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Official Title: The Severe Asthma Research Program at Wake Forest University - Longitudinal Phenomics and Genetics of Severe Asthma.

Date: 3/15/2021

WAKE FOREST
UNIVERSITY
HEALTH SCIENCES

**Research Subject Information and Consent Form**
**Core Consent**

**Study Title:** **Longitudinal Phenomics and Genetics of Severe Asthma**

**Principal Investigator:** Dr. Wendy Moore

*Note: From this point forward throughout this form "you" refers to the study participant. If you are a parent, this means that "you" refers to your child.

This consent form may contain words that you do not understand. Please ask the study physician or the study staff to explain any words or information that you do not clearly understand.

The purpose of this form is to give you information about the study, and by signing it you will give your permission to be in the study. The Wake Forest School of Medicine is part of a group of centers that are studying severe asthma. You should join in this study only if you want to do so. You may refuse to join or stop being in this study at any time. Your decision to join or not join this study will not affect your doctor-patient relationship or your medical treatment in any way. This study is voluntary.

## What Is the Purpose of This Study?

You have been invited to join in a research study. This is a research study that is being done to learn more about severe asthma by comparing people with severe asthma to those with milder forms of asthma over time. You are being asked to join a research study to follow your overall health and the health of your lungs for up to six and a half years. In this study, we will look at your breathing tests, your level of inflammation in your blood and breath, the number of and how bad your asthma attacks are, your medication use and other conditions related to asthma over time. We will also look at how steroids affect your asthma and the inflammation in your airways.

The job of the Severe Asthma Research Program (SARP) is to improve the understanding of severe asthma to develop better treatments. The SARP will gain a better understanding of asthma, in children and adults, by looking at the disease level in a very detailed way. You are being asked to join in this study because you have asthma.

## Who is Sponsoring the Study?

The Wake Forest School of Medicine is one of seven research groups, funded mainly by the National Institutes of Health, and partially by the private industry-supported SARP Research Fund, working together to study severe asthma. A list of current and past industry sponsors is available upon request for this study. This group of sites is part of the SARP.

Because severe asthma is uncommon, the seven centers were set up to work together to enroll enough people with severe asthma in research studies. Each of the centers will conduct a common longitudinal protocol and will share the information, test results and research samples collected across all seven centers. Each center will also have its own research study and questions they will look at specific to that center or a combination of a few centers. If you decide to join this research study at the Wake Forest School of Medicine, you will also be asked to allow the sharing of your study information and samples with other sites participating in this study. The data coordinating center for all sites will be Penn State University.

**Who are the other investigators involved in the SARP partnerships?**

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|---|---|
| Brigham and Women's Hospital, Boston, MA | Elliot Israel, M.D.; Bruce Levy, M.D. |
| Children's Hospital Boston | Wanda Phipatanakul, M.D. |
| Rainbow Babies and Children's Hospital | Benjamin Gaston, M.D. |
| Cleveland Clinic, Cleveland, OH | Serpil Erzurum, M.D. |
| Emory University, Atlanta, GA | Anne Fitzpatrick, Ph.D. |
| University of Virginia, Charlottesville, VA | Gerald Teague, M.D. |
| University of Pittsburgh, Pittsburgh, PA | Sally Wenzel, M.D. |
| University of California San Francisco, CA | John Fahy, M.D. |
| University of Wisconsin, Madison, WI | Nizar Jarjour, M.D. |
| Wake Forest School of Medicine, Winston-Salem, NC | Wendy Moore, M.D. |
| Washington University, St. Louis, MO | Mario Castro, M.D. |

**What Does this Study Involve?**

This study will last up to six and a half years and will involve up to eleven clinic visits, and up to eleven phone or mail contacts from research study staff. The last three years of the study are part of the SARP Long-Term Extension. There will be 700 subjects enrolled in this study across all centers. The Clinical Research Center will have 200 people sign the consent in order to enroll 100 subjects.

A detailed study grid can be found at the end of this consent form in Appendix 1. An explanation of each procedure can be found below. Procedures at Visits 2 and Visit 3 might take more than one day to complete.

**SARP Registration:**

Before you enroll in SARP, you must first be entered into the SARP Registry. This Registry has been set up to collect basic background information that will probably not change over time. This information is limited to: your initials, date of birth, gender, and race/ethnic identification. Your Registry information will be coded with a unique SARP identification number. No information that directly identifies you will be entered into the SARP database or sent to the Data Coordinating Center (Penn State University, Hershey, PA). Registry data

help us track your study over time and is useful in data analyses.

Your agreement to provide the information for the SARP Registry is voluntary. However, if you choose not to provide it, you cannot be screened for or enrolled into SARP. Once you consent to be entered into the Registry, your information cannot be removed and will be maintained in the study database into the future. You will only be asked to supply Registry information one time during your participation in SARP. Registration happens before or during your first study visit (Visit 1).

STUDY PROCEDURES:

I. QUESTIONNAIRES _____/_____
(Initials)

Visit 1, Visit 2, Visit 3, and every 6 months for a total of 6 and a half years. Some of these later questionnaires will be done over the phone while you need to come to the clinic for others (Visit 4, Visit 5, Visit 6, and Extension Visits 7-9).

This will include information on the development of asthma or breathing problems, current symptoms, your home and work environment, present and past treatment of shortness of breath, exacerbating factors (triggers) and how your breathing affects your life. In addition, you will be asked to give information on your age, place of birth and your parent's medical history. The questionnaires will take you approximately 1 hour to complete.

RISKS: The questionnaires are not tests; there are no right or wrong answers. There are no known risks to answering the questionnaires. The questionnaires might be considered long with repeating questions. You can skip any question you feel uncomfortable answering.

**II. Online asthma symptoms questionnaire:**

In addition to the questionnaires that you will be asked to answer, either by phone or in-person, you will also be asked to complete a brief monthly online questionnaire about your asthma control and any worsening asthma symptoms that you may have had recently. You will also be reminded to complete this questionnaire anytime you feel like you are having or have recently had worsening asthma symptoms.

The data collected about asthma symptoms will help the SARP researchers better understand how often people with severe asthma have worsening symptoms and how this compares with worsening symptoms experienced by people who have mild or moderate asthma. This information will help the SARP researchers better understand changes that happen to people with asthma when they have worsening symptoms. Let us know if we can contact you via email to remind you to complete the online asthma symptoms questionnaire:

_____ (initial) We **may** enroll you in the online questionnaire system. You will receive monthly reminders to complete this questionnaire.

