Vagus Nerve Simulation for Long-COVID-19

PI: David.Putrino
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STUDY INFORMATION:

Study Title: VNS Long COVID

Study site(s): Icahn School of Medicine at Mount Sinai, Mount Sinai Hospital

Lead Researcher (Principal Investigator): David Putrino, PT, PhD

Physical Address: 5 East 98th Street, Sub-basement 18, New York, NY 10029

Mailing Address: 5 East 98th Street, Sub-basement 18, New York, NY 10029

Phone: 212-824-8369

SUMMARY OF THIS RESEARCH STUDY:

This document explains a research study you might be interested in joining. Participation in the study is voluntary. You can agree to join or not. Your decision will not limit your ability to receive care at Mount Sinai. You should only agree to take part if you understand the study and if all of your questions about the research study are answered. If you do join the study, the research team must share any new information with you that may change your mind about taking part.

The purpose of this research study is to evaluate the effect of a non-invasive vagus nerve stimulation (VNS) on:
1) Symptom reporting through surveys and questionnaires
2) Blood test results that provide information about the health of some of your body's nerves.

Vagus nerve stimulation uses simple technology that provides a small vibration to the outside of the body wherever the device is placed. The vagus nerve is a nerve that is responsible for the actions of many organs in your body such as digesting food, making sweat, and making your heart beat faster or slower.

We aim to investigate how a 6-week VNS program creates meaningful changes in specific symptoms associated with post-COVID dysautonomia (PCD) PCD is a condition that occurs when the part of your nervous system that controls bodily functions that are usually under automatic control [e.g., heart rate, digestion, and temperature control] is not functioning normally. We will track changes to patient-reported outcomes (PRO) pre- and post-VNS study procedures. Additionally, we aim to investigate if there is an association between completion of the 6-week VNS treatment and symptoms of vagus nerve overactivity, by tracking changes in your blood and saliva before and after your VNS treatment.

The Parasym device system is non-invasive and does not present a potential for serious risk to the health, safety, or welfare of a subject. The device does not claim to and is not represented to be for use in supporting or sustaining human life and is not for a use of substantial importance in diagnosing, curing or treating disease or otherwise prevent the worsening of human health. The Parasym Device is approved for use in Europe and it is not approved in the United States outside of a research setting. It is being used in research studies in the United States studying several different indications. The Parasym Device is not currently available for purchase outside of the research environment by residents of the United States of America.

The device is labeled by Parasym will be used solely for the current clinical trial.

If you choose to participate, you will be asked to:

- Attend 5, in-person, visits to the Department of Rehabilitation and Human Performance Faculty Practice Associate (FPA)
- Have a blood draw at each study visit (approximately 1 fluid ounce or 2 tablespoons)
- Bring a morning saliva sample to each study visit (about 5ml or 1.5 tablespoons per sample)
- Complete PRO questionnaires at each study visit
- Be responsible for transportation to and from the visits

If you choose to take part, the main risks to you are minor VNS-related discomforts, mild discomfort during the blood test and potential loss of private information, for which we take several measures to prevent.

You may benefit from taking part in this research. Some potential benefits are a reduction in your symptoms.

Instead of taking part in this research, you may find other standard-of-care options through your healthcare provider.

If you are interested in learning more about this study, please continue to read below.

STUDY PARTICIPATION:

You may qualify to take part in this research study because:

- You are an adult ages 18+
- Have a clinical diagnosis of dysautonomia following an acute COVID-19 infection at least 3 months prior
- Speak English

Your participation in this research study is expected to last 12 weeks.

There are 40 people expected to take part in this research study at Mount Sinai.

Funds for conducting this research study are provided by Mount Sinai.

A description of this clinical trial will be available on http://www.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.

DESCRIPTION OF WHAT IS INVOLVED:

If you agree to take part in this research study, here is what may be involved:

- Research activities will take place at the Abilities Research Center (5 East 98th St, Sub-basement 18).
- There will be five required, in-person study visits, at weeks 0, 2, 5, 8, and 12. Each visit will take approximately 1 hour.
- If you agree to participate in this study: you will have a blood sample (approximately 11 milliliters or 2.2 teaspoons) taken by a Mount Sinai staff member in the same clinical area during each study visit.
- You will be asked to bring a saliva sample from the morning before each study visit.
- We will collect end-tidal CO2 levels at each study visit. This entails breathing into a small device for 15 seconds.
- You will be asked to complete several surveys/questionnaires after each study visit.
- After being randomized into either the “active VNS” or “sham VNS” group, you will take the non-invasive VNS device (Parasym) home with you to use according to the study protocol. This will be fully explained to you fully by a member of the study team. You will be explained how and when to perform the stim protocol.
- You will interact with the study coordinator(s) and Principal Investigator.
- Because this research study involves the use of a VNS device, a note must be included in your electronic medical record that you are taking part in the research. This way, anyone involved in your medical care will know that you are a study participant, and they can work to avoid any problems or negative outcomes that could arise if they do not know.

