
Macrophages_____**%**	**Someker Inclusions:**	**Few**	**Mod**	**Many**	**Many**	**None**	**<86%**
Lymphocytes_____**%**							**<2.6%**
Bronchial Epithelial cells_____**%**							**<4.4%**
Squamous cell:_____**% (<20%)**							

Reference Values	
Cells/g of sputum	4.2
Neut	37.50%
Eos	0.40%
Mac	58.80%
lymp	1%
BE	1.60%
Squamos	<20%

BELDA J, LEIGH R, et al.
Crit. Care Med. 2000; 161: 475-478

Comments and Interpretation:

TABLE 1
SPUTUM TOTAL AND ABSOLUTE DIFFERENTIAL CELL COUNTS ($\times 10^6$ cells/g)

	Mean ± SD	Normal Range		Median (IQR)	Percentiles	
		Mean −2 SD	Mean +2 SD		10	90
Total cell count	4.129 ± 4.814	−4.599	13.757	2.400 (3.188)	0.672	9.732
Eosinophils	0.013 ± 0.037	−0.061	0.087	0.000 (0.008)	0.000	0.042
Neutrophils	1.962 ± 3.027	−4.092	8.016	0.865 (1.959)	0.098	4.860
Macrophages	2.126 ± 2.027	−1.928	6.180	1.644 (1.873)	0.296	4.859
Lymphocytes	0.043 ± 0.069	−0.095	0.181	0.018 (0.048)	0.009	0.086
Metachromatic cells	0.000 ± 0.001	−0.002	0.002	0.000 (0.000)	0.000	0.001
Bronchial epithelial cells	0.014 ± 0.037	−0.06	0.088	0.006 (0.010)	0.000	0.031

TABLE 2
SPUTUM DIFFERENTIAL CELL PERCENTAGES

	Mean ± SD	Normal Range		Median (IQR)	Percentiles	
		Mean −2 SD	Mean +2 SD		10	90
Eosinophils	0.4 ± 0.9	−1.4	2.2	0.0 (0.3)	0.00	1.1
Neutrophils	37.5 ± 20.1	−2.7	77.7	36.7 (29.5)	11.0	64.4
Macrophages	58.8 ± 21.0	16.8	100.8	60.8 (28.9)	33.0	86.1
Lymphocytes	1.0 ± 1.1	−1.2	3.2	0.5 (1.8)	0.01	2.6
Metachromatic cells	0.0 ± 0.04	−0.1	0.1	0.0 (0.0)	0.00	0.04
Bronchial epithelial cells	1.6 ± 3.9	−6.2	9.4	0.3 (1.3)	0.00	4.4

BELDA J, LEIGH R, et al. Induced Sputum Cell Counts in Healthy Adults Am. J. Respir. Crit. Care Med. 2000; 161: 475-478

COMPOUND AUTHORIZATION AND CONSENT FOR PARTICIPATION IN A RESEARCH PROJECT
YALE UNIVERSITY SCHOOL OF MEDICINE-YALE-NEW HAVEN HOSPITAL

ESSENTIAL TESTING CONSENT

Study Title: Mechanisms and Mediators of Lung Disease

Principal Investigator: **Geoffrey Chupp, MD**
Yale University School of Medicine
Department of Pulmonary and Critical Care Medicine
TAC S-441
PO Box 208057
New Haven, CT 06520-8057

Funding Source: National Institute of Health, Yale Center for Clinical Investigation

Invitation to Participate and Description of Project

You are invited to participate in a research study designed to investigate the development and natural history of lung disease. You have been chosen to participate because you either have lung disease or have no history of lung disease. It is important for us to understand how people who do not have lung disease are different from people who do.

In order to decide whether or not you wish to be a part of this research study, you should know enough about its risks and benefits to make an informed judgment. This consent form provides detailed information about the research study that a member of the research team will discuss with you. This discussion should go over all aspects of this research: its purpose, the procedures that will be performed, any risk of the procedures, possible benefits and possible alternative treatments. Lung diseases can cause shortness of breath and progressive loss of lung function leading to death. This study is designed to understand the biologic pathways (molecules) that lead to lung disease.

Purpose: The purpose of this study is to investigate the development and natural history of lung disease by analyzing biological samples and measurements (blood, sputum, lung tissue and fluid) from subjects with or without lung disease over the course of time. We are determining the genes, molecules, and pathways that cause lung disease and how different genes, molecules, and pathways cause different types of lung disease. This will be done by comparing the different signals in patients with lung disease to each other and to patients without lung disease (controls). We will use several methods to do this. With a few tubes of blood, we can examine cells, serum, protein, and genes (DNA and RNA). Researchers in the lab will do the measurements on samples provided by you from a blood, sputum and/or samples taken during the course of this study The following are examples of our research: **DNA/RNA analysis:** one way we will study lung disease will

be to examine DNA/genetic material for abnormalities that can cause lung disease; **Protein:** another will be to examine the protein made by the DNA in serum, cells or tissue samples.

The researchers will obtain samples of your blood for various immunologic and cytokine (molecules produced by cells) analysis, including DNA (deoxyribonucleic acid), RNA (ribonucleic acid), cells and serum. DNA is a large chemical that carries our genetic, or hereditary information. The genes are specific pieces of DNA that carry the instructions for making all the proteins that are found in a cell. A gene is like a strand of multicolored beads, and the gene will not function right if it has a mistake or a mutation in it, (for example, extra or missing beads). In addition, genes can act differently in different people if the beads are in a slightly different order or pattern. Experiments have shown that these slight differences in genes can affect either the way disease develops, the way drugs act on disease cells, or the way drugs are broken down by your body. Research using DNA is an important way to try to understand airways disease and the role genes play. RNA is a substance that translates DNA into proteins and is present at different levels in cells of your body. Your study doctor can give you more information on the genes being studied.

Description of Procedures: If you agree to participate in this study, you will be asked to come to the Winchester Chest Clinic at Yale-New Haven Hospital, be seen in out-patient or in-patient areas of YNHH, Yale University Health Services, or be seen in your private physician's office at a convenient time.

During your first visit, we will obtain informed consent, a medical history, completion of a standardized questionnaire, and the collection of about 1-2 tablespoons of blood for genetic and various immunologic and cytokine (molecules produced by cells) testing. We may also do a pulmonary function (breathing) test that is explained below, urine chemistry testing for protein analysis, sputum collection, and exhaled breath condensate collection or breathalizer.

At additional visits, which may include an exacerbation of your lung disease, we may obtain a medical history focused on the stability of your lung disease, completion of a standardized questionnaire, a repeat blood draw (about 1-2 tablespoons of blood), up to four times per year at your regular visits, and a breathing test to compare to your initial visit test. We may also ask you to participate in additional testing as mentioned in the first visit.

If you are sick enough to require a machine to help you breathe, (ventilator), we will collect a mucus specimen from the tube in your lung. These specimens are routinely collected throughout the day in patients on ventilators**.** However, if you are intubated , (on a ventilator), the investigator may want to perform a mini-BAL, which involves placement of a special tube (catheter) just beyond the tip of the breathing (endotracheal) tube.
The procedure involved in obtaining blood specimens for laboratory analysis is conducted through the use of standard blood drawing methods by a highly trained nurse

or technician. We will keep you as comfortable as possible during this procedure, and if you should develop a bruise or swelling at the blood-drawing site, we will apply ice to the site.

We may collect blood for laboratory medicine testing (chemistry and hematology), and if we do, we will share the results with you. This may result in a follow-up if there are any significant abnormalities in the laboratory tests.
Collection of blood for genetic testing will be evaluated in the research laboratory of the Pulmonary Department of the Yale School of Medicine. The scope of this research is to study lung disease with a specific focus on airways disease. Personal information about your identity will be removed from the samples, (samples identified by a code number), and the person doing the tests will not know who you are. This is called "de-identification" of samples. (These tests are performed in Dr. Geoffrey Chupp's laboratory at the Yale School of Medicine, and Dr. Chupp may share this information with his collaborators in a "de-identified" manner). Your samples will be stored until they are exhausted or until you request withdrawal or destruction of your specimens. However, the data obtained from the specimens up to the point of withdrawal, will continue to be used. The results of the DNA tests will not be available to you, your family or your physician. We hope that these studies will lead to a further understanding of lung disease.

Urine for protein analysis will be evaluated in Dr. Chupp's laboratory in the Pulmonary Section.

Sputum collection by induction; we may ask you to deposit sputum you cough up spontaneously into a collection cup, or we may ask you to cough up sputum (lung fluid) from your lungs. This is called sputum induction. To begin, we will again do lung function testing. We will carefully watch your lung function and the amount of oxygen in your blood while we do the sputum induction. You will inhale a mist containing salt water, which will help you to cough up the sputum sample. This test will take place in our Research Room (LMP 5046), by personnel, trained for this procedure under the supervision of a physician.

Exhaled Breath Condensate collection is accomplished using a special plastic disposable device (R-tube device), which is a disposable plastic mouthpiece with a one-way valve attached to a trap to capture exhaled breath. The procedure involves the collection of exhaled breath over a 20 minute period. You will be given specific instructions as to the collection of your breath through the use of the device. This will take place in the Research Room also. The samples from the Exhaled Breath Condensate (EBC), will be collected for Dr. Chupp's laboratory at the Yale School of Medicine, and stored for further analysis.

Lung function testing is performed by highly trained technicians in the Pulmonary Function Laboratory at Yale-New Haven Hospital or the Research Room (LMP 5046), and involves breathing into a machine through a tube that measures lung function (while in a sitting position). You may also be asked to do plethysmography (another part of the

breathing test), which involves shallow and deep breathing maneuvers that are performed while seated in a clear box. At the conclusion of the breathing test, you will then be given a bronchodilator (a medicine that helps to open your airways) and the simple spirometry (breathing test) will be repeated to see if your lung function improves. A bronchodilator is available for you if you should experience a wheeze or cough during the procedure.

Endotracheal suction is a procedure that is routinely performed in patients on mechanical ventilation throughout the day to keep patients' airways free of mucus. The material removed is either analyzed or discarded. For this study some excess material will be saved for study purposes and analyzed later.

The mini-BAL is conducted in the intensive care unit of the hospital. This will only be done after you are given medication to help you relax and be sleepy (sedated) and placed on 100% oxygen. Patients who have endotracheal (breathing) tubes require frequent suctioning, and the placement of this catheter is very similar to the placement of a suction catheter. Through this catheter or tube, the physician will put in a small amount of sterile salt water based on your body weight, to try to wash fluid from the lower lung. Then, the physician will take the fluid out of your lung and send it to the laboratory located in the Pulmonary Department of Yale University School of Medicine, for further evaluation. Approximately 50% of this fluid will be suctioned out. The remaining fluid is normally reabsorbed from the lung within a short period of time.

The results of the DNA tests will not be available to you, your family or your personal physician and your results will not be placed in your medical records. This information may only be available to the laboratory that performed the tests, collaborators, or possibly our Human Investigation Committee during the auditing process. Personal information about your identity will be removed from the samples and the person doing the blood test will not know who you are. Any excess material may be saved for future studies of the lung.

If you develop any problems possibly related to the procedures, you or your doctor may contact Dr. Geoffrey Chupp at the Division of Pulmonary and Critical Care, Yale School of Medicine (203) 785-4198 at any time.

Risks and Inconveniences

Blood drawing from your vein is very safe and will be performed by a highly trained nurse or technician according to standard blood drawing methods. About 1-2 tablespoons will be taken at each time period; there may be mild pain or a bruise at the blood drawing site. You may feel dizzy or you may feel faint, but we will make every effort to make you as comfortable as possible. The scope of the genetic analysis will be limited to studying lung disease. We will protect against disclosure by storing specimens with a code number, called "de-identification" as described previously. Inadvertent disclosure of genetic information has the potential to cause anxiety to you or may pose other risks, such as your right to insurance and employment opportunities, or other unknown risks. Disclosure of this information could also cause people to have a certain view about you,

or even a psychological response, and possibly divulge a biological relationship within your family, not previously known. We will not share this information with your primary physician or your family and access to study records will be limited to investigators on the study and the Human Investigation Committee. These individuals are required to keep all information confidential.

Sputum induction can cause wheezing, but you will be watched very carefully during this procedure. It is possible that this procedure will cause you to cough, which may cause some shortness of breath, but this test will be monitored closely and the procedure will be stopped if your breathing test appears to have decreased. This will be performed by a trained health professional, under the supervision of a physician.

There are no risks to the collection of exhaled breath condensate or to the collection of urine.

The procedure of lung function, (breathing test) is performed in a sitting position for your safety, by a trained technician in the Pulmonary Function Laboratory at Yale-New Haven Hospital, or the Research Room (LMP 5046), and occasionally, a subject may experience dizziness while performing the test, but this is usually temporary. Very rarely, people with airway disease may actually start to wheeze or cough following these tests. If this occurs, a bronchodilator (medicine to help open your airway) is available.

Endotracheal suction is routinely performed on subjects on ventilators and therefore there is no additional risk to you, but can sometimes cause irritation and bleeding.

The mini-BAL may cause some slight discomfort. You will be given medication to help you relax and be sleepy (sedation), prior to the procedure. Investigations have shown that this procedure is as safe as routine suctioning of patients. You may have minor increases in your heart rate, blood pressure, and minor decreases in blood oxygen levels. To make sure you have enough oxygen in your blood, the amount of oxygen you breathe will be increased for the three minutes the procedure usually takes.

Under some circumstances, it can be a risk for genetic information to be known by the subject or others. Variation in some genes is known to be directly related to risk of certain illnesses. In some cases, knowledge of genetic information could have negative psychological consequences or could affect access to or retention of certain benefits or entitlements. For example, the information could potentially be used against you if it were revealed to insurance companies or potential employers. However, you will not get the results of the DNA portion of the study nor will the results be made available in your medical record. Additionally, we will take precautions to ensure that confidentiality is maintained and that genetic information is not unintentionally disclosed to inappropriate third parties. There is a federal law called the Genetic Information Nondiscrimination Act (GINA). In general, this law makes it illegal for health insurance companies, group health plans, and most employers, except those with less than 15 employees, to discriminate against you based on your genetic information. However, it does not protect you against

discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

Benefits:
You should not expect to benefit directly from your participation in this study. However, these tests may yield medical information that could be useful for your health care, or the care of others with airways disease. The results of these tests will be given to you or sent to your personal physician (excluding the genetic information). Information obtained may help identify those at risk for lung disease or for lung disease you can control.

Economic Considerations: You will be compensated for your participation in this study according to this compensation schedule:

1) $20 blood draw
2) $20 pulmonary function test
3) $20 sputum induction
4) $20 exhaled breath condensate

If you participate fully in this study you could receive a maximum of approximately $130 for each time point if you complete all of the above testing procedures. Neither you nor your insurance company will be charged for any of the tests that are performed as a part of this research study.

Alternatives:
The only alternative is to decline participation in the study.