_____ (initial) We **may not** enroll you in the online questionnaire system. You will not receive monthly reminders to complete this questionnaire.

If you agree to complete these monthly questionnaires, you will be asked to provide your email address. Your email address will be shared with the survey administrator, UCSF, who will use secure software to protect your email address. The SARP staff at your study site will enroll you in this online system. Only your SARP center and UCSF will have access to your email address. Your email address will not be shared with others and it will only be used to send you these monthly emails. Your email address will be permanently removed from the system once you complete the study or if you no longer want to participate in this part of the SARP study. If you do not agree to provide your email address, you will not receive monthly reminders to participate in this online questionnaire.
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RISKS:
You are being asked to report symptoms of worsening asthma or asthma attacks using this online questionnaire. It is important that you understand that the information you provide is not immediately reviewed by a healthcare provider. Therefore, if you feel you are having a medical emergency, you must not complete the questionnaire. Instead you should get immediate medical attention or dial 911.

III. PULMONARY FUNCTION TESTING _____/_____
(Initials)

Visit 1, Visit 2, Visit 3, and then once every year for a total of 6 and half years (Visit 4, Visit 5, Visit 6 and Extension Visits 7-9).

Pulmonary function testing (PFT) is a standard test that is used regularly by doctors to test breathing. You will be asked to breathe into a machine called a spirometer (spirometry) or pant into another breathing machine (body plethysmograph or body box). The technician will ask you to take a few normal breaths, then breathe in a deep breath, and then breathe out hard and fast. You will need to repeat this task several times. To make sure we measure all of your breaths exactly, you will be asked to wear nose clips. PFT's take approximately 10 minutes to complete.

RISKS: Pulmonary function testing can cause tiring, mild chest tightening and coughing. If your breathing is difficult after or during the test, we will give you 2-4 puffs of albuterol, an inhaled medicine to relax the airways (bronchodilator). In some people, albuterol can make your heart race, make you feel jittery or nervous, increase your blood pressure and cause nausea or headache. These feeling are temporary and should be gone within 15-30 minutes.

Maximum Bronchodilation

After you perform pulmonary function testing, we will ask you to take 4 puffs of albuterol (an inhaled medicine to relax the airways). 15 minutes later you will perform spirometry again and take another 2 puffs of albuterol. 15 minutes later you will repeat spirometry. If there is little to no difference between the last two sets of spirometry values, the test will stop. If comparison of the last two sets of spirometry values shows a continued increase in your breathing, you will take 2 more puffs of albuterol, and spirometry will be repeated one last time. For this test, you will receive no more than 8 puffs of albuterol.

**Ipratropium reversibility:** At Visit 1 or 2 for those older than 18 years, you may also be asked to take 4 puffs of ipratropium (Atrovent® HFA) and repeat spirometry 30 minutes later if your maximum bronchodilator response is not high enough to be classified as an asthmatic patent and included into SARP. Ipratropium is an anticholinergic bronchodilator that is FDA approved for the treatment of chronic bronchitis, emphysema and chronic obstructive pulmonary disease (COPD). Although ipratropium has not been FDA-approved for use in asthma, it is widely used for asthma, and an NIH Task Force and US and International guidelines all recommend ipratropium in this dose for characterization of asthma.

RISKS: You might have coughing or lightheadedness with pulmonary function testing. You may get up to 8 puffs of albuterol for this test. Taking up to 8 puffs of albuterol can make your heart race, make you feel jittery or nervous, increase your blood pressure and cause nausea or headache. These feelings are temporary and should be gone within 15-30 minutes.

Risks of **Ipratropium (Atrovent® HFA):** This drug is only used by adults (age 18 or older) once in this study for reversibility testing at Visit 1 or 2. Occasional side effects are headache, dry mouth, nausea, bronchitis, and shortness of breath. These side effects were reported in patients with COPD who took ipratropium for 12 weeks. Since you will only take ipratropium once, the likelihood of these side effects is much less.

IV. METHACHOLINE INHALATION CHALLENGE _____/_____
(Initials)

Visit 1

This test measures the reactivity or sensitivity of the airways. This consists of measuring the degree of narrowing that occurs after inhaling methacholine. Methacholine Challenge is an approved standard test used by physicians to test if a person has asthma or test how "sensitive" the airways are in people with asthma. Methacholine will cause some people's breathing tubes to narrow, especially if you have asthma. We will ask you to inhale increasing doses of a mist containing methacholine and then we will measure your breathing capacity by having you blow into a spirometer. You will receive albuterol after the test to reverse any shortness of breath or wheezing the test has caused. An inhalation study using methacholine will take approximately 60 minutes of your time. This will be done on Visit 1 if needed. If you have previously participated in an NIH study involving Methacholine Inhalation Challenge, you may not need to complete this procedure.

RISKS: Methacholine may cause your breathing tubes to narrow slightly after you inhale it, causing shortness of breath. You may feel this as tightness in your chest or experience a

coughing sensation. These symptoms usually go away in 10-15 minutes without treatment, but they can be reversed quickly with 2 puffs of albuterol at the end of the test. We have performed these tests on many people in the last 10 years and very few have had any difficulty. If your breathing is very bad (less than half of what is considered normal breathing), we will not perform this test.

V. BLOOD SAMPLING _____/_____
(Initials)

Visit 2, Visit 3, and then every year for a total of 6 and half years (Visit 4, Visit 5 and Visit 6 and Extension Visits 7 and either Visit 8 or 9).

You will be asked to donate a small amount of blood from your vein on visits 2, 3, 4, 5 and 6 and at Extension Visits 7 and either visit 8 or 9. During visit 2, 3, 4, 5, 6 and Extension Visits 7 and either visit 8 or 9, about 5 tablespoons will be collected at each visit. At visit 2, blood will be drawn for CBC with differential count, total IgE, ImmunoCap, serum, plasma and isolation of DNA for SARP genetic studies to evaluate genes that may be related to the development of asthma, allergy and related diseases. At visit 3, blood will be drawn for CBC with differential count, serum, plasma and isolation of DNA for SARP genetic studies to evaluate genes that may be related to the development of asthma, allergy and related diseases. At visit 4, visit 5 and visit 6 blood will be drawn for the collection of serum and plasma. Also at visit 6, a RNA (paxgene) sample and blood for HbA1c, cholesterol, HDL, triglycerides, along with an optional fasting blood for glucose and insulin will be collected. At the Extension visits 7 blood will be drawn for collection of serum, plasma and CBC with differential count. At either visit 8 or visit 9, blood will be drawn for a CBC with differential count, a DNA and RNA sample, and collection of serum and plasma. We will be collecting DNA and RNA as part of the study.DNA (deoxyribonucleic acid) and RNA (ribonucleic acid) are the genetic materials contained in all the cells of your body, including blood cells. This genetic material (genes) influences such things as your physical features, hair, and eye color. As part of this research project, your DNA and RNA will be studied in an effort to find out if there are genes that contribute to medical conditions that are part of this study. Your blood will also be tested for numbers of eosinophils (white blood cells important in asthma), immunoglobulins E [(IgE), proteins that are elevated in people with allergies] and other substances that may contribute to the airway inflammation seen in people with asthma.