Randomization

No one, not you, or anyone from your medical team or from the research team will be able to choose what group you are assigned to or what study device you get. It will be by chance, like flipping a coin You will have an equal chance of being given each study device. Neither you nor the Lead Researcher or your own doctor will know which study device you are getting. If there is an emergency, they can get this information.

Future Contact:

The researchers may wish to use your personal contact information to contact you in the future. Do you give the researchers permission to **contact you** in the future to request the collection of additional information about you, discuss how your private information, study data and/or samples might be used, or discuss possible participation in another research study?

Please initial your choice: Yes_____ No_____

If "Yes", please indicate your preferred method of contact: (initial all that apply)

[ ] Email [ ] Phone [ ] Letter [ ] Text

USE OF YOUR DATA AND/OR SAMPLES:

The research team will never use or share your personal information (such as, name, address, date of birth, social security number), study data and/or samples (blood, tissue, urine, saliva, or any other body matter) that are collected as part of this study for future research, even if your identity is removed. Your data and/or samples will only be used to complete this study and then they will be destroyed.

YOUR RESPONSIBILITIES IF YOU TAKE PART IN THIS RESEARCH:

If you decide to take part in this research study, you will be responsible for the following things:

- Ensure your contact information is accurate to allow scheduling for your study visits
- Transportation to and from study visits
- Completion of surveys and questionnaires
- Return of device at the last study visit

COSTS OR PAYMENTS THAT MAY RESULT FROM PARTICIPATION:

Researchers will not pay you for your travel or the time it will take for you to be in the study.

If you agree to take part in this study, you will be paid a total of $200 (in the form of a Visa gift card) for your time and effort, with $40 being earned every visit.

Tax law may require the Mount Sinai Finance Department to report the amount of payment you receive from Mount Sinai to the Internal Revenue Service (IRS) or other agencies, as

applicable. Generally, this happens if you receive payments that equal $600 or more from Mount Sinai in a calendar year. You would be responsible for the payment of any tax that may be due.

POSSIBLE BENEFITS:

There is a chance this study may benefit you, but this is not guaranteed. Others may benefit from what researchers learn from the study. Possible benefits to you include a reduction in your symptoms.

POSSIBLE RISKS AND DISCOMFORTS:

- Risk of loss of private information; this risk always exists, but there are procedures in place to minimize the risk.
- Side effects associated with Parasym VNS
    - Parasym has the highest safety profile of VNS technology, with 0 serious adverse events reported in clinical studies. Side effects are rare and typically resolve immediately after the stimulation is complete.
    - The most common side effects include:
        - Application site discomfort
        - Application site irritations
        - Tingling on the skin where the device is applied
        - The following risks and complications have been associated with other VNS devices and may potentially occur with Parasym.
            - Light-headedness/dizziness, fatigue, shortness of breath, headaches, abnormal heart rhythm, sweating, fatigue, tinnitus, diarrhea
- The risks of a blood draw include pain, bruising, and the slight possibility of infection at the place where the needle goes in. Some people feel dizzy or may faint during or after a blood draw.
- In addition to these risks, this research may hurt you in ways that are not known. The unknown risks might be minor or might be major (death).

OTHER OPTIONS TO CONSIDER:

You may decide not to take part in this research study. If you decide not to take part, this will not affect the clinical care you receive at Mount Sinai. The choice is totally up to you.

IN CASE OF INJURY DURING THIS RESEARCH STUDY

If you believe that being in this research study has harmed you, you should contact the Lead Researcher. Their contact information is listed at the beginning of this consent form.

ENDING PARTICIPATION IN THE RESEARCH STUDY:

You may stop taking part in this study at any time. No matter what you choose, your care and benefits through Mount Sinai will not be negatively impacted.

If you decide to stop being in the study, please contact the Lead Researcher or the research staff.