Confidentiality:
Any identifiable information that is obtained in connection with this study will remain confidential and will be disclosed only with your permission or as required by US or State law. When the results of the research are published or discussed in conferences, no information will be included that would reveal your identity unless your specific consent for this activity is obtained.

We understand that information about you obtained in connection with your health is personal, and we are committed to protecting the privacy of that information. If you decide to be in this study, the researcher will get information that identifies you and your personal health information. This may include information that might directly identify you, such as your name, medical record number, or date of birth. This information will be de-identified at the earliest reasonable time after we receive it, meaning we will replace your identifying information with a code that does not directly identify you. The principal investigator will keep a link that identifies you to your coded information, and this link will be kept secure and available only to the PI or selected members of the research team. Any information that can identify you will remain confidential. We also safeguard your confidentiality by storing research materials in a locked cabinet, and by using password-protected data entry. The research team will only give this coded information to others to carry out this research study. The link to your personal information will be kept until the research is completed, after which time the link will be

destroyed and the data will become anonymous. The data will be kept in this anonymous form until it is destroyed.

The information about your health that will be collected in this study includes: the entire research records and any medical records held by Yale-New Haven Hospital created from February 2009 through the end of your participation in the study. Information about you and your health which might identify you may be used by or given to:

- The US Department of Health and Human Services (DHHS) agencies
- Representatives from Yale University and the Human Investigation Committee (the committee that reviews, approves, and monitors research on human subjects), who are responsible for insuring research compliance. These individuals are required to keep all information confidential
- Those individuals at Yale who are responsible for the financial oversight of research including billings and payments
- The Principal Investigator: Geoffrey L. Chupp, MD
- The National Institutes of Health
- Health care providers who provide services to you in connection with this study
- Laboratories and other individuals and organizations that analyze your health information in connection with this study, according to the study plan
- Co-Investigators and other investigators
- Study Coordinator and Members of the Research Team
- Data and Safety Monitoring Boards and others authorized to monitor the conduct of the Study

By signing this form, you authorize the use and/or disclosure of the information described above for this research study. The purpose for the uses and disclosures you are authorizing is to ensure that the information relating to this research is available to all parties who may need it for research purposes.

All health care providers subject to HIPAA (Health Insurance Portability and Accountability Act) are required to protect the privacy of your information. The research staff at the Yale School of Medicine and Yale-New Haven Hospital are required to comply with HIPAA and to ensure the confidentiality of your information. Some of the individuals or agencies listed above may not be subject to HIPAA and therefore may not be required to provide the same type of confidentiality protection. They could use or disclose your information in ways not mentioned in this form. However, to better protect your health information, agreements are in place with these individuals and /or companies that require that they keep your information confidential.

You have the right to review and copy your health information in your medical record in accordance with institutional medical records policies.

In Case of Injury:

If you are injured as a result of your participation in this study, treatment will be provided. You or your insurance carrier will be expected to pay the costs of this

treatment. No additional financial compensation for injury or lost wages is available. You do not give up your legal rights by signing this form.

Voluntary Participation and Withdrawal:

Participating in this study is voluntary. You are free to choose not to participate in this study. Refusing to participate will involve no penalty or loss of benefits to which you are otherwise entitled (such as your health care outside the study, the payment for your health care, and your health care benefits. However, you will not be able to enroll in this research study and will not receive study procedures as a study participant if you do not allow use of your information as part of this study.

If you do become a subject, you are free to stop and withdraw from this study at any time during its course. If you sign this authorization, you may change your mind at any time, but the researchers may continue to use information collected before you changed your mind to complete the research. To withdraw, you can call a member of the research team at any time and tell them that you no longer want to take part. This will cancel any appointments in the future. You must also follow up your phone call by sending a written notice to revoke this authorization to the principal investigator (Geoffrey L. Chupp, MD, TAC S-441 [complete address on page 1 of this consent form]).

This authorization to use and disclose your health information will never expire unless and until you change your mind and revoke it. The researchers may withdraw you from participating in the research if necessary. You are not required to complete all aspects of this trial, so if there are procedures that you are not comfortable with, you will not have to participate in them. The only exception is for a subset of 200 participants who will be asked to complete specific procedures to meet the requirements of our National Institute of Health grant. Withdrawing from the study will involve no penalty or loss of benefits to which you are otherwise entitled. It will not harm your relationship with your own doctors or with Yale-New Haven Hospital.

Questions:

We have used some technical terms in this form. Please feel free to ask about anything you don't understand and to consider this research and the consent form carefully—as long as you feel is necessary—before you make a decision.

Authorization:

I have read (or someone has read to me) this form and have decided to participate in the project described above. Its general purposes, the particulars of involvement and possible hazards and inconveniences have been explained to my satisfaction. My signature also indicates that I have received a copy of this consent form. By signing this form, I give permission to the researchers to use [and give out] information about me for the purposes described in this form. By refusing to give permission, I understand that I will not be able to be in this research.

Name of Subject:_____

Signature:_____

Date:_____

_____ _____
Signature of Primary Investigator Date

or

_____ _____
Signature of Person Obtaining Consent Date

If you have further questions about this project or if you have a research related problem, you may contact the Principal Investigator, Geoffrey Chupp, MD at (203) 785-4198 or Carole Holm BSN, RN at (203) 737-4263. If you have any questions concerning your rights as a research subject, you may contact the Human Investigation Committee at (203) 785-4688. If, after you have signed this form, you have any questions about your privacy rights, please contact the Yale Privacy Officer at 203/436-3650.

THIS FORM IS NOT VALID UNLESS THE FOLLOWING BOX HAS BEEN COMPLETED IN THE HIC OFFICE

THIS FORM IS VALID ONLY UNTIL:
_____

HIC PROTOCOL #:
_____

INITIALED:
_____

AUTHORIZATION FOR DONATION OF EXCESS TISSUE
YALE UNIVERSITY SCHOOL OF MEDICINE

Title: Mechanisms and Mediators of Lung Disease

Principal Investigator: Geoffrey L. Chupp, MD

Funding Source: National Institutes of Health

Tissue Donation

You are invited to donate any tissue leftover from your participation in the asthma and COPD research trial, to a research tissue bank where it can be used for future research projects. The tissue collected in this bank is used by Yale University researchers to study a broad spectrum of medical research, such as techniques for improving the diagnosis and treatment of human diseases and fundamental studies exploring new areas of biology, biotechnology, biomedical engineering and informatics.

In order to decide whether or not you wish to donate your tissue, you should know enough about its risks and benefits to make an informed decision. This form gives you information about the research bank and how the tissue is used. Once you understand the tissue donation and banking process, you will be asked if you wish to participate; if so, you will be asked to sign this form.

How Does the Tissue Get Into the Bank

The tissue samples we refer to include (and will subsequently be referred to as "samples"): blood, sputum, tracheal aspirates (material suctioned from your lungs during your stay in the intensive care unit), and tissue and lavage (fluid from the lungs) during the bronchoscopy. These samples are sent to the research laboratories in the Department of Pulmonary and Critical Care at Yale University School of Medicine. The samples are analyzed by the researchers for the Asthma and COPD (chronic obstructive pulmonary disease) project and will be used to study human health, if you agree to donate your tissue for future research. The following information about you will be entered into the database that tracks your samples: your name, the name of your physician, the date of your bronchoscopy or blood draw, sputum collection of tracheal aspirate and your diagnosis. In most cases, the researchers will use your leftover samples in a de-identified manner. This means that they will use your samples without knowing who you are. In some cases, they may use information about you for research purposes, subject to an approval process.

Risks and Inconveniences

There are no known risks associated with donating your samples to research. You will not be required to give any more samples than that which will be taken at the time of the procedures for the study.

Under some circumstances, it can be a risk for genetic information to be known by the subject or others. Variation in some genes is known to be directly related to risk of certain illnesses. In

some cases, knowledge of genetic information could have negative psychological consequences or could affect access to or retention of certain benefits or entitlements. For example, the information could potentially be used against you if it were revealed to insurance companies or potential employers. However, you will not get the results of the DNA portion of the study nor will the results be made available in your medical record. Additionally, we will take precautions to ensure that confidentiality is maintained and that genetic information is not unintentionally disclosed to inappropriate third parties. There is a federal law called the Genetic Information Nondiscrimination Act (GINA). In general, this law makes it illegal for health insurance companies, group health plans, and most employers, except those with less than 15 employees, to discriminate against you based on your genetic information. However, it does not protect you against discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

Benefits

You will not receive any direct benefit from banking your samples into the bank. We hope that the information we learn in future research studies will increase our knowledge of human health and that this information will lead to better treatments in the future.

Economic Considerations

You will not receive any payments for donating your samples to the research bank.

Confidentiality

Any identifiable information that is obtained in connection with your samples will remain confidential and will be disclosed only with your permission. Only the members of the research tissue bank staff will know your identity. When the results of the research are published or discussed in conferences, no information will be included that would reveal your identity unless your specific consent for this activity is obtained.

Representatives from the Yale Human Investigation Committee, National Institutes of Health, Yale Center for Clinical Investigation, may inspect study records during internal auditing procedures. However, these individuals are required to keep all information confidential.

Voluntary Participation and Withdrawal

Participating in this study is voluntary. You are free to choose not to donate your samples to research and if you do become a donor, you are free to change your mind at any time, but the researchers may still use the information collected before you changed your mind in order to complete the research that has already started.

Withdrawing from the study will involve no penalty or loss of benefits to which you are otherwise entitled. It will not harm your relationship with your own doctors or Yale University or Yale-New Haven Hospital.

This form will never expire unless and until you change your mind and retract it. To retract the permission to use your information, please call Dr. Geoffrey Chupp @ 785-3207.

Questions

We have used some technical terms in this form. Please feel free to ask about anything you don't understand and to consider this research and the consent form carefully—as long as you feel is necessary—before you make a decision.

Privacy Rights

The health-related information that we gather about you in this study is personal. The researchers are required by law to protect the privacy of the information known as protected health information or PHI. All reasonable efforts will be made to protect the confidentiality of your PHI, which may be shared with others to support this research, to conduct public health reporting and to comply with the law as required. Despite these protections, there is a possibility that information about you could be used or disclosed in a way that it will no longer be protected.

By signing this form, you give permission for the researchers to use and/or disclose the information for this research bank. You have a right to refuse to sign this form. Your health care outside the study, the payment for your health care, and your health care benefits will not be affected if you do not sign this form. If you do not sign this form, your samples will not be banked for research purposes.

CONTACT INFORMATION

The contact information of the subject or personal representative who signed this form should be filled in below.

Address: Telephone

_____

_____ daytime _____

_____ evening _____

_____

e-mail address optional

Authorization

I have read (or someone has read to me) this form and have decided to participate in the project described above. Its general purposes, the particulars of involvement and possible hazards and inconveniences have been explained to my satisfaction. By signing below, I give permission for the described uses and disclosures of information. My signature also indicates that I have received a copy of this consent/authorization form.

CHECK ONE:

___I wish to donate my leftover samples to the Yale Department of Pulmonary and Critical Care Department for research

___I do not wish to donate my leftover samples to the Yale Department of Pulmonary and Critical Care Department for research

_____ _____
Signature of Subject or Personal Representative Date

_____ _____
Print Name of Subject or Personal Representative Description of Representative

_____ _____
Signature of Principal Investigator Date Received

Or

_____ _____
Signature of Person Obtaining Consent Date

If you have further questions about this project, or if you have a research-related problem, you may contact the Principal Investigator, Geoffrey Chupp, MD @ 785-4198. If you have any questions concerning your rights as a research subject, you may contact the Human Investigation Committee at (203) 785-4688. If, after you have signed this form, you have any questions about your rights, please contact the Yale Privacy Officer @ (203) 436-3650.

THIS FORM IS NOT VALID UNLESS THE FOLLOWING BOX HAS BEEN COMPLETED BY THE YALE HUMAN INVESTIGATION COMMITTEE OFFICE

THIS FORM IS VALID ONLY UNTIL: _____

HIC PROTOCOL #: _____

INITIALED: _____

COMPOUND AUTHORIZATION AND CONSENT FOR PARTICIPATION IN A RESEARCH PROJECT
YALE UNIVERSITY SCHOOL OF MEDICINE-YALE-NEW HAVEN HOSPITAL

PARENTAL PERMISSION FORM

ESSENTIAL TESTING CONSENT

Study Title: Mechanisms and Mediators of Lung Disease

Principal Investigator: **Geoffrey Chupp, MD**
Yale University School of Medicine
Department of Pulmonary and Critical Care Medicine
TAC S-441
PO Box 208057
New Haven, CT 06520-8057

Funding Source: National Institute of Health, Yale Center for Clinical Investigation

Invitation to Participate and Description of Project

Your child is invited to participate in a research study designed to investigate the development and natural history of lung disease. Your child has been chosen to participate because he/she either has lung disease such as asthma or have no history of lung disease, and your child is age twelve or older. It is important for us to understand how people who do not have lung disease are different from people who do.

In order to decide whether or not you and your child wish to be a part of this research study, you should know enough about its risks and benefits to make an informed judgment. This consent form provides detailed information about the research study that a member of the research team will discuss with you and your child. This discussion should go over all aspects of this research: its purpose, the procedures that will be performed, any risk of the procedures, possible benefits and possible alternative treatments. Lung diseases can cause shortness of breath and progressive loss of lung function leading to death. This study is designed to understand the biologic pathways (molecules) that lead to lung disease.

Purpose

The purpose of this study is to investigate the development and natural history of lung disease by analyzing biological samples and measurements (blood, sputum, lung tissue and fluid) from subjects with or without lung disease over the course of time. We are determining the genes, molecules, and pathways that cause lung disease and how different genes, molecules, and pathways cause different types of lung disease. This will be done by comparing the different signals in patients with lung disease to each other and to patients without lung disease (controls). We will use several methods to do this. With a few tubes of blood, we can examine cells, serum, protein, and genes (DNA and RNA). Researchers in the lab will do the measurements on samples provided by your child from

a blood, sputum and/or samples taken during the course of this study The following are examples of our research: **DNA/RNA analysis:** one way we will study lung disease will be to examine DNA/genetic material for abnormalities that can cause lung disease; **Protein:** another will be to examine the protein made by the DNA in serum, cells or tissue samples.

The researchers will obtain samples of your child's blood for various immunologic and cytokine (molecules produced by cells) analysis, including DNA (deoxyribonucleic acid), RNA (ribonucleic acid), cells and serum. DNA is a large chemical that carries our genetic or hereditary information. The genes are specific pieces of DNA that carry the instructions for making all the proteins that are found in a cell. A gene is like a strand of multicolored beads, and the gene will not function right if it has a mistake or a mutation in it, (for example, extra or missing beads). In addition, genes can act differently in different people if the beads are in a slightly different order or pattern. Experiments have shown that these slight differences in genes can affect either the way disease develops, the way drugs act on disease cells, or the way drugs are broken down by your child's body. Research using DNA is an important way to try to understand airways disease and the role genes play. RNA is a substance that translates DNA into proteins and is present at different levels in cells of your child's body. Your child's study doctor can give you more information on the genes being studied.