RISKS: You may experience a slight bruise or some discomfort at the site of the blood draw. Some people may feel faint or lightheaded during blood draws. The study doctor and nurse are available in these cases. There is also a very small risk of infection at the site of the needle insertion.

> **Fasting for V6.** If you choose to participate in the fasting blood draw, we will ask you not to eat for 12 hours before the blood draw. You will be allowed to drink water, and we would like you to drink plenty of water so that you do not get dehydrated. With fasting, there is also a risk that your blood sugar will get too low. To avoid this, we will encourage you to eat snacks (provided by us or you may bring your own) after your blood draw. Please let us know if you have a medical condition that could be made

worse by fasting or if you have had a low blood sugar or any problems with blood draws in the past. If you cannot fast or choose not to, then you will still be eligible for the study and we will go on with the study procedures by making a note that you have not fasted.

After your blood is drawn, your blood sample will be processed for DNA and RNA by technicians at the Center for Human Genomics. This DNA and RNA will be stored in a –70° freezer at the Center for Human Genomics. Your genetic samples will be identified only by an ID number (not your name), and no genetic analysis will be performed other than that associated with asthma, allergy, respiratory and related diseases. These DNA and RNA samples may be shared with our collaborators for research purposes. You authorize the Wake Forest University Health Sciences and members of its professional staff to use your DNA and RNA samples for these purposes. Your DNA and RNA sample will be used only for research purposes and will not be sold. Because we do not know how the results of this DNA study relate to your individual health, the results of the research will not be given to you or your doctor without your permission. These results will also not be placed in your medical records. The findings from this research may result in the future development of products that are of commercial value. There are no plans for you to share in any profits that may occur as a result of this research.

The Center for Human Genomics is a research facility only and does not have the capacity to provide genetic test results or genetic counseling on an individual basis. However, if, during the course of this research, an asthma gene is identified, you will be notified of the general results. The Center for Human Genomics will provide you with general information on how to obtain the appropriate genetic testing and counseling, such as a list of places where genetic testing and counseling is conducted.

As part of the genetic study, a sample of your DNA may have Genome Wide Association Studies (GWAS) or Whole Genome Sequencing (WGS) performed. The GWAS analysis creates a very detailed picture of your DNA for researchers using up to 2 million genetic markers. WGS is an analysis of your complete genetic code and has the capability to identify nearly all genetic mutations in your DNA.

In addition, information regarding your DNA and clinical information about you will be sent to the National Institute for Health's Genome Wide Association Study (GWAS) data repository, where it will undergo genome-wide analysis and be shared with other investigators for research purposes. DNA and information sent to the GWAS will help researchers better understand how genes affect the risk of developing diseases such as asthma, cancer, diabetes, and heart disease, and may lead to better methods to select the best treatment options. Before your information is sent to the GWAS data repository it will be de-identified, which means that we will remove any identifying information such as your name, date of birth, address, etc. Thus, researchers using your DNA and clinical data will not be able to link this information back to you.

VI. URINE _____/_____
(Initials)

Visit 2, Visit 3, then every year for a total of 6 and half years (Visit 4, Visit 5 and Visit 6 and Extension Visits 7-9)

The urine sample collected will be used to look for signs of inflammation that might be related to your asthma for visits 2-7. You will also be asked to provide a small amount of urine for pregnancy testing at all visits if you are a female of childbearing potential to make sure you are not pregnant before taking any study medication or doing some study procedures. You will not be enrolled if you are pregnant or breastfeeding. If you become pregnant during the longitudinal follow up phase you can stay in the study, but we will ask that you let us know.

Risk: There are no known risks for the collection of urine.

VII. EXHALED BREATH CONDENSATE _____/_____
(Initials)

Visits 2, Visit 3, then every year (Visit 4, Visit 5, Visit 6 and Extension Visit 7 only) (Note: EBC will not be collected at V8 and V9)

Exhaled breath condensate (EBC) is a liquid collection of the air you breathe out into a tube. We will ask you to collect a liquid version of your exhaled breath (EBC) by breathing into a tube for 10 minutes, which will allow the collection of exhaled breath vapor.

RISKS: Risks of these procedures include tiring, mild chest tightness and coughing. A medication (albuterol) can be given to open the air passages if wheezing develops.

VIII. NITRIC OXIDE MEASUREMENT _____/_____
(Initials)

Visits 2, Visit 3, and then every year (Visit 4 and Visit 5 and Extension visit 7) (Note: Nitric Oxide will not be collected at Visit 6, Visit 8 and Visit 9)

People with asthma are known to have inflammation in their airways. This test is a way to look at this inflammation. Nitric oxide (NO) is a gas in your breath that we can measure with a machine. We will ask you to undergo measurement of NO by having you blow out slowly through a mouthpiece while wearing nose clips. It feels much like blowing up a balloon. When breathing out you will notice some resistance (similar to blowing through a straw). You will be asked to repeat this maneuver up to two times. This test takes approximately 10 minutes to complete.

RISKS: Risks of this procedure includes tiring, mild chest tightness and coughing. A medication (albuterol) can be given to open the air passages if wheezing develops.

IX. Physical Exam _____/_____
(Initials)

Visit 1 (or 2), then every year for a total of 6 and half years (Visit 4, Visit 5 and Visit 6 and Extension visits 7-9)

At Visit 1 (or 2), the study doctor will listen to your heart and lungs, and look at your eyes, ears, nose and throat. Vital signs (blood pressure, temperature, height and weight) will also be collected by a study coordinator or designated representative at Visit 1 then every year for a total of 6 and half years. If needed a study physician is available to see you during other visits also.

RISK: There are no known risks for Physical Exams.

