Letter of Information and Consent to Participate in a Research Study

Before agreeing to take part in this research study, it is important that you read the information in this research consent form. It includes details we think you need to know in order to decide if you wish to take part in the study. If you have any questions, ask a study doctor or study staff.

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|---|---|
| **Study Title:** | **S**ustained **M**ood **I**mprovement with **L**aughing gas **E**xposure**:** A Randomized Controlled Pilot Trial. **(SMILE Trial)** – Sub-Study Protocol to include Neuroimaging |
| **REB Study Number:** | 22-139 |
| **Sponsor Investigator/Lead Investigator:** | Venkat Bhat, MD MSc FRCPC DABPN<br>St. Michael's Hospital<br>193 Yonge Street, Suite 6-013, Toronto, ON M5B 1M8<br>416-360-4000 ext. 76404 (24-hour contact) |
| **Co-Investigator:** | Karim Ladha, MD, MSc, FRCPC<br>Department of Anesthesia. St. Michael's Hospital<br>30 Bond Street, Toronto, ON M5B 1W8<br>416-864-5825 (Monday to Friday, 9:00 am to 5:00 pm) |
| **Study Coordinator:** | Walter Sim<br>St. Michael's Hospital<br>647-676-2317 (Monday to Friday, 9:00 am to 5:00 pm) |

## INTRODUCTION

You are invited to consider participating in this research sub-study because you have been diagnosed with depression and are participating in the Sustained Mood Improvement with Laughing gas Exposure (SMILE) trial.

Please read this Consent Form carefully and ask your primary doctor and study team as many questions as you would like before deciding whether to participate in this additional sub-study. You may also wish to discuss the study with others, such as a family member or a close friend. This consent form should inform you of what this research is about and what your participation will involve. If you would like more details about any information that is included or not included here, please ask the research team.

Please take your time in making your decision. Taking part in this study is voluntary. Deciding not to take part or deciding to leave the study later will not result in any penalty or affect your current or future health care.

If you choose to participate in this study, you will need to sign this Letter of Information and Consent form. You should not sign this form until you are sure you understand the information. You may also wish to discuss the study with others, such as a family member or a close friend.

## IS THERE A CONFLICT OF INTEREST?

The researchers have received funding for this study from the St. Michael's Hospital Medical Services Association Innovation Fund but receive no direct or personal benefit from any study activities.

## WHAT IS THE STUDY ABOUT?

The purpose of this sub-study is to provide us with a better understanding of the changes in the brain's activity in response to the nitrous oxide intervention. While many studies commonly include MRI scans (i.e. brain scans) alongside interventions proposed to reduce depression symptoms, the imaging performed in this sub-study will allow us to specifically identify changes in the brain's structure and blood flow linked to the nitrous oxide intervention.

As part of this sub-study, you will receive 2 MRI scans in addition to your nitrous oxide or placebo intervention visits. The first MRI scan will occur before or during the first treatment visit (Day 0). The second MRI scan will happen on the first follow-up visit (Day 28). Additional details about the study visit schedule can be found below.

At this time, the main purpose is to complete the study with 20 participants (also known as a pilot study) to learn whether it will be possible to plan for a larger study in the future.

## WHAT IS THE DESIGN OF THIS STUDY?

This study is designed as a prospective, observational study. This means that no part of the study procedure is designed to change your regular clinical care and that additional imaging data will be collected to better understand your response to the nitrous oxide intervention or midazolam placebo.

## CAN I TAKE PART IN THIS STUDY?

If you agree to take part in the sub-study, you will be screened to see if you are eligible to participate in the study. Please see the section below for details regarding the screening visit.

HOW WILL I BE INVOLVED IN THIS STUDY?

Your participation in the sub-study will last a total of 4 weeks. You will be asked to come to the St Michael's Hospital for the MRI scans twice in total (4 weeks apart). The other study assessments will be completed on the phone.

**Screening – Visit 1:**
At your appointment in the hospital, you will be asked to complete the following:

After you signed the consent form and have been screened for eligibility for the main study, the Research Coordinator will ask some additional questions about whether it is safe to undergo the MRI scan and will also ask about any medications or therapies you are currently receiving, which should take about 10 minutes in total.

The research staff will ask for your email address to send the study reminders to you. You also have the option of telephone reminders to remind you of the study visits.

**MRI Sessions – Visits 2 and 7 (Days 0 and 28):**
Before you are scheduled for your first dose of the study intervention, you will undergo the first MRI session. This visit will take place before or on the day of your first treatment visit. The second MRI session will take place four weeks after you have received the first intervention.