Description of Procedures

If you and your child agree to participate in this study, your child will be asked to come to the Winchester Chest Clinic at Yale-New Haven Hospital, be seen in out-patient or in-patient areas of YNHH, Yale University Health Services, or be seen in your child's private physician's office at a convenient time.

During the first visit, we will obtain informed consent, a medical history, completion of a standardized questionnaire, and the collection of a little more than 1 tablespoons of blood for genetic and various immunologic and cytokine (molecules produced by cells) testing. We may also do a pulmonary function (breathing) test that is explained below, urine chemistry testing for protein analysis and sputum collection.

At additional visits, which may include an exacerbation of your child's lung disease, we may obtain a medical history focused on the stability of your child's lung disease, completion of a standardized questionnaire, a repeat blood draw (about 1-2 tablespoons of blood), up to four times per year at regular visits, and a breathing test to compare to the initial visit test. We may also ask your child to participate in additional testing as mentioned in the first visit.

If your child is sick enough to require a machine to help them breathe, (ventilator), we will collect a mucus specimen from the tube in their lung. These specimens are routinely collected throughout the day in patients on ventilators**.** The procedure involved in obtaining blood specimens for laboratory analysis is conducted through the use of standard blood drawing methods by a highly trained nurse or technician. We will keep your child as comfortable as possible during this procedure, and if your child should develop a bruise or swelling at the blood-drawing site, we will apply ice to the site.

We may collect blood for laboratory medicine testing (chemistry and hematology), and if we do, we will share the results with you, your child and/or the primary care physician. This may result in a follow-up if there are any significant abnormalities in the laboratory tests.

Collection of blood for genetic testing will be evaluated in the research laboratory of the Pulmonary Department of the Yale School of Medicine. The scope of this research is to study lung disease with a specific focus on airways disease. Personal information about your child's identity will be removed from the samples, (samples identified by a code number), and the person doing the tests will not know who your child are. This is called "de-identification" of samples. (These tests are performed in Dr. Geoffrey Chupp's laboratory at the Yale School of Medicine, and Dr. Chupp may share this information with his collaborators in a "de-identified" manner). Your child's samples will be stored until they are exhausted or until you or your child request withdrawal or destruction of the specimens. However, the data obtained from the specimens up to the point of withdrawal, will continue to be used. The results of the DNA tests will not be available to your child, your family or your physician. We hope that these studies will lead to a further understanding of lung disease.

Urine for protein analysis will be evaluated in Dr. Chupp's laboratory in the Pulmonary Section.

Sputum collection by induction; we may ask your child to deposit sputum your child cough up spontaneously into a collection cup, or we may ask your child to cough up sputum (lung fluid) from your child's lungs. This is called sputum induction. To begin, we will again do lung function testing. We will carefully watch your child's lung function and the amount of oxygen in the blood while we do the sputum induction. Your child will inhale a mist containing salt water, which will help your child to cough up the sputum sample. This test will take place in our Research Room (LMP 5046), by personnel, trained for this procedure under the supervision of a physician.

Lung function testing is performed by highly trained technicians in the Pulmonary Function Laboratory at Yale-New Haven Hospital or the Research Room (LMP 5046), and involves breathing into a machine through a tube that measures lung function (while in a sitting position). Your child may also be asked to do plethysmography (another part of the breathing test), which involves shallow and deep breathing maneuvers that are performed while seated in a clear box. At the conclusion of the breathing test, your child will then be given a bronchodilator (a medicine that helps to open the airways) and the simple spirometry (breathing test) will be repeated to see if your child's lung function improves. A bronchodilator is available for your child if your child should experience a wheeze or cough during the procedure.

The results of the DNA tests will not be available to your child, your family or your personal physician and your child's results will not be placed in their medical records. This information may only be available to the laboratory that performed the tests, collaborators, or possibly our Human Investigation Committee during the auditing

process. Personal information about your child's identity will be removed from the samples and the person doing the blood test will not know who you or your child is. Any excess material may be saved for future studies of the lung.

If your child develops any problems possibly related to the procedures, your child or your doctor may contact Dr. Geoffrey Chupp at the Division of Pulmonary and Critical Care, Yale School of Medicine (203) 785-4198 at any time.

Risks and Inconveniences

Blood drawing from the vein is very safe and will be performed by a highly trained nurse or technician according to standard blood drawing methods. A little more than one (1) tablespoon will be taken at each time period; there may be mild pain or a bruise at the blood drawing site. Your child may feel dizzy or your child may feel faint, but we will make every effort to make your child as comfortable as possible. The scope of the genetic analysis will be limited to studying lung disease. We will protect against disclosure by storing specimens with a code number, called "de-identification" as described previously. Inadvertent disclosure of genetic information has the potential to cause anxiety to your child or may pose other risks, such as your child's right to insurance and employment opportunities, or other unknown risks. Disclosure of this information could also cause people to have a certain view about your child, or even a psychological response, and possibly divulge a biological relationship within your family, not previously known. We will not share this information with your child's primary physician or your family and access to study records will be limited to investigators on the study and the Human Investigation Committee. These individuals are required to keep all information confidential.

Sputum induction can cause wheezing, but your child will be watched very carefully during this procedure. It is possible that this procedure will cause your child to cough, which may cause some shortness of breath, but this test will be monitored closely and the procedure will be stopped if your child's breathing test appears to have decreased. This will be performed by a trained health professional, under the supervision of a physician.

The procedure of lung function, (breathing test) is performed in a sitting position for your child's safety, by a trained technician in the Pulmonary Function Laboratory at Yale-New Haven Hospital, or the Research Room (LMP 5046), and occasionally, a subject may experience dizziness while performing the test, but this is usually temporary. Very rarely, people with airway disease may actually start to wheeze or cough following these tests. If this occurs, a bronchodilator (medicine to help open the airway) is available.

Under some circumstances, it can be a risk for genetic information to be known by the subject or others. Variation in some genes is known to be directly related to risk of certain illnesses. In some cases, knowledge of genetic information could have negative psychological consequences or could affect access to or retention of certain benefits or entitlements. For example, the information could potentially be used against you if it were revealed to insurance companies or potential employers. However, you will not get the results of the DNA portion of the study nor will the results be made available in your

medical record. Additionally, we will take precautions to ensure that confidentiality is maintained and that genetic information is not unintentionally disclosed to inappropriate third parties. There is a federal law called the Genetic Information Nondiscrimination Act (GINA). In general, this law makes it illegal for health insurance companies, group health plans, and most employers, except those with less than 15 employees, to discriminate against you based on your genetic information. However, it does not protect you against discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

Benefits

Your child should not expect to benefit directly from their participation in this study. However, these tests may yield medical information that could be useful for their health care, or the care of others with airways disease. The results of these tests will be given to your child or sent to their personal physician (excluding the genetic information). Information obtained may help identify those at risk for lung disease or for lung disease you can control.

Economic Considerations

You will be compensated for your participation in this study according to this compensation schedule:

1) $20 blood draw
2) $20 pulmonary function test
3) $20 sputum induction

If your child participates fully in this study your child could receive a maximum of approximately $60 for each time point if your child completes all of the above testing procedures. Neither your child nor your child's insurance company will be charged for any of the tests that are performed as a part of this research study.

Alternatives

The only alternative is to decline participation in the study.

Confidentiality

Any identifiable information that is obtained in connection with this study will remain confidential and will be disclosed only with your permission or as required by US or State law. When the results of the research are published or discussed in conferences, no information will be included that would reveal your child's identity unless a specific consent for this activity is obtained.

We understand that information about your child obtained in connection with their health is personal, and we are committed to protecting the privacy of that information. If your child decides to be in this study, the researcher will get information that identifies your child and your child's personal health information. This may include information that might directly identify your child, such as your child's name, medical record number, or date of birth. This information will be de-identified at the earliest reasonable time after we receive it, meaning we will replace your child's identifying information with a code

that does not directly identify your child. The principal investigator will keep a link that identifies your child to their coded information, and this link will be kept secure and available only to the PI or selected members of the research team. Any information that can identify your child will remain confidential. We also safeguard their confidentiality by storing research materials in a locked cabinet, and by using password-protected data entry. The research team will only give this coded information to others to carry out this research study. The link to your child's personal information will be kept until the research is completed, after which time the link will be destroyed and the data will become anonymous. The data will be kept in this anonymous form until it is destroyed.

The information about your child's health that will be collected in this study includes: the entire research records and any medical records held by Yale-New Haven Hospital created from February 2009 through the end of your child's participation in the study. Information about your child and your child's health which might identify your child may be used by or given to:

- The US Department of Health and Human Services (DHHS) agencies
- Representatives from Yale University and the Human Investigation Committee (the committee that reviews, approves, and monitors research on human subjects), who are responsible for insuring research compliance. These individuals are required to keep all information confidential
- Those individuals at Yale who are responsible for the financial oversight of research including billings and payments
- The Principal Investigator: Geoffrey L. Chupp, MD
- The National Institutes of Health
- Health care providers who provide services to your child in connection with this study
- Laboratories and other individuals and organizations that analyze your child's health information in connection with this study, according to the study plan
- Co-Investigators and other investigators
- Study Coordinator and Members of the Research Team
- Data and Safety Monitoring Boards and others authorized to monitor the conduct of the Study

By signing this form, you authorize the use and/or disclosure of the information described above for this research study. The purpose for the uses and disclosures you are authorizing is to ensure that the information relating to this research is available to all parties who may need it for research purposes.

All health care providers subject to HIPAA (Health Insurance Portability and Accountability Act) are required to protect the privacy of your child's information. The research staff at the Yale School of Medicine and Yale-New Haven Hospital are required to comply with HIPAA and to ensure the confidentiality of your child's information. Some of the individuals or agencies listed above may not be subject to HIPAA and therefore may not be required to provide the same type of confidentiality protection. They could use or disclose your child's information in ways not mentioned in this form. However, to better protect your child's health information, agreements are in place with

these individuals and /or companies that require that they keep your child's information confidential.

Your child has the right to review and copy your child's health information in your child's medical record in accordance with institutional medical records policies.

In Case of Injury

If your child is injured as a result of participation in this study, treatment will be provided. Your child or your child's insurance carrier will be expected to pay the costs of this treatment. No additional financial compensation for injury or lost wages is available. Your child does not give up any legal rights by signing this form.

Voluntary Participation and Withdrawal

Participating in this study is voluntary. Your child is free to choose not to participate in this study. Refusing to participate will involve no penalty or loss of benefits to which you are otherwise entitled.However, your child will not be able to enroll in this research study and will not receive study procedures as a study participant if your child do not allow use of information as part of this study.

If your child does become a subject, your child is free to stop and withdraw from this study at any time during its course. If you sign this authorization, you may change your mind at any time, but the researchers may continue to use information collected before your child changed their mind to complete the research. To withdraw, you can call a member of the research team at any time and tell them that your child no longer wants to take part. This will cancel any appointments in the future. You must also follow up your phone call by sending a written notice to revoke this authorization to the principal investigator (Geoffrey L. Chupp, MD, 1 Gilbert Street, TAC S-441, New Haven, CT 06520).

This authorization to use and disclose your child's health information will never expire unless and until your child changes their mind and revokes it. The researchers may withdraw your child from participating in the research if necessary. Your child are not required to complete all aspects of this trial, so if there are procedures that your child are not comfortable with, your child will not have to participate in them. The only exception is for a subset of 200 participants who will be asked to complete specific procedures to meet the requirements of our National Institute of Health grant. Withdrawing from the study will involve no penalty or loss of benefits to which you are otherwise entitled. It will not harm your child's relationship with their own doctors or with Yale-New Haven Hospital.

Questions:

We have used some technical terms in this form. Please feel free to ask about anything you don't understand and to consider this research and the consent form carefully—as long as you feel is necessary—before you make a decision.

Authorization

I have read (or someone has read to me) this form and have decided that my child may participate in the project described above. Its general purposes, the particulars of involvement and possible hazards and inconveniences have been explained to my satisfaction. My signature also indicates that I have received a copy of this consent form. By signing this form, I give permission to the researchers to use [and give out] information about my child for the purposes described in this form. By refusing to give permission, I understand that my child will not be able to be in this research.

Name of Subject: _____

Signature: _____

Date: _____

_____ _____
Signature of Primary Investigator Date

or

_____ _____
Signature of Person Obtaining Consent Date

If you have further questions about this project or if you have a research related problem, you may contact the Principal Investigator, Geoffrey Chupp, MD at (203) 785-4198 or Carole Holm BSN, RN at (203) 737-4263. If you have any questions concerning your rights as a research subject, you may contact the Human Investigation Committee at (203) 785-4688. If, after you have signed this form, you have any questions about your privacy rights; please contact the Yale Privacy Officer at 203/436-3650.

THIS FORM IS NOT VALID UNLESS THE FOLLOWING BOX HAS BEEN COMPLETED IN THE HIC OFFICE

THIS FORM IS VALID ONLY UNTIL:
_____

HIC PROTOCOL #:
_____0102012268_____

INITIALED:
_____

AUTHORIZATION FOR DONATION OF EXCESS TISSUE
YALE UNIVERSITY SCHOOL OF MEDICINE

PARENTAL PERMISSION FORM

Title: Mechanisms and Mediators of Lung Disease

Principal Investigator: Geoffrey L. Chupp, MD

Funding Source: National Institutes of Health

Tissue Donation

Your child is invited to donate any tissue leftover from their participation in the asthma and COPD research trial, to a research tissue bank where it can be used for future research projects. The tissue collected in this bank is used by Yale University researchers to study a broad spectrum of medical research, such as techniques for improving the diagnosis and treatment of human diseases and fundamental studies exploring new areas of biology, biotechnology, biomedical engineering and informatics.

In order to decide whether or not you wish for your child to donate tissue, you should know enough about its risks and benefits to make an informed decision. This form gives you information about the research bank and how your child's tissue is used. Once you and your child understand the tissue donation and banking process, you and your child will be asked if you both agree to participate; if so, you will be asked to sign this form.

How Does the Tissue Get Into the Bank

The tissue samples we refer to include (and will subsequently be referred to as "samples"): blood, sputum. These samples are sent to the research laboratories in the Department of Pulmonary and Critical Care at Yale University School of Medicine. The samples are analyzed by the researchers for the Asthma and COPD (chronic obstructive pulmonary disease) project and will be used to study human health, if you agree to allow your child to donate tissue for future research. The following information about your child will be entered into the database that tracks the samples: your child's name, the name of their physician, the date of their blood draw, sputum collection and their diagnosis. In most cases, the researchers will use leftover samples in a de-identified manner. This means that they will use the samples without knowing who your child is. In some cases, they may use information about your child for research purposes, subject to an approval process.

Risks and Inconveniences

There are no known risks associated with donating your child's samples to research. Your child will not be required to give any more samples than that which will be taken at the time of the procedures for the study.