X. SPUTUM INDUCTION _____/_____
(Initials)

Visits 2, Visit 3, Visit 4, Visit 5, Visit 6 and Extension visits 7

Sputum induction is a method of obtaining fluid secretions from your breathing airways to better understand airway inflammation in asthma. You will be asked to inhale a nebulized mist of 3% saline solution (salt solution) and collect your airway secretions in a cup. Prior to inhaling saline solution, you will be given 4 puffs of albuterol to help prevent you from developing wheezing from inhaling the salt solution, which may happen in some participants. You will be asked to inhale this saline mist for 12 minutes. During this period, you will be encouraged to cough and your secretions will be collected in a cup. If you develop difficulty breathing or excessive coughing during this procedure, the inhalation of saline will be stopped. Before and after the inhalation period, you will also be asked to perform a pulmonary function test. Subjects with low lung function will not be asked to inhale the saline mist for 12 minutes. These subjects will be asked to spontaneously cough and their secretions will be collected in a cup.

RISKS: This is a commonly performed procedure to try to obtain a sputum (respiratory secretions) sample from patients in the hospital to see if they have pneumonia. You may experience some discomfort or coughing but this will only be temporary. Some patients experience bronchospasm (narrowing of the airways) from inhaling saline, which may cause some chest tightness, wheezing, and shortness of breath. This is reversible with a bronchodilator (albuterol). If you experience any of these symptoms and/or your breathing decreases by 20%, you will be given 2 puffs of a bronchodilator. In addition, should you develop any symptoms during the inhalation of saline the procedure will be stopped. You should experience no other effects from the inhalation of the saline solution.

XI. Corticosteroid Treatment _____/_____
(Initials)

Visit 2

**Triamcinolone acetonide treatment:** At the end of Visit 2, if the study physician thinks it is safe for you, you will be given a shot of Triamcinolone acetonide. This will be given as a single shot into your butt. Triamcinolone acetonide is a steroid medication that is approved by the FDA for the treatment of inflammation in people with asthma. The purpose for this treatment is to allow the researchers to look at different measures of inflammation before and after you receive the steroid treatment to see if there are any changes. The dose of study medicine that you will receive is within the safe range. You will continue your usual asthma medications throughout the duration of this study.

RISKS:

Triamcinolone taken during pregnancy may expose the unborn baby to unknown risks, including the possibility of birth defects. If you are a woman who may be able to become pregnant, you must use a medically acceptable method of birth control beginning at the time of enrollment and continuing until 12 weeks following the triamcinolone injection. If you become pregnant during that time, you should notify the study doctor promptly. The study doctor will ask to follow the progress of your pregnancy until the end of your pregnancy. Acceptable birth control methods include: abstinence, birth control pills, diaphragm, intra-uterine device (IUD, IUS), Depo-Provera, NuvaRing, birth control patches, single or double barrier methods (condom plus foam/jelly) or surgical sterility.
Side effects with this steroid are not very common. However, side effects of a shot in the muscle have been reported, including atrophy (a “dimple”) at the injection site and changes in skin color. These side effects are kept low by placing the drug deep into the muscles. All triamcinolone shots will be given by an experienced member of the study staff. Side effects in the body after a single shot of triamcinolone are rare. However, with continuous or repeated use, muscle weakness, bone fractures, ulcers, impaired wound healing, and growth suppression may occur. To lower these risks, you will be screened thoroughly by a physician for the likelihood of side effects before the shot is given. We will tell you what problems to look for and we will call you within 72 hours to make sure that you are OK. Also you will have 24-hour access to an on-call physician while you are participating in this study.

XII. Computed Tomography Scan (CT scan) _____/_____
(Initials)

Visit 1

You may be asked to undergo CT scan as part of this study. Not everyone will be asked to have this test. This test requires one extra visit to the laboratory that will last between 30-90 minutes. CT scans show your lungs in greater detail and will allow us to see how thick your

airways are and how much air is trapped in your lungs. It is a new way of looking at the severity of your lung disease. The exam will require that you lie still on your back on a table that moves slowly through a dough-nut shaped machine. The machine takes a series of x-rays to create a three-dimensional picture of your lungs. Before the scan you will be given 4 puffs of albuterol. Then you will be asked to take a deep breath and hold your breath for 20-25 seconds while you are being scanned (full inspiration). Then we will ask you to blow all your air out and hold your breath for 20-25 seconds (full expiration).

RISKS: This research study involves exposure to radiation from ct of the chest. The risk of this procedure is small and is similar to that received from clinical x-ray and nuclear medicine studies. The amount of radiation exposure that you will receive from this procedure is equivalent to a uniform whole body exposure of 956 millirem. This is equal to 3.19 times the amount of background radiation that the average person in the United States receives each year (annual background = 300 millirem).

## XIII. BRONCHOSCOPY

Bronchoscopy with lavage, brushing and/or biopsy _____/_____
(Initials)

Visit 2 and Visit 3

You may be asked to undergo a Bronchoscopy as part of this study. Not everyone will be asked to have this test. This test requires two extra visits to the laboratory that will last between 6-12 hours, but could require overnight hospitalization in some participants with severe asthma. Bronchoscopy is a test designed to examine the inside of your lungs to obtain fluid and biopsy samples (pieces of lung tissue) from your lung. Bronchoscopy is a common medical test, we do it very often to examine the lungs, and airways of subjects with suspected lung disease. The use of bronchoscopy in the study of asthma, however, is an experimental procedure. This test involves taking a soft, flexible, bronchoscope (about the same size and flexibility as a lamp cord) and inserting it through your nose or mouth into your lungs. During this test, the physician performing the bronchoscopy will look through this fiberoptic scope to examine your lungs and to make sure he/she is placing the scope in the correct portion of your lung. You must not eat or drink for
at least six (6) hours before the bronchoscopy study. In general, you may take your usual medications in the morning with a sip of water, but you should discuss this issue with the study doctors. We will monitor your heart activity (EKG, electrocardiogram), blood pressure, pulse oximetry (a clip on the finger that tells us how much oxygen is in the blood), and breathing continuously throughout the test. In case of an emergency, fully trained physicians are immediately available with all the necessary medications and emergency equipment that would be needed.

We will place an intravenous catheter (“IV” line; a small, soft, plastic tube) into a vein in your arm or hand. This “IV” will be removed at the end of the test. You will be offered intravenous injections (shots) of one or two sedative medications to make you drowsy, relaxed and comfortable during the bronchoscopy. These sedative medications are similar to morphine

(Fentanyl) and Valium™ (Versed™), and are used routinely in the clinical bronchoscopy laboratory at the Wake Forest University Baptist Medical Center. Versed™ and Fentanyl are sometimes used together to allow smaller doses of medication to be given. After discussion with the study doctor, you may decide not to have intravenous sedation during bronchoscopy.

