Letter of Information and Consent

Title:	**Novel Pulmonary Imaging of Lung Structure and Function in Symptomatic and Asymptomatic e-cigarette Smokers**
Sponsor:	**Robarts Research Institute, Schulich School of Medicine & Dentistry, Western University**
Protocol:	**ROB0048**
Investigator:	**Dr. Grace Parraga** **519-931-5265** **Robarts Research Institute** **1151 Richmond St N** **London ON Canada N6A 5B7**
Funding:	This study is funded by a grant from the Canadian Institutes of Health Research

You are being invited to voluntarily take part in a research study because you use e-cigarettes. This study is looking at the effects of using e-cigarettes on the structure and function of the lungs. We are looking for half of our participants to be exclusively e-cigarette users who have never smoked regular (combustible) cigarettes and half to be current or former regular (combustible) cigarette smokers.

This letter of information contains information to help you decide if you would like to participate. Take your time, read this letter of information carefully, and ask the study investigator or staff any questions you may have. You will be given a copy of the consent document once it has been signed.

Purpose of the Study

This study is being conducted at Robarts Research Institute, Western University. Up to 150 people will participate in this study.

The purpose of this study is to evaluate the structure and function of e-cigarette users' lungs over time. Participants in this study will attend up to 4 study visits over a period of up to 3 years. Each study visit will take approximately 2 hours. One visit is a phone call for a health update and completion of questionnaires.

There may be reasons why you may not be eligible to participate in the study. The study investigator and staff will discuss these with you. Some reasons you would not be eligible for the study are listed below:

- You are younger than 18 years old
- You have not used e-cigarettes weekly for at least 1 year
- You have used e-cigarettes for longer than 5 years
- You are pregnant
- You have an unstable medical condition
- You cannot perform the breathing tests
- It is unsafe for you to go into an MRI
- If you are female, you must ensure that you are using an effective form of birth control for 2 months before each imaging visit. Examples of effective birth control include:
    - True sexual abstinence
    - A vasectomized sexual partner
    - Implanon®
    - Female sterilization by tubal occlusion
    - Any effective intrauterine device (IUD)/levonorgestrel intrauterine system (IUS)
    - Depo-Provera™ injections
    - Oral Contraceptive
    - Erva Patch™
    - Nuvaring™

What will happen during the study visit?
There will be up to 4 study visits over a period of up to 3 years. Visits will be scheduled every 12 ± 3 months. Study visits 1 and 4 will include the following procedures:

Each test will be explained in more detail below.

- Review your medical history and current medications
- Take your vital signs (blood pressure, heart rate, oxygen saturation) and height and weight
- Pulmonary (Lung) Function Tests
- MRI using Hyperpolarized Xenon (^{129}Xe) gas
- Exercise testing
    - Cardio pulmonary exercise testing (CPET)
- Sputum induction
- Blood draw
- Women of childbearing potential will undergo a urine pregnancy test at visit 1, prior to undergoing any study assessments
- Questionnaires
- Computed tomography (CT) of the lungs
    - The CT will be done at the first study visit and may be repeated 3 years after the first study visit.

Study visit 2 will be a telephone call to complete questionnaires. Study visit 3 will include pulmonary function testing of spirometry and questionnaires only.

Medical history and current medications

A member of the study staff will review the medications you are taking, any medical conditions you may have, and ask if you have had to see a doctor or go to the hospital because of a breathing problem.

Vital Signs

We will measure your blood pressure, heart rate, breathing rate and oxygen saturation at each visit. Oxygen saturation is measured using a pulse oximeter clip on your finger to measure the amount of oxygen in your blood. We will also measure your height and weight at each visit.

Pulmonary (lung) function tests

You will be asked to perform lung function tests before and after inhaling a medication called salbutamol (Ventolin). These tests include:

- Spirometry
  - Measures lung function
  - You will breathe through a mouthpiece, breathe all the way in and blow all the way out as fast as you can
- Body plethysmography
  - Measures lung volumes and function
  - You will sit in a closed Plexiglas chamber and breathe in and out through a mouthpiece
- Diffusing capacity of the lungs for carbon monoxide (DL_{CO})
  - Measures how well oxygen is able to move from the lungs to the blood
  - You will breathe in a gas mixture and hold your breath for 8 seconds
- Forced oscillation technique (FOT)
  - Measures the mechanics of the lungs
  - You will breathe normally through a mouthpiece
- Multiple breath nitrogen washout (MBNW)
  - Measures how evenly the air you breathe spreads throughout your lungs
  - You will breathe normally through a mouthpiece
- Fractional exhaled nitric oxide (FeNO)
  - Measures inflammation in your lungs
  - You will breathe in and out once through a mouthpiece

These tests will take approximately 20 minutes and will be done twice per visit.