Under some circumstances, it can be a risk for genetic information to be known by the subject or others. Variation in some genes is known to be directly related to risk of certain illnesses. In some cases, knowledge of genetic information could have negative psychological consequences or could affect access to or retention of certain benefits or entitlements. For example, the

information could potentially be used against you if it were revealed to insurance companies or potential employers. However, you will not get the results of the DNA portion of the study nor will the results be made available in your medical record. Additionally, we will take precautions to ensure that confidentiality is maintained and that genetic information is not unintentionally disclosed to inappropriate third parties. There is a federal law called the Genetic Information Nondiscrimination Act (GINA). In general, this law makes it illegal for health insurance companies, group health plans, and most employers, except those with less than 15 employees, to discriminate against you based on your genetic information. However, it does not protect you against discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

Benefits

Your child will not receive any direct benefit from banking samples into the bank. We hope that the information we learn in future research studies will increase our knowledge of human health and that this information will lead to better treatments in the future.

Economic Considerations

Your child will not receive any payments for donating their samples to the research bank.

Confidentiality

Any identifiable information that is obtained in connection with your child's samples will remain confidential and will be disclosed only with your permission. Only the members of the research tissue bank staff will know your child's identity. When the results of the research are published or discussed in conferences, no information will be included that would reveal your identity unless your specific consent for this activity is obtained.

Representatives from the Yale Human Investigation Committee, National Institutes of Health, Yale Center for Clinical Investigation, may inspect study records during internal auditing procedures. However, these individuals are required to keep all information confidential.

Voluntary Participation and Withdrawal

Participating in this study is voluntary. You and your child are free to choose not to donate samples to research and if your child does become a donor, you and your child are free to change your mind at any time, but the researchers may still use the information collected before you and your child changed your mind in order to complete the research that has already started.

Withdrawing from the study will involve no penalty or loss of benefits to which you or your child are otherwise entitled.It will not harm you or your child's relationship with your own doctors or Yale University or Yale-New Haven Hospital.

This form will never expire unless and until you change your mind and retract it. To retract the permission to use your child's information, please call Dr. Geoffrey Chupp at 203-785-3207.

Questions

We have used some technical terms in this form. Please feel free to ask about anything you don't understand and to consider this research and the consent form carefully—as long as you feel is necessary—before your make a decision.

Privacy Rights

The health-related information that we gather about your child in this study is personal. The researchers are required by law to protect the privacy of the information known as protected health information or PHI. All reasonable efforts will be made to protect the confidentiality of your child's PHI, which may be shared with others to support this research, to conduct public health reporting and to comply with the law as required. Despite these protections, there is a possibility that information about your child's information could be used or disclosed in a way that it will no longer be protected.

By signing this form, you give permission for the researchers to use and/or disclose the information for this research bank. You have the right to refuse to sign this form. Your child's health care outside the study, the payment for your child's health care, and your child's health care benefits will not be affected if you do not sign this form. If you do not sign this form, your child's samples will not be banked for research purposes.

CONTACT INFORMATION

The contact information of the subject or personal representative who signed this form should be filled in below.

Address: Telephone

_____

_____ daytime _____

_____ evening _____

_____

e-mail address optional

Authorization

I have read (or someone has read to me) this form and have decided to participate in the project described above. Its general purposes, the particulars of involvement and possible hazards and inconveniences have been explained to my satisfaction. By signing below, I give permission for the described uses and disclosures of information. My signature also indicates that I have received a copy of this consent/permission authorization form.

CHECK ONE:

___I wish to donate my child's leftover samples to the Yale Department of Pulmonary and Critical Care Department for research

___I do not wish to donate my child's leftover samples to the Yale Department of Pulmonary and Critical Care Department for research

_____ _____
Signature of Subject or Personal Representative Date

_____ _____
Print Name of Subject or Personal Representative Description of Representative

_____ _____
Signature of Principal Investigator Date Received

Or

_____ _____
Signature of Person Obtaining Consent Date

If you have further questions about this project, or if you have a research-related problem, you may contact the Principal Investigator, Geoffrey Chupp, MD @ 785-4198. If you have any questions concerning your child's rights as a research subject, you may contact the Human Investigation Committee at (203) 785-4688. If, after you have signed this form, you have any questions about your child's rights, please contact the Yale Privacy Officer @ (203) 436-3650.

THIS FORM IS NOT VALID UNLESS THE FOLLOWING BOX HAS BEEN COMPLETED BY THE YALE HUMAN INVESTIGATION COMMITTEE OFFICE

THIS FORM IS VALID ONLY UNTIL: _____

HIC PROTOCOL #: _____

INITIALED: _____

ADOLESCENT ASSENT FOR PARTICIPATION IN A RESEARCH PROJECT YALE UNIVERSITY SCHOOL OF MEDICINE-YALE-NEW HAVEN HOSPITAL

ESSENTIAL TESTING CONSENT ASSENT FORM (Ages 12-17)

Study Title: **Mechanisms and Mediators of Lung Disease**
Principal Investigator: **Geoffrey Chupp, MD**
Yale University School of Medicine
Department of Pulmonary and Critical Care Medicine
TAC S-441
PO Box 208057
New Haven, CT 06520-8057

Funding Source: **National Institute of Health, Yale Center for Clinical Investigation**

Invitation to Participate and Description of Project (Why would you like for me to participate in this study?)

You are invited to participate in a research study designed to investigate the development and natural history of lung disease. You have been chosen to participate because you either have lung disease such as asthma or have no history of lung disease, and you are age twelve or older. It is important for us to understand how people who do not have lung disease are different from people who do.

In order to decide whether or not you wish to be a part of this research study, you should know enough about its risks and benefits (how the study will help or might harm you) to make an informed judgment. This assent form provides detailed information about the research study that a member of the research team will discuss with you. This discussion should go over all aspects of this research: its purpose, the procedures that will be performed, any risk of the procedures, possible benefits and possible alternative treatments. Lung diseases can cause shortness of breath and progressive loss of lung function leading to death. This study is designed to understand the biologic pathways (molecules) that lead to lung disease.

Purpose (Why are they doing this study?): The purpose of this study is to investigate the development and natural history of lung disease by analyzing biological samples and measurements (blood, sputum, lung tissue and fluid) from subjects with or without lung disease over the course of time. We are determining the genes, molecules, and pathways that cause lung disease and how different genes, molecules, and pathways cause different types of lung disease. This will be done by comparing the different signals in patients with lung disease to each other and to patients without lung disease (controls). We will use several methods to do this. With a few tubes of blood, we can examine cells, serum, protein, and genes (DNA and RNA). Researchers in the lab will do the measurements on

samples provided by you from a blood, sputum and/or samples taken during the course of this study The following are examples of our research: **DNA/RNA analysis:** one way we will study lung disease will be to examine DNA/genetic material for abnormalities that can cause lung disease; **Protein:** another will be to examine the protein made by the DNA in serum, cells or tissue samples.

The researchers will obtain samples of your blood for various immunologic and cytokine (molecules produced by cells) analysis, including DNA (deoxyribonucleic acid), RNA (ribonucleic acid), cells and serum. DNA is a large chemical that carries our genetic or hereditary information. The genes are specific pieces of DNA that carry the instructions for making all the proteins that are found in a cell. A gene is like a strand of multicolored beads, and the gene will not function right if it has a mistake or a mutation in it, (for example, extra or missing beads). In addition, genes can act differently in different people if the beads are in a slightly different order or pattern. Experiments have shown that these slight differences in genes can affect either the way disease develops, the way drugs act on disease cells, or the way drugs are broken down by your body. Research using DNA is an important way to try to understand airways disease and the role genes play. RNA is a substance that translates DNA into proteins and is present at different levels in cells of your body. Your study doctor can give you more information on the genes being studied.

Description of Procedures (What procedures will I have to have? How long do they last?): If you agree to participate in this study, you will be asked to come to the Winchester Chest Clinic at Yale-New Haven Hospital, be seen in out-patient or in-patient areas of YNHH, Yale University Health Services, or be seen in your private physician's office at a convenient time.

During your first visit, we will obtain your assent to participate (using this form), a medical history, completion of a standardized questionnaire, and the collection of about a little more than one tablespoon of blood for genetic and various immunologic and cytokine (molecules produced by cells) testing. We may also do a pulmonary function (breathing) test that is explained below, urine chemistry testing for protein analysis, sputum collection, and exhaled breath condensate collection or breathalizer.
If you have lung disease, at additional visits, which may include an exacerbation of your lung disease, we may obtain a medical history focused on the stability of your lung disease, completion of a standardized questionnaire, a repeat blood draw (a little more than 1 tablespoon of blood), up to four times per year at your regular visits, and a breathing test to compare to your initial visit test. We may also ask you to participate in additional testing as mentioned in the first visit.

If you are sick enough to require a machine to help you breathe, (ventilator), we will collect a mucus specimen from the tube in your lung. These specimens are routinely collected throughout the day in patients on ventilators**.** However, if you are intubated, (on a ventilator), the investigator may want to perform a mini-BAL, which involves

placement of a special tube (catheter) just beyond the tip of the breathing (endotracheal) tube.

The procedure involved in obtaining blood specimens for laboratory analysis is conducted through the use of standard blood drawing methods by a highly trained nurse or technician. We will keep you as comfortable as possible during this procedure, and if you should develop a bruise or swelling at the blood-drawing site, we will apply ice to the site.

We may collect blood for laboratory medicine testing (chemistry and hematology), and if we do, we will share the results with you and/or your primary care physician. This may result in a follow-up if there are any significant abnormalities in the laboratory tests.

Collection of blood for genetic testing will be evaluated in the research laboratory of the Pulmonary Department of the Yale School of Medicine. The scope of this research is to study lung disease with a specific focus on airways disease. Personal information about your identity will be removed from the samples, (samples identified by a code number), and the person doing the tests will not know who you are. This is called "de-identification" of samples. (These tests are performed in Dr. Geoffrey Chupp's laboratory at the Yale School of Medicine, and Dr. Chupp may share this information with his collaborators in a "de-identified" manner). Your samples will be stored until they are exhausted or until you request withdrawal or destruction of your specimens. However, the data obtained from the specimens up to the point of withdrawal, will continue to be used. The results of the DNA tests will not be available to you, your family or your physician. We hope that these studies will lead to a further understanding of lung disease.

Urine for protein analysis will be evaluated in Dr. Chupp's laboratory in the Pulmonary Section.

Sputum collection by induction; we may ask you to deposit sputum you cough up spontaneously into a collection cup, or we may ask you to cough up sputum (lung fluid) from your lungs. This is called sputum induction. To begin, we will again do lung function testing. We will carefully watch your lung function and the amount of oxygen in your blood while we do the sputum induction. You will inhale a mist containing salt water, which will help you to cough up the sputum sample. This test will take place in our Research Room (LMP 5046), by personnel, trained for this procedure under the supervision of a physician.

Lung function testing is performed by highly trained technicians in the Pulmonary Function Laboratory at Yale-New Haven Hospital or the Research Room (LMP 5046), and involves breathing into a machine through a tube that measures lung function (while in a sitting position). You may also be asked to do plethysmography (another part of the breathing test), which involves shallow and deep breathing maneuvers that are performed

while seated in a clear box. At the conclusion of the breathing test, you will then be given a bronchodilator (a medicine that helps to open your airways) and the simple spirometry (breathing test) will be repeated to see if your lung function improves. A bronchodilator is available for you if you should experience a wheeze or cough during the procedure.

The results of the DNA tests will not be available to you, your family or your personal physician and your results will not be placed in your medical records. This information may only be available to the laboratory that performed the tests, collaborators, or possibly our Human Investigation Committee during the auditing process. Personal information about your identity will be removed from the samples and the person doing the blood test will not know who you are. Any excess material may be saved for future studies of the lung.

If you develop any problems possibly related to the procedures, you or your doctor may contact Dr. Geoffrey Chupp at the Division of Pulmonary and Critical Care, Yale School of Medicine (203) 785-4198 at any time.

Risks and Inconveniences (Will the any of the study procedures hurt?)

Blood drawing from your vein is very safe and will be performed by a highly trained nurse or technician according to standard blood drawing methods. A little more than 1 tablespoon will be taken at each time period; there may be mild pain or a bruise at the blood drawing site. You may feel dizzy or you may feel faint, but we will make every effort to make you as comfortable as possible.

The scope of the genetic analysis will be limited to studying lung disease. We will protect against disclosure (telling others) by storing specimens with a code number, called “de-identification” as described previously. Inadvertent disclosure (telling someone else by accident) of genetic information has the potential to cause anxiety to you or may pose other risks, such as your right to insurance and employment opportunities, or other unknown risks. Disclosure of this information could also cause people to have a certain view about you, or even a psychological response, and possibly divulge a biological relationship within your family, not previously known. We will not share this information with your primary physician or your family and access to study records will be limited to investigators on the study and the Human Investigation Committee (the committee that approves and monitors research studies). These individuals are required to keep all information confidential (private).

Sputum induction can cause wheezing, but you will be watched very carefully during this procedure. It is possible that this procedure will cause you to cough, which may cause some shortness of breath, but this test will be monitored closely and the procedure will be stopped if your breathing test appears to have decreased. This will be performed by a trained health professional, under the supervision of a physician.

The procedure of lung function, (breathing test) is performed in a sitting position for your safety, by a trained technician in the Pulmonary Function Laboratory at Yale-New Haven

Hospital, or the Research Room (LMP 5046), and occasionally, a subject may experience dizziness while performing the test, but this is usually temporary. Very rarely, people with airway disease may actually start to wheeze or cough following these tests. If this occurs, a bronchodilator (medicine to help open your airway) is available.

Benefits (Will the study help me?):
You should not expect to benefit directly from your participation in this study. However, these tests may yield medical information that could be useful for your health care, or the care of others with airways disease. The results of these tests will be given to you or sent to your personal physician (excluding the genetic information). Information obtained may help identify those at risk for lung disease or for lung disease you can control.

Economic Considerations (Will I be paid anything for being in this study?): You will be compensated for your participation in this study according to this compensation schedule:

1) $20 blood draw
2) $20 pulmonary function test
3) $20 sputum induction

If you participate fully in this study you could receive a maximum of approximately $60 for each time point if you complete all of the above testing procedures. Neither you nor your insurance company will be charged for any of the tests that are performed as a part of this research study.

Alternatives (What are my other choices besides participating in this study?):
The only alternative is to decline participation in the study.

Confidentiality (Will you keep all of my information private or confidential?):
Any identifiable information (information that can identify you) that is obtained in connection with this study will remain confidential and will be disclosed only with your permission or as required by US or State law. When the results of the research are published or discussed in conferences, no information will be included that would reveal your identity unless your specific consent for this activity is obtained.

We understand that information about you obtained in connection with your health is personal, and we are committed to protecting the privacy of that information. If you decide to be in this study, the researcher will get information that identifies you and your personal health information. This may include information that might directly identify you, such as your name, medical record number, or date of birth. This information will be de-identified at the earliest reasonable time after we receive it, meaning we will replace your identifying information with a code that does not directly identify you. The principal investigator will keep a link that identifies you to your coded information, and this link will be kept secure and available only to the PI or selected members of the research team. Any information that can identify you will remain confidential. We also

safeguard your confidentiality by storing research materials in a locked cabinet, and by using password-protected data entry. The research team will only give this coded information to others to carry out this research study. The link to your personal information will be kept until the research is completed, after which time the link will be destroyed and the data will become anonymous. The data will be kept in this anonymous form until it is destroyed.

