Research Subject Information and Consent Form

Title of study: BARD - Best African American Response to Asthma Drugs
Study investigator: Robert F. Lemanske, Jr, MD, University of Wisconsin-Madison
608-263-6184
Co-Investigator: Lisa Sullivan Vedder, MD, Aurora Health Care, Milwaukee
414-219-5970

In this consent form, ‘you’ always refers to the participant (person who is taking part in the study). If you are a legally authorized representative of a minor (such as the parent), please remember that ‘you’ refers to the child.

This consent describes a study being done at the University of Wisconsin-Madison and at Aurora Health Care in Milwaukee, WI. Research studies help us learn more about conditions and possible new treatments. Research studies are voluntary, which means that it is your choice whether or not to take part in the study. The study staff will explain the study and answer any questions that you may have before you make a decision.

You are invited to join this research study because you are least 5 years of age, are of African American/Black ancestry (have at least 1 African American/Black grandparent) and you have asthma. This consent form explains the study and any risks that may be involved. Please take your time making a decision. Feel free to discuss the study with your family and doctors. Please ask the study doctor or the study staff to explain anything that is not clear to you. If you decide not to take part in the study, the relationship you have with the study site and its doctors (including your health care providers) will not change in any way.

WHAT IS THE PURPOSE OF THIS STUDY?
African American/Black children and adults with asthma sometimes don’t get better when they take the usual dose of inhaled steroid used to treat asthma. When this happens, doctors do not know if they should increase the dose of the inhaled steroid, or add a long-acting bronchodilator medication like Serevent®, or have the person start a combination medication like Advair®, Symbicort® or Dulera®.

The purpose of this study is to compare asthma treatments for African American/Black people who have asthma that is not well controlled on a low dose of inhaled steroid. This study will also try to find out if African American/Black adults and children differ in how they respond to the medications used in this study.

The study will also try to see if your genes (DNA) or chemicals in your blood, urine or phlegm (lung mucus) can predict the response to asthma treatment. It will also study whether your home or work environment might have an effect on the response to asthma treatment. Lastly, this study will try to see if taking different asthma medications makes economic sense.

WHO IS THE SPONSOR OF THIS STUDY?
The sponsor of this study is ‘AsthmaNet’, a network of centers funded by the National Institutes of Health (NIH) National Heart, Lung, and Blood Institute (NHLBI). The Network’s purpose is to develop and carry out research on asthma and the best
treatments for it. Nine AsthmaNet research centers across the United States are taking part in this study. UW-Madison is one of them. Aurora Health Care in Milwaukee is collaborating with the UW-Madison site for this study.

**HOW MANY PEOPLE WILL BE ENROLLED?**
As many as 1000 people across the nation may need to be screened for this study so that 494 can take part in the study. Up to 50 people will take part at the Wisconsin sites.

**WHAT WILL HAPPEN IF I TAKE PART IN THIS RESEARCH STUDY?**

**AsthmaNet Registration**
Before you enroll in an AsthmaNet study, you must first be entered into the AsthmaNet 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 AsthmaNet identification number. No information that directly identifies you will be entered into the AsthmaNet Registry database or sent to the Data Coordinating Center (Penn State University, Hershey, PA). Registry data help us track your being in multiple AsthmaNet studies over time. Knowing that you were in more than one study is useful when we look at study results.

Your agreement to provide the information for the AsthmaNet Registry is voluntary. However, if you choose not to provide it, you cannot be screened for or take part in any AsthmaNet study. Once you consent to be entered into the Registry, your information cannot be removed and will be kept in the study database into the future. You will only be asked to supply Registry information one time. Registration happens before or during your first study visit.

**African American/Black Ancestry**
You will be able to join this study if you identify yourself as being of African American/Black ancestry. You must have at least one African American/Black grandparent (blood relative). We will estimate your degree of African descent by a genetic blood sample. The genetic blood sample is required for this study. The results of the genetic testing will not be provided to you. This is because we will be looking at hundreds of thousands of genes to look for clues that could help us learn more about asthma, and no one knows what such tests mean for a given person.

**Study Parts**
This study has two main parts: run-in and treatment. The whole study lasts 66-68 weeks (about 1 year and 4 months) with 15-18 study visits and 10 scheduled telephone calls. Study visits are from 15 minutes to 2.5 hours long, with most visits taking about an hour. Phone calls usually take less than 10 minutes to complete. If your asthma worsens during the study, you may be asked to come in for extra safety visits.

**Run-in (2-12 weeks long):** The study run-in has between 2 and 5 visits over 2-12 weeks. Run-in visits take place every 2-4 weeks. The length of the run-in will vary from person to person. There will be up to 2 scheduled telephone calls.

The purpose of the run-in is to find out if you qualify for the study. Those people who are not well controlled on a low dose (amount) of inhaled steroid will qualify. We may need to
switch your asthma controller medication to a low dose of inhaled steroid. We will check you to make sure that you are safe on this dose. If you are taking a high dose of a controller medication when you sign up for the study, we will switch you to a medium dose for 2 weeks and then step your dose down to the low dose, as long as it is safe for you. If you need to start the study on the higher dose of the study controller medication, an extra study visit will be needed.

