

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

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RESEARCH PROTOCOL

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

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1. PREVIOUS STUDY HISTORY

Has this study ever been reviewed and rejected/disapproved by another IRB prior to submission to this IRB?

No Yes – if yes, please explain:

2. BRIEF SUMMARY OF RESEARCH

- *The summary should be written in language intelligible to a moderately educated, non-scientific layperson.*
- *It should contain a clear statement of the rationale and hypothesis of your study, a concise description of the methodology, with an emphasis on what will happen to the subjects, and a discussion of the results.*
- *This section should be ½ page*

Stroke is the fifth leading cause of death and the leading cause of serious long-term disability in the U.S. [1]. Post-stroke impairment is often characterized by hemiparesis or weakness of the upper and lower limbs, rendering the individual dependent for most activities of daily living. Traditional stroke rehabilitation medicine consists of a combination of one-on-one treatment and group therapy with physical, occupational and speech therapists, focusing on both labor-intensive motor training of the affected limbs, as well as compensatory training of the unaffected side of the body. Even with aggressive standard rehabilitation, 65 percent of patients cannot incorporate their affected hand in functional activities six months after stroke, and only 25 percent of patients return to the level of life participation equivalent to that of community-matched healthy controls [2].

We have previously demonstrated that robotic therapy provides functionally and clinically significant benefits to upper limb motor recovery after stroke, and has been consequently acknowledged by the American Heart Association as an effective form of stroke rehabilitation [3-5]. Robotic intervention operates through a series of interactive motors with low impedance which move a patient's limb when the patient cannot move and progressively intervene less as the patient improves. The advantage of this technology is to deliver reproducible movement without tiring, increasing the level of training intensity and potentially decreasing the level of impairment. Though the clinical benefit of robotic interventions to reduce motor impairment after stroke is well established, the results are generally not curative.

Promising new animal research suggests that vagus nerve stimulation paired with motor intervention induces movement-specific plasticity in the motor cortex and improves limb function after stroke [6-7]. These results were recently extended to the first clinical trial, in which patients with stroke demonstrated significant improvements in upper limb function following rehabilitation paired with implanted

VNS [8]. Currently, vagus nerve stimulation is being used clinically to treat a number of human diseases including migraine headaches, epilepsy, and depression [9-11]. Many of these treatments are non-invasive, activating the auricular branch of the vagus nerve transcutaneously through the cymba concha at the pinna of the ear [9-10, 23, 40]. We propose here a pilot study combining non-invasive stimulation of the vagus nerve with upper limb robotic therapy to investigate the potential of tVNS to augment improvements gained with robotic therapy in patients with chronic hemiparesis after stroke.

3. INTRODUCTION/BACKGROUND MATERIAL/PRELIMINARY STUDIES AND SIGNIFICANCE

- *Describe and provide the results of previous work by yourself or others, including animal studies, laboratory studies, pilot studies, pre-clinical and/or clinical studies involving the compound or device to be studied.*
- *Include information as to why you are conducting the study and how the study differs from what has been previously researched, including what the knowledge gaps are.*
- *Describe the importance of the knowledge expected to result*

Vagus nerve stimulation (VNS) is an FDA approved form of therapy to treat refractory epilepsy, depression, and cluster headaches. Because VNS is believed to drive activation of neuromodulatory nuclei associated with plasticity (e.g. cholinergic basal forebrain and noradrenergic locus coeruleus), it has also been recently investigated for use in the treatment of neurological diseases and injuries. Animal models of tinnitus, ischemic stroke, intracerebral hemorrhage, and traumatic brain injury benefitted from repetitive bursts of VNS during rehabilitative interventions [12-15]. Khondaparast et al (2013) reported that VNS paired with intensive forelimb motor rehabilitation improved force generation recovery in rats with chronic motor impairment following ischemic infarction of the primary motor cortex. Specifically, rats who received VNS during motor rehabilitation tasks improved twice as much as those who received rehabilitation alone, and returned to near pre-lesion levels of motor performance [7]. These results were also replicated in animal models of cerebral hemorrhage and TBI [12-13]. Taken together, these pre-clinical studies suggest VNS may be a viable additive rehabilitation intervention to deliver greater functional outcomes following neurological injury.

