INDIANA UNIVERSITY INFORMED CONSENT STATEMENT FOR RESEARCH
Healthy Volunteers

EFFECT OF ELECTRICAL STIMULATION OF THE AURICULAR BRANCH OF THE VAGUS NERVE ON CERVICAL VAGUS NERVE COMPOUND ACTION POTENTIALS- Phase 2

About this research
You are being asked to participate in a research study. Scientists do research to answer important questions which might help change or improve the way we do things in the future.

This consent form will give you information about the study to help you decide whether you want to participate. Please read this form, and ask any questions you have, before agreeing to be in the study.

Taking part in this study is voluntary
You may choose not to take part in the study or may choose to leave the study at any time. Deciding not to participate, or deciding to leave the study later, will not result in any penalty or loss of benefits to which you are entitled, and will not affect your relationship with your doctor or Indiana University or IU Health University Hospital.

WHY IS THIS STUDY BEING DONE?
The purpose of this study is to find out if we can stimulate the vagus nerve. The vagus nerve is a largely-internal nerve that controls many bodily functions, including stomach function. We hope that electrically stimulating the nerve around the external ear will also stimulate the internal vagus nerve. If it does, then we hope that this will help our treatment of patients with nausea and vomiting and disordered stomach function.

We hope to be able to measure the activity of the vagus nerve when it is stimulated in other ways. This could help us learn more about studying this nerve in the future.

We also hope to be able to measure the activity of the heart and vagus nerve in volunteers who are currently undergoing vagal nerve stimulation (VNS) as a part of their therapy for partial or focal seizures. This could help us determine if heart rate is affected by VNS therapy.

You were selected as a possible participant because you are either a healthy volunteer who does not suffer from any stomach disorders and are not taking any medications that affect stomach motility or you are a healthy volunteer who does not suffer from any stomach disorders and is undergoing VNS Therapy for the treatment of partial or focal seizures

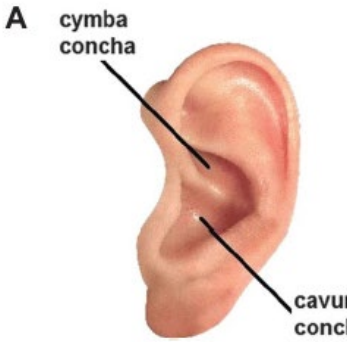
The study is being conducted by Dr. Thomas Nowak at the Indiana University School of Medicine. It is funded by the National Institutes of Health (NIH).

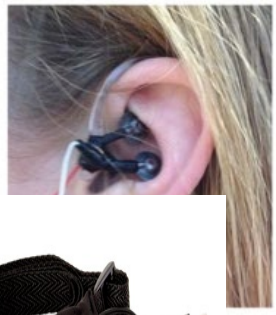
HOW MANY PEOPLE WILL TAKE PART?
If you agree to participate, you will be one of]175 participants taking part in this research.

WHAT WILL HAPPEN DURING THE STUDY?
If you agree to be in the study, you will do the following things:

<u>Healthy Human Subjects Group:</u>

You will sign this document called an informed consent that tells in detail about the study and confirm that you agree to all the study procedures. This document can be signed either in person or virtually online.
You will complete a Health History questionnaire that asks in detail about your health history along with any medications that you may be on. If you have been diagnosed with COVID 19 and are experiencing GI symptoms due to that then you can still enroll in the study if the study team feels so. You will be asked to complete another questionnaire related to some symptoms that you may or may not be experiencing.
If you meet all the requirements for the study, then you will do the following





