Letter of Information

Title: **HYPERPOLARIZED MAGNETIC RESONANCE IMAGING IN ASTHMA PRE- AND POST-BRONCHIAL THERMOPLASTY**

Sponsors: **Robarts Research Institute**

Protocol: **ROB0039**

Investigator: **Dr. Grace Parraga**

You are being invited to voluntarily take part in a research study because you have been diagnosed with asthma and are undergoing bronchial thermoplasty as a part of your normal clinical care and asthma treatment plan. This letter of information has information to help you decide if you want to participate. Take your time, read this letter of information carefully, and ask the study investigator or staff any questions you may have.

About This Study

The purpose of this study is to:

- Use Magnetic Resonance Imaging (MRI) using an inhaled contrast agent called either Hyperpolarized Helium or Hyperpolarized Xenon to evaluate the effect of Bronchial Thermoplasty, and to guide Bronchial Thermoplasty treatment to abnormal airways. Hyperpolarized Helium or Hyperpolarized Xenon gives us more information about the structure and function of the lungs.

- Compare the effect of bronchial thermoplasty on MRI of lungs with standard pulmonary function tests and asthma quality of life and symptom questionnaires.

There may be reasons why you may not be eligible for the study. The study investigator or staff will discuss these with you.

This study is being conducted in one centre, at the Robarts Research Institute. About 14 people will be in the study.

What will you be asked to do?

If you take part in this study, you will have to visit the clinic five times at Robarts Research Institute, which is located next to University Hospital. Each visit will take

approximately two hours. The study duration will be approximately nine months. Three visits will take place before your first bronchial thermoplasty session, one visit six weeks after bronchial thermoplasty, and your final visit will be 24 weeks after your final bronchial thermoplasty session.

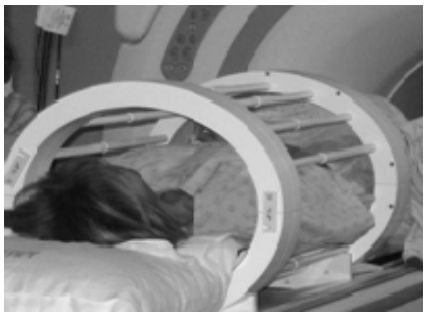
At your first visit to Robarts, you will be randomized (like the flip of a coin) to one of two groups: One group will receive the conventional Bronchial Thermoplasty treatment as explained by the study doctor. The other group will receive treatment that is guided by the inhaled contrast MRI. If you are in the conventional group, you will undergo three Bronchial Thermoplasty treatments. If you are in the guided treatment group, you will undergo a single Bronchial Thermoplasty treatment.

At these visits, we will ask you to do all of the study procedures listed below.

What will happen during the study visits?

Visits 1 and 2

- Take your vital signs (height, weight, blood pressure, heart rate, breathing rate and pulse oximetry test (a test in which a clip is placed on your finger to measure the amount of oxygen in your blood).
- Ask you to complete two questionnaires about your breathing. These questionnaires will take about 5 minutes to complete.
- Perform lung function tests such as spirometry (test to measure how much air you can breathe in and out), body plethysmography, airwave oscillometry (measures the mechanics of the respiratory system), Lung Clearance Index, and diffusing capacity of carbon monoxide (DL_{CO}). For the body plethysmography test, you will sit in a closed Plexiglas chamber and breathe in and out into a mouth-piece. This test measures the different volumes of air in your lungs. The DL_{CO} test measures how well the lungs exchange gases. For airway oscillometry as well as Lung Clearance Index, you will breathe normally throughout the measurement sequence via a disposable mouth piece. These tests will take approximately 20 minutes.
- Perform an MRI using an inhaled gas (hyperpolarized ^{129}Xe or ^{3}He). The MRI does not have radiation. A special coil will be placed around your torso and chest during the MRI. This coil receives a signal from the magnet and helps to create the image. You will be observed by a technologist during the entire procedure and may be spoken to through an intercom in the scanner. The MRI takes about 20 minutes or less.