We will check your asthma by having you do breathing tests at study visits and at home. Breathing tests at study visits include pulmonary function tests (these are described in study procedures, below). Breathing tests at home are peak flow measurements. You will keep track of your symptoms in an electronic diary called a Spirotel®. We want to make sure that your asthma is not too mild or too severe for the study. This part of the study may take up to 12 weeks.

**Treatment (56 weeks long):** If you qualify before the end of the run-in, you will have 13 more study visits over 56 weeks. These visits will happen every 2-6 weeks. Breathing tests and questionnaires will be done at each visit. Height will be measured at all visits for participants less than 21 years of age. Spirotel® information and medication use will be reviewed. Used medicines will be collected and new medicines will be given to you. Eight telephone calls will be scheduled during this time to check your asthma. If your asthma worsens during the study, you may be asked to come to the clinic for one or more extra safety visits.

**Study Procedures**

**Spirometry:** For this breathing test, you will wear a nose clip and breathe hard into a machine, called a spirometer. The machine measures how fast and how much air moves out of your lungs. You will be asked to blow into the spirometer several times during each visit. This test will be done at most visits.

**Albuterol reversibility:** This test measures improvement in your breathing. You will perform spirometry and take 4 puffs of albuterol. You will repeat spirometry 15 minutes later. This will be done 5 times during the study to see if the study treatments change your results. If you are doing sputum induction (explained below), you will have this test done one additional time, at the sputum induction visit.

**Methacholine challenge testing:** You will be asked to breathe in gradually increasing doses of methacholine. Methacholine is a drug that can cause narrowing of the airways in people with asthma. Spirometry will be done before the methacholine test is started and after you breathe in each dose of the methacholine. The test will stop after you have been given the last dose or if your spirometry drops by a certain level (20% or more). You may have asthma symptoms during this test. The study staff will give you albuterol to make any symptoms go away. This test will be performed by trained staff, and a study doctor will be available at all times. This test will be done 1 time.

**Sputum induction (only Madison participants):** This test will be done 1 time if you are at least 12 years old. You will take 4 puffs of albuterol to open your airways. You will then be asked to breathe in a salty mist for up to 12 minutes. Every 2 minutes you will be asked to cough deeply and strongly to bring up mucus from your lungs (sputum).
Urine cortisol: This test is done to see how your body responds to the different doses of study inhaled steroid. You will be asked to collect all of your urine from bedtime at night to when you get up in the morning. The collections will be done the night before 5 scheduled visits to the clinic (5 collections during the study). You will bring the collected urine to your visit. Leftover urine will be saved to study markers of asthma and allergy.

Urine pregnancy testing: If you are a female and can become pregnant you will have a urine pregnancy test up to 6 times during the study. You cannot join or continue in the study if the pregnancy test is positive. The study doctor will inform you of a positive pregnancy test result.

If you are able to get pregnant (that is, you are a female who has begun menstruating and you are not surgically sterile or post-menopausal), you must use birth control during the entire study. 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.

If you are sexually active, there is a risk that pregnancy could still occur despite using birth control. You should notify the study doctor or staff as soon as possible of any birth control failure or if you become pregnant. If you become pregnant, the clinical center will ask you for permission to call you to ask about your pregnancy. If you are willing to provide it, this information would be given to the companies who make the drugs used in the study. (Drug companies are required to report the effects of exposures to drugs during pregnancy in a clinical trial.)

Pregnancy testing in minors. Urine pregnancy testing will be performed on every female who has begun menstruation (has had at least one period). The first pregnancy test is done to find out if the participant is eligible for the study. If this first pregnancy test is positive, she will not be able to join the study. Results from pregnancy tests done during the study may be reported to both the minor and her parent/guardian.

Blood draw: You will give a blood sample once during the study. All of the blood can usually be collected with 1 needle stick. However, if we are unable to take the full sample at visit 1, then we may try again at another visit. Blood tests include a complete blood count, serum cotinine level (a measure of cigarette smoke exposure), and markers of allergy and asthma. We will also take a blood sample for genetics testing. Much more information about the genetic test is explained in its own section at the end of this consent form.

Blood will be taken from a vein in the arm using a needle. Children ages 5-11 will be asked to provide about 20 ml (about 1.5 tablespoon). Half of this will be used for genetic analysis. Adults and adolescents (ages 12 and up) will give about 42 ml (about 3 tablespoons). 30 ml (2 tablespoons) will be used for genetic analysis.

Medical history: You will be asked about your current and past health. You will also be asked about prescription and over-the-counter medications, nutritional/herbal supplements and vitamins that you use.
**Physical examination:** A thorough examination (check-up) will be done at the first visit to make sure that it is safe for you to participate. Another will take place at the last visit. The exam may include listening to your lungs and heart, looking into your ears, nose and throat, and measuring your height, weight, blood pressure and heart rate. If you are under 21 years of age, you will have your height measured at most visits. If you are 18 or older, at certain visits we will also measure the size of your waist, neck, and hips. A short check-up will be done at the randomization visit.