The information about your health that will be collected in this study includes: the entire research records and any medical records held by Yale-New Haven Hospital created from February 2009 through the end of your participation in the study. Information about you and your health which might identify you may be used by or given to:

- The US Department of Health and Human Services (DHHS) agencies
- Representatives from Yale University and the Human Investigation Committee (the committee that reviews, approves, and monitors research on human subjects), who are responsible for insuring research compliance. These individuals are required to keep all information confidential
- Those individuals at Yale who are responsible for the financial oversight of research including billings and payments
- The Principal Investigator: Geoffrey L. Chupp, MD
- The National Institutes of Health
- Health care providers (doctors, nurses and technicians, etc.) who provide services to you in connection with this study
- Laboratories and other individuals and organizations that analyze your health information in connection with this study, according to the study plan
- Co-Investigators and other investigators
- Study Coordinator and Members of the Research Team
- Data and Safety Monitoring Boards and others authorized to monitor the conduct of the Study

You have the right to review and copy your health information in your medical record in accordance with institutional medical records policies.

In Case of Injury (What will happen if I am injured as a result of this study?):

If you are injured as a result of your participation in this study, treatment will be provided. You or your parent's insurance carrier will be expected to pay the costs of this treatment. No additional financial compensation for injury or lost wages is available. You do not give up your legal rights by signing this form.

Voluntary Participation and Withdrawal (Do I have to participate? Can I leave this study at any time?):

You are free to choose not to participate in this study. Your health care outside the study, the payment for your health care, and your health care benefits will not be affected if you do not agree to participate. However, you will not be able to enroll in this research study

and will not receive study procedures as a study participant if you do not allow use of your information as part of this study.

If you do become a subject, you are free to stop and withdraw from this study at any time during its course. If you sign this authorization, you may change your mind at any time, but the researchers may continue to use information collected before you changed your mind to complete the research. To withdraw, you can call a member of the research team at any time and tell them that you no longer want to take part. This will cancel any appointments in the future. You and your parents must also follow up your phone call by sending a written notice to revoke this authorization to the principal investigator (Geoffrey L. Chupp, MD TAC S-441 [complete address on page 1 of this consent form]).

The researchers may withdraw you from participating in the research if necessary. You are not required to complete all aspects of this trial, so if there are procedures that you are not comfortable with, you will not have to participate in them. The only exception is for a subset of 200 participants who will be asked to complete specific procedures to meet the requirements of our National Institute of Health grant. If you choose not to participate or if you withdraw, it will not harm your relationship with your own doctors or with Yale-New Haven Hospital.

Questions:

We have used some technical terms in this form. Please feel free to ask about anything you don't understand and to consider this research and the consent form carefully—as long as you feel is necessary—before you make a decision.

Authorization:

I have read (or someone has read to me) this form and have decided to participate in the project described above. Its general purposes, the particulars of involvement and possible hazards and inconveniences have been explained to my satisfaction. My signature also indicates that I have received a copy of this assent form. By signing this form, I give permission to the researchers to use [and give out] information about me for the purposes described in this form. By refusing to give permission, I understand that I will not be able to be in this research.

Name of Subject: _____

Signature:_____

Date:_____

_____ _____

Signature of Primary Investigator Date

or

_____ _____

Signature of Person Obtaining Consent Date

If you have further questions about this project or if you have a research related problem, you may contact the Principal Investigator, Geoffrey Chupp, MD at (203) 785-4198 or Carole Holm BSN, RN at (203) 737-4263. If you have any questions concerning your rights as a research subject, you may contact the Human Investigation Committee at (203) 785-4688. If, after you have signed this form, you have any questions about your privacy rights; please contact the Yale Privacy Officer at 203/436-3650.

THIS FORM IS NOT VALID UNLESS THE FOLLOWING BOX HAS BEEN COMPLETED IN THE HIC OFFICE

THIS FORM IS VALID ONLY UNTIL:
_____

HIC PROTOCOL #:
_____

INITIALED:
_____

AUTHORIZATION FOR DONATION OF EXCESS TISSUE
YALE UNIVERSITY SCHOOL OF MEDICINE

ASSENT FORM Ages 12-17

Title: Mechanisms and Mediators of Lung Disease

Principal Investigator: Geoffrey L. Chupp, MD

Funding Source: National Institutes of Health

Tissue Donation

You are invited to donate any tissue leftover from your participation in the main study, to a research tissue bank where it can be used for future research projects. The tissue collected in this bank is used by Yale University researchers to study different types of medical research.

In order to decide whether or not you wish to donate your tissue, you should know enough about its risks and benefits to make an informed decision. This form gives you information about the research bank and how the tissue is used. Once you understand the tissue donation and banking process, you will be asked if you wish to participate; if so, you will be asked to sign this form.

How Does the Tissue Get Into the Bank

The tissue samples include: blood and sputum. These samples are sent to the research laboratories in the Department of Pulmonary and Critical Care at Yale University School of Medicine. The samples are analyzed by the researchers for the Asthma and COPD (chronic obstructive pulmonary disease) project and will be used to study human health, if you agree to donate your tissue for future research. The following information about you will be entered into the database that tracks your samples: your name, the name of your physician, the date of your blood draw, sputum collection and your diagnosis. In most cases, the researchers will use your leftover samples in a de-identified manner. This means that they will use your samples without knowing who you are. In some cases, they may use information about you for research purposes, subject to an approval process.

Risks and Inconveniences (Will the donation of samples hurt or harm me?)

There are no known risks associated with donating your samples to research. You will not be required to give any more samples than that which will be taken at the time of the procedures for the study.

Benefits (Will the donation of samples help me?)

You will not receive any direct benefit from banking your samples into the bank. We hope that the information we learn in future research studies will increase our knowledge of human health and that this information will lead to better treatments in the future.

Economic Considerations (Will I be paid anything for donating my samples?)

You will not receive any payments for donating your samples to the research bank.

Confidentiality (Will you keep my information private?)

Any identifiable information that is obtained in connection with your samples will remain confidential and will be disclosed only with your permission. Only the members of the research tissue bank staff will know your identity. When the results of the research are published or discussed in conferences, no information will be included that would reveal your identity unless your specific consent for this activity is obtained.

Representatives from the Yale Human Investigation Committee, National Institutes of Health, Yale Center for Clinical Investigation, may inspect study records during internal auditing procedures. However, these individuals are required to keep all information confidential.

Voluntary Participation and Withdrawal (Do I have to donate my samples? If I donate my samples, can I change my mind?)

You are free to choose not to donate your samples to research and if you do become a donor, you are free to change your mind at any time, but the researchers may still use the information collected before you changed your mind in order to complete the research that has already started.

If you choose not to donate or if you withdraw your permission, it will not harm your relationship with your own doctors or Yale University or Yale-New Haven Hospital.

This form will never expire unless and until you change your mind and retract it. To retract the permission to use your information, please call Dr. Geoffrey Chupp @ 203-785-3207.

Questions

We have used some technical terms in this form. Please feel free to ask about anything you don't understand and to consider this research and the consent form carefully—as long as you feel is necessary—before you make a decision.

Privacy Rights

The health-related information that we gather about you in this study is personal. The researchers are required by law to protect the privacy of the information known as protected health information or PHI. All reasonable efforts will be made to protect the confidentiality of your PHI, which may be shared with others to support this research, to conduct public health reporting and to comply with the law as required. Despite these protections, there is a possibility that information about you could be used or disclosed in a way that it will no longer be protected.

By signing this form, you give permission for the researchers to use and/or disclose the information for this research bank. You have a right to refuse to sign this form. Your health care outside the study, the payment for your health care, and your health care benefits will not be affected if you do not sign this form. If you do not sign this form, your samples will not be banked for research purposes.

CONTACT INFORMATION

The contact information of the subject or personal representative who signed this form should be filled in below.

Address: Telephone

_____

_____daytime_____

_____evening_____

_____

e-mail address optional

Authorization

I have read (or someone has read to me) this form and have decided to participate in the project described above. Its general purposes, the particulars of involvement and possible hazards and inconveniences have been explained to my satisfaction. By signing below, I give permission for the described uses and disclosures of information. My signature also indicates that I have received a copy of this consent/authorization form.

CHECK ONE:

___ I wish to donate my leftover samples to the Yale Department of Pulmonary and Critical Care Department for research

___ I do not wish to donate my leftover samples to the Yale Department of Pulmonary and Critical Care Department for research

_____ _____

Signature of Subject or Personal Representative Date

_____ _____

Print Name of Subject or Personal Representative Description of Representative

_____ _____

Signature of Principal Investigator Date Received

Or

_____ _____

Signature of Person Obtaining Consent Date

If you have further questions about this project, or if you have a research-related problem, you may contact the Principal Investigator, Geoffrey Chupp, MD @ 785-4198. If you have any questions concerning your rights as a research subject, you may contact the Human Investigation Committee at (203) 785-4688. If, after you have signed this form, you have any questions about your rights, please contact the Yale Privacy Officer @ (203) 436-3650.

Yale Center for Asthma & Airways Disease Questionnaire Version 17

Study ID	_ _ _ - _ _ _
Visit Date	_ _ / _ _ /_ _ _ _ **MM DD YYYY**
Visit Number	**1 2 3 4 5 6**
Yale MRN	
Interviewer	
Consent Signed Date	_ _ / _ _ /_ _ _ _ **MM DD YYYY**
Participant's Last Name	
Participant's First Name	
Participant's Middle Initial	
D.O.B.	_ _ / _ _ /_ _ _ _ **MM DD YYYY**
Gender	**Male** **Female**
Address **Street** **Apartment Number**	_____ _____
City	
State	
Zip Code	
Home Phone	
Cell Phone	

PULMONARY HISTORY

1. How old were you when you first experienced pulmonary symptoms?	Age=_____ (If less than 1, enter 1)
2. At what age did a health care provider tell you that you had lung disease?	Age =_____ | N/A| Unknown
3. Where you working at the time?, if so what was your occupation	Yes No
Occupation	
4. What were you diagnosed with?	
5. Who do you see **primarily** for your lung problems now?	1 = General Practitioner/ your primary care doctor 2 = Pulmonologist 3 = Allergist 4 = Other → Write in _____ 5 = Not seeing anyone
6. After age of diagnosis (above answer) did you ever experience a time when your lung symptoms went away (for a period greater than a year)?	Yes → go to number **7** No → skip to question **10**
7. Describe the interval free of symptoms (to be expressed in years)	Age from ____ to _____
8. Was there a main trigger when your lung disease symptoms returned?	Yes No
9. What was your main trigger when the symptoms returned?	Respiratory infection Exposure Change of household Work place related Other
10. How many urgent clinic/office or Emergency Department visits have you had for worsening pulmonary symptoms in the past year?	# of urgent/ ED visits = ___
11. In the past year, how many courses of steroids did you have?	
12. When did you complete your last course of steroids?	(weeks)
13. Are you currently being treated with oral corticosteroids for a flare of your disease?	Yes No
14. Are you currently being treated with antibiotics for a flare of your disease?	Yes No→ if no go to q16
15. How many days ago did the flare start?	(Days)
16. Have you been treated with antibiotics recently? If No skip to question 18	Yes No
17. If you completed antibiotics recently, when was the course completed	(weeks)
18. How many hospitalizations have you had for pulmonary disease in the past year?	# of hospitalizations = ___
19. How many hospitalizations have you had for pulmonary disease in your lifetime?	# of hospitalizations = ___
20. How many ICU admissions have you had for pulmonary disease in the past year?	# of ICU admissions = ___
21. How many ICU admissions have you had for pulmonary disease in your lifetime?	# of ICU admissions = ___

22. Have you ever been intubated?	Yes, If so how many times__ No
23. Have you been intubated (ie placed on a ventilator/respirator) in the past year?	Yes No
24.Have you experienced an increase in your asthma symptoms over the last week?	Yes No

25. If so how severe is the change from your baseline (scale)

1 2 3 4 5 6 7 8 9 10

MENSES RELATED ASTHMA SYMPTOMS

If male gender skip to question 32

26.Is worsening of your asthma symptoms ever associated with menstruation?	Yes No Not applicable
27. How many weeks ago was your menstrual period? _____	Not applicable
28. Do you use any form of hormonal contraception?	Yes No
29. If menopausal, do you use any form of hormone replacement therapy? (Can also be applied if the ovaries have been removed)	Yes No
30. Have you experienced any change in your asthma symptoms while pregnant?	1. I have never been pregnant 2. My asthma improved during pregnancy 3. My asthma worsened during pregnancy 4. My asthma was the same during pregnancy 5. Not applicable
31. If pregnant in the past, did you take the same, more or less asthma medication while you were pregnant?	1. The same | 3. More 2. Less | 4. Not applicable

EXERCISE RELATED ASTHMA SYMPTOMS

32. Does your asthma limitsyour activities of daily living? (ie. Dressing, eating, walking, climbing stairs, carrying weight)	Yes No
33.Do you experience worsening of your asthma symptoms when you exercise?	Yes No
34. If so what kind of exercise **(If the patient describes ADLS, please skip to question 35)**	
35. Do you experience worsening of your asthma symptoms when exposed to cold weather? **(This is an exercise induced asthma only response, no ADLS)**	Yes No

COMORBIDITIES

SINUS HISTORY	Self-Report Yes=Y No = N	
36. Do you have a history of sinus disease?	Y | N→ If No skip to Q 43	
37. Are you taking any medications for sinus disease	Y N	
38. Number of antibiotic courses for your sinuses in the last year	[redacted]	# =
39. CT scan with evidence of chronic sinusitis changes	Y N	√ EMR Y N
40. Do you have a history of nasal polyps?	Y N	
41. Have you had any surgeries for your sinuses?	Y N	how many?# =
42. Is your sinus disease controlled?	Y N	

GERD HISTORY	Self-Report Yes=Y No=N	
43. Do you have a history of GERD?	Y | N → If No skip to Q 52	
44. How many days a week you experience symptoms?	[redacted]	#
45. Do you take medications for GERD?	Y N	
46. How often you take medications for GERD?	[redacted]	
47. Endoscopy with evidence of changes consistent with GERD	Y N	
48. Laryngoscopy with evidence of changes consistent with GERD	Y N	
49. Any esophageal probe (pH, esophageal manometry, other)	Y N	
50. Surgery for GERD	Y N	
51. Is your GERD controlled?	Y N	