MRI Coil

Visit 3

- Take your vital signs (height, weight, blood pressure, heart rate, breathing rate and pulse oximetry test (a test in which a clip is placed on your finger to measure the amount of oxygen in your blood).
- Ask you to complete two questionnaires about your breathing. These questionnaires will take about 5 minutes to complete.
- Perform lung function tests such as spirometry (test to measure how much air you can breathe in and out), body plethysmography, airwave oscillometry (measures the mechanics of the respiratory system), Lung Clearance Index, and diffusing capacity of carbon monoxide (DL_{CO}) (tests of lung volumes and function). For the body plethysmography test, you will sit in a closed Plexiglas chamber and breathe in and out into a mouth-piece. This test measures the different volumes of air in your lungs. The DL_{CO} test measures how well the lungs exchange gases. For airway oscillometry as well as Lung Clearance Index, you will breathe normally throughout the measurement sequence via a disposable mouth piece. These tests will take approximately 20 minutes.
- Perform an MRI using an inhaled gas (hyperpolarized ^{129}Xe or ^{3}He) before and after a methacholine challenge. The MRI does not have radiation. A special coil will be placed around your torso and chest during the MRI. This coil receives a signal from the magnet and helps to create the image. You will be observed by a technologist during the entire procedure and may be spoken to through an intercom in the scanner. The MRI takes about 30 minutes or less.

- Chest CT (Computed Tomography). This test will be done at University Hospital, located next door to Robarts Research Institute. You will be escorted to and from the radiology department by study staff. A chest CT will be acquired at this visit only.

- Undergo a methacholine challenge test:

    - The methacholine test is performed by inhaling a medication (methacholine) in increasing doses in an attempt to produce a change in your spirometry results. The test will continue until you reach a 20% drop in your FEV_1 (the amount of air you exhale in the first second) or you finish all the dosages of the medication.
    - After the testing is completed, you may be given salbutamol (“Ventolin”) that will reverse the action of the methacholine, if it has caused your results to change.
    - After each dose and after the salbutamol, you will be asked to perform several spirometry tests (a test that measures how much air you can breathe in and out)

Visit 4 – this visit will take place six weeks after your Bronchial Thermoplasty treatment. It will be the same as Visit 3 but without the Chest CT.

Visit 5 – This visit will take place approximately six months after your Bronchial thermoplasty treatment and will be the same as visits 1 and 2.

- In between visits, we will ask you to complete some asthma questionnaires: one every week and another one every other week. We will ask you to upload these questionnaires monthly to our secure website using a confidential password. Instructions for these questionnaires will be given to you at your first visit by study staff.

Potential Risks and Discomforts of Study Participation

You may feel discomfort during some of these tests and some may have risks, such as:

- Spirometry breathing tests may result in shortness of breath and light-headedness
- Tests done in the Body Plethysmograph may cause claustrophobia, nausea, or vomiting.
- Methacholine challenge test: You may become short of breath during the testing, and may experience an "asthma attack" as a result. The study doctor will be present for the testing, and rescue medication is available in the testing room.
- Part of your participation in this study will involve a research test with Magnetic Resonance Imaging (MRI) system, a common medical diagnostic tool that uses a strong magnetic field, a low frequency magnetic field, and a radio frequency field. No X-rays are used. As with any technology there is a risk of death or injury. For MRI the risk of death is less than 1 in 10 million and the risk of injury is less than 1 in 100,000. These risks do not arise from the MRI process itself, but from a failure to disclose or detect MRI incompatible objects in or around the body of the subject or the scanner room. It is therefore very important that you answer all the questions honestly and fully on the MRI screening questionnaire.

  Almost all the deaths and injuries related to MRI scans have occurred because the MRI operator did not know that surgically implanted metal hardware (such as a cardiac pacemaker) was present inside the subject during the MRI scan. Other remote risks involve temporary hearing loss from the loud noise inside the magnet. This can be avoided with ear headphone protection that also allows continuous communication between the subject and staff during the scan.

  For comparison, the risk of death in an MRI is similar to travelling 10 miles by car, while the risk of injury during an MRI is much less than the risks associated with normal daily activities for 1 hour.