EAR STIMULATION:
This is a onetime visit only

1. Two MRI compatible electrodes (small piece of metal or other substance that is used to take an electric current to or from a source of power like a stimulator) will be placed on the external (outer) surface of your left ear. (See Fig A and B) The leads from the electrodes are connected to a stimulator (a device that sends signals to the electrodes to function).
2. A pneumatic belt (which is a belt operated by air pressure) (see Fig C) that measures breathing, will be placed around your lower chest. Plastic tubes connected to this belt tell a laptop computer whether you are inhaling or exhaling.
3. Two electrocardiography (ECG) electrodes are placed on both sides of your neck overlying the area near the carotid pulse (which overlies the carotid artery in the neck) where the vagus nerve is located. This is performed in order to measure the vagal nerve electrical impulses in the neck (electrical signal travelling in the nerve).
4. Two ECG electrodes are placed, one on each side of your clavicle area, near the base of the neck, for measurement of heart function
5. Three ECG electrodes are placed on your stomach to measure the electrical activity of the stomach
6. A butterfly catheter will be placed by a trained person under aseptic conditions into a vein to collect blood so you don't have to have multiple needle sticks. 15 ml (1 tablespoon) of blood will be drawn at this time
7. After the electrodes have been placed in the ear, neck and on the arms, and the butterfly catheter is in place. you will undergo what we call a baseline recording. No current will be delivered to the ear electrodes, but you will be connected to the recording system to see if any activity can be recorded in any or all of the electrodes. The recordings will be made for 5- 10 minutes.
8. After the end of the baseline recording, electrical stimulation will then be sent to the ear electrodes. The intensity of the current will be such that you should not experience pain. You will be asked to grade the intensity based on a 10 point scale with "0" being no sensation and "10" being mild discomfort. The aim is to achieve a comfortable level for you. The intensity of the current will be increased by 10 percent and a recording will be made for 60 seconds. It will then be decreased by 10 percent and a recording made for another 60 seconds.

The current will be increased and decreased by 10 percent and recordings made till you feel that a comfortable level of sensation has been reached for you. This is 4 out of 10 and is labeled as "100 percent." The stimulus will be delivered when you are breathing out and not breathing in. You will be taking normal breaths during the duration of the study, and the study team will be closely observing your breathing to deliver the stimulus at the right time.
It may take you anywhere from 5 minutes to 15 minutes to reach the target 100% or 4/10 level of sensation.

9. Once the “100 percent” (4/10) or “target” level has been achieved, the stimuli will be delivered for a total of 2 minutes and recordings will be made.
10. After 20 minutes of stopping the stimulus, another 15 ml (1 tablespoon) of blood will be drawn. This is our second time point of blood draw.
11. You will then be asked to rest for additional 20 minutes and the final draw of 15 ml (1 tablespoon) will be made.

Consent for Blood Draw:

☐ I give my permission to have blood drawn for the purpose of the study.

☐ I do not want to have blood drawn for the study, but would still like to take part in the rest of the study procedures.

VAGAL MANEUVER:
You will be asked to not eat or drink for 2 hours before the study

1 MEA (Multi electrode Array) devices that contain multiple (tens to thousands of small electrodes) will be placed on either one, or both sides of the neck. This film will help capture the vagus signal from a large area and help define the path of the vagus nerve.
2 Two ECG electrodes are placed one on each of your arms or your chest for measurement of heart function
3 Three ECG electrodes are placed on your stomach to measure the electrical activity of the stomach
4 After the electrodes have been placed on the neck and on the arms, you will undergo what we call a baseline recording of 8-10 minutes.
5 After that the following procedures will be conducted to stimulate your vagus nerve. You will be monitored throughout and the electrical impulses made by your vagus nerve will be recorded.
    a. Cough: You will be asked to generate approximately 6 to 8 forceful and sustained coughs over 10 seconds.
    b. Cold stimulus to face: We will place a washcloth soaked in ice water on your face for about 10 seconds.
    c. Carotid Massage: This technique is performed with your neck in an extended position, the head turned away from the side being massaged. Only one side is massaged at a time. Pressure is applied underneath the angle of the jaw in a gentle circular motion for about 10 seconds.
    d. Gagging: A tongue depressor is briefly inserted (10 seconds) into the mouth touching the back of the throat, which causes you to reflexively gag.
    e. Valsalva maneuver: You will be asked to bear down as if you were having a bowel movement. You will be asked to blow through a mouthpiece that is hooked to a machine that measures how hard you are blowing. Alternatively, we can have you blow through the barrel of a 10 ml syringe for 10 seconds.
    f. Eating: You will be asked to drink water (8oz or 1 cup) or/ and Ensure Original (8 oz or 1 cup) that has 220 calories after fasting overnight to see that effect on vagal activity during eating. After 10 seconds of each maneuver, another 5-10 minutes of recording will be made. You are encouraged to drink water or ensure as per your capacity.