By using a nebulizer, you will inhale an albuterol breathing treatment, followed by a nebulized mist of numbing medicine (lidocaine) into your mouth and airways to decrease your discomfort and to decrease any cough you might experience during the bronchoscopy. To do the bronchoscopy, we will place a small black tube (fiberoptic bronchoscope) into your lungs through your nose or mouth. In your airways, brushings/biopsies will be taken from the large parts of your breathing tubes using tiny brushes and special tweezers (biopsy forceps) to take very small pieces of tissue. We will take between four and six evaluable samples of brushes and biopsies. Finally, a small amount of salt water (100-200 ml or 4 to 8 oz.) saline will be put into your airways through the bronchoscope in order to wash your airways and to collect cells from your breathing passages. The cells from the brushes and washing and the tissue from the biopsies will be tested in the laboratory. When the bronchoscopy is completed, you will inhale another treatment with albuterol to treat any wheezing the bronchoscopy may have caused. You will be asked not to eat until the numbing medicine wears off (usually about 1 hour). You will perform breathing tests (spirometry) every few hours after the bronchoscopy until your breathing has returned to the level it was before the test.

Your asthma may worsen temporarily after the bronchoscopy, especially if you have severe asthma. All subjects will be treated with corticosteroids (trimacinolone acetonide) after bronchoscopy would should treat any worsening of your asthma that you experience. The study physician will follow you until your asthma symptoms and breathing tests are back to within 10% of what they were before the test. If your breathing does not improve to baseline after three albuterol treatments, we may ask you to spend the night in the hospital to monitor your breathing. If your asthma worsens after you go home, treatment in an emergency room/urgent care facility might be required on rare occasions. The study staff will call you every day for 3 days to check on how your asthma is doing and to be certain you are not having any side effects from the bronchoscopy.

MAJOR RISKS OF BRONCHOSCOPY: Although bronchoscopy is a common test performed by physicians to check for lung diseases, you should be aware that the use of bronchoscopy for research purposes is an experimental procedure. If you have severe asthma, these risks may be greater for you.

The three most serious risks of this procedure are:

1) Severe worsening of your breathing during the test (respiratory distress)
2) Apnea (stopping breathing) due to too much sedation
3) Decrease or change in your heart rate/rhythm or breathing that could lead to death.

These complications are very rare and have never occurred in our laboratory, but you should be aware that these are potential risks of the procedure. If you have problems with your breathing or your heart rate during the procedure, the physician and laboratory staff will

provide emergency care including transfer to the emergency room if necessary.

One death has been reported after research bronchoscopy. Many thousands of research bronchoscopies have been performed, so the risk of death is very rare. Please notify your study doctor or their representative for any major complication at 713-8550. If any minor complication continues for more than 24 hours, please also contact your study doctor at the same number.

There are several MINOR RISKS to bronchoscopy and these are detailed below.

There is a small risk that the numbing medicine (lidocaine) or bronchoscopy may cause some irritation of the airways in your lung that could cause minor degrees of narrowing of your airways (wheezing). If there is narrowing of your airways, it can be stopped by inhaling a medicine such as albuterol, which will be provided to you in the clinic. If you become very wheezy after the lidocaine, we will not do the bronchoscopy.

The intravenous catheter (IV) placed in your arm may cause local pain, bleeding, swelling or rarely, infection (< 1 in 100 people). Fentanyl may cause bradycardia (slowing of the heart rate) which can be stopped by giving a medication (atropine) through your IV. Other possible side effects include mild lowering of blood pressure, a decrease in alertness, rare nausea, and vomiting. The side effects of Versed are similar to Fentanyl. Slowed-down breathing has been noted at higher doses of this medication. Because these medications may decrease alertness and cause lightheadedness or dizziness, you will have to have another adult drive you home from the clinic.

Bronchoscopy may result in nosebleeds, gagging or coughing (< 25 out of 100 people), but the test is generally not painful. This test will take less than 30 minutes. If you cough during the bronchoscopy, medications are available to stop you from coughing and from feeling discomfort during the bronchoscopy. However, if you cough or gag and become uncomfortable, the test will be stopped. We will ask you to remain in the laboratory for several hours after the test is completed for observation (or possibly overnight). If you received sedative medications, you will receive instructions for the next 24 hours and someone will have to give you a ride home (a responsible adult).

Occasionally fever (10-15 out of 100 people), a respiratory infection (pneumonia, rare), narrowing/collapse of the washed area of lung (atelectasis, rare) or a small hole in the lung (pneumothorax, < 1 in 1000 procedures) might occur. If these occur, they will be treated with albuterol, and, if necessary, an antibiotic (an anti-infection medicine). If a hole in the lung occurs you will have to undergo several chest x-rays and rarely, a procedure to remove the air from your chest. A physician will be available during and after the bronchoscopy test to treat any complaints.

In addition to the risks outlined above, subjects undergoing biopsies may have a small amount of bleeding after the biopsy. This bleeding usually stops in a few minutes, but if bleeding continues a small amount of medication called epinephrine will be applied to the area of bleeding. Epinephrine causes the blood vessels to constrict (narrow) and stop bleeding. The epinephrine may cause your heart rate to increase a small amount, but

otherwise it should not cause any problems. The epinephrine may actually reverse any airway narrowing you may have experienced during the test. It is common to cough up small flecks of blood for 24 hours after bronchoscopy, but if the amount of bleeding increases, you should call [redacted] or (after hours) have the study doctor on-call paged at [redacted].

**Holding asthma medication:** For some visits, the study staff may ask you to not take your asthma medication before the visit. If your asthma symptoms get worse and you feel that you need to take your medication, please take your asthma medicine and call the study staff to let them know.

**Risk of disclosure:** Your research samples and data will not be labeled with your name or other items that might identify you. All data will be stored in a password protected, study specific database and will be labeled with a code number. There will be very limited access to the link between your name or other personal information and the study code. Because this link will exist, there is a small risk that your name may become known in association with this research study.

## What are the Benefits of Study Participation?

You are not guaranteed any benefit from participation in this study. Your participation in this study will help researchers understand more about severe asthma. The results from this study may help us find a better way to treat asthma and may benefit other asthma patients in the future.