However, these previous rehabilitation trials have shown that such improvements are often selective only to the task which has been paired with VNS. Specifically, in rats, motor behaviors paired with implanted VNS following stroke demonstrated selective increases in the size of the motor representations within the motor cortex for trained behaviors, while motor representations for untrained tasks or tasks performed without VNS remained relatively unchanged [19]. Human and animal models of tinnitus rehabilitation involving selective pairing of VNS with tones outside of the tinnitus white noise perceptual range resulted in significant reductions in the perception of tinnitus for up to three months [20-21]. In stroke rehabilitation, one of the most notable hindrances to motor recovery is the persistence of

maladaptive upper and lower limb flexor synergy patterns. Upper extremity flexor synergy is characterized by a fixed pattern of scapular retraction, shoulder abduction/external rotation, elbow/wrist/finger flexion, and wrist supination, resulting a 'curling in' of the arm towards the body with a rigid, closed hand. It is caused by damage to the corticospinal tract (CST), and subsequent upregulation of interneuron spinal networks and other descending spinal pathways, ultimately resulting in movement limitations, which are greatest for extensor movements [22]. Given the apparent task-selectivity of VNS training, current delivered only during extensor movements of a motor therapy task might lead to more efficient recovery of arm function after stroke.

Preliminary clinical evidence suggests that implanted VNS augments the benefits of upper limb rehabilitation for individuals with chronic upper limb hemiparesis post-stroke. Dawson et al (2015) randomized twenty-one patients who were greater than 6 months from an ischemic stroke to receive either VNS plus rehabilitation (N=9) or upper limb rehabilitation alone (N=11). Rehabilitation intervention was intensity matched across groups, and consisted of three 2hr treatment sessions per week for 6 weeks. VNS was delivered manually by the therapist via button press while the patient completed all prescribed motor tasks. Results from the per-protocol analysis demonstrated a significant improvement in upper limb Fugl Meyer scores for the VNS plus rehabilitation group as compared with the rehabilitation group alone (between group difference= 6.5 points). There were no serious adverse device effects, though side effects included transient dysphagia and vocal fold paralysis following implantation, and temporary nausea and taste disturbances following stimulation [8]. Overall, this first clinical trial of stimulator implanted VNS suggests a promising augmentative tool may become available to enhance post-stroke motor rehabilitation. However, given that vagus nerve stimulation appears to be task-selective and dose-sensitive, refinement of stimulation parameters is still needed. Thus, we propose an investigation of specific vagus nerve stimulation timing parameters via a transcutaneous route to potentially improve intervention efficacy and decrease side effects.

For this study, investigators in the Laboratory of Rehabilitation Robotics are collaborating with investigators in the Center for Bioelectronic Medicine (CBEM) to test the hypothesis that vagus nerve stimulation via an external electrode placed on the ear and timed to deliver stimulation during upper limb extensor movements will improve the outcome in patients after stroke. Currently, CBEM investigators have experience with 8 healthy controls and 8 patients with lupus delivering transcutaneous auricular vagus nerve stimulation (tVNS) without any serious adverse events. The advantages of non-invasive tVNS device for use in stroke rehabilitation are to eliminate the need for surgical implantation, reducing untoward side effects in an already vulnerable population, and to potentially develop a clinical tool for better and more efficient functional recovery.

In our previous research, the Laboratory for Rehabilitation Robotics employed robotic devices to train movement in paralyzed limbs with well over 300 patients, and have established robotic intervention as a recommended standard of care [3]. We have demonstrated that robotic interventions alone provide safe, targeted, impairment altering upper and lower limb motor rehabilitation in the chronic phase of stroke recovery [3-5]. We have subsequently investigated the combination of robotic training with two bioelectronic interventions, transcranial direct current stimulation (tDCS) and trans-spinal direct current stimulation (tsDCS), and specifically examined the optimal timing parameters for administration of non-invasive brain and spinal stimulation devices during upper limb recovery. To that end, we demonstrated that tDCS improves robotic kinematic scores in patients with post-stroke hemiparesis, but only when it is used prior to robotic training, and not when applied during or after robotic therapy [14]. These results suggest tDCS increases cortical excitability and neural plasticity for a time period, and that robotic therapy is more effective when applied at that time. In another group of experiments, we are testing the efficacy of tsDCS in order to pair it with robotic intervention. We have demonstrated that tsDCS significantly reduces both objective measures of the spastic catch response (e.g. changes in peak amplitudes measured with force transducer and EMG) as well as clinical measures (Tardieu/MAS) of upper extremity spasticity in twenty-one patients in the chronic phase after stroke. Importantly, these improvements are seen immediately following 5 days of stimulation compared to the sham condition, and are maintained for three weeks or greater. While these studies have been crucial in characterizing optimal treatment windows and sensitively measuring kinematic profiles of motor recovery, the stimulation interventions were delivered in an “open loop,” which is to say the stimulation was not interactively timed with a motor task. Recent evidence suggests that delivery of closed loop stimulation, in which stimulation is provided precisely online during a motor therapy task, may yield greater recovery of function [16-18]. However, better understanding of task-selectivity and the timing of tVNS stimulation parameters is still needed.