**Questionnaires:** You will be asked to complete different types of questionnaires dealing with medical facts about you and your family and your environment. You will be asked how your quality of life is affected by asthma and how asthma affects your work and/or schoolwork. You will also be asked about your socioeconomic status (household income, educational level) and stress in your life (ages 12 and older only). Lastly, when you leave the study you will be asked to complete an optional anonymous questionnaire about how you felt about being in the study.

**Peak flows/e-diary entries and medication use:** You will get a small device (tool) to use to check your breathing and record your asthma symptoms twice every day. The device is called a Spirotel®. Study staff will teach you how to use the Spirotel®.

At each visit, study staff will review your peak flows and symptom scores collected with your Spirotel®. The purpose is to look over your asthma symptoms and asthma control since your last visit. The coordinator will also check your medication use. These steps are to ensure that you are doing as asked with the at-home study procedures.

**Telephone contacts:** You will be called for scheduled telephone interviews with study staff to find out about your symptoms and medication use and to see if you have had any problems or if you have any questions.

**Study Medications (fluticasone and salmeterol).**

**Run-in medication (2-12 weeks long):** All study participants will be asked to take fluticasone (Flovent®) one puff twice a day during the run-in. Fluticasone is an inhaled steroid (an asthma controller medication). It is FDA-approved for the treatment of asthma and has been described as being very safe and well tolerated in millions of people. It can be given to children as young as 4 years of age. The run-in fluticasone will always be active medication. It will never be placebo (fake or inactive) medication.

The run-in dose for participants who are 5-11 years old will be 50 micrograms (mcg) of fluticasone per puff. Participants 12 years and older will receive 100 mcg of fluticasone per puff.

It may take more than one run-in visit to have your current asthma controller medication switched over to this dose of run-in fluticasone. People who are taking a high dose of an asthma controller medicine when they enter the study will take a higher dose of run-in fluticasone for the first 2 weeks (participants ages 5-11 will be given 100 mcg of fluticasone per puff and participants ages 12 and older will be given 250 mcg of fluticasone per puff for 2 weeks). These participants will have an extra run-in visit to decide if it is safe to put them on the lower run-in dose and continue in the study.
Treatment medication (56 weeks long): Once you finish the run-in, you will have a randomization visit (Visit 1) to start the treatment phase. During this part of the study, the medications become a secret and will change every 14 weeks. You might get a higher dose of fluticasone, or a long-acting beta-agonist might be added, or both. The long-acting beta-agonist is called salmeterol. It acts like a 12-hour albuterol and should be taken every day on a schedule, rather than just to treat symptoms. Salmeterol is FDA approved for the treatment of asthma. It can be prescribed to someone as young as 4 years of age. Salmeterol and fluticasone will be packaged together in one Diskus® so that puffs are taken from only one inhaler (like Advair®). Fluticasone will also be given to you in the Diskus® form.

Each person will have 14 weeks on each of the four possible treatment regimens. The order of these treatments will be decided randomly, like flipping a coin. You and the study staff will not know which treatment you are getting at any point in the study after you are randomized.

Treatment regimens (taken twice a day) for participants who are 5-11 years old:
- fluticasone 100 mcg PLUS salmeterol 50 mcg per puff
- fluticasone 100 mcg per puff alone
- fluticasone 250 mcg PLUS salmeterol 50 mcg per puff
- fluticasone 250 mcg per puff alone

Treatment regimens (taken twice a day) for participants who are at least 12 years old:
- fluticasone 100 mcg PLUS salmeterol 50 mcg per puff
- fluticasone 250 mcg per puff alone
- fluticasone 250 mcg PLUS salmeterol 50 mcg per puff
- fluticasone 500 mcg per puff alone

Rescue medication: An FDA approved short-acting ‘rescue’ bronchodilator medication called albuterol will be given to you. It will help open the airways and take care of asthma symptoms. You can use it as needed during the study to treat asthma symptoms. You will be given an action plan that explains proper use of this medication. Children will be given a spacer for use with this medication, if needed or preferred.

Prednisone ‘Rescue’ Pills (for emergency use only): You will be given a supply of prednisone to keep at home. This prednisone can only be used if you are having a bad asthma attack AND study staff or a treating physician tells you to take it. Your asthma action plan will tell you when and who to call for prednisone instructions. You should not take prednisone without first informing the study staff.

At Home Procedures
Completing all of the home procedures should take a few minutes twice each day. Try to do the procedures about the same time each day. It is VERY important that you understand how to measure your peak flow, how to complete the electronic diary, and how to take the study drugs. Please ask questions until these procedures are CLEAR to you. If you don’t do the home procedures, you might be asked to leave the study.
Please bring all study supplies and inhalers with you to ALL study visits, **including empty inhalers and your Spirotel®.**

**Peak flow monitoring:** You will be asked to check your peak flow in the morning and evening every day of the study. The study will give you a Spirotel® device to use, but it must be returned at your last visit. The electronic peak flow meter is combined with an electronic or e-diary in the Spirotel® device. Peak flow and e-diary data will be stored in the device until your next study visit when it will be transferred to a study database.

**E-diary:** Before you use the Spirotel® device to take your peak flow in the morning and the evening, it will present you a series of questions about your asthma symptoms and rescue medication use. You will be expected to answer these questions twice a day.