## Will I be Paid for My Participation?

You will be paid for your participation. The amount you receive depends on which parts of the study you complete. If you qualify for the study after screening and complete all the study visits outlined in this consent form for which you are eligible, you will be paid up to $1775. Not all subjects will be asked to undergo all procedures. If you stop participating before the end of the study or if the study is discontinued through no fault of yours, you will receive a partial payment based upon your participation in the study.

| | | |
|---|---|---|
| **Visit 1** | **Questionnaires** | **$15** |
| | **Maximum Bronchodilation** | **$35** |
| | **Methacholine** | **$ 30** |
| | **CT Scan (optional)** | **$ 50** |

| | | |
|---|---|---|
| **Visit 2** | **Questionnaires with Blood Draw** | **$ 25** |
| | **Maximum Bronchodilation** | **$35** |
| | **Sputum Induction** | **$30** |
| | **Exhaled Nitric Oxide** | **$15** |
| | **Exhaled Breath Condensate** | **$20** |
| | **Bronchoscopy (optional)** | **$300** |

| | | |
|---|---|---|
| **Visit 3** | **Questionnaires with Blood Draw** | **$ 25** |

| | | |
|---|---|---|
| | **Maximum Bronchodilation** | **$35** |
| | **Sputum Induction** | **$30** |
| | **Exhaled Nitric Oxide** | **$15** |
| | **Exhaled Breath Condensate** | **$20** |
| | **Bronchoscopy (optional)** | **$300** |
| **6 month telephone follow up** | | **$15** |
| **Visit 4** | **Questionnaires with Blood Draw** | **$ 25** |
| | **Maximum Bronchodilation** | **$35** |
| | **Sputum Induction** | **$30** |
| | **Exhaled Nitric Oxide** | **$15** |
| | **Exhaled Breath Condensate** | **$20** |
| **18 month telephone follow up** | | **$15** |
| **Visit 5** | **Questionnaires with Blood Draw** | **$ 25** |
| | **Maximum Bronchodilation** | **$35** |
| | **Exhaled Nitric Oxide** | **$15** |
| | **Exhaled Breath Condensate** | **$20** |
| | **Sputum Induction** | **$30** |
| **30 month telephone follow up** | | **$15** |
| **Visit 6** | **Questionnaires with Blood Draw** | **$ 25** |
| | **Maximum Bronchodilation** | **$35** |
| | **Sputum Induction** | **$30** |
| | **Exhaled Breath Condensate** | **$20** |
| **Visit 6 (fasting blood draw if needed)** | | **$25** |
| **42 month telephone follow up** | | **$15** |
| **Visit 7** | **Questionnaires with Blood Draw** | **$ 25** |
| | **Maximum Bronchodilation** | **$35** |
| | **Exhaled Nitric Oxide** | **$15** |
| | **Exhaled Breath Condensate** | **$20** |
| | **Sputum Induction** | **$30** |
| **54 month telephone follow up** | | **$15** |
| **Visit 8** | **Questionnaires** | **$ 10** |
| | **Blood Draw** | **$15** |
| | **Maximum Bronchodilation** | **$35** |

| | | |
|---|---|---|
| **66 month telephone follow up** | | **$15** |
| **Visit 9** | **Questionnaires** | **$ 10** |
| | **Blood Draw** | **$15** |
| | **Maximum Bronchodilation** | **$35** |
| **78 month telephone follow up** | | **$15** |

**What Are My Alternatives to Participating?**
Your participation in this study is voluntary. You may choose not to participate in this research study.

**Who Will See The Study Records?**
To the extent possible, your participation in this study will remain private. The principal investigator as well as people from the NIH (National Institute of Health) and the Data and Safety Monitoring Committee may review your medical records about this study. However, private industry supporters will not have access to your medical records about the study. The SARP investigators will have access to the information that you have agreed to share. The results of this study may be published in scientific journals or be presented at medical meetings; however, individual patients will not be identified by name. The data will be coded with a number. Only the Investigator and his study staff at this site have access to the code that links your name with your study number and data. Paper copies are kept in a locked file cabinet in locked rooms, electronic data is password protected.

## WHAT ABOUT MY HEALTH INFORMATION?

In this research study, any new information we collect from you and information we get from your medical records or other facilities about your health or behaviors is considered Protected Health Information. The information we will collect for this research study includes**:** questionnaire information, blood and serum, DNA, RNA, sputum cells, and bronchoscopy fluid.

If this research study involves the diagnosis or treatment of a medical condition, then Protected Health Information collected from you during this study may be placed in your medical record, and may be used to help treat you, arrange payment for your care, or assist with Medical Center operations.

We will make every effort to keep your Protected Health Information private. We will store records of your Protected Health Information in a cabinet in a locked office or on a password protected computer. Only the following people or organizations will be granted access to your Protected Health Information:

1) The study investigator and his/her staff, or others at Wake Forest University Health Sciences who oversee research

2) Other people or laboratories providing services for this research project on behalf of Wake Forest University Health Sciences and Wake Forest University Baptist Medical Center

3) Brigham and Women's Hospital, Boston, MA, Cleveland Clinic, Cleveland, OH, Emory University, Atlanta, GA, University of Virginia, Charlottesville, VA ,University of Pittsburgh, Pittsburgh, PA, University of California San Francisco, CA, University of Wisconsin, Madison, WI and Washington University, St. Louis, MO
4) FDA (Food and Drug Administration)
5) SARP Data Coordinating Center, Penn State University College of Medicine, Hershey PA
6) SARP Data Safety Monitoring Board (DSMB)
7) NIH/NHLBI (National Institute of Health/ National Heart, Lung, and Blood Institute)

If required by law or court order, we might also have to share your Protected Health Information with a judge, law enforcement officer, government agencies, or others. If your Protected Health Information is shared with any of these groups it may no longer be protected by federal or state law.

Any Protected Health Information collected from you in this study that is maintained in the research records will be kept for an indeterminate period of time. This authorization does not expire and any research information entered into your medical record will be kept for as long as your medical record is kept by the Medical Center. You will not be able to obtain a copy of your Protected Health Information in the research records until all activities in the study are completely finished.

You can tell Dr. Wendy Moore that you want to take away your permission to use and share your Protected Health Information at any time by sending a letter to this address:

Dr. Wendy Moore
[redacted]

However, if you take away permission to use your Protected Health Information you will not be able to be in the study any longer. We will stop collecting any more information about you, but any information we have already collected can still be used for the purposes of the research study.

By signing this form you give us permission to use your Protected Health Information for this study.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the

website will include a summary of the results. You can search this Web site at any time.