Magnetic Resonance Imaging (MRI)

You will perform an MRI using an inhaled gas (hyperpolarized ^{129}Xe). The MRI does not have radiation. One of three special coils will be placed around your torso and chest during the MRI. The ^{129}Xe Radio Frequency Coil for Human Lung Imaging, CMRS Flexible Lung Coil or ^{129}Xe Lung Coil will be used during the MRI. All of these coils are investigational devices that are not licensed in Canada but authorized for use in this study. These coils receive a signal from the magnet and helps to create the image. You will be asked to breathe in the gas from a special bag made for this procedure. You will be observed by an MRI technologist during the entire procedure and may be spoken to through an intercom in the scanner. The MRI takes about 40 minutes or less.

Exercise Testing

Participants may complete a cardio pulmonary exercise test (CPET). You will first complete a questionnaire to assess exercise readiness. The study doctor may decide not to do this test with you if it is deemed unsafe. You will perform the exercise test on a stationary bicycle. You will breathe through a mouthpiece during this test. You will pedal

for approximately 10 minutes, and the effort needed to pedal will increase as the test goes on.

Blood Test

A blood test will be performed to measure the level of eosinophils in your blood. Eosinophils are a type of white blood cell (part of the immune system). The number of eosinophils in the blood can be greater in individuals with lung conditions.

This test will either be done at University Hospital, located next door to Robarts Research Institute, or at Robarts Research Institute by the study staff/coordinator. If you have the blood test done at University Hospital, you will be escorted to and from the laboratory by study staff.

Blood samples will be taken by inserting a needle into a vein in your arm. Up to 4mL (less than a teaspoon) of blood will be taken at each visit. These blood samples will be analysed at the laboratory at University Hospital, then they will be destroyed.

Please let study staff know if you would like to know the results of this test, or if you no longer want your samples to be used in this research.

Sputum Test

A sputum test shows how many eosinophils and neutrophils are present in your sputum (phlegm). Eosinophils and neutrophils are types of white blood cells (part of the immune system). Eosinophils and neutrophils may be higher in the sputum of individuals with lung conditions.

To obtain a sputum sample, you will inhale a salty mist that will help loosen secretions, or mucous from the chest so that you can cough them up easily into a specimen container. You will inhale this mist for up to 7 minutes at a time for up to 3 times. You will be asked to perform breathing tests during this process to make sure you may continue. You may stop at any time if you wish to.

Sputum samples will be analysed by study staff at Robarts Research Institute. Please let study staff know if you would like to know the results of this test, or if you no longer want your samples to be used in this research.

CT

A CT of your chest will be performed either at Robarts Research Institute or at University Hospital, which is located next door to Robarts Research Institute. You will perform an 8-9 second breath-hold of medical grade nitrogen from a special bag made for this procedure. Similar to MRI, you will be observed by a technologist during the entire procedure and may be spoken to through an intercom in the scanner. You will be personally escorted to and from the radiology department by study staff and if you prefer, you may go by wheelchair. The CT will be performed at your first visit.

Questionnaires

You will be asked to complete questionnaires about your breathing history. These questionnaires will take you about 5-10 minutes to complete. You will be offered assistance to complete these as needed.

Instructions before study visits

Some activities may affect the results of the breathing tests. Because of this, we ask that you do not use e-cigarettes or tobacco products within 4 hours of your study visit, and that you do not eat or drink for 1 hour before study visits. If you are not able to do this, please let study staff know.

If you are on any medications for your breathing, these may need to be held before study visits. Study staff will tell you what medications you need to hold and for how long. If you need to use your medication for medical reasons during this time period, please do so and let study staff know.

If you are not able to follow any of these instructions, please let study staff know during the study visit. You will still be allowed to participate in the study if you do not follow these instructions, however some tests may not be done.

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.
- You may experience side effects related to the salbutamol (Ventolin). The most common adverse reactions to salbutamol (3-14%) are throat irritation, viral respiratory infections, upper respiratory inflammation, cough, and musculoskeletal pain. Less common side effects (1-3%) are diarrhea, laryngitis, tachycardia (increased heart rate), palpitation and dizziness.
- The sputum induction process may cause gagging, coughing and a sore/burning throat, but these are usually not bothersome and they will not interfere with the test. Sometimes the procedure may cause you to hyperventilate and may cause some chest tightness and discomfort. You will do this test after you have inhaled salbutamol (Ventolin), which helps reduce the chance of chest discomfort.
- When you do blood tests, a needle will be used to puncture the skin. When the skin is punctured, there is always a very small chance of introducing an infection into the body. If you notice a fever, persistent redness or persistent pain at the injection site, please follow up with your physician to rule out an infection.
- The CT delivers a radiation dose to your lungs, the mean total effective dose is approximately 1.8 mSv. The cancer risk related to this radiation dose is the same as the cancer risk related to smoking 23 cigarettes over a lifetime and the same as one third to half the annual natural background radiation in London, Ontario.
- Bicycle exercise testing is generally well tolerated. The reported risk of death is 2 to 5 per 100,000, and these events are usually related to an underlying disease. For reference, the risk of being struck by lightening in a given year is about 1 in 100,000.
- Bicycle exercise testing may cause you to experience leg fatigue from pedaling or breathlessness from exertion
- There are no known biological risks associated with MR imaging. Some people cannot have an MRI because they have some type of metal in their body. For instance, if you have a heart pacemaker, artificial heart valves, metal implants such as metal ear implants, bullet pieces, chemotherapy or insulin pumps or any other metal such as metal clips or rings, you cannot have an MRI. During this test, you will lie in a small closed area inside a large magnetic tube. Some people may get scared or anxious in small places (claustrophobic). An MRI may also cause possible anxiety for people due to the loud banging made by the machine and the confined space of the testing area. You will be given earplugs to help reduce the noise.

