Harlem Hospital Center
Columbia University, New York, NY

Consent to Participate in a Research Study

IRB# _____ **IRB Approval Date:** ___/___/___ **IRB Expiration Date:** ___/___/___

STUDY TITLE: **Beta Adrenergic Response by Genotype (BARGE)**

A study to compare the effects of regularly scheduled use of inhaled albuterol versus placebo in patients with mild to moderate asthma who are members of two distinct haplotypes expressed at the β_2-adrenergic receptor.

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STUDY PURPOSE

We invite you to participate in **BARGE,** a research study to examine the effect of regularly administered albuterol on asthma control, in patients who have two different forms of the gene for the β_2-adrenergic receptor. This receptor is the site of action of albuterol, a common medicine in inhaler form that is used to treat asthma. Information gathered from several research studies indicates that the effect of albuterol may vary among individuals, depending on their gene for the β_2-adrenergic receptor. The information that we collect during this study may help us determine whether we can improve asthma treatment by considering an individual's gene for the β_2-adrenergic receptor.

The **BARGE** study is being conducted at six clinical centers in the United States, which are a part of the Asthma Clinical Research Network of the National Heart, Lung and Blood Institute (NHLBI). We have invited you to be a part of this study because at screening we confirmed that you have mild to moderate asthma, and that you have one of two forms of the β_2-adrenergic receptor gene that are required in order for you to be in the study.

We also require that you have not used any oral, intramuscular or intravenous corticosteroids (such as prednisone or methylprednisolone), inhaled corticosteroids (such as Aerobid, Azmacort,

Beclovent, Pulmicort, Vanceril, Flovent), or Cromolyn/Nedocromil (such as Intal or Tilade) over the previous 6 weeks.

If you decide to be in this study, you need to be able to withhold some medications for the time period that you are in the study. A doctor or study coordinator will gather more facts about your medication use and will decide if you should be in the study according to your need for medication. The study coordinator, the person who will coordinate the study, will give you a list of medications that you can use during the study.

STUDY PROCEDURES

The study is about a year long (54 weeks), and you will have to make a total of 24 visits to our clinical center. The visits will be 1-3 weeks apart. Also, we will contact you by telephone on several occasions during the study. After the initial six (6) weeks in the study, if your asthma is under control while on the study medications, you will be randomized (assigned by chance, like flipping a coin or lottery), to receive one of two treatments. This study has two stages. During the first stage you will be assigned to one of the two treatments; and during the second stage you will be assigned to the other.

The treatments consist of an inhaler that contains either albuterol or placebo (a non-active medication). The placebo is harmless and is meant to hide who has the treatment. This is so that our study doctors will give each person in the study the same attention and not look harder at one group over the other. This gives our research the fairest test and allows us to know the true facts of treatment. You will be switching between albuterol and placebo during the course of the study but you will not know which medication you are receiving at each visit. Similarly, during certain periods of the study we will not know what medication you are taking; but this information can be known anytime, if medically necessary.

Throughout the study, you will monitor your asthma symptoms using a diary, and your peak expiratory flow (PEF, a test of lung function), using a peak flow meter. You will receive an Atrovent® (Ipratropium) inhaler to be used as rescue medication (as needed) to treat your asthma when you have symptoms, or when your PEF falls to a certain level below your baseline PEF. You will also be given a Ventolin® (albuterol) inhaler, in case Atrovent® does not relieve your symptoms or bring your lung function close enough to your baseline value. You will be given instructions for situations where you have more asthma symptoms than usual.

You will be asked not to use your inhalers for at least 6 hours before each visit, and not to use your rescue medication (Atrovent®) for at least 24 hours prior to some of the visits.