ALLERGIES/RHINITIS HISTORY	Self-Report Yes = Y No = N	
52. Do you have allergies/rhinitis?	Y N→ If No skip to Q 56	
53. Do you take medications for your allergies/rhinitis?	Y N	
54. Have you ever received any allergy shots? (immunotherapy)	Y N	
55. Are you currently receiving allergy shots?	Y N	
56. Have you had anaphylaxis in the past?	Y | N → If No skip to Q 60	
57. If anaphylactic reaction, what was it to?	[redacted]	Name | N/A
58. Do you use antihistamines for your allergies?	Y | N → If No skip to Q 60	
59. Do you take antihistamines daily or as needed?	Daily	As needed
60. Allergy skin prick tests. If yes, include report	Y N	
61. RAST testing. If yes, list results	Y N	
62. Are your allergies under control?	Y N	

Allergies

63. Are you allergic to any medication?	Y | N | Multiple Meds (>3) |Name up to three:	
64. Are you allergic to any vaccine?	Y | N | N/Applicable	Name
65. Do your pulmonary symptoms get worse with aspirin or non-steroidal anti-inflammatory drugs (NSAIDS) like Advil (ibuprofen) or Aleve (Naproxen)?	Y | N	

Immunizations

66. When was your last influenza vaccination?	**Mo**	**|Yr**	**N/A**	**No**
67. When was your last H1N1 Vaccination?	**Mo**	**|Yr**	**N/A**	**No**
68.When was your last pneumonia vaccination? At leastYear	**Mo**	**|Yr**	**N/A**	**No**

MEDICATION COMPLIANCE AND PERCEPTION

69. Do you believe you are able to take your asthma medications as directed.? (ATAQ)	Y N
70.Do you believe your asthma medications are useful in controlling your asthma? (ATAQ)	Y N

71. Which of the following statements best describes how you took your asthma controller medications last week?	Prior Week Adherence 1. I took my asthma controller medications every day 2. I missed doses of my asthma controller medications 1-2 days 3. I missed doses of my asthma controller medications 3-4 days 4. I missed doses of my asthma controller medications 5-6 days 5. Not applicable
72. In general, which of the following statements best describes how you take your asthma controller medications?	General Adherence 1. Less than 25% of the time 2. 25% to 49% of the time 3. 50% to 74% of the time 4. More than 75% of the time 5. Not applicable

ASTHMA MEDICATIONS

Corticosteroids

73. Do you take oral steroids daily as part of your maintenance therapy?	Yes No

Oral Corticosteroid Name	Formulation	Dose (mg)	Total Dose

Inhaled Corticosteroids

Drug	Brand Name	Formulation	Dose (ug)	Total Daily Dose
Beclomethasone	Qvar	MDI-HFA	40 or 80	
Budesonide	Pulmicort	DPI or solution for nebs	90 or 180 Neb: 250 or 500	
Ciclesonide	Alvesco	MDI-HFA	80 or 160	
Fluticasone	Flovent	MDI-HFA or DPI	MDI-HFA 44,110,220 DPI 50 or 100	
Mometasone	Asmanex	DPI	110 or 220	

Inhaled Corticosteroids in Combination with LABA

Drug	Brand Name	Formulation	Dose (ug)	Total Daily Dose
Budesonide with formoterol	Symbicort	MDI-HFA	80 or 160 (with 4.5 ug of formoterol	
Fluticasone with salmeterol	Advair	MDI-HFA or DPI	MDA-HFA 45, 115, or 230 with 21 ug of salmeterol DPI 100, 250,500 with 50 ug of	

			salmeterol	

Inhaled Long-Acting B-Agonist Bronchodilators

Drug	Brand Name	Formulation	Dose (ug)	Total Daily Dose
Arformoterol	Brovana	Liquid for aerosolization	15/vial	
Formoterol	Foradil	Single dose DPI	12/capsule	
	Performist	Liquid for aerosolization	20/vial	
Salmeterol	Serevent	DPI	50/inhalation	

Leukotriene Modifiers

Drug	Brand Name	Formulation	Dose (mg)	Total Daily Dose
Montelukast	Singulair	Granules, chewable tabs, or tabs	Granules 4 Chew Tabs 4 or 5 Tabs 10	
Zafirlukast	Accolate	Tablets	10 or 20	
Zileuton	Zyflo	Extended Release Tabs	600	

Short Acting Beta Agonist

Drug	Brand Name	Formulation	Dose (mg)	Total Daily Dose
Albuterol		MDI		
Albuterol		Nebulized		
Other				

Anticholinergics

Drug	Brand Name	Formulation	Dose (mg)	Total Daily Dose
Ipratropium	Atrovent			
Tiotropium	Spiriva			
Ipratropium & Albuterol	Combivent			
Ipratropium & Albuterol	Duoneb			

Biologic Modifier

Drug	Brand Name	Formulation	Dose (mg)	Total Dose
Omalizumab	Xolair			
Mepolizumab				

Methylxanthines

Drug	Brand Name	Formulation	Dose (mg)	Total Dose
Theophylline	Theodur			

Nasal Inhalers

Drug	Brand Name	Formulation	Dose (mg)	Total Dose
Fluticasone	Flonase			
Mometasone	Nasonex			
Budesonide	Rhinocort			
Omnaris	Ciclesonide			
Ipratropium nasal	Atrovent nasal			
Other				

GERD medications

Drug	Brand Name	Formulation	Dose (mg)	Total Dose
Pantoprazole	Protonix			
Esomeprazole	Nexium			
Rabeprazole	Aciphex			
Lansoprazole	Prevacid			
Omeprazole	Prilosec			
Ranitidine	Zantac			
Famotidine	Pepcid			
Other				

Antihistamines

Drug	Brand Name	Formulation	Dose (mg)	Total Dose
Loratadine	Claritin			
Hydroxyzine	Vistaril			
Fexofenadine	Allegra			
Cetirizine	Zyrtec			
Desloratadine	Clarinex			
Pseudoephedrine	sudafed			
Other				

Inhaled Medication

Drug				
DNAse				
Pulmozyme				
Aztreonam				
Tobramycin (Tobi)				
Other				

74. Do you use a spacer?	Y N		
75. Do you use a nebulizer?	Y N		Frequency

76. Do you use supplemental oxygen	Y N	How many L/min	Frequency

Alternative Therapies

77. Do you use any Alternative Therapies for asthma? (ie. Yoga/herbal/other)	Y N	o Yoga o Herbal o Nasal saline o Acupuncture o Other	

78. Select **ONE** of the statements that best describes your thinking or behaviors related to your asthma today? . (Prochaska – change processes)

1. I have taken an interest in learning more about asthma.
2. I have been thinking about how I take care of my asthma and how I might change.
3. I have been thinking about how my asthma affects my family.
4. I have told my family about my intentions to change how I take care of my asthma.
5. I talk to others with asthma and make suggestions about how they might improve.
6. I reward myself when I reach personal goals related to my asthma.
7. I have made major changes in my life to reduce my exposure to known triggers.
8. I really have not thought about or done any of these things at this time.

Change Process =_____

OBESITY HISTORY	Self-Report Yes=Y No=N
79. How would you describe your weight before age 18	☐Low weight ☐Normal ☐Overweight ☐Obese
80. Do your pulmonary symptoms worsen with a weight gain of more than 10 lbs? If No skip to Q **84**	Y N N/A
81. Did your pulmonary symptoms improve after weight loss?	Y N N/A
82. Have you ever had bariatric surgery – gastric bypass or lap-band, if No skip to question **84**	Y N
83. Did you experience any change on your pulmonary symptoms after the obesity surgery?	Y N

Have you ever been told by a health care provider that you have any of the following illnesses/conditions? If Yes, list medications. Only check on the self report box if yes

Illness/Condition	Self-Report	Medical Record Confirmation	**Medications**
	Check only if yes	Check only if yes	
84. Heart Disease	☐	☐	
85. Hypertension	☐	☐	
86. Elevated Cholesterol	☐	☐	
87. Stroke	☐	☐	
88. Diabetes	☐	☐	
89. Liver Disease	☐	☐	
90. Sleep apnea	☐	☐	[redacted]
91. CPAP/BIPAP Machine Use?	☐	☐	
92. Seizure	☐	☐	
93. Birth defects	☐	☐	
94. Kidney disease	☐	☐	
95. Kidney stones	☐	☐	
96. Bleeding Problems	☐	☐	
97. Rheumatologic disorders (ie. Rheumatoid arthritis, lupus)	☐	☐	
98. Do you take any biologic response modifiers/biologics (e.g. Enbrel, Humira, Remicade, Orencia?)	☐	☐	
99. Are you taking any immunosuppressants? (cellcept, tacrolimus, sirolimus, cyclosporine)			
100. Thyroid Disease	☐	☐	
101. Cancer	☐	☐	Type Chemo XRT
102. Chronic Viral Infections/HIV	☐	☐	
103. Other	☐	☐	
104. Surgical history	☐	☐	If so list surgeries

Organ Transplantation

Have you ever had an organ or bone marrow transplantation? If no skip to question **109**

Organ Transplantation	Self-Report	Medical Record Confirmation	**Medications**
	Check only if yes	Check only if yes	
105. Bone Marrow	☐	☐	
106. Stem Cell	☐	☐	
107. Solid Organ	☐	☐	
108.Which organ?	☐	☐	

ENVIRONMENTAL EXPOSURES

109. Which of the following best describes where you lived most of the time until age 18.	1. In a rural area (countryside) 2. Outside of a city (suburban) 3. In a city (urban)
110. Which of the following best describes where you lived most of the time after age 18?	1. In a rural area (countryside) 2. Outside of a city (suburban) 3. In a city (urban)
111. What locations make your asthma symptoms worse? Select all that apply.	1 = Home 2 = Work 3 = Outdoors 4 = Other (list location) _____ 5 =Not applicable (not worse)
112. What are your hobbies?	
113. Do you currently have any exposure to the following in your home? If yes, does it make your asthma worse?	

Exposures	**Current**	**Previous**	**Frequency**	**Does it make your asthma worse?**
	Check if Yes	Check if Yes		Yes = Y No = N Unknown =N/A
Mold	☐	☐	Daily Few days a week Few times a month Few times a year Never	N | Y | N/A
History of Pipe or Roof Leaks	☐	☐	Daily Few days a week Few times a month Few times a year Never	N | Y | N/A
Dampness /Wet or Damp Basement/Crawlspace	☐	☐	Daily 1-6 days a week	N | Y | N/A

			Weekly Monthly 2-11 Months Never	
Radiator/Baseboard	☐	☐	Daily 1-6 days a week Weekly Monthly 2-11 Months Never	N | Y | N/A
Wood Burning Stove, fireplace	☐	☐	Daily 1-6 days a week Weekly Monthly 2-11 Months Never	N | Y | N/A
Gas Stove	☐	☐	Daily 1-6 days a week Weekly Monthly 2-11 Months Never	N | Y | N/A
Kerosene Heater	☐	☐	Daily 1-6 days a week Weekly Monthly 2-11 Months Never	N | Y | N/A
Cigarette Smoke, cigar smoke or pipe	☐	☐	Daily 1-6 days a week Weekly Monthly 2-11 Months Never	N | Y | N/A
Wall to wall carpet	☐	☐	Daily 1-6 days a week Weekly Monthly 2-11 Months Never	N | Y | N/A
Dust	☐	☐	Daily 1-6 days a week Weekly Monthly 2-11 Months Never	N | Y | N/A

Animals	☐	☐	Daily 1-6 days a week Weekly Monthly 2-11 Months Never	N | Y | N/A
Cat	☐	☐	Daily 1-6 days a week Weekly Monthly 2-11 Months Never	N | Y | N/A
Dog	☐	☐	Daily 1-6 days a week Weekly Monthly 2-11 Months Never	N | Y | N/A
Bird	☐	☐	Daily 1-6 days a week Weekly Monthly 2-11 Months Never	N | Y | N/A
Other Pet	☐	☐	Daily 1-6 days a week Weekly Monthly 2-11 Months Never	N | Y | N/A

114. "Have you used any of the following products? ***If yes how often?***
If yes, does it make your asthma worse?"

Product examples	**Current**	**Previous**	**Frequency**	**Does it make your asthma worse?**
	Check if Yes	Check if Yes		Yes = Y No = N Unknown =N/A
Cleaning products (ie. Disinfectant, chlorine bleach, carpet cleaner, oven cleaner, window or glass cleaner)	☐	☐	Daily Few days a week Few times a month Few times a year Never	N | Y | N/A
Personal care products (ie.Hairspray, hair coloring products, hair bleaching products)	☐	☐	Daily Few days a week Few times a month Few times a year Never	N | Y | N/A
Air Fresheners – spray, stick, aerosol, plug-in, other	☐	☐	Daily Few days a week Few times a month Few times a year Never	N | Y | N/A
Perfumes or Fragrances	☐	☐	Daily Few days a week Few times a month Few times a year Never	N | Y | N/A
Home maintenance and repair products (ie. Turpentine, paint thinner, paint or varnish, Home insulation products)	☐	☐	Daily Few days a week Few times a month Few times a year Never	N | Y | N/A
Glues or adhesives	☐	☐	Daily Few days a week Few times a month Few times a year Never	N | Y | N/A
Polyurethane	☐	☐	Daily Few days a week Few times a month Few times a year Never	N | Y | N/A
Pesticides / Insect Killers	☐	☐	Daily Few days a week Few times a month Few times a year Never	N | Y | N/A

EMPLOYMENT

115. Which of the following best describes your **current employment situation**?	**If 1,2 or 3 is checked go to 116** **If 4-10 is checked go to 117** 1= Working full time 2 = Working part time 3 = On leave, but still employed 4 = Temporarily laid off 5 = Unemployed and able to work – looking for work 6 = Unemployed – unable to work – disability related to lung disease 7 = Unemployed – unable to work – disability unrelated to lung disease 8 = Student, not working 9 = Full time mother/homemaker/caregiver 10 = Retired
116. If working, what is your current work title?	
117. Thinking about your **longest held or most typical employment**: what kind of work do/did you do?	
118. How **many years**, did or have you work(ed) in the job above? (If < 1 yr, enter decimal)?	# of Years
119. Is your asthma worse at work?	Yes No N/Applicable
120. Is yout asthma better away from work?	Yes No N/Applicable

WORKPLACE TRIGGERS / EXPOSURES

The following is a list of common substances in the workplace that can cause occupational asthma.

121. Do you currently have or have you had any exposure to the following at work? If yes, did or does it make your asthma worse?

Substances	Check if Yes	Current	Previous	Unknown	Does it make your asthma worse? Yes = Y / No = N / Not applicable=N/A
Chemicals	☐				N | Y | N/A
Cleaning products	☐				N | Y | N/A
Dust, fumes, vapors	☐				N | Y | N/A
Mold	☐				N | Y | N/A
Poor ventilation	☐				N | Y | N/A
Isocyanates	☐				N | Y | N/A
Foam coating	☐				N | Y | N/A
adhesives	☐				N | Y | N/A
polyurethane	☐				N | Y | N/A
Construction	☐				N | Y | N/A

Substances	Check if Yes	Current	Previous	Unknown	Does it make your asthma worse? Yes = Y / No = N / Not applicable=N/A
Welding machines	☐				N | Y | N/A
Animals	☐				N | Y | N/A
Agricultural products	☐				N | Y | N/A
Farm exposure	☐				N | Y | N/A
122. Are there any other WORKPLACE triggers or exposures that make your asthma worse?					