**Study Diskus®:** You will be asked to take one puff twice each day throughout the study, and to bring the Diskus® to study visits.

**WHERE WILL THE STUDY VISITS TAKE PLACE?**
All study visits and procedures will be done at the University of Wisconsin-Madison and/or at Aurora Health Care in Milwaukee, WI.

**CAN I STOP BEING IN THE STUDY?**
Yes, you can decide to stop at any time. It is important to tell the study doctors if you are thinking about stopping. They can check for and explain any risks from stopping your study medications. They may wish to discuss follow-up care and testing after you leave the study. The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest, if you do not follow the study rules, or if the study is stopped by the sponsor.

**ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?**
There is no guarantee of direct benefit to you from participating in this study. But there is a chance for improved asthma control from one or more of the treatment arms of this study. You will be getting FDA-approved and recommended asthma treatments while in this study. No one will be deprived of asthma treatment. While you are in the study you will have asthma care provided by a study doctor. It is likely that your asthma will be monitored more closely than if you went to your usual health care provider. We will give you information about asthma and about staying away from asthma triggers. Your asthma may or may not improve while in this study. However, the results of this study will help doctors learn more about treating people with asthma in the future.

**WHAT SIDE EFFECTS OR RISKS CAN I EXPECT FROM BEING IN THE STUDY?**
You might experience some side effects and discomfort while in this study. The study doctors and study staff will check you closely. During the study, you should contact the study staff immediately if you experience any severe side effects, or if you need medical advice. Madison participants, please call Robert Lemanske, Jr. MD at 608-263-6184. Milwaukee participants, please call Lisa Sullivan Vedder, MD at 414-219-5970.

The medications and procedures in this study may have risks that are not possible to predict. Below is a list of the risks we know about for each medication and procedure. If you have any of these problems, you should tell the study doctor or study staff.
Study procedure risks

Blood collection: A blood draw may cause pain, bleeding, bruising and rarely, infection. Lightheadedness and fainting rarely occur. A numbing cream called EMLA may be put on the skin before the blood draw to reduce the pain of the needle stick. Side effects from this cream (mainly skin rash) are rare, but may occur. Study staff will take care to prevent these blood draw risks or to correct them should they arise.

Spirometry: Breathing fast and hard into a spirometry machine or peak flow meter can cause coughing, lightheadedness, and chest tightness. This should go away shortly after the test is finished.

Methacholine challenge: This test can cause coughing, chest tightness, shortness of breath, and wheezing. Albuterol will be given at the end of this test to reverse any symptoms. If your symptoms are severe, albuterol will be given immediately and the challenge will be stopped. There is a small chance that a severe asthma attack could occur while doing this test. A study doctor will always be available to treat you immediately if this occurs.

Albuterol reversibility: Taking the 4 puffs of albuterol required for this test can cause a fast heart rate and high blood pressure, nausea, headache, and a jittery or nervous feeling. These symptoms usually go away without treatment in less than an hour.

Sputum Induction (Madison participants only, done once if you are at least 12 years old): Breathing in salty mist may cause an unpleasant salty taste. Coughing hard to produce sputum can cause a sore throat. This test can also cause coughing, chest tightness and shortness of breath. These symptoms are usually prevented by the albuterol treatment given before sputum induction. The 12-minute test will be stopped if your lung function gets worse.

Urine Pregnancy Test: There are no known risks for the pregnancy test. There may be unknown risks to the fetus/unborn child if you become pregnant while in this study. Although there is the requirement for birth control explained above, you should notify your study doctor or study staff immediately if you become pregnant during the study. You must stop the study if you become pregnant.

Questionnaires: There are no known risks to answering the questions. You may refuse to answer any questions that make you feel uncomfortable. The questionnaires are not tests, and there are no right or wrong answers.

Risks related to study medications.
Your asthma treatment might change when you join this study. You will have to stop taking your own asthma medications and start taking the study medication, fluticasone. It is possible that changing asthma medications might worsen your asthma.

This study plans to enroll people who are not well controlled on a low dose of inhaled steroid. You may have asthma symptoms during the study that would need to be evaluated and possibly treated with additional medications.
During the study your asthma treatment will change among 4 different treatment regimens. It is possible that changing the study medication might worsen your asthma.

There is a chance that you could be allergic to any medication given in this study. If your breathing suddenly worsens, your face, throat, lips or tongue swell, you get hives, itching or a rash, you could be having an allergic reaction. If signs of an allergic reaction occur, stop the medication and contact the study staff/study doctor immediately.

**Fluticasone (Flovent® Diskus®, also present in Advair® Diskus®):** Fluticasone is an FDA-approved inhaled corticosteroid. Inhaled steroids are the most common medications used for asthma control. The most common side effects from inhaled steroids are throat irritation, hoarseness and a yeast infection of the mouth or throat (known as thrush or oral candidiasis). To avoid these side effects, you will be asked to rinse your mouth with water and spit the water out each time you use the inhaler. Some people get a headache from taking fluticasone.