Our experience treating patients in post-stroke condition, and with robotics combined with non-invasive stimulation, and also with tVNS will facilitate the experiment we propose. Specifically, we will deliver tVNS in a closed loop approach during only extensor movements for consecutive upper limb robotic therapy training sessions in order to test whether task-specific closed loop tVNS combined with upper limb robotic intervention can significantly improve arm function compared to a sham condition.

4. OBJECTIVE(S)/SPECIFIC AIMS AND HYPOTHESES

- *A concise statement of the goal(s) of the current study.*
- *The rationale for and specific objectives of the study.*
- *The goals and the hypothesis to be tested should be stated.*

Specific Aim 1: To evaluate whether 3 weeks of robotic therapy paired with tVNS delivered only during extensor movements will significantly change

EMG activation patterns of up the upper extremity during unassisted gravity-eliminated movements in approximately 18 patients with chronic post-stroke hemiparesis compared to sham condition.

In patients with chronic upper-limb hemiparesis post-stroke, we will use a within-subjects repeated measure design to determine if 9 sessions of active tVNS during only extensor movements significantly alters EMG activation of the biceps brachii and triceps as compared to a sham condition.

Specific Aim 2: To determine whether 3 weeks of robotic therapy paired with tVNS will significantly improve clinical measures of upper extremity motor function in approximately 18 patients with chronic hemiparesis after stroke compared to a sham condition.

We will use a within-subjects repeated measures design to determine if 9 sessions of robotic therapy paired with active tVNS during only extensor movements significantly improves upper extremity motor function in patients with chronic post-stroke hemiparesis as compared to sham tVNS paired with robotic therapy.

5. RESOURCES AVAILABLE TO CONDUCT THE HUMAN RESEARCH

- *Explain the feasibility of meeting recruitment goals of this project and demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period*
 - *How many potential subjects do you have access to?*
- *Describe your process to ensure that all persons assisting with the trial are adequately informed about the protocol and their trial related duties and functions*

The study will involve approximately 36 subjects with chronic hemiparesis following stroke. The research team will be led by Dr. Bruce Volpe, who has extensive experience recruiting for clinical trials related to stroke. Additionally, the Northwell Health System treats over 1000 patients with stroke annually, and provides an excellent recruitment population eligible for participation in this study.

The team in the Laboratory of Rehabilitation Robotics has substantial experience in the field of stroke rehabilitation. Dr. Volpe is a treating neurologist, investigator, and lecturer with over 30 years of clinical and research experience with neurological recovery. Dr. Maira Saul is a Physiatrist and Research Coordinator with over ten years of clinical experience in the treatment of neurological injuries and neurodegenerative impairment. Johanna Chang is a Research Coordinator and Speech-Language Pathologist with extensive clinical and research experience related to neurological injury. Alexandra Paget-Blanc is a Research Assistant with a background in neuroscience, and an expertise in EMG spike analysis.

Additionally, the team in the Center for Bioelectronic Medicine has extensive experience in engineering, programming, and clinical administration of vagus

nerve stimulation via tVNS devices. The team has developed a wireless all-in-one tVNS stimulator, the device was co-designed with an ISO 13485 certified company (MIDI), and fabricated by MIDI, and supplied to the CBEM team.

In order to ensure everyone assisting on the study is well versed in the protocol requirements, there will be a study team meeting after institutional approval is obtained. At this meeting, everyone will be reminded of the study design and all of the study processes. In addition, there will be a delegation of responsibility log created to outline the specific tasks of each study member during the course of the study. The study team will also routinely meet to discuss study progress and address any questions that arise.