You may also withdraw your permission for the researchers to use and share any of your protected information for research, but you must do so in writing to the Lead Researcher at the address on the first page. Even if you withdraw your permission, the Lead Researcher may still use the information that was already collected if that information is necessary to complete the research study. Your health information may still be used or shared after you withdraw your authorization if you have an adverse event (a bad effect) from taking part in the research study.

If you stop being in the research study, the research team may not remove information they have already placed in the study database, and may continue to use that data as part of this study. The research team may ask you whether they can continue to collect information from your medical record.

If you decide you don't want your data and/or samples to be used for research anymore, you can contact the researcher and ask to have your data and/or samples withdrawn or labeled so that they will not to be used in additional projects or shared. If your data and/or samples have already been shared with researchers, those researchers will be asked to stop using them. However, if any data and/or samples have already been shared without your identity or a linking code, it won't be possible to retrieve them. Data and/or samples that have already been used will not be affected by your decision. If your data and/or samples have already been deposited in an external repository, the study team will request that your data and/or samples be removed.

Withdrawal without your consent: The Lead Researcher, the funder or Mount Sinai may stop your involvement in this research study at any time without your consent. This may be because the research study is being stopped, the instructions of the research team have not been followed, the Lead Researcher believes it is in your best interest, or for any other reason. If data and/or samples have been stored as part of the research study, they too can be destroyed without your consent.

CONTACT INFORMATION:

If you have any questions, concerns or complaints at any time about this research, or you think the research has harmed you, please contact the office of the research team and/or the Lead Researcher at phone number 212-824-8369.

DISCLOSURE OF FINANCIAL INTERESTS:

Researchers sometimes get paid for consulting or doing work for companies that produce drugs, biologics or medical devices. If you have questions regarding industry relationships, you are encouraged to talk to the Lead Researcher or visit our website at http://icahn.mssm.edu/ where Mount Sinai publicly discloses the industry relationships of our faculty.

MAINTAINING CONFIDENTIALITY – HIPAA AUTHORIZATION:

As part of this study, some of your private and/or protected health information will be obtained, used, and shared with your permission. There is a Federal Health Insurance Portability and Accountability Act (HIPAA) that makes sure this is done correctly and safely.

What is protected health information (PHI)?
PHI is the combination of two things:

1. PHI contains information that identifies you. It will be used to contact you and link you to your health information, like name, date of birth, medical record number, and address.
2. PHI also contains health information, including information about your mental and physical health from your visits to doctors or hospitals, or from study visits.

Every time you visit a hospital or your doctor, PHI is created and recorded in your medical record by your healthcare providers. In the same way, the PHI created as part of this study will be linked to who you are and your medical information.

What PHI is collected and used in this research study, and might also be shared with others?
As part of this study, the research team at the hospital(s) involved in the research will collect your:

- Name
- Phone number
- Email
- Date of birth
- Past and current medical history

During the study, the researchers will gather information by:

- Taking a medical history (includes current and past medications or therapies, illnesses, conditions or symptoms, family medical history, allergies, etc.)
- Completing the tests, procedures, questionnaires, and interviews explained in the description section of this consent.

Why is your PHI being used?
Researchers need the information that identifies you so they can contact you during the study. They need your health information and the results of any tests and procedures being collected as part of this study to answer the questions posed in the study. The purpose of the study is discussed earlier in this consent form. Before researchers analyze the data, they remove any information that would let others know who you are or that you took part in the study. If researchers publish or present study results at scientific meetings, lectures, or other events, their presentations would not include any information that would let others know who you are, unless you give separate permission to do so.

The Lead Researcher may also use and share the results of these tests and procedures with other healthcare providers at Mount Sinai who are involved in your care or treatment. The research team and other authorized members of The Mount Sinai Health System ("Mount Sinai") workforce may use and share your information to ensure that the research meets legal, institutional or accreditation requirements. For example:

- The Mount Sinai Program for the Protection of Human Subjects is responsible for overseeing research on human participants and may need to see your information.
- If you receive any payments for taking part in this study, the Mount Sinai Finance Department may need your name, address, social security number, payment amount, and related information for tax reporting purposes.
- I*f the research team uncovers abuse, neglect, or reportable diseases, this information may be disclosed to appropriate authorities.*

Who, outside Mount Sinai, might receive your PHI?
As part of the study, the Lead Researcher, research team and others in the Mount Sinai workforce may disclose your PHI, including the results of the research study tests and procedures, to the following people or organizations: (It is possible that there may be changes to the list during this research study; you may request an up-to-date list at any time by contacting the Lead Researcher.)