Other less common risks include upper respiratory tract infection or inflammation (for example, the common cold, sinus infection, runny or stuffy nose), nausea and vomiting, gastrointestinal discomfort, viral gastrointestinal infection, non-specific fever, viral infection, viral respiratory infection, cough, bronchitis, muscle injury, musculoskeletal pain, and injury.

Long-term use of steroid medications taken by mouth or inhaled like fluticasone may cause thinning of the skin, changes to your bones or eyes, and may weaken your body's ability to handle stress due to other medical conditions like infections. The risk is greater when the steroid doses are higher and used for a long time. These side effects are not expected because you will be taking the study doses for only a short time.

The biggest concern for young children taking fluticasone is the possible effect on growth. “Catch-up” growth after stopping this medication has not been fully studied. The height of all children in the study will be carefully measured at each study visit.

**Salmeterol (also present in Advair® Diskus®):** Salmeterol is an FDA-approved long-acting beta-agonist (LABA) medication that relaxes the airways. It acts like a 12-hour albuterol and has side effects similar to albuterol. The main risks from salmeterol are headache, nervousness, dizziness, cough and nasal congestion. Less frequent side effects are difficulty sleeping, chest pain and irregular heartbeat.

The FDA has required that there be a “boxed warning” about the small risk of death that was seen in a large study of people with asthma who were treated with LABA medications. In that study more patients who used salmeterol died from asthma problems (13 out of 13,176) compared with patients who did not use it (3 out of 13,179).

National consensus guidelines for the treatment of asthma have reviewed this information and have included LABA medications in the suggested treatment plan for patients with asthma of your severity as long as they are combined with an inhaled corticosteroid. We are only providing the LABA medication with an inhaled steroid as recommended by these guidelines. If you have any questions or concerns about this information, please discuss them with the study staff or doctor.
**Prednisone:** Prednisone is an oral steroid. It will only be used if you develop severe asthma symptoms that are not controlled with your daily asthma medications or albuterol. The most common side effect from taking prednisone is heartburn. The risk is less if the medicine is taken with food. Other common side effects include increased appetite (the “munchies”), nervousness, restlessness, or trouble sleeping. Oral steroids can cause hoarseness, sore throat, and yeast infections of the mouth or throat if taken at high doses for long periods of time. They can also cause weight gain, growth delay, bruises of the skin, cataracts (cloudiness in your vision), and diabetes. These effects are more likely if the medicine is taken at very high doses for long periods of time. These side effects are not likely in this study because of the short length of time (5 days) that oral prednisone will be taken, if it is needed.

A very uncommon side effect has been reported with prednisone in which the hip bone weakens or breaks down. While this effect tends to be related to longer prednisone use, it has been reported after short courses.

**Albuterol:** Albuterol is the “rescue” inhaler used to treat sudden worsening of asthma symptoms. Risks include fast heart rate and high blood pressure, nausea, dizziness, nervousness, difficulty sleeping, headache, and a jittery or nervous feeling. These symptoms usually go away within one hour. It is likely that you already use albuterol and you are familiar with how you react to this medication.

**Other study risks.**
There is always the risk of having a previously unknown side effect. You will be told of any major new findings. The investigator or study staff is willing to discuss any questions you might have about these possible risks and discomforts.

There is a very small risk of loss of confidentiality through unintentional disclosure of protected health information (PHI).

**WHAT OTHER CHOICES DO I HAVE IF I DO NOT TAKE PART IN THIS STUDY?**
Taking part in this research study is voluntary. You may choose not to participate. You do not have to join this study to receive treatment for asthma. There are many alternative asthma treatments. Feel free to talk to your doctor before deciding if you will take part in this study. If you join the study and want to start another asthma treatment, you must first tell the study doctor or coordinator.

**WILL MY MEDICAL INFORMATION BE KEPT PRIVATE?**
Study personnel will treat your identity with professional standards of confidentiality. They may look at your medical records to confirm information related to deciding if you are eligible to join the study. Some aspects of the medical information gathered from this study may become part of your permanent medical record (routine asthma and allergy information). Your identity, medical records and data related to this study will be kept confidential, except as required by the law. Your records regarding this study may be subject to review by appropriate officials of the UW Hospital and Clinic and Aurora, the National Institutes of Health (NIH) and their agents, and the FDA, should the need arise. The results of this study may be published or presented at medical meetings. However, you will not be identified by name.
ClinicalTrials.gov is a website that provides information about clinical trials. A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time. To help protect your privacy, AsthmaNet has received a Certificate of Confidentiality from the NIH/NHLBI. 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/evaluating federally funded projects or for information that must be disclosed in order to meet the requirements of the 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 in cases of suspected child abuse or intent to hurt self or others. The research team will only use and share your samples and data as explained in this form. When possible, the research team will make sure information and samples cannot be linked to you (they will be de-identified). Once information is de-identified, it may be used and shared for other purposes not discussed in this consent form. If you have questions or concerns about your privacy and the use of your PHI, please contact Robert Lemanske, Jr. MD at 608-263-6184 (Madison participants) or Lisa Sullivan Vedder, MD at 414-219-5970 (Milwaukee participants).