Following is a list of procedures you will have during each visit:

Visit 1: (*This visit will last approximately 4 hours)*
Electrocardiogram or EKG: (small metal leads will be placed on your chest and arms and legs to measure electrical activity of your heart)
Medical history and physical examination
Urine pregnancy test (women only)
Spirometry is a test where you will wear a nose clip and breathe out forcefully into an instrument that measures the amount of air you can blow out in one breath. FEV1 (Forced Expiratory Volume in one second) is a measure of the amount of air you can blow out in the one second, after taking a very deep breath.
Nitric oxide is a gas that comes from your airway (bronchial tubes) in increased amounts if you have asthma. It will be measured after you simply breathe out slowly into a balloon.
Instruction in the use of the AirWatch™ device for measuring lung function (peak expiratory flow, PEF).
Quality of life Questionnaire is a questionnaire that assesses the impact of asthma on your daily life. It takes about 10 minutes to complete the first time and 5 minutes at subsequent visits.
Methacholine challenge test is a common asthma test that requires 30-60 minutes to complete. Methacholine is a chemical used to estimate the sensitivity of the airways (your bronchial tubes) to nonspecific environmental stimuli. The methacholine challenge test is a procedure which consists of inhaling increasing amounts of methacholine. After each dose of methacholine, spirometry is performed, as described above. The procedure will be stopped if you demonstrate a significant change in your lung function. You will be monitored in our laboratory for approximately one-half hour after the procedure, to be sure your lung function has returned to baseline. You will be given a medication to improve your lung function, if needed, based on your symptoms and lung function.
Instruction in proper inhaled medication technique. A study inhaler will be given to you at the end of the visit to use at a scheduled dose of 2 puffs 4 times a day. Instruction on use of the inhaler will be given. You will also receive the medications, ipratropium (Atrovent®) and albuterol (Ventolin®), with instructions on how to use them in case your asthma symptoms are not controlled. These inhalers will be replaced periodically, throughout the study. You will also be given an AirWatch™ and diary cards to use on a daily basis. These will be used to establish your baseline lung function and monitor your symptoms and inhaler use. If you cannot use the study inhaler correctly, you will be dropped from the study.
Blood drawing for determination of IgE level and eosinophil count. These tests are indicators that are used commonly to assess disease activity in asthma.

Visit 2 (2 weeks after Visit 1): (*This visit will last approximately 1½ hours)*
Spirometry (as described above)
Measurement of exhaled nitric oxide (as described above)

Allergy skin testing: The allergy skin test is used to determine your sensitivity to certain environmental irritants (allergens). Fourteen drops of dissolved extract of common allergens (such as house dust mite, pollen, grass, etc.) will be placed on the skin of your forearm, and your skin will be lightly pricked with a sterile disposable needle. Fifteen minutes later, your skin will be inspected for localized redness and swelling. This commonly results in itching of the area tested.
Review of the use of medication, symptoms and peak flow diary and AirWatch™ data.

Visit 3 (2 weeks after visit 2): (*This visit will last approximately 2 hours*)
Spirometry (as above)
Measurement of exhaled nitric oxide (as above)
Maximal bronchodilator effect: In this test, spirometry will be repeated 15 minutes after you inhale 4 puffs of albuterol. You will then receive an additional 2 puffs of albuterol, and spirometry will be performed again after 15 minutes. Depending on the results of this spirometry test you may receive an additional 2 puffs of albuterol, for a maximum dose of 8 puffs. Spirometry will be repeated 15 minutes after the last dose, to a cumulative dose of 8 puffs, or until the change in FEV1 is $\leq$ 5%.
Review of your medication use, diary cards, and AirWatch™

Visit 4 (2 weeks after visit 3): (*This visit will last approximately 3 hours)*
Spirometry (as above)
Measurement of exhaled nitric oxide (as above)
Urine pregnancy test (women only)
Quality of life questionnaire
Albuterol-protected methacholine challenge: consists of inhaling 2 puffs of albuterol followed by a methacholine challenge (as described above) 15 minutes later.
Review of your medication use, diary cards, and AirWatch™

At this point in time in the study, if you meet all criteria, you will be randomized (assigned by chance, like a flip of a coin) to one of two initial phases of the study where you will receive an inhaler containing one of the study medications for your use.