MRI sessions will be booked for 45 minutes. During the scan, you will be instructed to lie on your back on the scanner bed. The scanner itself is tube-shaped, and you will be inserted headfirst into the scanner up until your shoulders. You may be offered a blanket as it can get cold in the room. Additionally, due to the fact that the MRI scan components are rather loud, you will be offered ear plugs. You may at all points contact the MRI technician in order to stop the scan.

**Table 1: Timeline of Study Visits**

| TIMEPOINT | Screening (Visit 1) | Before/on Day 0 (Visit 2) | Day 28 (Visit 7) |
|---|---|---|---|
| **ENROLLMENT:** | | | |
| Eligibility screen | x | | |
| Informed consent | x | | |
| **ASSESSMENTS:** | | | |
| MRI safety screening | x | | |
| Neuroimaging (MR scan) | | x | x |

WHICH RESEARCH ACTIVITIES OR STUDY PROCEDURES WILL BE DONE?

**Magnetic Resonance Imaging (MRI)**

MRI scans are specialized imaging procedures that are necessary for measuring your response to this study drug. For most patients, the risks or side effects associated with undergoing MRI are minimal. An MRI scan does not involve ionizing radiation like conventional X-rays. Scanning is a painless procedure and there is no radiation emitted from the scan. You will be monitored the entire time.

MRI is a method of taking pictures of the brain and of the blood flow in the brain using a large magnet and radio signals. Because an MRI scanner uses strong magnets, you cannot have any metal implants in your body to have an MRI scan. People with an artificial heart valve, metal plate, pin, or other metallic objects in their body (including gun shots or shrapnel) are not eligible for MRI scans. Study personnel will ask you questions to make sure you can safely have an MRI scan.

Before you start and after you finish the treatment sessions, the study team will do the approximately 45-minute magnetic resonance imaging (MRI) to map your brain, to make sure that the stimulator will be aimed correctly during the intervention. This will be performed for research purposes, to help the study team learn who will best respond to the Nitrous Oxide treatment.

An MRI imaging coil, which is made from special wires that are covered in plastic, will be placed around your head. Foam pads will be placed around your head to limit head movement during the scan. Cardiovascular and respiratory activity will be monitored throughout the scan to avoid the impact of physiological processes such as heart rhythm and rate of respiration on your brain scan. The term cardiovascular refers to the heart (cardio) and the blood vessels (vascular). You will be asked to put on a belt around your chest during the MRI scan to monitor cardiovascular and respiratory activity,.

During the scan:

- You will be asked to lie still on your back for approximately 45 minutes.
- You will hear a loud knocking or hammering noise while the MRI is taking pictures, but the process itself will be painless. You will be given disposable earplugs to use to help make the noise less noticeable.
- You will be in constant contact with the MRI technician through an intercom.

If at any time during the scan, you feel too uncomfortable to continue, no matter what the reason, the procedure will be immediately stopped, and you will be removed from the MRI scanner.

The brain imaging scan is being done for research purposes only and will not be reviewed for clinical purposes. The technical staff involved in the study are not trained or qualified to diagnose

pathologies. During brain imaging procedures, however, there is a small chance of discovering a potential abnormality during the scan. In the rare case of an unexpected finding, your images will be reviewed by a radiologist. If follow-up is deemed necessary, you will be contacted directly by the principal investigator and asked to provide permission for the findings to be shared with your primary physician. Your physician can then provide you with a referral for further testing and clinical follow-up. If you do not have a primary physician, a study physician will provide you with a referral and follow-up.

For safety reasons, if your abdomen, shoulder, or hip circumference is greater than 180 cm you may need to be excluded from the study as the MRI scanner may not accommodate you.

## WHAT ARE THE RISKS OR DISCOMFORTS RELATED TO THE STUDY ACTIVITIES?

For the MRI scan, there is also a risk of discomfort due to lying on your back for the time of the scan, claustrophobia, and exposure to loud noise (although hearing protection is provided during scans). There are also several conditions that could make MRI unsafe, such as:

- Certain implanted medical devices
- Foreign metal objects in the body
- Metal fragments in the eyes

MRI personnel will review these with you in detail prior to scanning. Those with the conditions listed above should not participate in the study, as it may be dangerous to undergo the MRI scan. Before completing any MRI associated with this study, MRI personnel at St. Michael's Hospital will review these with you prior to undergoing any scans. If based on this screen, you are deemed ineligible for the MRI (e.g. there is metal in your body that is incompatible with the MRI), you will be excluded from participating in the MRI component of this study for safety reasons and will not be eligible to complete all other aspects of this study.

