
Protocol Title: Evaluating the use of transcutaneous vagus nerve stimulation (tVNS) to improve upper limb motor recovery after stroke

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Consent for Participation in a Research Study

Protocol Title: Evaluating the use of transcutaneous vagus nerve stimulation (tVNS) to improve upper limb motor recovery after stroke
Principal Investigator: Bruce T. Volpe, MD
Sponsor: Department of Functional Neuroanatomy

This consent form is written from the point of view of a research subject. If consent will be obtained from a legally authorized representative or next of kin, the words “you” and “your” should be read as “the research subject.”

As the subject’s legally authorized representative or next of kin, you are being asked to give consent for the subject to be in a research study. You are being asked to do this because the subject is not able to give consent. When making this decision you should take into account the wishes of the subject. If you agree to allow the subject to take part in this research, the subject will also be asked to give consent, but only if he/she regains the ability to make healthcare decisions.

Introduction

You are being asked to join a research study. The purpose of a research study is to answer specific questions, sometimes about the safety of a drug or device and how well it works. Being in a research study is different from being a patient. When you are a patient, you and your doctor have freedom in making decisions about your healthcare. When you are in a research study, the researcher will follow the rules of the research study as closely as possible, while monitoring your health.

This consent form will explain:

- the purpose of the study
- what you will be asked to do
- the potential risks and benefits

It will also explain that you do not have to be in this study to receive medical care. You should ask questions before you decide if you want to participate. You can also ask questions at any time during the study.

Why is this research study being done?

The goal of this research study is to better understand and improve the treatment of upper limb muscle weakness (e.g. hemiparesis) after stroke with the hope of maximizing this recovery. Specifically, we wish to examine if multiple sessions of non-invasive vagus nerve stimulation of the ear with an investigational device combined with robotic shoulder/elbow therapy, can improve motor function of the arm after stroke.

You are being asked to participate because you have had a stroke with resulting muscle weakness of the arm.

How many people will take part in this study?

We hope to enroll a total of 36 post-stroke participants in this study.

How long will you be in this study?

If you choose to participate in this research study, the duration of participation will be 16 weeks. During this time, there will be 14 study visits, up to 90 minutes each. These study visits will take place at the Feinstein Institute for Medical Research (350 Community Drive, Manhasset, NY).

What will happen in this research study?

There are several procedures that you will be asked to complete during the study visits and are described below:

Screening questionnaire

You will be asked to complete a questionnaire about your health history to see if you have any risk factors that would prevent you from undergoing transcutaneous vagus nerve stimulation. This will take only a few minutes. Additionally, during the study you will be given a device tolerance questionnaire after every stimulation session. This will also only take a few minutes.

Clinical measures

You will complete a series of evaluations to assess the strength and function of your muscles. This will take approximately 45 minutes.

Instrumental assessment with EMG

You will be seated in a chair and hold onto a joystick while resting your forearm in the trough of the robotic therapy device. You will be prompted by a video display on the screen to take your arm through a series of unassisted movements. A set of surface EMG electrodes will be placed on your arm to measure your muscle activation during these movements. This will take approximately 15 minutes.

Robot-assisted training

During the planar robot therapy, you will be seated in a chair facing a video screen and the robot. You will hold onto the end of the robotic arm. If you cannot grip the robot with your affected hand and arm, then your hand and forearm will be attached to the robot by a foam lined plastic support pad and Velcro straps. You will move, as best you can, the robotic arm through a series of exercises guided by the visual display on the video screen in front of you. You will be able to see your arm move and you will see the movements recorded on the video screen. If you cannot move the robotic arm within 1.5 seconds, the device will move your arm through the exercises. For the arm movements, the elbow will be supported by a foam pad that slides on a tabletop in front of you. The force, speed, and position of the robotic device and whether it is driving the movement of being moved by you will be recorded. This exercise will take approximately 1 hour.

Transcutaneous Vagus Nerve Stimulation (tVNS)

During the hour-long robotic therapy session, this device will apply a low-grade, non-invasive electrical current through the ear, targeting the auricular branch of the Vagus Nerve. The current will be delivered via an ear clip containing two electrodes, with one electrode contacting the back of the ear and the other electrode on a spring loaded arm, contacting the cymba conchae

(e.g. the upper hollow of the external ear closest to the ear canal). Transcutaneous Vagus Nerve Stimulation (tVNS) is not currently approved by the FDA for the purposes of this study, and is thus considered an investigational device. However, tVNS has been successfully used in several human and animal research studies to change motor function after brain injury, suggesting a potential therapeutic benefit to patients with upper limb hemiparesis (arm weakness) after stroke.