Visit 5 (2 weeks after visit 4): (*The visit will last approximately 2 1/2 hours)*
Spirometry
Measurement of exhaled nitric oxide
Quality of life questionnaire
Urine pregnancy test (women only)
Albuterol-protected methacholine challenge (as described above)
Review of your medication use, diary cards, and AirWatch™

Visits 6 and 7 (at 3-week intervals): *(These visits will last approximately 1 hour each)*
Spirometry
Measurement of exhaled nitric oxide
Review of your medication use, diary cards, and AirWatch™

Visit 8 (3 weeks after visit 7): (This visit will last approximately 2 hours)
Spirometry
Measurement of exhaled nitric oxide
Quality of life questionaire
Urine pregnacy test (women only)
Methacholine challenge
Review of your medication use, diary cards, and AirWatch ™

Visit 9 (3 weeks after visit 8): (*This visit will last approximately 2 hours)*
Spirometry
Measurement of exhaled nitric oxide
Review of your medication use, diary cards, and AirWatch™
Maximum bronchodilator effect (as described above)

Visit 10 (2 weeks after visit 9): (*The visit will last approximately 2 1/2 hours)*
Spirometry
Measurement of exhaled nitric oxide
Review of your medication use, diary cards, and AirWatch™
Quality of life questionnaire
Urine pregnancy test (women only)
Albuterol-protected methacholine challenge (as described above)

Visit 11 (1 week after visit 10): (*The visit will last approximately 2 1/2 hours)*
Spirometry
Measurement of exhaled nitric oxide
Review of your medication use, diary cards, and AirWatch™
Quality of life questionnaire
Urine pregnancy test (women only)
Albuterol-protected methacholine challenge (as described above)

Visit 12 (3 weeks after visit 11): (*This visit will last approximately 1 hour)*
Spirometry
Measurement of exhaled nitric oxide
Review of your medication use, diary cards, and AirWatch™

Visit 13 (3 weeks after visit 12): *(This visit will last approximately 2 hours)*
Spirometry
Measurement of exhaled nitric oxide
Review of your medication use, diary cards, and AirWatch™
Maximum bronchodilator effect

Visit 14 (1 week after visit 13): (*The visit will last approximately 2 1/2 hours)*
Spirometry
Measurement of exhaled nitric oxide
Review of your medication use, diary cards, and AirWatch™
Quality of life questionnaire
Urine pregnancy test (women only)
Albuterol-protected methacholine challenge

Visit 15 (2 weeks after visit 14): (*The visit will last approximately 2 1/2 hours)*
Spirometry
Measurement of exhaled nitric oxide
Review of your medication use, diary cards, and AirWatch™
Quality of life questionnaire
Urine pregnancy test (women only)
Albuterol-protected methacholine challenge

Visits 16 and 17 (at 3-week intervals): (*These visits will last approximately 1 hour each)*
Spirometry
Measurement of exhaled nitric oxide
Review of your medication use, diary cards, and AirWatch™

Visit 18 (3 weeks after visit 17): (*This visit will last approximately 2 hours)*
Spirometry
Measurement of exhaled nitric oxide
Quality of life questionaire
Urine pregnancy test (women only)
Methacholine challenge
Review of your medication use, diary cards, and AirWatch™

Visit 19 (3 weeks after visit 18): (*This visit will last approximately 2 hours)*
Spirometry
Measurement of exhaled nitric oxide
Review of your medication use, diary cards, and AirWatch™
Maximum bronchodilator effect

Visit 20 (2 weeks after visit 19): (*The visit will last approximately 2 1/2 hours)*
Spirometry
Measurement of exhaled nitric oxide
Urine pregnancy test (in women)
Review of your medication use, diary cards, and AirWatch™
Quality of life questionnaire
Albuterol-protected methacholine challenge

Visit 21 (1 week after visit 20): (*The visit will last approximately 2 1/2 hours)*
Spirometry
Measurement of exhaled nitric oxide
Urine pregnancy test (women only)
Review of your medication use, diary cards, and AirWatch™
Quality of life questionnaire
Albuterol-protected methacholine challenge

Visit 22 (3 weeks after visit 21): (*This visit will last approximately 1 hour)*
Spirometry
Measurement of exhaled nitric oxide
Review of your medication use, diary cards, and AirWatch™