- The United States Department of Health and Human Services (DHHS) and the Office of Human Research Protection (OHRP) (the government organization that is responsible for protecting human research participants).

In all disclosures outside of Mount Sinai, you will not be identified by any direct identifier unless disclosure of the direct identifier is required by law. Some records and information disclosed may be identified with a unique code number. The Lead Researcher will ensure that the key to the code will be kept in a locked file, or will be securely stored electronically. The code will not be used to link the information back to you without your permission, unless the law requires it, or rarely if the Institutional Review Board (IRB) allows it after determining that there would be minimal risk to your privacy. It is possible that a sponsor or their representatives, a data coordinating office, a contract research organization, may come to inspect your records. Even if those records are identifiable when inspected, the information leaving the institution will be stripped of direct identifiers. Additionally,

when applicable, the monitors, auditors, the IRB, *OHRP, as well as the Food and Drug Administration (FDA) will be granted direct access to your medical records for verification of the research procedures and data. OHRP and FDA are authorized to remove information with identifiers if necessary to complete their task. By signing this document you are authorizing this access.* The results of this research may be published. However, your name and other identifying information will be kept confidential.

For how long will Mount Sinai be able to use or disclose your PHI?
Your authorization for use of your PHI for this specific study does not expire.

Will you be able to access your records?
During your participation in this study, you will have access to your medical record and any study information that is part of that record. The research team is not required to release research information to you that is not part of your medical record.

Do you need to give the researchers permission to obtain, use or share your PHI?
NO! If you decide not to let the research team obtain, use or share your PHI, you should not sign this form, and you will not be allowed to volunteer in the research study. If you do not sign, it will not affect your treatment, payment, or enrollment in any health plans or affect your eligibility for benefits.

Can you change your mind?
If you decide to stop being in the study, please contact the Lead Researcher or the research staff. The research team may ask you whether they can continue to collect information from your medical record. You will also have to decide if you wish to limit the continued use of the information collected during the study. Under US privacy laws you may also withdraw your permission for the researchers to use and share any of your protected information for research, but you must do so in writing to the Lead Researcher at the address on the first page.

Even if you withdraw your permission, the Lead Researcher may still use the information that was already collected, but only to complete this research study. Your health information may still be used or shared after you withdraw your authorization if you have an adverse event (a bad effect) from taking part in the research study.

It is important for you to understand that once information is disclosed to others outside Mount Sinai, the information may be re-disclosed and will no longer be covered by the federal privacy protection regulations. However, where possible, Mount Sinai has entered into agreements with those who will receive your information to continue to protect your confidentiality.

If researchers are reviewing your medical records or asking questions about your medical history or conditions, it is possible that they may learn information related to your HIV status. If that is the case,

the following information concerns you. If researchers are not reviewing your medical records or asking questions about your medical history or conditions, then you may ignore the following section.

Notice Concerning HIV-Related Information

If you are authorizing the release of HIV-related information, you should be aware that the recipient(s) is (are) prohibited from re-disclosing any HIV-related information without your authorization unless permitted to do so under federal or state law. You also have a right to request a list of people who may receive or use your HIV-related information without authorization. If you experience discrimination because of the release or disclosure of HIV-related information, you may contact the New York State Division of Human Rights at (888) 392-3644 or the New York City Commission on Human Rights at (212) 416-0197. These agencies are responsible for protecting your rights.

How the Institutional Review Board (IRB) can help you:

This research has been reviewed and approved by an Institutional Review Board (IRB). You may reach a representative of the Mount Sinai Program for Protection of Human Subjects at telephone number (212) 824-8200 during regular work hours (Monday-Friday, 9am-5pm, excluding holidays) for any of the reasons listed below. This office will direct your call to the right person within the Mount Sinai Health System:

- Your questions, concerns, or complaints are not being answered by the research team.
- You cannot reach the research team.
- You are not comfortable talking to the research team.
- You have questions about your rights as a research participant.
- You want to get information or provide input about this research.

ADULT PARTICIPANT:

Your signature below documents your permission to take part in this research study and to the use and disclosure of your protected health information. A signed and dated copy will be given to you.

Signature of Participant	Printed Name of Participant	Date	Time

PERSON EXPLAINING STUDY AND OBTAINING CONSENT:

Signature of Consent Delegate	Printed Name of Consent Delegate	Date	Time

WITNESS SECTION:

My signature below documents that the information in the consent document and any other written information was accurately explained to, and apparently understood by, the participant, and that consent was freely given by the participant.

Signature of Witness	Printed Name of Witness	Date	Time