You will receive a total of 9 sessions of combined tVNS and robotic arm therapy. Half of the participants in this research study will be randomized to receive stimulation with active electric current while the other half will receive stimulation without electric current (“sham” stimulation). Randomization is a procedure used to assign research subjects, by chance, to a study group in a research study. It is used to make sure study results are not influenced by the selection of subjects in one group as compared to another. In this study you have a 50/50 chance of being assigned to one group or another.

Neither you nor the investigators will know which group to which you are randomized. This is called double blinding and is a process used to prevent the researcher and the subject from knowing which study group a subject is in. It is used to make sure the study data will not be biased. You will be asked at the end of the study whether or not you believe you received active transcutaneous vagus nerve stimulation.

Sham stimulation has no actual electric current. It is compared to stimulation with active electric current to see if the stimulation has a real effect. A sham is often used in research studies in order to “blind” the study so that the doctor and the subject are not biased by knowing the subject’s study group. In case of emergency, the investigators can be “un-blinded” to find out which stimulation you are receiving.

Schedule of Visits

The schedule of study visits is below and describes what procedures will be done at each study visit:

Lead-in Period

- Week 1, Visit 1 (approximately 90 minutes)
 - Baseline clinical outcome measures
 - Instrumental measures with EMG
 - Medical screening
 - Consent
- Week 1, Visits 2-3 (approximately 60 minutes each)
 - Baseline clinical outcome measures
 - Instrumental measures with EMG

Training Period

- Weeks 2-4, Visits 4-12 (approximately 60 minutes)
 - robotic therapy + tVNS
 - Device tolerance questionnaires

Discharge Evaluation

- Week 4, Visit 13 (approximately 60 minutes)
 - Clinical outcome measures
 - Instrumental measures with EMG

No study visits: Weeks 5-15

Follow-Up Evaluation

- Week 16, Visit 14 (approximately 60 minutes)
 - Clinical outcome measures
 - Instrumental measures with EMG

Participation in this study also allows investigators access to your medical records. They will record your age, gender, and date of stroke/results of the medical imaging you had done following the stroke.

What are the risks of the research study? What could go wrong?

tVNS has the potential to cause discomfort at the site of the stimulation. The discomfort occurs from stimulation of the sensory nerves innervating the ear. During the stimulation period, we will monitor for discomfort and can adjust the stimulation intensity reduce/relieve the physical discomfort. This physical discomfort is not serious and the side effects are reversible. Another risk of electrical stimulation is the rare occurrence of an increased or decreased heart rate as a result of activating the cervical vagus nerve via transcutaneous electrical stimulation of the ear. Consequently, patients with known cardiac arrhythmias have been excluded from this study, and all participants will be monitored closely during stimulation. If you experience any discomfort during the stimulation, the stimulation intensity will be reduced and/or ceased immediately. Finally, if you have a loop recorder, there is a small risk of disruption to the cardiac monitoring data. You will only be approved to participate if your Cardiologist has cleared you for the study.

There are no known risks associated with robot-assisted exercise. Some patients have pain in the shoulder after a stroke. There is a small risk that this pain may be increased with robotic intervention. However, our experience has demonstrated a comparable incidence of shoulder pain in groups that were or were not treated by the robot.

There may be risks that are unknown at this time.

What are the benefits of this research study?

We cannot predict whether you will experience direct benefits from the stimulation. However, knowledge may be gained which may benefit patients with stroke in the future.

If you do not want to take part in this research study, what are your other choices?

If you do not join this study, you have other choices for treatment. Talk to your doctor about your choices. Your other choices may include:

- Standard treatment

Your doctor can also tell you the important risks and benefits associated with the alternative treatment.

Are there any costs for being in this research study?

You will not have any added costs from being in this study.

Will you receive any payments for participating in this research study?

Parking during your study participation will be provided on site at no cost to you. You will not be paid for participating in this study.

If the research produces marketable products, will you receive any payment?

If this research produces a marketable product, there are no plans for you to receive any money.

What happens if you are injured while participating in this study?

If you are hurt from being in the study, you will receive medical care and treatment as needed from Northwell Health. However, you will be responsible for the costs of such medical treatment, directly or through your medical insurance and/or other forms of medical coverage. No money will be given to you.

What are your rights as a research participant?

Your participation in this project is voluntary. The quality of your medical care will be the same, whether you join, refuse to join, or decide to leave the study.

If you do not join the study, you will not be penalized or lose benefits to which you are entitled. If you join the study you may withdraw at any time without prejudice to your future care at Northwell Health. Follow-up examinations may be needed to assure your well-being.