Visit 23 (3 weeks after visit 22): (*This visit will last approximately 2 hours)*
Spirometry
Measurement of exhaled nitric oxide
Review of your medication use, diary cards, and AirWatch™
Maximum bronchodilator effect

Visit 24 (1 week after visit 23): (*The visit will last approximately 3 1/2 hours)*
Spirometry
Measurement of exhaled nitric oxide
Urine pregnancy test (women only)
Review of your medication use, diary cards, and AirWatch™
Quality of life questionnaire
Albuterol-protected methacholine challenge

Termination from the Study

Blood from your parents/siblings for DNA analysis

During your period of participation in this study we would like to contact your biological parents or siblings for a blood sample for DNA analysis. This blood sample will allow us to perform specific tests, which will give us the most reliable genetic information about the nature of your responses to treatment. It does not matter whether or not they have asthma. Other than the blood sample, they will not participate in any other testing. In addition, regardless of what decision you make, they will have the opportunity to either refuse or accept participation in the study. Your answering of the questions given below will NOT impact your participation in BARGE study.

Please check the appropriate box:

1. Are both of your biological parents alive? Yes☐ No☐ DK☐
2. Do you have any siblings (full-blooded brother or sister) Yes☐ No☐
3. Do you allow us to contact your parents to request a blood sample for DNA analysis? Yes ☐No☐ N/A ☐
4. Do you allow us to contact your siblings to request a blood sample for DNA analysis? Yes ☐No☐ N/A ☐

RISKS/DISCOMFORTS

Following is a summary of the potential risks of being in this study. We expect these risks to be rare but we cannot rule them out.

Methacholine Challenge Test: Methacholine is a chemical used to check the sensitivity of the airways (bronchial tubes). This chemical is mixed with sterile solutions and then diluted into various concentrations before it is used for testing. Within the last few years, supplies of methacholine have been inconsistently available due to corporate decisions to restrict and/or cease its production. Therefore, the methacholine used in this protocol has been purchased in chemical form from Canada and was prepared, standardized and quality controlled by centers participating in the Asthma Clinical Research Network, in order to provide a uniform and reliable supply of this material on a daily basis. This procedure might produce mild symptoms such as cough, chest tightness, and/or wheezing. The methacholine challenge test is carried out in such a way that the danger of an asthmatic reaction is minimized. Should an asthmatic reaction become more severe, medication will be promptly given to reverse the effect.

Spirometry with beta-agonist reversal: This maneuver of rapid, forced exhalation of air can be associated with temporary coughing or lightheadedness. We will monitor you carefully for these possibilities. Spirometry is a common way to measure lung function and is performed safely many times each day in our institution. Potential risks associated with the use of β_2-agonist inhalation

aerosols such as albuterol (Ventolin®) are palpitations (abnormally rapid beating of the heart), accelerated heart rate, increased blood pressure, tremor, nausea, headache, nervousness, lightheadedness, coughing and dizziness.

Blood drawing: You will feel a slight sting or "pinch" in your arm when the blood is drawn. You may also get a small bruise where needle went in. Some people faint but this is rare.

Exhaled nitric oxide: There are no risks involved. You simply exhale slowly into a balloon.

Measurement of Peak Flow: Blowing out hard may cause temporary coughing or lightheadedness.

Allergy skin testing: This test is commonly used to determine your sensitivity to certain allergens. Fourteen drops of dissolved extract of common allergens (such as house dust mite, pollen, grass) will be placed on the skin of your back or your forearm and your underlying skin will be lightly pricked with a sterile disposable needle. Fifteen minutes later, your skin will be inspected for localized redness and swelling. This commonly results in itching of the area tested.

Pregnancy testing: If you are a woman of childbearing potential, a urine pregnancy test will be performed several times throughout the study. If your urine test shows that you are pregnant, you will not be permitted to enter the study. If you become pregnant during the course of the study, your participation will be ended. You will be allowed to use study-approved contraceptive pills and other methods of contraception.