**Certificate of Confidentiality**

To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of Federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

The Certificate of Confidentiality does not prevent the researchers from disclosing voluntarily, without your consent, information that would identify you as a participant in the research project if required by law (e.g. child abuse, reportable communicable disease, threat of harm to self or others) or as required by state or federal agencies who may review our records under limited circumstances, (e.g. such as a U.S. Department of Health and Human Services (DHHS) request for information for an audit or program evaluation or an FDA request under the Food, Drug and Cosmetics Act.)

**Will There Be Any Costs To Me?**

There will be no charge to you for participation in this study.

**Will There Be Compensation For Injury?**

Should you experience a physical injury or illness as a direct result of your participation in this study, Wake Forest University Health Sciences maintains limited research insurance coverage for the usual and customary medical fees for reasonable and necessary treatment of such injuries or illnesses. To the extent research insurance coverage is available under this policy the reasonable costs of these necessary medical services will be paid, up to a maximum of $25,000. Wake Forest University Baptist Medical Center holds the insurance policy for this coverage. It provides a maximum of $25,000 coverage for each claim and is limited to a total of $250,000 for all claims in any one year. The Wake Forest University Health Sciences, and the North Carolina Baptist Hospitals, Incorporated do not assume responsibility to pay for these medical services or to provide any other compensation for such injury or illness. Additional information may be obtained from the Medical Center's Director of Risk and Insurance Management, at [redacted].

**If I Start This Study, Can I Stop?**

If you choose not to participate in this study, your doctor will continue to treat your asthma. Your participation is voluntary. You are free to refuse to participate in the study and may stop participating in the study at any time without any change in the quality of medical care to which you are entitled. Your physician may also end your participation in the study if he/she judges it to be in your best interest. Your participation in the study may be stopped for any of the following reasons:

A. Failure to follow the investigator's instructions
B. A serious adverse reaction, which may require evaluation
C. If the investigator feels it is in the best interest of your health and welfare

In addition the investigator or the NIH may end your participation in the study at any time with or without your consent.

**Sample Storage and Shared Procedures:**

Below, we describe the different kinds of information that we will collect about you for this research study.

1. *Sharing and Storing of* ***Questionnaires, Test Results and Samples****:* During the course of this study, the study investigator Dr. Wendy Moore, or a member of the study team will ask you to answer questionnaires about your medical history including information on your asthma, current symptoms, present and past medical treatment, asthma triggers and the impact of asthma on your life, your age and place of birth. You will also be asked to do breathing tests, blood tests and other research related studies, and collect sputum cells/fluid, urine, exhaled breath condensate and blood samples. The results of these questionnaires, tests, and some of the samples will be used now. Some of the information and left over samples will be stored for studies to be done in the future. The information and samples may be stored for up to 50 years to look at scientific questions related to asthma, allergies and related diseases. The questionnaires, test results and samples will be handled in a manner that protects your privacy; they will only be identified by a code. Only Dr. Wendy Moore and the Wake Forest University Health Sciences study team will have the link between the code and your name. The investigators may share the stored questionnaire data, test results or tissue/samples with other investigators in the SARP or other groups for research related to asthma, allergy and inflammation. However, your identity will be kept private as only the code will identify your sample now and in the future.

   The sharing and storing of the questionnaire data, test results and samples is not optional. If you do not want to have your questionnaire data, test results or samples shared or stored with the other investigators in SARP or other groups researching asthma, allergy and inflammation, you will not be allowed to join this study.

2. ***Genetic*** *Studies* - A blood sample (3 tablespoons) will be collected to evaluate genetic information (DNA, RNA) that may be related to the development of asthma, allergy, respiratory and related diseases. No other genes will be studied. DNA is the genetic

material contained in all the cells of your body, including blood cells. RNA is genetic material that carries instructions from DNA for controlling the building of proteins. Your blood will also be tested for the numbers of eosinophils (white blood cells thought to be important in asthma) and IgE (a protein that is elevated in people with allergies). The samples will be collected and coded such that only the primary investigator at the Wake Forest University Health Sciences will be able to link your genes to you.

. Work with your DNA and RNA will be done mainly at Wake Forest School of Medicine (Winston-Salem, NC) but also at other SARP centers as well. Your name and participation in these studies will be private. Your genetic samples will be identified only by an ID number (not your name), and no genetic testing will be performed other than that associated with asthma, allergy, respiratory and related diseases. Any identifying data is kept in a locked drawer or in a password protected computer file. Only the Principal Investigator of this study and his designated data manager will have access to the numeric code, which identifies you by name. These results will NOT be put in your medical records. No HMOs or insurance companies will ever be allowed access to the genetic results.

As part of the genetic study, a sample containing your genetic information may have Genome Wide Association Studies (GWAS) or Whole Genome Sequencing (WGS) performed. The GWAS analysis creates a very detailed picture of your genetic information for researchers using up to 2 million genetic markers. WGS is an analysis of your complete genetic code and has the capability to identify nearly all genetic mutations in your genetic information.

In addition, your genetic information and clinical information about be sent to the National Institute for Health's Genome Wide Association Study (GWAS) data repository, where it will undergo genome-wide analysis and be shared with other investigators for research purposes. Genetic information will be sent to the GWAS will help researchers better understand how genes affect the risk of developing diseases such as asthma, cancer, diabetes, and heart disease, and may lead to better methods to select the best treatment options. Before your information is sent to the GWAS data repository it will be de-identified, which means that we will remove any identifying information such as your name, date of birth, address, etc. The code that once linked the data back to you will be removed prior to the data being sent to the NIH GWAS data repository. Thus, researchers using your DNA and clinical data will not be able to link this information back to you.

The laboratories that are processing genetic information are research facilities and do not have the ability to provide genetic test results or genetic counseling Genetic information about you or other information obtained from your sample will not be given to you, your family or your doctor. You may withdraw consent for the use of your genetic information at any time by contacting Dr. Wendy Moore at [redacted]. What about my genetic information:

a) Although the genetic information about you is shared with other investigators in the network, it is identified with a code number and not your name or other identifiable information. Only researchers at the Wake Forest University Health Sciences will

be able to link your information with your name.

b) Results from research using your samples may be presented in publications and meetings but individual names will not be identified.

c) Absolute privacy cannot be guaranteed as the U.S. Department of Health and Human Services has the right to inspect your medical records relating to this research for the purposes of verifying data. Demographic information on the subjects is released only to characterize our populations for the National Institutes of Health.

d) In order to protect records, 1) only allowed users will be able to see the records, 2) the records will be kept in offices that are locked when not in use, and 3) access is strictly controlled. The records collected in this study will be subject to the Privacy Act. Records will not be shown to any person or agency, unless the person who the records are about gives a written request or prior consent. The request should be made in writing to the Privacy Act Coordinator, NHLBI, NIH, [redacted].