6. RECRUITMENT METHODS

- *Describe the source of potential subjects*
- *Describe the methods that will be used to identify potential subjects*
- *Describe any materials that will be used to recruit subjects. A copy of any advertisements (flyers, radio scripts, etc.) should be submitted along with the protocol.*
- *If monetary compensation is to be offered, this should be indicated in the protocol*

Stroke subjects who meet inclusion criteria will be recruited by consenting professionals through the Departments of Physical Medicine and Rehabilitation, Neurology, and Outpatient Stroke Rehabilitation at NSUH, LIJMC, GCH, SSH, Transitions of Long Island, and STARs Outpatient Rehabilitation Center. Recruitment will be done with direct contact and flyers.

Northwell Health physicians and clinicians who have appropriate patient populations will be made aware of the research study protocol and procedures, and given an overview of the study through contacts with the study personnel. These clinicians will identify potential study participants, and either: 1.) provide the patient with the study coordinator's contact information or 2.) provide the patient's contact information to study personnel.

Investigators may contact (or be contacted by) a potential subject or subject's LAR/next-of-kin by telephone or email to discuss participation in this research protocol. The investigator will provide the subject/LAR/next-of-kin with all the information contained in the written consent form. The investigator will answer any questions regarding the research and give the subject/LAR/next-of-kin ample time to consider participation in the study which may require a follow-up phone conversation or an in-person appointment at the Feinstein for a brief study enrollment screening visit.

7. ELIGIBILITY CRITERIA

- Describe the characteristics of the subject population, including their anticipated number, age, ranges, sex, ethnic background, and health status. Identify the criteria for inclusion or exclusion of any subpopulation.
- Explain the rationale for the involvement of special classes of subjects, such as fetuses, pregnant women, children, prisoners or other institutionalized individuals, or others who are likely to be vulnerable. You cannot include these populations in your research, unless you indicate such in the protocol
- Similarly, detail exclusionary criteria: age limits, special populations (minors, pregnant women, decisionally impaired), use of concomitant medications, subjects with other diseases, severity of illness, etc.

Inclusion Criteria:

- Individuals between 18 and 85 years of age
- First single focal unilateral supratentorial ischemic stroke with diagnosis verified by brain imaging (MRI or CT scans) that occurred at least 6 months prior
- Cognitive function sufficient to understand the experiments and follow instructions (per interview with Speech Pathologist or PI)
- Fugl-Meyer assessment 12 to 44 out of 66 (neither hemiplegic nor fully recovered motor function in the muscles of the shoulder, elbow, and wrist).

Exclusion Criteria:

- Botox treatment within 3 months of enrollment
- Fixed contraction deformity in the affected limb
- Complete and total flaccid paralysis of all shoulder and elbow motor performance
- Prior injury to the vagus nerve
- Severe dysphagia
- Introduction of any new rehabilitation interventions during study
- Individuals with scar tissue, broken skin, or irremovable metal piercings that may interfere with the stimulation or the stimulation device
- Highly conductive metal in any part of the body, including metal injury to the eye; this will be reviewed on a case by case basis for PI to make a determination
- Pregnant or plan on becoming pregnant or breastfeeding during the study period
- Significant arrhythmias, including but not limited to, atrial fibrillation, atrial flutter, sick sinus syndrome, and A-V blocks (enrollment to be determined by PI review)
- Presence of an electrically, magnetically or mechanically activated implant (including cardiac pacemaker), an intracerebral vascular clip, or any other electrically sensitive support system; Loop recorders will be reviewed on a case by case basis by PI and the treating Cardiologist to make a determination

8. NUMBER OF SUBJECTS

- *Indicate the total number of subjects to be accrued locally. If applicable, distinguish between the number of subjects who are expected to be pre-screened, enrolled (consent obtained), randomized and complete the research procedures.*
- *If your study includes different cohorts, include the total number of subjects in each cohort.*
- *If this is multisite study, include total number of subjects across all sites.*

This is a double-blind, sham-controlled pilot study. The total target enrollment is 36 subjects with post-stroke hemiparesis. Only patients who meet inclusion criteria following screening will be enrolled. We have anticipated a 10-15% drop-out rate in determining target enrollment.