  You may not be allowed to continue in this research study if you are unable to have a MRI scan because, for example, you have some MRI incompatible metal in your body, you may be pregnant or attempting to become pregnant, or you may have a drug patch on your skin that contains a metal foil. Should you require a medically necessary MRI scan in the future, the final decision as to whether you can be scanned will be made by a qualified physician considering all the risks and benefits.

  The MRI experiments carried out for this study are performed solely for scientific purposes. The data which is collected is not optimized to make clinical diagnoses, and the research team involved in these experiments are not trained to make medical evaluations. By participating, you agree that the

experimenters are not expected to arrive at a clinical interpretation of the data collected.

Nevertheless, there is a small possibility that a potential abnormality might be observed – otherwise known as an incidental finding. If this occurs you will be notified of the issue by the principal investigator of the study who will assist you with your options for following up. Investigators are not responsible for the outcome of medical follow-up or for any incurred costs during medical follow-up. By participating, you agree to the possibility of being informed about a potential incidental finding, according to the above-described procedure. If you do not agree to the potential risk of an incidental finding you should not participate in this study.

MRI Exclusion Criteria

If you have any history of head or eye injury involving metal fragments, if you have some type of implanted electrical device (such as a cardiac pacemaker), if you have severe heart disease (including susceptibility to heart rhythm abnormalities), you should not have an MRI scan unless supervised by a physician. Additionally you should not have a MRI scan if you have conductive implants or devices such as skin patches, body piercing or tattoos containing metallic inks because there is a risk of heating or induction of electrical currents within the metal element causing burns to adjacent tissue.

- CT: The CT does deliver a radiation dose to your lungs which is similar to the dose for approximately 10 chest x-rays, or <u>one half to two-thirds of</u> the same radiation dose you receive from the background radiation from the ground in London, Ontario over the course of a year.

About The Agents

^{3}He

Hyperpolarized Helium gas (^{3}He) is an “investigational” agent that is similar to the helium used in balloons, but is used in MRI to better visualize (see) the lungs. “Investigational” means the study drug or study procedure has not yet been approved for clinical use by Health Canada. Health Canada has approved the use of Hyperpolarized Helium gas in this study. The agent has been studied in over 800 people worldwide.

What side effects can happen to you from inhaling hyperpolarized Helium gas?

Recent summaries of adverse or bad side effects have been reported by people who have inhaled hyperpolarized ^{3}He gas at a hospital research centre (University of Virginia in Charlotteville VA, USA); 10% had adverse side effects, all were mild and improved during the study without any treatment. Approximately 6% of people who have inhaled helium gas experienced side effects related to the dryness of the gas and included: dry mouth or throat (3.5%), throat soreness (less than .005%), lung irritation (.005%), tickle in throat (less than .005%), chest tightness (.01%) and wheezing (less than .005%).

In similar studies sponsored by General Electric Health Care (the manufacturer of the ^{3}He hyperpolarized gas), 9% of all persons inhaling the gas had adverse side effects, all reported to be mild and improved during the study without any treatment. These side effects include breathlessness (4.5%), dry mouth (1.5%),

throat pain (1.5%), throat irritation (0.75%), dizziness (0.75%), vague chest pain (0.75%) and bad taste in the mouth (0.75%).

^{129}Xe

Hyperpolarized Xenon gas (^{129}Xe) is an "investigational" agent that is used in MRI to better visualize (see) the lungs. "Investigational" means the study drug or study procedure has not yet been approved for clinical use by Health Canada. Health Canada has approved the use of Hyperpolarized Xenon gas in this study. The agent has been approved by Health Canada for other procedures, and has been studied in over 400 people worldwide.

What side effects can happen to you from inhaling hyperpolarized Xenon gas?

Some adverse or bad side effects have been reported by people who have inhaled hyperpolarized ^{129}Xe gas for different procedures. The amount of gas inhaled by these people was approximately 70 times the amount you will be asked to inhale. The effects reported include respiratory depression (slow, shallow breathing) greater than 10 seconds (3.6%), seizures (0.2%), change in how you feel (0.1%), headache (0.4%), nausea and/or vomiting (0.2%) and change in sensorium (your senses may be affected) (0.1%). It should be noted that in the cases of seizure, 3 of the 4 patients who experienced seizures were being studied because they were having seizures, and the status of the 4th patient was unknown.