**3. Long Term Extension -** We would like to extend the SARP study beyond the original three years to the SARP Long-term Extension. This is still part of the same SARP study with up to 3 additional years of visits, which will make SARP up to six years in total. Details of these visits can be found at the end of the consent form in Appendix 1. An explanation of each procedure is found in the main part of the consent form. Study procedures at each of these Long-term Extension visits include a medical and asthma history, asthma questionnaires, online asthma symptoms questionnaire, urine pregnancy test, urine for lab studies, physical exam, spirometry, maximum bronchodilator response, exhaled nitric oxide (ENO), exhaled breath condensate (EBC), sputum induction, and blood draw. Blood will also be drawn at either Visit 8 or Visit 9 for genetics and other test. If you do not agree, then you will stop the study after Visit 6 (Year 3). If you do agree, then you will continue in the study beyond Visit 6. Let us know whether you agree to stay in SARP for the Long-term Extension:

_____ (initial) I agree to stay in the SARP study after Visit 6 for the Long-term Extension.

_____ (initial) I DO NOT agree to stay in the SARP study after Visit 6 for the Long-term Extension.

4. **Fasting Blood Draw –** We would like to collect a sample of blood from you at Visit 6 after you have fasted for 12 hours, details of which are discussed above. If you are unable to fast for your SARP visit, we will either ask you to return another day for a brief visit to collect the fasting sample or we will not perform the fasting blood draw at all. If you cannot fast or elect not to, then you will still be eligible for the study and we will go on with the study procedures by making a note that you have not fasted.

_____ (initial) I agree to provide a fasting blood sample at Visit 6 or a subsequent brief visit, if necessary.

_____ (initial) I DO NOT agree to provide a fasting blood sample at Visit 6 or a subsequent brief visit

**Future Contact**

Occasionally we may want to contact subjects who did our studies in the past to see if they are interested in new projects. Your name and contact information will be kept in a database at the Wake Forest University Health Sciences. If you agree to be in this database, you may be contacted in the future to see if you are interested in participating in more studies. The results of your breathing tests will be included in this database, and this information may be used to see whether you qualify for future research studies. The database is password protected, and only immediate research staff will have access to the information. There is a very small chance that your name, contact information and your screening information could, in error, be made public. Please let us know whether you would like to be called or not by putting your initials in one of the spaces below.

_____ I would like to be contacted for future research studies.

_____ I **DO NOT** want to be contacted for future research studies.

**Who Will Answer Questions?**

You may freely ask questions about this informed consent or the study now or at any time during the study. If you experience an adverse reaction, have questions about the research or experience a research related injury you may contact Dr. Wendy Moore or one of his associates at [redacted].

If you have questions about your rights as they relate to your participation in this study, you may contact the Chairman of the Institutional Review Board at The Office of Research, Wake Forest University Health Sciences, [redacted] or by telephone at [redacted]. The Institutional Review Board is a group of people who review research to protect your rights

**Authorization**

Subject **Name (Printed):**_____

Subject Signature: _____Date: _____Time:_____ am pm

Person Obtaining
Consent: _____Date:_____Time:_____ am pm



WFU School of Medicine
Institutional Review Board
IRB Number: IRB00021507
Meeting Date Approved 3/15/2021
Version Valid Until: 9/17/2021

WAKE FOREST UNIVERSITY HEALTH SCIENCES

Appendix 1

| | Characterization | | | Longitudinal Follow-up | | | | | | Long-term Extension | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Minimum Procedure Set** | Baseline | Steroid Responsiveness | | 6 mos[2] | 12 mos | 18 mos[2] | 24 mos | 30 mos[2] | 36 mos | Annual PC[2] | Annual clinic visit | |
| | V1[1] | V2 (pre) | V3 (post) | | V4 | | V5 | | V6 | | V7 | V8-V9 |
| Visit scheduling window (6 month to V6 calculated from time of enrollment) | Max BD must be w/in 6 weeks of V2 | | 18 ± 3 days from V2 | 6 mos ± 60 days | 12 mos ± 90 days | 18 mos ± 60 days | 24 mos ± 90 days | 30 mos ± 60 days | 36 mos ± 90 days | ± 60 days | ± 90 days | |
| Consent and eligibility | x | | | | | | | | | | | |
| SARP 3 Questionnaires | x | | | x | x | x | x | x | x | x | x | X |
| Validated questionnaires | x | x | x | x | x | x | x | x | x | x | x | X |
| Physical exam/VS/Hgt/Wgt/BMI | x | | | | x | | x | | x | | x | X |
| Spirometry | x | x | x | | x | | x | | x | | x | X |
| Max bronchodilation | x | x | x | | x | | x | | x | | x | X |
| Methacholine | x | | | | | | | | | | | |
| Urine pregnancy test | x | x | x | | x | | x | | x | | x | X |
| Urine collection | | x | x | | x | | x | | x | | x | |
| Sputum induction (ages 12 and above) | | x | x | | x | | x | | x | | x | |
| Exhaled nitric oxide | | x | x | | x | | x | | | | X3 | |
| Exhaled breath condensate | | x | x | | x | | x | | x | | X4 | |
| Blood sample | | x | x | | x | | x | | x | | x | X5 |
| CT Scan (only some subjects) | x | | | | | | | | | | | |
| Bronchoscopy (only some subjects) | | x | x | | | | | | | | | |
| ImmunoCap (includes IgE) | | x | | | | | | | | | | |
| Corticosteroid treatment | | x | | | | | | | | | | |
| Online Asthma Exacerbation Ques. | Monthly or as exacerbations occur | | | | | | | | | | | |

[1]Testing in V1 may be completed on several days as determined by individual site standard operating procedures

[2]Subject contact by telephone only. (PC = Phone Contact)

[3]Exhaled Nitric Oxide will only be collected at Visit 7 of the Extension Study. Exhaled nitric oxide will not be collected at Visit 8 and Visit 9 of the Extension Study.

[4]Exhaled Breath Condensate will only be collected at Visit 7 of the Extension Study. Exhaled breath condensate will not be collection at Visit 8 and Visit 9 of the Extension Study.

[5]At either visit 8 or Visit 9