Some participants may experience discomfort while trying to remain motionless inside the scanner. Participants may be bothered by feelings of claustrophobia (i.e., the fear of enclosed spaces) while inside the scanner or by the noise levels made by the scanner during the study. You will also be provided with both earplugs and earphones to help reduce scanner noise exposure. Any discomfort experienced is generally mild. There is no exposure to harmful x-rays. If you have metallic objects in your body, we will not allow you to take part in the scans because the strong magnetic field in the scanner could cause these objects to change position and may cause injuries.

## WILL I BENEFIT IF I TAKE PART?

There will not be any direct benefits to you for participation in this sub-study. There will be no difference in your care if you choose to take part in the study or not. Your participation may allow the

researchers to establish whether nitrous oxide is a feasible and safe procedure for those with depression. Further studies looking at the efficacy of nitrous oxide will be needed to learn whether it can treat depression, which may be of benefit to future patients.

## ALTERNATIVES TO PARTICIPATION

This sub-study is not researching ways to provide you with medical treatment, so the alternative to taking part in this study is to not take part in the study. Whether you choose to take part in this study or not, you will receive the same standard and level of care at Unity Health Toronto.

## NEW INFORMATION ABOUT THE RESEARCH STUDY

During the study, we may make changes to the study. We may also learn new things about the study that you may need to know. Some of the new information or changes might affect your decision to take part in the study. If so, you will be notified about the new or changed information in a timely manner and we will ask you if you consent to remain in the study. You may be asked to sign a new consent form at that time.

## NEW INFORMATION ABOUT YOUR HEALTH (INCIDENTAL FINDINGS)

The tests or procedures that we do during this study might reveal medical information about you that is not part of the objectives of this study but may be relevant to your health. This type of medical information is called an incidental finding. Some incidental findings could be related to treatable conditions, or they could be related to factors that may affect your current or future health care. With your consent, we will communicate all medically actionable incidental findings to you.

## PARTICIPATION IN THE STUDY

Your participation in this study is voluntary. If you choose not to participate, you and your family will continue to have access to standard care at St Michael's Hospital.

## DOES THIS STUDY AFFECT PREGNANCY?

It is not known if there is any risk to a fetus posed by the magnet in the MRI scanner, therefore, we will not allow you to take part in the sub-study if you are pregnant.

## WITHDRAWAL FROM THE STUDY

If you choose to take part in this sub-study, you can change your mind without giving a reason, and you may withdraw from the study at any time without any effect on the care you or your family will receive at St Michael's Hospital. If at any time you choose to withdraw from this sub-study, please contact a member of the study team.

You will be allowed to continue your participation in the main SMILE study if you withdraw from this sub-study. You will, however, be withdrawn from the sub-study component if you withdraw from the main study.

Your participation in the study may be stopped without your consent for the following reasons:

- If continuation in the study appears to be harmful to you;
- If it is discovered that you do not meet the eligibility requirements;

The study may be terminated by the investigators at any time for any reason.

**Continued collection and use of your data after withdrawal:**

If you withdraw from the sub-study, any data collected about you up to that time will still be used. Any study data collected about you up to the time you withdraw will still be used for analysis. We may be required to retain the personally identifying information and study data that we have already collected until after the end of this study (described in the Privacy and Confidentiality section). If you withdraw or are withdrawn from this study, no more data about you will be collected.

HOW WILL MY INFORMATION BE MANAGED AND KEPT SAFE?

The study personnel will make every effort to keep your personally identifying information private and confidential in accordance with all applicable privacy legislation, including the Personal Health Information Protection Act (PHIPA) of Ontario.

Any information that is recorded for study purposes will be de-identified by using a unique study identification number instead of any of your personal identifiers. To complete our data analysis, please note that we will need to know your assigned intervention from the main study in order to determine if there were any changes to your brain's function as a result of the study intervention assigned to you. The principal investigator at St. Michael's Hospital is in control of the key that links your study number to you personally and will keep it stored separately from the study data.

No personally identifying information will be allowed off site in any form, unless required by law or as described in this consent form.

All the study data will be collected on paper forms and later transferred to a database for analysis. The paper forms on which your data is collected will be stored securely in locked cabinets and only authorized research personnel will have access to these forms. The data will be stored on a secure internal hospital server and will be password protected so that it is only accessible to authorized research personnel.

Your research records will be kept for 7 years after study completion at St. Michael's Hospital in a highly secure and confidential manner, as this is the length of time required by the institution. The information will then be anonymized (any link to you will be destroyed) or completely destroyed.