Could you be taken off the study before it is over?

It is also possible that your participation in this study may end without your consent. This decision may be made by an investigator or the IRB. Reasons for withdrawal may include:

- failure to show up for study visits,
- it is not in your best interests to continue on this study
- the study is stopped.

If you withdraw from this study or if you are withdrawn from the study, any data (or samples) already collected will continue to be used. However, no new information will be collected.

What happens if new information is learned?

You will be told of any new findings that may change your decision to continue to participate. Your consent to continue to take part in this study may be obtained again.

What information will be collected and used for this study?

If you agree to be in this study, we will collect health information that identifies you. We may collect the results of tests, questionnaires, and interviews. We may also collect information from your medical record. Additionally, we may contact your relevant treating physicians/clinicians to obtain further information about your health history and care, and/or to provide them with

information about this study. We will only collect information that is needed for research. Such information has been described in this consent form. If you sign this consent form, you are giving us permission to collect, use and share your health information. This permission is called authorization. If you do not want to provide authorization, then you cannot participate in this research study.

Who else will see your information?

Study records that identify you will be kept private. You will not be identified in study records or publications disclosed outside Northwell Health, except as detailed below.

- Investigators may share the results of your study tests and procedures with your doctors or clinical staff not involved in the study, but who may be involved in your treatment.

The following reviewers may access your study and medical records to make sure that this study is being done properly:

- Representatives from federal and state government oversight agencies such as the National Institutes of Health (NIH) and/or the Food and Drug Administration (FDA),
- Representatives from the Northwell Health Human Research Protection Program (the group of people that oversee research at this institution)

The data from this study may also be used to support regulatory approvals of the tVNS device used in the study. This means that your health information and test data related to this study may be disclosed to regulatory agencies including the US Food and Drug Administration as well as regulatory agencies in other countries. However, data disclosed for this purpose will not identify you by name, address, telephone number or any other personal identifier; only a patient ID code will be used.

We will do our best to protect the privacy of your records but it is possible that once information is shared with people listed on this form, it will be released to others. If this happens, your information may no longer be protected by the federal law.

In the future, we may publish results of this study in scientific journals and may present it at scientific meetings. If we do we will not identify you.

If the researchers learn about potential serious harm to you or someone else or other public health concerns, it will be shared with the appropriate authorities.

Will you be able to access your records?

If your research records are used for decisions related to your clinical care, then you have the right to review this information and request changes. This is limited to information about your treatment, and does not include information related to procedures or tests that are for research purposes only. You may access this information only after the study analysis is complete. You have the right to know who has and who will see your records. To request this information, please call the Human Research Protection Program at 516-321-2100.

How long will your health information be kept?

There is no limit on the length of time we will keep your information for this research because it may be analyzed for many years. We will keep it as long as it is useful, unless you decide you no longer want to take part or we close the study. You are allowing access to this information indefinitely.

Can you change your mind?

If you change your mind about being in the study, you may withdraw at any time. If you want us to stop collecting your health information, you need to send a letter to the researcher at the following address:

Bruce T. Volpe, MD
Feinstein Institute for Medical Research
350 Community Drive
Manhasset, NY 11030

Your letter needs to say that you have changed your mind and do not want the researcher to continue to collect and share your health information. You may also need to leave the research study if we cannot collect any more health information. We may still use the information we have already collected. We need to know what happens to everyone who starts a research study, not just those individuals who stay in it.

Will information about this study be available to the public?

A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this website at any time.

Does the investigator of this study receive money if you take part?

The investigators on this study do not receive money for your participation in this study.

Who can answer your questions about this study?

If you have any questions about the study, or about side effects or injury caused by research, call Bruce T. Volpe, MD at (516) 562-3384. If you need emergency care go to the nearest Emergency Department or dial 911. If you have questions about your rights as a research subject you may contact the Office of the Institutional Review Board (the committee that oversees research at this institution) at (516) 465-1910.

A signed copy of this consent form will be given to you.

SUMMATION & SIGNATURES: You have read the above description of the research study. You have been told of the risks and benefits involved and all your questions have been answered to your satisfaction. A member of the research team will answer any future questions you may have. You voluntarily agree to join this study and know that you can withdraw from the study at any time without penalty. By signing this form, you have not given up any of your legal rights.