WHAT ARE THE COSTS OF TAKING PART IN THIS STUDY?
There will be no costs to you as a result of participating in this study.
WILL I BE PAID FOR TAKING PART IN THIS STUDY?
You will be paid a total of $1360 if you complete the study, plus an additional $15 per visit to cover travel expenses to/from the clinic. If you do not complete the study, you will be reimbursed for the visits you have completed. Payment for participation in a study is taxable income. Payments will be given at the end of each completed visit as follows:

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<tr>
<td>TOTAL</td>
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<td>$1360</td>
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</table>

*These amounts are for participants who bring all study supplies to the visits, including medications and Spirotel®. Participants who do not bring study medications and their Spirotel® to a given visit will receive $30 less than the amount in the table.

+Madison participants ages 12 and older who complete a sputum collection at visit 1 will receive an extra $50.

WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THIS STUDY?

**Milwaukee Participants:** If you get hurt or ill from your participation in this study, you should seek medical treatment as soon as possible.
- You will not have to pay for the costs of this medical treatment if the unexpected illness or injury is caused by your participation in this research study.
- There is no plan to provide you with other payments for such illness or injury.
- The costs associated with medical treatment that is not related to your participation in the research will be billed at the usual charge to your health insurance, if you have health insurance. You are responsible for any co-pays or deductibles of your health insurance. If you do not have health insurance or if your health insurance
does not pay the costs associated with your medical treatment that is not related to your participation in the research, these costs will be billed to you.

- You do not give up your legal rights by signing this form.
- If you think that you’ve been hurt because you were in this research study, you can call the principal investigator at the Aurora Health Care site, Lisa Sullivan-Vedder, M.D. at 414-219-5970 anytime or the Department of Clinical Research at 414-649-5397 during normal business hours to let you know what you should do next.

**Madison Participants** In the event that you are physically injured as a result of participating in this research, emergency care will be available. You will, however, be responsible for the charges for the emergency care. There is no commitment to provide any compensation for research-related injury. You should realize, however, that you have not released this institution from liability for negligence. Please contact the Robert F. Lemanske, Jr. MD, at 608-263-6184 if you are injured or for further information.

**IF I JOIN THE STUDY, CAN I CHANGE MY MIND?**
Taking part in this study is your choice. You may choose to not take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

If you choose to leave the study, please talk with your study doctor. He or she can help you stop the study medications in the safest way possible. We will ask you to come in for a final visit. We may perform procedures such as questionnaires and spirometry at your final visit. We will also collect all study supplies, including the Spirotel®. The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest, if you do not follow the study rules, or if the study is stopped by the sponsor.

**WILL I BE TOLD ABOUT NEW INFORMATION?**
While you are in this study, we may learn about new information that may affect your willingness to continue to participate. If this happens, we will tell you about this new information and you can choose to continue or stop your participation.

**WHO CAN ANSWER MY QUESTIONS ABOUT THIS STUDY?**

**Milwaukee participants.** For general questions, concerns, or complaints about the study, contact Lisa Sullivan Vedder, MD at 414-219-5970. If you want to talk to someone not part of this study about your rights as a human subject or to address concerns, complaints or provide input about the study, contact the Human Protections Administrator in the Aurora Research Subject Protection Program office at 414-219-7744 or toll free at 1-877-219-7744 (outside the Milwaukee area).

**Madison participants.** If you have questions about this research, please contact Robert Lemanske at 608-263-6184. If you have questions about your rights as a research subject, please contact the UWHC Patient Relations Representative at 608-263-8009.
GENETIC BLOOD DRAW AND TESTING SECTION

WHAT IS THE PURPOSE OF GENETIC TESTING?
This part of the study involves giving a blood sample for genetic testing (DNA analysis). Deoxyribonucleic acid (abbreviated DNA) is the genetic material contained in all cells of your body, including blood cells. DNA stores information in the form of a code. It is the material that determines, among other things, your physical characteristics such as your height and the color of your eyes. Genetic testing can be used to find out if you are more likely to develop a particular disease or to determine how you might respond to different medications. Another purpose of genetic testing is to identify genes and/or variations in genes. Genes are parts of DNA that have complete messages for building the proteins that make our bodies work.

For this study we will perform DNA tests for the molecules related to your response to asthma medications such as albuterol, salmeterol, and inhaled steroids. We will try to find out if your DNA results are associated with your response (or lack of response) to different medications, and whether your results are related to information we collect about you in the study. We will also look for genes and/or variations in genes related to asthma, allergies, and related diseases. Identifying genes and their variations may help develop a new treatment approach for people with asthma who have certain genes. We will also perform a test for proteins present in the plasma leftover from your blood sample. Other tests on the plasma may be performed at a later time, but they have not yet been defined. Any future tests will need to be approved by the AsthmaNet Steering Committee.

In addition to the asthma-related DNA tests described above, we will also perform tests that find out how much African and European ancestry you have. Your ancestry is your blood-related family who came before you. We want to find out in this study if the amount of African ancestry is related to how individuals respond to the four treatments we are studying. We might find that those who have more African ancestry respond better or worse to certain treatments, which will help to find the best treatment for individuals of different racial backgrounds in the future.