## ARE THERE ANY RISKS OF USING EMAIL FOR RESEARCH?

There are common risks of using email to communicate:

- Information travels electronically and is not secure in the way a phone call or regular mail would be.
- If someone sees these emails they may know that you are a participant in this study or see the health information included in the email.
- Emails may be read or saved by your internet provider (i.e. Rogers, your workplace, "free internet" providers).
- Copies of an email may continue to exist, even after efforts to delete the email have been made.
- There is always a chance with any unencrypted email, however remote, that it could be intercepted or manipulated.

Do not use email messaging for medical emergencies. If you require immediate help, call your clinic or care provider, or seek emergency services.

## WHAT IS THE COST TO PARTICIPATE IN THE STUDY?

There are no costs to you for participation in the imaging sub-study. You will be compensated $25 per in-person visit for the sub-study component to cover travel expenses, but we are not able to provide compensation for additional expenses such as parking or food.

If you withdraw from this study before completing it, you will receive compensation for the parts of the study that you have completed.

## WHAT IF I AM HURT DURING MY PARTICIPATION IN THE STUDY?

If you experience side effects from study interventions or study procedures, you should inform the study team as soon as possible. If you have any other concerns about safety or unexplained symptoms, contact us immediately.

## COMPENSATION FOR INJURY:

If you are injured because of your participation in this study, medical care will be provided to you in the same manner as you would ordinarily obtain any other medical treatment. In no way does signing this form waive your legal rights nor release the study doctor(s), sponsor, or involved institution(s) from their legal and professional responsibilities.

STUDY RESULTS:

The results of this study may be presented at a scientific conference or published in a scientific journal. If you are interested in obtaining the results of this study, you can contact the study team. We estimate that the results of this study will be available in 2 years.

You will never be personally identified in any publication, report, or presentation that may come from this study.

RESEARCH ETHICS BOARD CONTACT:

If you have any questions regarding your rights as a research participant, you may contact the Unity Health Toronto Research Ethics Board Office at:

**Unity Health Toronto Research Ethics Board**
Monday to Friday, 9:00 a.m. to 5:00 p.m.
416-864-6060 ext. 42557

Unity Health Toronto is a health network that includes Providence Healthcare, St. Joseph's Health Centre, and St. Michael's Hospital.

The Unity Health Toronto Research Ethics Board is made up of a group of scientists, medical staff, and individuals from other backgrounds (including law and ethics) as well as members from the community. The Board is established by Unity Health Toronto to review studies for their scientific and ethical merit. The Board pays special attention to the potential risks and benefits to the research participant, as well as the potential benefit to society.

STUDY CONTACT:

If you have questions about taking part in this study, or if you suffer a research-related injury, you can talk to the research team, or the person who is in charge of the study at this institution. That person is:

**Venkat Bhat, MD, MSc, FRCPC, DABPN**

St. Michael's Hospital
24 Hour Contact: 416-360-4000 ext. 76404
(You will be asked to leave your phone number to be called)

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| **Study Title:** | **S**ustained **M**ood **I**mprovement with **L**aughing gas **E**xposure**:** A Randomized Controlled Pilot Trial (**SMILE Trial**) – Sub-Study Protocol to include Neuroimaging |
| **Sponsor Investigator/Lead Investigator:** | Venkat Bhat, MD, MSc, FRCPC, DABPN<br>416-360-4000 ext. 76404 (24-hour contact) |

SIGNATURE

The research study has been explained to me, and my questions have been answered to my satisfaction. I have been informed of the alternatives to participation in this study. I have the right not to participate and the right to withdraw without affecting the quality of medical care at St. Michael's Hospital for me and for other members of my family. As well, the potential harms and benefits (if any) of participating in this research study have been explained to me.

I have been told that I have not waived my legal rights nor released the investigators or involved institutions from their legal and professional responsibilities. I know that I may ask now, or in the future, any questions I have about the study. I have been told that records relating to me and my care will be kept confidential and that no information will be disclosed without my permission unless required by law. I have been given sufficient time to read the above information.

I consent to participate. I have been told I will be given a signed copy of this consent form.

| _____ | _____ | _____ |
|---|---|---|
| PARTICIPANT (Print Name)<br>Person providing consent | SIGNATURE | DATE |

I have explained to the above-named participant the nature and purpose, the potential benefits, and possible risks associated with participation in this research study. All questions that have been raised about the research have been answered.

| _____ | _____ | _____ |
|---|---|---|
| STUDY STAFF (Print Name)<br>Person obtaining consent | SIGNATURE | DATE |