After 10 seconds of each maneuver, another 10-20 minutes of recording will be made before doing the next maneuver.

Not all procedures for the vagal study may be done in one day. You may be asked to come in on a separate day for the rest of the procedures. Also, you may not be required to do all the procedures and the study team will ask you before the procedure if you are comfortable with any or all before starting the procedure.

VNS THERAPY GROUP:
This is a one time visit only.

You will be asked to not eat or drink 2 hours before the study.

1. MEA (Multi electrode Array) devices that contain multiple electrodes (tens to thousands of small electrodes) will be placed on either one, or both sides of the neck. This film will help capture the vagus signal from a large area and help define the path of the vagus nerve.
2. Two ECG electrodes are placed either one on each arm or on the chest for measurement of the electrocardiogram (ECG)
3. Three ECG electrodes are placed on the abdomen in a line parallel to the longitudinal axis of the stomach to record the electrogastrogram (EGG).
4. After the electrodes have been placed on the neck and on the arms, you will undergo what we call a baseline recording of 20 minutes.

WHAT ARE THE RISKS OF TAKING PART IN THE STUDY?

While participating in the study, the risks, side effects, and/or discomforts include:
EAR STIMULATION GROUP:

There is a small chance of slight and temporary discomfort at the site where the ear electrodes are placed. Before starting the electrical stimulation study, you will be asked at which point you experience discomfort. We will call this a "10" on a scale of 1 to 10 (0= no sensation, 10= mild discomfort). The rest of the electrical impulses will be given at a level of 4 or less.

It is possible that you may experience some dizziness or light-headedness in which case the ear electrodes will be removed, and you may be asked to lie down in a flat position. Additionally, you may experience some skin irritation due to the ECG electrodes placed on the skin.

It is possible that electrical stimulation may cause anxiety. In this case, the electrodes will be removed and the study discontinued. You will be required to remain under supervision until all symptoms subside. A study physician will be available at all times to discuss the study with you should you have any concerns.

VAGAL STIMULATION GROUP:

The maneuvers may cause discomfort to you. You may feel dizzy or light-headed, or you may feel like vomiting. Cough may lead to feeling of vomiting which is normal if you are trying to cough knowingly. The cold towel may cause wetness and coldness to your face which lasts for 10 seconds. Carotid massage (near the carotid artery in the neck) may cause slight discomfort to your neck area. Very rarely, carotid massage may lead to transient ischemic attack (TIA or "mini-stroke") or a stroke. Gagging may lead to feeling of vomiting. Drinking Ensure may cause fullness to your stomach.

BOTH EAR STIMULATION AND VAGAL STIMULATION GROUPS:

You may experience some pain during venipuncture. An indwelling catheter is used to decrease the discomfort of multiple venipunctures. The procedure is performed using aseptic technique to minimize the risk of infection. Pressure and a bandage are applied over the venipuncture site to minimize the risk of bleeding.

There also may be other side effects that we cannot predict.

There is a risk of potential loss of confidentiality.

VNS THERAPY GROUP:

There is no additional risk as part of the recording for VNS Therapy subjects that are research related.

WHAT ARE THE POTENTIAL BENEFITS OF TAKING PART IN THE STUDY?
We don't expect you to receive any benefit from taking part in this study, but we hope to learn things which will help scientists in the future.