About ^{129}Xe gas

Hyperpolarized ^{129}Xe gas is an "investigational" agent that is used to see inside 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 ^{129}Xe gas in this study. The agent has been approved by Health Canada for other procedures and has been studied in over 2000 people worldwide, including about 150 participants in London Ontario. Neither the Xenon gas nor the MRI will expose participants to radioactivity.

What side effects can happen from inhaling hyperpolarized xenon gas?

Some adverse or bad side effects of hyperpolarized ^{129}Xe gas that have been reported at Robarts Research Institute include light-headedness (less than 1%), which resolved within 2 minutes, and nausea/headache (less than 1%). It was determined that the nausea and headache were unrelated to inhalation of hyperpolarized ^{129}Xe gas. Overall, inhalation of ^{129}Xe gas has been well tolerated by study participants.

Another study using ^{129}Xe gas has reported other adverse or bad side effects. The amount of gas used in this study was approximately 2-3 times the amount of gas you will be asked to inhale. The most common side effects reported were dizziness (59%), paresthesia (tingling sensation) (34%), euphoria (30%) and hypoesthesia (numbness) (30%). All side effects were mild and resolved within 3 minutes.

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

There may be other side effects or risks that are not known at this time. You will be told in a timely manner about significant new information that might affect your decision to stay in the study.

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 this study may help improve understanding of the effects of e-cigarette use in the future.

Voluntary Participation

Your participation in this study is voluntary. You may decide not to be in this study, or to be in the study now and then change your mind later. Even if you consent to participate, you have the right to not answer individual questions or to withdraw from the study at any time. You may leave the study at any time without affecting your medical care.

If you withdraw from the study, you will not need to do any additional activities related to this study, and any information that has been collected already may still be used.

We will give you new information that is learned during the study that might affect your decision to stay in the study.

You may be asked to leave the study without your consent if it is no longer safe for you to continue, if you have a study-related injury, or for any other reason.

What other choices are there?

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

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

If you are injured or become ill as a direct result of participating in this research study, you should contact your study doctor as soon as possible and treatments you may need according to the current medical practice that are not covered by healthcare insurance will be covered.

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

What if researchers discover something about a research participant?

This study involves blood tests, sputum tests, chest CT, lung MRI, lung function tests, exercise tests and questionnaires. There is a small possibility that an abnormality might be found on these tests, called an incidental finding.

If an incidental finding occurs, you will be notified of the finding by the principal investigator of the study. If you would like the incidental finding to be sent to your healthcare team, this will be arranged.

Information collected for this study is performed for research purposes only and is not optimized to make clinical diagnoses.

During the study, the researchers may learn something about you that they didn't expect. For example, the images or bloodwork done during your study visit may show an unexpected abnormality.

By participating, you agree to the possibility of being informed about a potential incidental finding, according to the procedure described above. If you do not agree to the potential risk of an incidental finding you should not participate in this study.

How will your privacy be protected?

By signing the Consent Form you agree that the study investigator and the regulatory agencies listed below may collect, use and disclose information about you. This may include your name, address, phone number, medical history and information from your study visits. 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. If you do not wish to consent to the collection, use and disclosure of information about you as described, you will not be able to participate in this study.

Unless required by law, only the principal investigators, collaborators, study staff and inspectors from regulatory agencies listed below will have direct access to your medical records to check the study information. A list linking your study number with your name, date of birth and contact information will be kept by the researcher in a secure place, separate from your study file. 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.

Regulatory agencies that will have direct access to your medical records are representatives of The University of Western Ontario Health Sciences Research Ethics Board, representatives of the Lawson Quality Assurance Education Program and Health Canada. These agencies may require access to your study-related records or may follow up with you to monitor the conduct of the research.

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
1151 Richmond St N
London ON Canada N6A 5B7

If you do this, you will not be studied any further and no new health data that identifies you will be gathered after that date.

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.

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 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.

General information about the status of this study and publication information can be found on wwww.clinicaltrials.gov

Contacts

If you have any questions about your rights as a research participant or the conduct of this study, you may contact the Patient Experience Office at LHSC at (519) 685-8500 ext. 52036.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) 931-5777 ext. 24197.

Western

Consent Form

Title:	**Novel Pulmonary Imaging of Lung Structure and Function in Symptomatic and Asymptomatic e-cigarette Smokers**
Sponsor:	**Western University, Robarts Research Institute**
Protocol:	**ROB0048**
Investigator:	**Dr. Grace Parraga** **Robarts Research Institute** **1151 Richmond St N** **London ON Canada N6A 5B7**

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

My signature means that I have explained the study to the participant named above. I have answered all questions.

_____
Name of person obtaining informed consent

_____
Signature of person obtaining informed consent