Because of the importance of the DNA tests to the goals of the study, if you do not agree to give a blood sample for genetic testing, you cannot participate in this study.

WHAT DOES PARTICIPATION INVOLVE?
We will use a needle to collect blood from a vein in your arm. For individuals ages 12 and older, we will collect 30 ml (about 2 tablespoons) of blood for genetics. For individuals ages 5-11 years old, we will collect 10 ml (about 2 teaspoons) of blood for genetics. DNA will be removed from your blood sample and stored in a lab. Plasma (the liquid part of your blood in which blood cells float) leftover from the DNA removal process also will be stored for future research in the areas of asthma, allergies and related diseases.

HOW WILL MY BLOOD BE HANDLED?
Your blood sample collected for genetic testing will be labeled with a code number, your initials, and blood draw date and transferred to the Tucson Genetics of Asthma Lab in
Tucson, Arizona for DNA removal and storage, and storage of the leftover plasma. The Data Coordinating Center in Hershey, Pennsylvania will provide the Tucson lab a new genetics code number (unrelated to the original) along with your gender and birth year (not complete date of birth). The genetics code number will not contain any information about you or your clinical site. After the DNA removal process is complete, the genetics lab will have access only to the new genetics code number, your gender, and your year of birth to identify your samples. The Tucson lab will not store your initials with your samples and will not be able to see your initials in the study database following processing of your sample.

The clinical site where you are seen for study visits will not have access to the genetics code number linked to your samples. Therefore, it would be very difficult for staff at the clinical site or at the Tucson lab to identify the person belonging to any given DNA/plasma sample.

For this study, samples of your DNA will be transferred to a lab at Wake Forest University Health Sciences in Winston-Salem, North Carolina. This lab will run the tests related to genetic ancestry described above. Only the genetics code number, your gender, and birth year will be transferred to the lab with your samples.

In the future, with the permission of the AsthmaNet Steering Committee, your DNA and/or plasma samples may be transferred to other laboratories for analysis. In each case, only the genetics code number, gender, and birth year will be transferred with your samples.

**HOW WILL THE GENETICS INFORMATION BE HANDLED?**

The coded results (that do not identify you) of the genetic testing will be sent to our central Data Coordinating Center in Hershey, Pennsylvania. The Hershey site will keep the links among all the code numbers and will be able to join the clinical data from the study, such as results of your breathing tests, with genetics data in order to perform analyses. The Hershey site does not have access to your name, address, social security number or other personal identifying information.

The coded analysis results will only be released to other scientists working on this study. It is almost impossible for the genetics results to be associated with you personally, unless your clinical site gives additional identifying information to the Data Coordinating Center (which it will not do) or unless the Data Coordinating Center gives additional information to your clinical site (which it may do under specific conditions which require approval as outlined in the next paragraph).

In the future, we may want to perform studies where it would be necessary to get in touch with you based on your genetic information. Only your specific clinical site will have enough information to do this, with your approval. Your specific clinical site will only be provided enough information to contact you based on your genetic information if both the AsthmaNet Steering Committee approves and the local clinical site’s Human Subjects’ Protection Board agrees that doing such testing and contacting you are appropriate. If you agree to future contact, you will always be able to opt out of (not take
part in) the future study. You do not have to agree to future contact to participate in this study.

WHO WILL SEE THE RESULTS OF THE GENETICS TESTING?
Coded (not identifiable to you) genetic information will be seen by the study investigators
at your site and in the AsthmaNet and by other NIH/NHLBI research centers/investigators with whom the AsthmaNet agrees to share such information.

Currently, individual genetic results will not be known and you will not be notified of your results. Therefore, your genetic results will not become part of your medical record. However, the investigators at your center, with the Human Subjects’ Protection Board approval, might carry out a study in which they do genetic analysis specific to you in order to contact you about a study based on your genes related to asthma, allergies or related diseases, or on your response to medications used to treat those conditions. At that point, if approved by the AsthmaNet Steering Committee and the Human Subjects’ Protection Board, only the investigators at your site would be made aware of any results linked to you and would contact you to find out if you are interested in providing more information or participating in a study. You can tell us whether or not you would like to be contacted for this purpose at the end of this section. You do not have to agree to future contact to participate in this study.

HOW LONG WILL MY SAMPLES AND INFORMATION (DATA) BE STORED AND USED FOR RESEARCH?
Your DNA and plasma samples will be stored for as long as they are useful to the AsthmaNet researchers. There is no limit on the length of time your information will be stored for research.

WILL THE GENETIC SAMPLES HAVE COMMERCIAL VALUE?
This genetic testing or other follow-up studies may lead to the development of a test that might tell in advance if a person will respond to certain asthma treatments, but you or your heirs will not be able to share in the profits made by the company that sells it. Commercial products may be developed from the samples you provide for this research study. However, it is not expected that you will be able to share in the profits from commercialization of products developed from your tissue or blood samples.

WHAT IF I CHANGE MY MIND?
Your agreement to provide a blood sample for DNA analysis and plasma storage is voluntary. You may refuse to provide a blood sample without any loss of rights or privileges to which you are otherwise entitled. However, as explained previously, if you do not wish to provide a sample for DNA analysis, you cannot take part in this study.