TOBACCO HISTORY

CIGARETTES	
123. Did you ever smoke cigarettes? If No, Skip to question **132**	Yes No
124. At what age did you start to smoke cigarettes?	
125. Are you currently smoking cigarettes? If No go to question **127**	Yes No
126. If smoking, how many cigarettes do you smoke per day?	Number of Cigarettes _____
127. If you quit smoking, at what age did you quit?	Age =
128. How many cigarettes were you smoking per day when you were smoking the most?	Number of Cigarettes
129. Total number of pack years	Number
130. Did your pulmonary symptoms start before or after starting to smoke cigarettes?	Before Starting to Smoke Cigarettes After Starting to Smoke Cigarettes
131. Does or did smoking cigarettes make your asthma worse?	Yes No

CIGARS	
132. Did you ever smoke cigars? If No, Skip to question **140**	Yes No
133. At what age did you start to smoke cigars?	Age
134. Are you currently smoking cigars? If No go to question **136**	Yes No
135. If smoking, how many cigars do you smoke per day?	Number of Cigars
136. If you quit smoking cigars, at what age did you quit?	Age =
137. How many cigars were you smoking per day when you were smoking the most?	Number of Cigars
138. Did your pulmonary symptoms start before or after starting to smoke cigars?	Before Starting to Smoke Cigars After Starting to Smoke Cigars

139. Does or did smoking cigars make your asthma worse?	Yes No

PIPE		
140. Did you ever smoke a pipe? If No, Skip to question **148**	Yes No	
141. At what age did you start to smoke a pipe?	Age =	
142. Are you a currently smoking a pipe? If No go to question **144**	Yes No	
143. If smoking, how many bowls of pipe tobacco do you smoke per day?		# of Bowls
144. If you quit smoking a pipe, at what age did you quit?	Age =	
145. How many bowls were you smoking per day when you were smoking the most?	Number of Bowls	
146. Did your pulmonary symptoms start before or after starting to smoke a pipe?	Before Starting to Smoke a Pipe=1 After Starting to Smoke a Pipe = 2	
147. Does or did smoking a pipe make your asthma worse?	Yes No	

Second Hand and Other Smoke Exposures	
148. Were you ever exposed to second hand smoke for at least 4 hours per day?	Never Exposed = 1 Currently Exposed = 2 Previously Exposed = 3
149.Where were you exposed to second hand smoke?	1=Home 2=Work 3=Other
150. How many years were you exposed to second hand smoke?	Number of years
151. Did you ever smoke anything else on a regular basis (ie. Marijuana, cocaine)	Never = 1 Currently = 2 Previously = 3
152. Write in the name of the substance	
153. How often were you smoking? (write in frequency in years)	

SELF & FAMILY RACE AND ETHNICITY

154. Are you adopted?	Yes No
155. Are you a twin?	Yes No
156. If you are a twin, are you an identical twin?	Yes No Uncertain

157. Fill in race and ethnicity in the table below using the categories below.

How would you describe the race and ethnicity of yourself and your ancestors? (Record all that apply)	1=White/Caucasian 2=Black or African-American 3=American Indian or Alaska Native 4=Asian 5=Pacific Islander 8=Other
Are you or your ancestors Hispanic or Latino origin?	A=Yes B= No
Specify country of origin, is more informative than the race/Census description	

Race and Ancestral Country of Origin (ACO)

	Race	**Ancestral (racial diversity) country of origin**
Self		
Mother		
Maternal Grandmother		
Maternal Grandfather		
Father		
Paternal Grandmother		
Paternal Grandfather		

158. FAMILY HISTORY: ASTHMA and ASTHMA RELATED CO-MORBIDITIES

Yes No

Please check for Yes

	MOTHER	**FATHER**
Asthma	☐	☐
Intubation for asthma	☐	☐
Fatal Asthma	☐	☐
Allergies or eczema	☐	☐
COPD/emphysema	☐	☐
Lung cancer	☐	☐
Cystic fibrosis	☐	☐
Cystic fibrosis carrier	☐	☐
Sarcoidosis	☐	☐
Interstitial lung disease	☐	☐

	Sibling 1	**Sibling 2**	**Sibling 3**	**Sibling 4**
Gender (Male/Female)	M F	M F	M F	M F
Half brother/sister	☐	☐	☐	☐
Asthma	☐	☐	☐	☐
Intubation for asthma	☐	☐	☐	☐
Fatal Asthma	☐	☐	☐	☐
Allergies or eczema	☐	☐	☐	☐
COPD/emphysema	☐	☐	☐	☐
Lung cancer	☐	☐	☐	☐
Cystic fibrosis	☐	☐	☐	☐
Cystic fibrosis carrier	☐	☐	☐	☐
Sarcoidosis	☐	☐	☐	☐
Interstitial lung disease	☐	☐	☐	☐

	Child 1	**Child 2**	**Child 3**	**Child 4**
Gender (Male/Female)	M F	M F	M F	M F
Asthma	☐	☐	☐	☐
Intubation for asthma	☐	☐	☐	☐
Fatal Asthma	☐	☐	☐	☐
Allergies or eczema	☐	☐	☐	☐
COPD/emphysema	☐	☐	☐	☐
Lung cancer	☐	☐	☐	☐
Cystic fibrosis	☐	☐	☐	☐
Cystic fibrosis carrier	☐	☐	☐	☐
Sarcoidosis	☐	☐	☐	☐
Interstitial lung disease	☐	☐	☐	☐

SOCIOECONOMIC	
159. What is your current marital status?	1 = Married 2 = Divorced 3 = Separated 4 = Widowed 5 = Never married 6 = Not available/declined
160. What is your family's gross income?	1 = Less than $19,999 2 = $20,000 to $39,999 3 = $40,000 to $59,000 4 = $60,000 to $99,000 5 = Over $100,000 6= Not available/declined
161. Please indicate which of the following best describes your educational level:	1 = Grade 8 or less 2 = Some High School 3 = High School Graduate 4 = College Graduate 5 = Graduate Education

End of Participant Interview

CLINICAL DATA - to be completed by staff

Airflow Obstruction Category

1	Spirometry with BD response; documented > in FEV1 ≥ 12%
2	Positive methacholine challenge; documented by PC20
3	PEF diurnal variability ≥ 20%; documented by MD
4	≥ 12% improvement in FEV1 after treatment with ICS or OCS; documented by MD/PFTs
5	Persistent obstruction defined as FEV1/FVC ratio less than LLN
0	None of the above

PHYSICIAN DESIGNATED STUDY GROUP CODE

Check all that apply

Group Code	Participant Designation	Definitions
1 = Control	☐	≤ 10 pack years smoking, no pulmonary symptoms or history of pulmonary disease
2 =Smoker Control	☐	> 10 pack years smoking, no pulmonary symptoms or history of pulmonary disease
3 = Asthma	☐	≤ 10 pack years smoking, symptoms/clinical picture compatible per MD
4 = COPD	☐	> 10 pack years smoking, symptoms, compatible per MD; NOTE DOES NOT NEED FEV1/FVC RATIO < 70%, GOLD class 0 included in this group
5 =Asthma/COPD	☐	>10 pack years smoking, but also with symptoms compatible with asthma per MD which PRE-DATE smoking; any FEV1/FVC ratio permissible
6 =Exercise Induced Bronchospasm	☐	Symptoms compatible with EIB per MD; subjects must be only treated for EIB, if also treated for persistent asthma,then select **3**
7 =Cough Variant Asthma	☐	Symptoms compatible per MD; cough should be primary or only symptom. Normal lung function.
8 =Sampter's Syndrome	☐	Physician documents asthma, nasal polyps and ASA allergy
9 =Alpha-1 Antitrypsin deficiency	☐	MD confirmed based on documentation.
10 = ABPA	☐	MD confirmed based on documentation.
11 =Churg Strauss	☐	MD confirmed based on documentation.
12 =Cystic Fibrosis	☐	MD confirmed based on documentation.
13 =Chronic eosinophilic pneumonia	☐	MD confirmed based on documentation.
14 =Bronchiectasis	☐	CT documentation
15 = Bronchiolitis Obliterans	☐	MD confirmed based on documentation.
16 = Pulmonary Hypertension	☐	MD confirmed based on documentation.
17 = ILD	☐	MD confirmed based on documentation.
18 = OSA/OHS	☐	MD confirmed based on documentation.
19=Work related asthma	☐	Symptoms are exacerbated by work and/or the diagnosis of asthma is compatible with occupational asthma
20 = Other	☐	All subjects with primary pulmonary pathology, not listed above, or with significant overlap between 2 or more diagnoses. List known or suspected diagnoses

First study group code _____ Second study group code _____
Third study group code _____ Fourth study group code _____

Classification	Criteria	Check all that apply
MILD	SABA only or ICS ≤ 200 mcg fluticasone per day or equivalent	
MODERATE	Daily ICS > 200 but < 880 fluticasone or equivalent AND does not meet Severe criteria	
SEVERE	*One Major & Two Minor Criteria Required*	
Major Criteria	On oral steroids ≥ 50% of the year	
	On high dose inhaled steroids ≥ 880 mcg/day fluticasone	
Minor Criteria	Daily LABA, theophylline or LTA	
	SABA use ≥ 3 days/wk other than for exercise	
	Persistent Obstruction (FEV1< 80%; diurnal PEF variability > 20%	
	Any urgent visits, ER visits, or hospitalizations in the past year	
	More than 2 steroid tapers in the past year	
	Prompt deterioration with ≤ 25% reduction in steroid use	
	Near fatal event (intubation) in past	

Yale Center for Asthma & Airways Disease Questionnaire Version 17-Pedi

Study ID	_ _ _ - _ _ _
Visit Date	_ _/ _ _/_ _ _ _ MM DD YYYY
Visit Number	1 2 3 4 5 6
Yale MRN	
Interviewer	
Consent Signed Date	_ _/ _ _/_ _ _ _ MM DD YYYY
Participant's Last Name	
Participant's First Name	
Participant's Middle Initial	
D.O.B.	_ _/ _ _/_ _ _ _ MM DD YYYY
Gender	Male Female
Address Street Apartment Number	_____ _____
City	
State	
Zip Code	
Home Phone	
Cell Phone	

Study Group: ___ Asthma ____ Control

Tonsillectomy Indication:

1. Airway obstruction (including OSA)
2. Chronic/Recurrent Infection
3. Peritonsillar Abscess
4. Rule out neoplastic pathology
5. Other

PULMONARY HISTORY

1. How old was your child when he/she first experienced pulmonary symptoms?	Age=_____ (If less than 1, enter 1)
2. At what age did a health care provider tell you that your child had Asthma?	Age =_____ | N/A| Unknown
3. For Patients who WORK: Where you working at the time?, if so what was your occupation Likely NA	Yes No NA
Occupation	
4. What were you diagnosed with?	
5. Who do you see **primarily** for your lung problems now?	1 = Pediatrician/ your primary care provider 2 = Pulmonologist 3 = Allergist 4 = Other → Write in _____ 5 = Not seeing anyone
5a. What is the most important trigger for your child's asthma?	Respiratory infection Seasonal allergies Home exposures Environmental exposures Exercise Other
5b. Which of the following are triggers for your child's asthma?	Respiratory infection Seasonal allergies Home exposures Environmental exposures Exercise Other
6. After age of diagnosis (above answer) did your child ever experience a time when his/her asthma symptoms went away (for a period greater than a year)?	Yes → go to number **7** No → skip to question **10**
7. Describe the interval free of symptoms (to be expressed in years)	Age from ____ to _____
8. Was there a main trigger when the lung disease symptoms returned?	Yes No
9. What was the main trigger when the symptoms returned?	Respiratory infection Exposure Change of household Work place related Other (allergy)
10. How many urgent clinic/office or Emergency Department visits has your child had for worsening pulmonary symptoms in the past year?	# of urgent/ ED visits = ___
11. In the past year, how many courses of steroids did your child have?	
12. When did he/she complete the last course of steroids?	(weeks)
13. Is your child currently being treated with oral corticosteroids for a flare of his/her disease?	Yes No
16. Has your child been treated with antibiotics recently? If No skip to question 18	Yes No
17. If you completed antibiotics recently, when was the course completed	(weeks)

18. How many hospitalizations has your child had for Asthma in the past year?	# of hospitalizations = ___
19. How many hospitalizations has your child had for asthma in his/her lifetime?	# of hospitalizations = ___
20. How many ICU admissions has your child had for asthma in the past year?	# of ICU admissions = ___
21. How many ICU admissions has your child had for Asthma in his/her lifetime?	# of ICU admissions = ___
22. Has your child ever needed a breathing tube because of an asthma attack?	Yes, If so how many times__ No
23. Has your child been intubated because of asthma (ie placed on a ventilator/respirator) in the past year?	Yes No
24.Have your child experienced an increase in his/her asthma symptoms over the last week?	Yes No

25. If so how severe is the change from your baseline (scale)

1 2 3 4 5 6 7 8 9 10

MENSES RELATED ASTHMA SYMPTOMS

If male gender or child is prepubertal skip to question 32

26.Is worsening of your asthma symptoms ever associated with menstruation?	Yes No Not applicable
27. How many weeks ago was your menstrual period? _____	Not applicable
28. Do you use any medication with hormones including a birth control ?	Yes No

EXERCISE RELATED ASTHMA SYMPTOMS

32. Does your child's asthma limit his/her activities of daily living? (ie. Dressing, eating, playing, walking, climbing stairs)	Yes No
33.Does your child experience worsening of his/her asthma symptoms when he/she exercises?	Yes No
34. If so what kind of exercise **?**	
35. Does your child experience worsening of your asthma symptoms when exposed to cold weather and exercising?	Yes No

COMORBIDITIES

SINUS HISTORY	Self-Report Yes=Y No = N	
36. Does your child have a history of sinus disease?	Y | N→ If No skip to Q 43	
37. Does your child take any medications for sinus disease	Y N	
38. Number of antibiotic courses for your child's sinuses in the last year	[redacted]	# =
39. CT scan with evidence of chronic sinusitis changes	Y N	√ EMR Y N
40. Does your child have a history of nasal polyps?	Y N	
41. Has your child had any surgeries for his/her sinuses?	Y N	how many?# =
42. Is your child's sinus disease controlled?	Y N	

42a. EAR HISTORY – frequency of ear infections in past 12 months
42b. # antibiotic courses for ear infections in past 12/months
42c. # antibiotic courses for any other reason (prolonged URI)
42d History of pneumonia? Y N
42e #antibiotics for pneumonia _____

GERD HISTORY	Self-Report Yes=Y No=N	
43. Does your child have a history of GERD?	Y | N → If No skip to Q 52	
44. How many days a week does your child experience symptoms?	[redacted]	#
45. Does your child take medications for GERD?	Y N	
46. How often you take medications for GERD?	[redacted]	
47. Endoscopy with evidence of changes consistent with GERD	Y N	
48. Laryngoscopy with evidence of changes consistent with GERD	Y N	
49. Any esophageal probe (pH, esophageal manometry, other)	Y N	
50. Surgery for GERD	Y N	
51. Is your child's GERD controlled?	Y N	