SIGNATURE PAGE TO FOLLOW

Please sign as “subject” if you agree to participate in the study and have the capacity to self-consent:

_____ Subject's Printed Name	_____ Subject's Signature	_____ Date
_____ Witness's Printed Name	_____ Witness's Signature	_____ Date
<p>Investigator's Statement: In addition to advising the above subject about the research study, I have offered an opportunity for further explanation of the risks and discomfort which are, or may be associated with this study and to answer any further questions relating to it.</p>		
_____ Investigator's Printed Name		
_____ Investigator's Signature	_____ Date	

OR

Please sign as the designated “Legally Authorized Representative” on behalf of the participant, if the participant has the capacity to self-consent, but was unable to sign due to a physical disability (e.g. hand weakness, visual deficits):

Subject’s Printed Name

Date

Legally Authorized Representative’s
or Next-of-Kin Printed Name

Legally Authorized Representative’s
or Next-of-Kin Signature

Date

Witness’ Statement: I was present during the consent process of the above mentioned research study. A member of the research team explained the research study entirely and allowed ample opportunity for the subject to ask any questions or express any concerns. The subject was unable to sign the consent form due to a physical disability, however, voluntarily agreed to participate in the research study by providing verbal assent. By signing below, I attest to this statement.

Witness Printed Name

Witness Signature

Date

Investigator’s Statement: In addition to advising the above subject about the research study, I have offered an opportunity for further explanation of the risks and discomfort which are, or may be associated with this study and to answer any further questions relating to it.

Investigator’s Printed Name

Investigator’s Signature

Date

OR

Please sign as the designated “Legally Authorized Representative” on behalf of the participant, if the participant does not have the capacity to self-consent:

Legally Authorized Representative’s or Next-of-Kin Printed Name	Legally Authorized Representative’s or Next-of-Kin Signature	Date
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Description of signer’s authority to act on behalf of the subject:

Witness’s Printed Name	Witness’s Signature	Date
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☐ Witness signature waived (signed consent emailed, faxed, or mailed to investigator)

Investigator’s Statement: In addition to advising the above subject about the research study, I have offered an opportunity for further explanation of the risks and discomfort which are, or may be associated with this study and to answer any further questions relating to it.

Investigator’s Printed Name

Investigator's Signature	Date
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**If you have signed the above consent as the legally authorized representative (LAR), please attempt to have the study participant sign this assent, in order to include him/her in his/her consent process:*

ASSENT BY ADULT SUBJECT WITH A LEGALLY AUTHORIZED REPRESENTATIVE

I have been asked to join this research study. I have the right to find out what will or might happen to me if I am in the study. I have the right to tell the doctor, and the person legally allowed to make decisions for me, that I do or do not want to participate.

The person legally allowed to make decisions for me will also be asked to give permission for me to join this study.

(Investigator's name) _____ and _____, the person legally allowed to make decisions for me, have explained what I will have to do in the study.

(Investigator's name) _____ and _____, the person legally allowed to make decisions for me, have explained the discomforts, risks and inconveniences I may have if I join the study.

I have asked any questions I had, and all my questions have been answered.

_____ I agree to be in this study.

_____ I do not want to be in this study.

Subject's name

Put your name here ↑

Date

Witness's Printed Name

Witness's Signature

Date

All procedures, risks and discomforts have been explained to the subject.

Investigator's printed name

Investigator's Signature

Date

**If you have signed the consent as the legally authorized representative (LAR), and during the study the participant regains the capacity to self-consent, please have him/her sign as “subject”:*

Addendum to Consent by Research Proxy for Continuing Participation in a Research Study

Protocol Title: Evaluating the use of transcutaneous vagus nerve stimulation (tVNS) to improve upper limb motor recovery after stroke

Principal Investigator: Bruce T. Volpe, MD

Sponsor: Department of Functional Neuroanatomy

- I have been told that my research proxy gave consent for me to be in the above titled research study.
- I am now able to give my own consent to be in the research study.
- I have been told of the purpose of the research, what my participation will entail, as well as all of the potential risks and benefits.
- I have discussed the research study with the study doctor and have received satisfactory answers to any questions.
- I have been told that I may ask more questions at any time.
- I do not have to stay in this research study. My decision to continue is completely voluntary. If I wish to leave the study, I may have to undergo final follow-up tests to assure my well-being. If I leave the study I will not suffer any penalty or loss of benefits to which I am entitled.
- I have been told that all of the elements of informed consent in the attached consent form, signed by my research proxy, are still applicable.
- I have reviewed the consent document and have discussed all of the elements of informed consent with the study doctor. I agree to stay in the above titled research study.

Signature of Subject

Date

Printed Name of Subject

Witness Signature

Date

Printed Name of Witness

In addition to advising the above subject about the research study, I have offered an opportunity for further explanation of the risks and discomfort which are, or may be associated with this study and to answer any further questions relating to it.

Investigator's Signature

Date