Who will see the study records?
Your doctor/investigator and coordinator will treat your identity with professional standards of confidentiality. Your medical records may be accessed and reviewed by study personnel for the purpose of verifying medical history pertinent to determining your study eligibility. Additionally, the study sponsor, the National Institutes of Health, the U.S. Dept. of Health and Human Service and the Food and Drug Administration have the right to inspect your medical records relating to this research for the purpose of verifying data. The results of this study may be published in medical journals or presented at medical meetings; however, you will not be identified by name.

What alternative therapies for asthma are available?
There are a number of medications available for the condition that you are being treated for, including other short or long-acting beta-agonists, cromolyn (Intal®, nedocromil (Tilade®, theophylline products, leukotriene modifiers (Zyflo®, Accolate®, and Singulaire®) and inhaled corticosteroids (Vanceril®, Beclovent®, Aero-Bid®, and Azmacort®). Should you decide not to participate or be discontinued from the study, or at the time of study completion, the study investigator may recommend another method of treatment and/or other medication. However, if you decide to take part in this study, you must agree to use only the medications allowed for the duration of your participation in the study.

What If I Change My Mind?
Your participation in this study is entirely voluntary. You are free to refuse to participate in this study and you may withdraw from the study at any time without any change in the quality of medical care or loss of benefits to which you are entitled. Any new findings, which may affect your willingness to continue in this study, will be communicated to you. Your study doctor may also end your participation in the study if s/he judges it to be in your best interest. Should this occur, you may be asked to return to the center for final safety evaluation including a physical examination, laboratory results, and breathing tests. After completion of the study, you may be contacted by phone or mail to determine your opinions about participation.

Who will answer my questions?
If you have any questions, please ask, and we will do our best to answer them. If you have additional questions in the future, you can reach the Harlem Lung Center at 212-939-8360 or the Principal Investigator, Dr. Jean Ford, at 212-939-1459.
If you have additional questions about your rights as a research subject you can reach the Columbia Institutional Review Board at Harlem Hospital at 212-939-4160.

BENEFITS

What are the benefits of study participation?
There is no long-term medical benefit to you for participating in this study. The benefits of being in this study include knowing your present health status and asthma control. The results of this study may be helpful in future for treating patients with asthma in general.

Will there be any costs to me or any compensation for participating?
There will be no charge to you or your insurance company for any of the medication, pulmonary function tests, laboratory tests, or health care and visits involved in this study.

You will be compensated a total of $2,800.00 for your participation. If you do not complete the study, your compensation will be prorated. The breakdown in compensation will be $ 25 for visit 0, $75 each for visits 6, 7, 8 12, 16, 17, 18 and 22, $ 300 for visit 1 and $ 125 each for visits 2, 3, 4, 5, 9, 10,11, 13,14,15, 19, 20, 21, 23 and 24.

Will There Be Compensation For Injury?
Federal regulations require us to state that in the event that physical injury occurs as a direct result of this research, only immediate, essential, short term medical treatment as determined by the doctors will be made available without charge to you. However, there will be no monetary compensation or non-emergency care provided by Harlem Hospital Center.

If physical injury is suffered in the course of the study or you experience any side effects or medical problem, you should contact Dr. Ford at 212-939-1459 or the study personnel at 212-939-8360

immediately. At night or during weekends you can contact either Dr. Ford or the Doctor on call at 800-396-1945.

Authorization

I have discussed this research study with Dr._____ to my satisfaction. I understand that my participation is voluntary and that I can withdraw from the study at any time without prejudice. I have read the above and agree to enter this research study. Signing this form does not waive any of my legal rights.

I have been informed that if I believe that I have sustained injury as a result of participating in this research study, I may contact the Principal Investigator, Dr. Jean Ford, at 212-939-1459, or the Columbia University Institutional Review Board at Harlem Hospital, at 212-939-4160, so I can review the matter and identify the medical resources which may be available to me. I have received a copy of the consent form. My signature below shows that I agree to participate in the BARGE study.

Signatures

_____ _____
Subject's Signature Date

_____ _____
Investigator Date

I observed the process of consent. The prospective participant read this form, was given a chance to ask questions, appeared to accept the answers, and signed to enroll in the study.

_____ _____
Witness Signature Date

The solicitation of subjects into this study has been approved by the Columbia University Institutional Review Board at Harlem Hospital Center.