ALLERGIES/RHINITIS HISTORY	Self-Report Yes = Y No = N	
52. Does your child have allergies/rhinitis?	Y N	
52a. Does your child have eczema	Y N	
53. Does your child take medications for his/her allergies/rhinitis?	Y N	
53. Does your child take medications for his/her eczema?	Y N	
54. Has your child ever received any allergy shots? (immunotherapy)	Y N	
55. Is your child currently receiving allergy shots?	Y N	
56. Has your child had anaphylaxis in the past?	Y | N → If No skip to Q 60	
57. If anaphylactic reaction, what was it to?	[redacted]	Name | N/A
58. Does your child use antihistamines for his/her allergies?	Y | N → If No skip to Q 60	
59. Does your child take antihistamines daily or as needed?	Daily | As needed	
60. Allergy skin prick tests. If yes, include report	Y N	
61. RAST testing. If yes, list results	Y N	
62. Are your allergies under control?	Y N	

Allergies

63. Is your child allergic to any medication?	Y | N | Multiple Meds (>3) |Name up to three:	
64. Is your child allergic to any vaccine?	Y | N | N/Applicable	Name
65. Does your child's pulmonary symptoms get worse with aspirin (for children over the age of 8) or non-steroidal anti-inflammatory drugs (NSAIDS) like Advil (ibuprofen) or Aleve (Naproxen)?	Y | N	

Immunizations

66. When was your child's last influenza vaccination?	**Mo |Yr | N/A | No**
68. Are routine childhood immunizations UTD? 68a: Received Pneumococcal 23? (not routine) Y N	**Mo |Yr | N/A | No**

MEDICATION COMPLIANCE AND PERCEPTION

69. Do you believe your child is able to take your asthma medications as directed.? (ATAQ)	Y N
70.Do you believe your child's asthma medications are useful in controlling his/her asthma? (ATAQ)	Y N
71. Which of the following statements best describes how your child took his/her asthma controller medications last week?	Prior Week Adherence 1. I took my asthma controller medications every day 2. I missed doses of my asthma controller medications 1-2 days 3. I missed doses of my asthma controller medications 3-4 days 4. I missed doses of my asthma controller medications 5-6 days 5. Not applicable- Not on controller
72. In general, which of the following statements best describes how your child takes his/her asthma controller medications?	General Adherence 1. Less than 25% of the time 2. 25% to 49% of the time 3. 50% to 74% of the time 4. More than 75% of the time 5. Not applicable

74. Does your child use a spacer? Added comment box in this section	Y N		
75. Does your child use a nebulizer?	Y N		Frequency
76. Does your child use supplemental oxygen	Y N	How many L/min	Frequency

Alternative Therapies

77. Does your child use any Alternative Therapies for asthma? (ie. Yoga/herbal/other)	Y N	○ Yoga ○ Herbal ○ Nasal saline ○ Acupuncture ○ Other	

78. Select **ONE** of the statements that best describes your thinking or behaviors related to your child's asthma today? . (Prochaska – change processes)

1. I have taken an interest in learning more about my child's asthma.
2. I have been thinking about how I take care of my child's asthma and how I might change.
3. I have been thinking about how my child's asthma affects our family.
4. I have told my family about my intentions to change how I take care of my child's asthma.
5. I talk to others who have children with asthma and make suggestions about how they might improve.
6. I reward myself when I reach personal goals related to my child's asthma.
7. I have made major changes in my life to reduce my child's exposure to known triggers.
8. I really have not thought about or done any of these things at this time.

ASTHMA MEDICATIONS

Name	Formulation/Route	Dose (unit)	Total Daily Dose
Short Acting Bronchodilators:			
Inhaled Corticosteroids:			
Inhaled LABA:			
Combination ICS+LABA:			
Oral Corticosteriods:			
Leukotriene Modifiers:			
Anticholinergics:			
Biologic Modifiers:			
Methylxanthines:			
Nasal Inhalers:			
GERD Medications:			
Antihistamines:			
Inhaled Medications:			

OBESITY HISTORY	Self-Report Yes=Y No=N
79. How would you describe your child's weight before age 18	□Low weight □Normal □Overweight □Obese
80. Does your child's pulmonary symptoms worsen with a weight increase of more than 10 percent (describe)? If No skip to Q **84**	Y N N/A
81. Did your child's pulmonary symptoms improve after weight loss?	Y N N/A

MEDICAL HISTORY

Have you ever been told by a health care provider that your child has any of the following illnesses/conditions? If Yes, list medications. Only check on the self report box if yes

Illness/Condition	Self-Report	Medical Record Confirmation	**Medications**
	Check only if yes	Check only if yes	
84. Heart Disease	□	□	
85. Hypertension	□	□	
86. Elevated Cholesterol	□	□	
87. Stroke	□	□	
88. Diabetes	□	□	
89. Liver Disease	□	□	
90. Sleep apnea Can make category to state if clinical diagnosis or PSG	□	□	
91. CPAP/BIPAP Machine Use?	□	□	
92. Seizure	□	□	
93. Birth defects	□	□	
94. Kidney disease	□	□	
95. Kidney stones	□	□	
96. Bleeding Problems	□	□	
97. Rheumatologic disorders (ie. Rheumatoid arthritis, lupus)	□	□	
98. Does your child take any biologic response modifiers/biologics (e.g. Enbrel, Humira, Remicade, Orencia?) \ *should this and #99 be with med section?	□	□	

Illness/Condition	Self-Report	Medical Record Confirmation	**Medications**
	Check only if yes	Check only if yes	
99. Is your child taking any immunosuppressants? (cellcept, tacrolimus, sirolimus, cyclosporine)			
100. Thyroid Disease	☐	☐	
101. Cancer	☐	☐	Type Chemo XRT
102. Chronic Viral Infections/HIV	☐	☐	
103. Other	☐	☐	
104. Surgical history	☐	☐	If so list surgeries
105 Muscle disease/myopathy			
106 Ciliary dyskinesia			
107: Immune deficiency?			
108 Cystic Fibrosis?			
109 Cerebral Palsy?			
110 Genetic disorder			

Organ Transplantation

Has your child ever had an organ or bone marrow transplantation? If no skip to question **109**

Organ Transplantation	Self-Report	Medical Record Confirmation	**Medications**
	Check only if yes	Check only if yes	
105. Bone Marrow	☐	☐	
106. Stem Cell	☐	☐	
107. Solid Organ	☐	☐	
108.Which organ?	☐	☐	

ENVIRONMENTAL EXPOSURES

109. Which of the following best describes where you lived most of the time until age 18.	1. In a rural area (countryside) 2. Outside of a city (suburban) 3. In a city (urban)
111. What locations made your child's asthma symptoms worse? Select all that apply.	1 = Home 2 = Work 3 = Outdoors 4 = Other (list location) _____ 5 =Not applicable (not worse)
112. What are your child's hobbies?	
113. Does your child currently have any exposure to the following in your home?	

Exposures	**Current**	**Previous**	**Frequency**	**Does it make your child's symptoms worse?**
	Check if Yes	Check if Yes	Daily Few days a week Few times a month Few times a year Never	Yes = Y No = N Unknown =N/A
Mold	☐	☐		N | Y | N/A
History of Pipe or Roof Leaks	☐	☐		N | Y | N/A
Dampness /Wet or Damp Basement/Crawlspace	☐	☐		N | Y | N/A
Radiator/Baseboard	☐	☐		N | Y | N/A
Wood Burning Stove, fireplace	☐	☐		N | Y | N/A
Gas Stove	☐	☐		N | Y | N/A
Kerosene Heater	☐	☐		N | Y | N/A
Cigarette Smoke, cigar smoke or pipe	☐	☐		N | Y | N/A
Wall to wall carpet	☐	☐		N | Y | N/A
Dust	☐	☐		N | Y | N/A
Animals	☐	☐		N | Y | N/A
Cat	☐	☐		N | Y | N/A
Dog	☐	☐		N | Y | N/A
Bird	☐	☐		N | Y | N/A
Other Pet	☐	☐		N | Y | N/A

114. "Have you used any of the following products near your child or in areas he/she frequents? ***If yes how often?***
If yes, does it make your child's asthma worse?"

Product examples	**Current**	**Previous**	**Frequency**	**Does it make your asthma worse?**
	Check if Yes	Check if Yes	Daily Few days a week Few times a month Few times a year Never	
Cleaning products (ie. Disinfectant, chlorine bleach, carpet cleaner, oven cleaner, window or glass cleaner)	□	□		N | Y | N/A
Personal care products (ie.Hairspray, hair coloring products, hair bleaching products)	□	□		N | Y | N/A
Air Fresheners – spray, stick, aerosol, plug-in, other	□	□		N | Y | N/A
Perfumes or Fragrances	□	□		N | Y | N/A
Home maintenance and repair products (ie. Turpentine, paint thinner, paint or varnish, Home insulation products)	□	□		N | Y | N/A
Glues or adhesives	□	□		N | Y | N/A
Polyurethane	□	□		N | Y | N/A
Pesticides / Insect Killers	□	□		N | Y | N/A

EMPLOYMENT

115. Which of the following best describes your child's **current employment situation**? Only 1, 2,8 apply	**If 1,2 or 3 is checked go to 116** **If 4-10 is checked go to 117** 1= Working full time 2 = Working part time 8 = **Student, not working**
116. If working, what is your current work title?	
117. Thinking about your **longest held or most typical employment**: what kind of work do/did you do?	
118. How **many years**, did or have you work(ed) in the job above? (If < 1 yr, enter decimal)?	# of Years
119. Is your asthma worse at work?	Yes No N/Applicable
120. Is yout asthma better away from work?	Yes No N/Applicable

WORKPLACE TRIGGERS / EXPOSURES

The following is a list of common substances in the workplace that can cause occupational asthma.

121. Do you currently have or have you had any exposure to the following at work?
If yes, did or does it make your asthma worse?

Substances	Check if Yes	Current	Previous	Unknown	Does it make your asthma worse? Yes = Y / No = N / Not applicable=N/A
Chemicals	□				N | Y | N/A
Cleaning products	□				N | Y | N/A
Dust, fumes, vapors	□				N | Y | N/A
Mold	□				N | Y | N/A
Poor ventilation	□				N | Y | N/A
Isocyanates	□				N | Y | N/A
Foam coating	□				N | Y | N/A
adhesives	□				N | Y | N/A
polyurethane	□				N | Y | N/A
Construction	□				N | Y | N/A
Welding machines	□				N | Y | N/A
Animals	□				N | Y | N/A
Agricultural products	□				N | Y | N/A
Farm exposure	□				N | Y | N/A
122. Are there any other WORKPLACE triggers or exposures that make your asthma worse?					

TOBACCO HISTORY

	CIGARETTES	**CIGARS**	**PIPE**
123. Did you ever smoke…? If No, Skip to question **132**			
124. At what age did you start?			
125. Are you currently smoking? If No go to question **127**			
126. If smoking, how many ___ do you smoke per day?			
127. If you quit smoking, at what age did you quit?	Age =		
128. How many ____ were you smoking per day when you were smoking the most?			
129. Total number of pack years		xxx	xxxx
130. Did your pulmonary symptoms start before or after starting to smoke?	Before After	Before After	Before After
131. Does or did smoking make your asthma worse?	Yes No	Yes No	Yes No

Second Hand and Other Smoke Exposures	
148. Has your child ever exposed to second hand smoke ? This is without the "for atleast 4hr/day) 148a Is the second hand smoke direct or indirect exposure (parent smokes outside	Never Exposed = 1 Currently Exposed = 2 Previously Exposed = 3 Direct Indirect
149.Where has your child been exposed to second hand smoke?	1=Home 2=Work 3=Other
150. How many years was your child exposed to second hand smoke?	Number of years
151. Did you ever smoke anything else on a regular basis (ie. Marijuana, cocaine)	Never = 1 Currently = 2 Previously = 3
152. Write in the name of the substance	
153. How often were you smoking? (write in frequency in years)	

SELF & FAMILY RACE AND ETHNICITY

154. Is your child adopted?	Yes No
155. Is your child a twin?	Yes No
156. If he/she is a twin, is he/she an identical twin?	Yes No Uncertain

157. Fill in race and ethnicity in the table below using the categories below.

How would you describe the race and ethnicity of your child and his/her ancestors? (Record all that apply)	1=White/Caucasian 2=Black or African-American 3=American Indian or Alaska Native 4=Asian 5=Pacific Islander 8=Other
Is your child or his/her ancestors Hispanic or Latino origin?	A=Yes B= No
Specify country of origin, is more informative than the race/Census description	

Race and Ancestral Country of Origin (ACO)

	Race	**Ancestral (racial diversity) country of origin**
Self		
Mother		
Maternal Grandmother		
Maternal Grandfather		
Father		
Paternal Grandmother		
Paternal Grandfather		

158. FAMILY HISTORY: ASTHMA and ASTHMA RELATED CO-MORBIDITIES

Please check for Yes

	MOTHER	**FATHER**
Asthma	☐	☐
Intubation for asthma	☐	☐
Fatal Asthma	☐	☐
Allergies or eczema	☐	☐
COPD/emphysema	☐	☐
Lung cancer	☐	☐
Cystic fibrosis	☐	☐
Cystic fibrosis carrier	☐	☐
Sarcoidosis	☐	☐
Interstitial lung disease	☐	☐

Siblings (also children if applicable):

Gender (Male/Female)	M F	M F	M F	M F
Half brother/sister	☐	☐	☐	☐
Asthma	☐	☐	☐	☐
Intubation for asthma	☐	☐	☐	☐
Fatal Asthma	☐	☐	☐	☐
Allergies or eczema	☐	☐	☐	☐
COPD/emphysema NA	☐	☐	☐	☐
Lung cancer likely NA	☐	☐	☐	☐
Cystic fibrosis	☐	☐	☐	☐
Cystic fibrosis carrier	☐	☐	☐	☐
Sarcoidosis	☐	☐	☐	☐
Interstitial lung disease	☐	☐	☐	☐

SOCIOECONOMIC	
159. What is your current marital status?	1 = Married 2 = Divorced 3 = Separated 4 = Widowed 5 = Never married 6 = Not available/declined
160. What is your family's gross income?	1 = Less than $19,999 2 = $20,000 to $39,999 3 = $40,000 to $59,000 4 = $60,000 to $99,000 5 = Over $100,000 6= Not available/declined
161. Please indicate which of the following best describes mothers highest educational level	1 = Grade 8 or less 2 = Some High School 3 = High School Graduate 4 = College Graduate 5 = Graduate Education mother = father =
162. Number of missed school days/year for asthma related symptoms	
162a. **# missed school days total.	
163. Number of missed work days for parent/guardian per year for asthma related symptoms	
163a **#of missed work days due to child illness (non-asthma)	

End of Participant Interview