This study will use a randomized controlled study design to determine whether nine repeated treatments of upper extremity robotic therapy paired with tVNS delivered only during extensor movements significantly changes objective EMG activation patterns and significantly improves clinical measures of upper extremity motor function in patients with chronic post-stroke hemiparesis as compared to a sham condition.

9. STUDY TIMELINES

- *Describe the duration of an individuals participation in the study*
- *Describe the duration anticipated to enroll all study subjects*
- *The estimated date of study completion*

The duration of an individual's participation in the study is approximately 4 months from providing consent to completing the study procedures. It is anticipated that enrollment will be completed within 20 months from receiving institutional approval, with all study procedures completed within 2 years. After the completion of data analysis and any subsequent presentations or publications, the study will be closed. It is estimated that the study will be completed by December 2020.

10. ENDPOINTS

- *Describe the primary and secondary study endpoints*
- *Describe any primary or secondary safety endpoints*

The primary measure of treatment efficacy will be an increase in EMG activation peak amplitude for upper extremity extensor muscles of at least 10%. The secondary measure of treatment efficacy will be an improvement in Upper Extremity Fugl Meyer score of at least 3 points (out of 66).

The primary safety endpoint will be any serious adverse events of suspected relationship with the tVNS investigational device. Any serious adverse events will be reported to the PI, research team, and IRB immediately for determination if the study should be discontinued. However, given that there were no serious adverse device effects of implanted VNS in individuals with stroke [8], it is anticipated that transcutaneous auricular vagus nerve stimulation will pose an even lower risk.

11. RESEARCH PROCEDURES

- *Include a detailed description of all procedures to be performed on the research subject and the schedule for each procedure.*
- *Include any screening procedures for eligibility and/or baseline diagnostic tests*
- *Include procedures being performed to monitor subjects for safety or minimize risks*
- *Include information about drug washout periods*
- *If drugs or biologics are being administered provide information on dosing and route of administration*
- *Clearly indicate which procedures are only being conducted for research purposes.*
- *If any specimens will be used for this research, explain whether they are being collected specifically for research purposes.*
- *Describe any source records that will be used to collect data about subjects*
- *Indicate the data to be collected, including long term follow-up*

Consecutive Sessions of tVNS during robotic therapy intervention

Thirty-six patients with chronic, post-stroke upper extremity hemiparesis will be accepted into this study, and randomized to receive either sham or active tVNS treatment coupled with robotic therapy. There will be 2-3 baseline measurement periods prior to treatment. Following the lead-in period, subjects will participate in a training period consisting of approximately 1 hour sessions robotic therapy paired with tVNS 3x/week for 3 weeks, for a total of 9 sessions. Following the training period, subjects will complete clinical and objective measures both immediately at discharge and again a 3-month follow-up 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 (every session)

Discharge Evaluation

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

Follow-Up Evaluation

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

**Phase II
Schedule**

	Screen 1	Screen 2	Screen 3	taVNS Tx + robotics	DC eval	3 mo FU
	Visit 1	Visit 2	Visit 3	Visit 4-12	Visit 13	Visit 14
Informed Consent	X					
Medical Hx	X					
Demographic Info	X					
Inclusion Criteria	X					
Neurological Exam	X					
Medication check	X					
Outcome Measures	X	X	X		X	X
Instrumental Assessment	X	X	X		X	X
tVNS (sham or real) + robotics				X		

Clinical Outcome Measures

Fugl-Meyer (Primary): The Fugl-Meyer scale is a valid and reliable evaluation instrument used for measuring performance-based impairment in stroke patients [4, 24-25].

Medical Research Council motor power score (MRC): The MCR is a valid and reliable score that measures strength in isolated muscle groups of the involved shoulder and elbow on an ordinal scale (scale range: 0, no muscle contraction; 5, normal strength) [5, 26].

Wolf Motor Function: The Wolf Motor Function Test is a valid and reliable assessment of upper extremity function by asking the patient to complete 15 motor-based tasks and two strength-based tasks [27].