If you experience any side effects, please notify your study doctor immediately.

It is not known what effects the MR scan may have on an unborn baby. Therefore if you are a female of childbearing potential, you must be using an acceptable method of birth control in order to be enrolled in the study. The contrast gas has not been shown to interact with your body and therefore there is no evidence that it would have an effect on an unborn baby, or any future planned or unplanned unborn babies or on a partner of yours who may participate in the conception of a baby.

You will be told in a timely manner about significant new information that might affect your decision to stay in the study.

There may be other side effects or risks that are not known at this time.

If you are injured from the study procedure, who will pay the doctor and hospital bills?

If you have any injury, illness, or side effect as a direct result of your participation in this study, the hospital will pay the necessary medical expenses to treat the injury to the extent you are not otherwise reimbursed by Ontario Health Insurance Plan [OHIP] or personal medical insurance.

You do not waive any legal rights by signing the consent form.

Voluntary Participation

Participation in this study is voluntary. You may refuse to participate, refuse to answer any questions or withdraw from the study at any time with no effect on your future care.

You may be asked to leave the study without your consent if you need other treatment, have a study-related injury, or for any other reason.

What benefit could there be from taking part in the study?

Since this study does not provide treatment, there is no direct benefit to you. Information learned from the study may help other people with asthma in the future.

How will your privacy be protected?

A file containing your study related information will be established by the principal investigator and maintained in connection with the study. Your research records will be stored in a locked cabinet in a locked office.

Unless required by law, only the principal investigators and staff and inspectors from regulatory agencies including Health Canada will have direct access to your medical records to check the study information. Instead, it may include a study number and study visit dates. While we will do our best to protect your information there is no guarantee that we will be able to do so. The inclusion of your initials and date of birth may allow someone to link the data and identify you.

Your information will be kept strictly confidential as stated above. If the results of this study are published, no one will know you were a part of the study.

Representatives of The University of Western Ontario Health Sciences Research Ethics Board may require access to your study-related records or may follow up with you to monitor the conduct of the research. Health Canada may also have access to the study data.

Your study-related records will be kept for a period of 25 years as per Health Canada Regulations.

You may take away your permission to use and share health data about you at any time by contacting the study investigator in person, by telephone or in writing at the following address:

Dr. Grace Parraga
Robarts Research Institute
Box 5015, 100 Perth Dr.
London ON Canada N6A 5K8

If you do this, you will not be able to stay in this study. No new health data that identifies you will be gathered after that date. However, health data about you that has already been gathered may still be used.

When the study is over you may write to the study doctor to ask to see study related health data about you that was collected during the study.

If you decide not to sign the consent form, you will not be able to participate in the study.

Alternatives to Study Participation

An alternative to the procedures described above is not to participate in the study and continue on just as you do now.

Will you be compensated?

You will receive up to $50.00 per study visit to reimburse you for travel and any other reasonable out of pocket expenses, which are directly related to your

participation in the study. There will be no charge to you for clinic visits, or any tests done as part of the study. If you are not able to complete all the visits in this trial you will be reimbursed for the visits you do complete.

Contacts

If you have questions about your rights as a research participant or the conduct of the study, you may call Dr. David Hill, Scientific Director, Lawson Health Research Institute (519) 667-6649.
If at any time you have any questions or need further information about this study, you may contact the study investigator, Dr. Grace Parraga at 519- 931-5265 or the study coordinator at (519) 663-5777 Ext. 24197

Consent Form

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Sponsors: **Robarts Research Institute**

Protocol: **ROB0039**
Investigator: **Dr. Grace Parraga**

I have read the Letter of Information, have had the nature of the study explained to me and I agree to participate. All questions have been answered to my satisfaction.

I will receive a signed and dated copy of the Letter of Information and Consent.

_____
Name of participant (please print)

_____
Signature of participant

_____
Date of signature

_____
Name of person obtaining informed consent

_____
Signature of person obtaining informed consent