WILL I RECEIVE MY RESULTS?
We may learn things about you from the study activities, which could be important to your health or to your treatment. If this happens, you can decide whether you want this information to be provided to you. For example, we may find that you have an abnormal rhythm (arrhythmia) of your heartbeat. In that case we can immediately inform you verbally of this abnormality and, if indicated, recommend further medical evaluation. If you decide that you want this information, you may need to meet with professionals with expertise to help you learn more about your research results. The study team/study will not cover the costs of any follow-up consultations or actions.

Please initial one of the following options:

_____ Yes, I want to be provided with this information.

_____ No, I do NOT want to be provided with this information.

HOW WILL MY INFORMATION BE PROTECTED?
Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. No information which could identify you will be shared in publications about this study

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as the study investigator and his/her research associates, the Indiana University Institutional Review Board or its designees, and (as allowed by law) state or federal agencies, specifically the Office for Human Research Protections (OHRP), the Food and Drug Administration (FDA) and the National Institutes of Health (NIH), who may need to access your medical and/or research records.

A description of this clinical trial will be available on ClinicalTrials.gov as required by U.S. law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

For the protection of your privacy, this research is covered by a Certificate of Confidentiality from the National Institutes of Health. The researchers may not disclose or use any information, documents, or specimens that could identify you in any civil, criminal, administrative, legislative, or other legal proceeding, unless you consent to it. Information, documents, or specimens protected by this Certificate may be disclosed to someone who is not connected with the research:

(1) if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases);
(2) if you consent to the disclosure, including for your medical treatment;

(3) if it is used for other scientific research in a way that is allowed by the federal regulations that protect research subjects;
(4) for the purpose of auditing or program evaluation by the government or funding agency;
(5) if required by the federal Food and Drug Administration (FDA).

A Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the researchers to release it.

WILL MY INFORMATION BE USED FOR RESEARCH IN THE FUTURE?
Information or specimens collected from you for this study may be used for future research studies or shared with other researchers for future research. If this happens, information which could identify you will be removed before any information is shared. Since identifying information will be removed, we will not ask for your additional consent.

WILL I BE PAID FOR PARTICIPATION?
You will be paid $50 in gift cards for each completed visit and for participating in this study. You may receive up to $50 for the ear stimulation study part and $50 for each visit for the vagal maneuver study up to 4 maximum visits. You will be paid $25 if you start but are unable to complete the visit. Parking voucher will be provided to you for the study visit.

WILL IT COST ME ANYTHING TO PARTICIPATE?
There is no cost to you for taking part in this study.

WHO WILL PAY FOR MY TREATMENT IF I AM INJURED?
In the event of physical injury resulting from your participation in this study, necessary medical treatment will be provided to you and billed as part of your medical expenses. Costs not covered by your health care insurer will be your responsibility. Also, it is your responsibility to determine the extent of your health care coverage. There is no program in place for other monetary compensation for such injuries. However, you are not giving up any legal rights or benefits to which you are otherwise entitled.

WHO SHOULD I CALL WITH QUESTIONS OR PROBLEMS?
For questions about the study or a research-related injury, contact the researcher, Dr. Thomas Nowak at 317-948-9227 or gimotili@iupui.edu. After business hours, please call 317-944-5000 and ask for the GI fellow on call.

In the event of an emergency, you may contact Dr. Nowak at 317-944-5000.

For questions about your rights as a research participant, to discuss problems, complaints, or concerns about a research study, or to obtain information or to offer input, please contact the IU Human Subjects Office at 800-696-2949 or at irb@iu.edu.

CAN I WITHDRAW FROM THE STUDY?
If you decide to participate in this study, you can change your mind and decide to leave the study at any time. The study team will help you withdraw from the study safely.

Your participation may be terminated by the investigator without regard to your consent if he feels that continuation in the study may affect your health or personal welfare.

PARTICIPANT'S CONSENT

In consideration of all of the above, I give my consent to participate in this research study. I will be given a copy of this informed consent document to keep for my records. I agree to take part in this study.

Participant's Printed Name:_____

Participant's Signature:_____**Date**:_____

Printed Name of Person Obtaining Consent:_____

Signature of Person Obtaining Consent:_____**Date**:_____