As explained above, it will be very difficult to link your blood sample to you. It will be very hard to withdraw your sample after it has been sent for genetic analysis, but we will make a good faith effort to ensure that all stored genetic material is destroyed. Please think very carefully about your decision to provide a blood sample for DNA analysis.

If you wish to withdraw your permission for your DNA and/or your plasma to be used for purposes outside of this research study, please contact Dr. Lemanske or Sullivan Vedder by calling the phone number on the front page of this consent form.
RISKS AND DISCOMFORTS RELATED TO GENETIC TESTING

Blood Draw. If possible, the genetic blood sample will be taken when other blood samples are needed for the study so that you will not have to undergo an extra needle stick. Blood drawing may cause a small amount of pain. In addition, a temporary bruise or "black and blue mark" may develop. Rarely, people faint after blood drawing. Very rarely, the vein in which the needle has been inserted may become inflamed (red and swollen) or infected, but this can be treated.

Confidentiality/Disclosure. Information about your participation in a genetics study may influence insurance and/or employers regarding your health status. If a result is accidentally disclosed and you are considered a high insurance risk as a result, this could lead to loss of health insurance, difficulty obtaining insurance, or an increase in premiums. If your employer becomes aware of the result, this could lead to the loss of your job or make it harder to get a new one. To help prevent disclosure, information about your participation and the results of the research will not be placed in your medical records. In addition, your blood sample will be coded and the key to the code kept in a separate locked physical or password-protected electronic file at your clinical site. Once the sample is processed at the genetics lab in Tucson, Arizona, a new unrelated code number will be used and no key linking your identity (name, address, etc.) to the DNA and plasma samples will exist. Not sharing information about your participation in this study with others will lower these risks. Although every effort will be made to keep your participation confidential, the investigators cannot guarantee absolute confidentiality. Even though we will remove identifying information and do not intend to tell you or anyone else the results of the genetic testing on your sample, there is a very small chance that this information could accidentally become known to you, your doctor, or others.

In some cases, a new federal law call the Genetic Information Nondiscrimination Act (GINA) makes it illegal for health insurers and employers to discriminate against you based on your genetic information. But you should know that there are limitations to this law; for example, it does not apply to businesses that employ fewer than 15 people or life insurance, disability insurance or long term care insurance. An abnormal genetic test could result in denial or much higher rates for life insurance, disability insurance, or long term care insurance if your genetic test results were to become known.

Other Risks. There might be other risks associated with genetic testing that we do not know about yet.

As we learn more about asthma-related or ancestry-related genetic testing, we may contact you to provide or request more information.
Do you agree to genetic testing and the sharing of your (or your child’s) coded genetic samples with AsthmaNet and NIH/NHLBI research centers/investigators for the purposes of identifying genes and/or variations in genes related to asthma, allergies, and related diseases (to be performed only with the agreement of the AsthmaNet Steering Committee)? For this study, this agreement also includes the tests related to ancestry described above.

(Please initial)   YES___________ NO___________

Do you agree to allow your clinical site to identify and get in touch with you in the future based on the results of genetic testing (to be performed only with the agreement of the AsthmaNet Steering Committee and the local Human Subjects’ Protection Board)?

(Please initial)   YES___________ NO___________

Your authorization to participate in the genetics blood draw and testing part of the BARD study was provided in the previous section through your initials on the appropriate lines for the two stated questions.

REQUEST FOR PERMISSION TO CONTACT YOU ABOUT FUTURE STUDIES:

1. May we contact you for future studies conducted by the University of Wisconsin-Madison, Aurora Health Care or AsthmaNet?
   If yes, we may need to look at your Protected Health Information (PHI) to check for study eligibility.
   [___ Yes  ___ No]

2. May other University of Wisconsin-Madison or Aurora Health Care physicians conducting asthma research contact you?
   If yes, your PHI may be shared with those physicians.
   [___ Yes  ___ No]

If you checked “Yes” to being contacted, the investigators will explain the future studies to you, and you can decide whether to take part. You may still refuse to join those future studies. Also, you can ask us at any time to take your name off of our contact list.
CONSENT TO PARTICIPATE IN THE BARD RESEARCH STUDY:

I have read the information in this consent form and reviewed any questions. I voluntarily agree to participate (or have my child participate) in this study. I have received a copy of this consent form.

PRINT NAME OF PARTICIPANT:____________________________________________________

Date Participant's (or parent/legal guardian) signature ___________________________

Date Person Obtaining Consent _____________________________________________
### BARD Study Procedure Table

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1. Scr = Screening Visits. Screening visits take place during the study run-in. Everyone completes Screening Visit A and Screening Visit B. Some participants may need to be seen for Screening Visit C and Screening Visit D.

   The run-in is of variable length and can range from 2 weeks long to 12 weeks long, depending on your controller dose at enrollment and your asthma control.

2. The Visit 1 overnight urine collection may be done earlier in the run-in and turned in at an earlier screen visit, if convenient.

3. This test will be done at Visit 1 only for those who may be eligible to proceed with sputum induction (ages 12 and older).

4. Sputum collection will be done only for Madison participants who are ages 12 and older.