Robotic Therapy

The MIT-MANUS (the planar robot) was developed in the Newman Laboratory of Biomechanics and Human Rehabilitation at the Massachusetts Institute of Technology and provides customized, goal-directed, robot assisted arm therapy. The hallmark of this system is an impedance controller that modulates the way the robot reacts to mechanical perturbation from a patient or clinician and ensures a gentle compliant behavior. The stability of most robot controllers is vulnerable when contacting objects with unknown dynamics. In contrast, dynamic interaction with highly variable and poorly characterized objects (e.g. neurologically impaired patients) will not de-stabilize the impedance controller, as its stability is extremely robust to the uncertainties due to physical contact [28-32]. Impedance control has been the central contribution of Dr. Hogan's engineering research since the early eighties and has been extensively adopted by other robotics researchers concerned with human-machine interaction [29]. At present the MIT-MANUS impedance controller is implemented using coupled nonlinear position and velocity feedback structured to produce a constant isotropic end-point stiffness and damping. High-bandwidth current-controlled amplifiers produce motor output torques directly proportional to commanded input. These facts make the robot a stable device for operation in a clinical context [28, 30-32].

During planar robot therapy, the patient's hand and wrist are held in a rigid support affixed to the robotic arm, and the patient must reach towards points in space that correspond to the positions of the targets on a screen. Throughout each therapy session, the participant completes a series of flexions, extensions, and rotational movements across the elbow and shoulder joints. If a limb is initially paralyzed, the robot will move it passively, but as motor function returns, the robot will require the patient to initiate progressively more voluntary movement. In this way, the robot safely delivers reproducible movement without tiring and can render the level of training intensity required to alter impairment.

Robotic therapy has been established as a safe and effective tool for upper limb motor recovery after stroke, and is presently a recommended intervention by the American Heart Association [1].

Transcutaneous auricular vagus nerve stimulation (tVNS)

Electrical auricular stimulation will be accomplished using either the Roscoe Medical Transcutaneous Electrical Nerve Stimulation (TENS) 7000 device paired

with ear clip electrodes available from Lhasa Ohms or an Auricular Branch Vagus Nerve Stimulation device co-designed by the CBEM team and fabricated by the MIDI Product Development Corporation. The study will only use one device throughout its conduct for all study participants since using multiple devices will create unnecessary variability. If the Auricular Branch Vagus Nerve Stimulation device from the MIDI Product Development Corporation is received prior to the anticipated study start date and passes internal reviews for design, comfort, and performance, the study will use the Auricular Branch Vagus Nerve Stimulation device from the MIDI Product Development Corporation for the entirety of the study for all subjects. If it is not received by the anticipated start date of this study, the study will utilize only the Roscoe TENS 7000 unit for the entirety of the study for all subjects.

Study Procedure:

tVNS will target the left VNS in order to avoid cardiac side effects associated with right VNS stimulation. The tVNS device will be applied to the left ear using a pair of conductive silicone electrodes, with one electrode contacting the back of the ear and the other electrode on a spring loaded arm, contacting the cymba conchae. Patients will wear the tVNS device for the duration of each 1 hour robotic therapy session. During each session, patients will perform approximately 1000 shoulder/elbow flexion and extension movements and will receive stimulation during only the extensor movements, for a total of 300 stimulations per session. The tVNS current will be delivered during each extensor movement in single 500msec bursts with a frequency of 30Hz and a pulse width of 0.3msec. The current intensity will be individually adjusted to a level just below the patient's reported pain threshold, with amplitudes ranging from 0.1-5.0mA in steps of 100 μ A. The FDA guidance for document for powered muscle stimulators (FDA document 2246) specifies a maximum power density at the electrode site of 250 mW/cm². The MIDI fabricated stimulator has a maximum power density of less than 100 mW/cm², which falls well below the guidance limit for thermal burns. A portable, battery-powered oscilloscope will be used to confirm peak current (for the Roscoe device). These stimulation parameters are similar to parameters that have been demonstrated to be safe in several other tVNS clinical trials [8, 23, 34, 41].

To ensure participant tolerance of stimulation, current will be introduced at the lowest 0.1mA intensity and gradually increased to a level at which the patient just begins to report discomfort, or a maximum of 5mA. The device will then be immediately adjusted to an intensity just below the reported discomfort level, and will remain at this intensity for 10 seconds to confirm patient tolerance. This will be considered the maximum tolerated stimulation intensity threshold for the patient, and stimulation bursts during robotic therapy will then be administered at this level. This tolerability dose will be determined prior to every treatment session for all patients, and recorded in the stimulation tolerance monitoring log. Sham tVNS will have a comparable set-up to active tVNS, with 10 seconds of real current ramping to the maximally tolerated current intensity at commencement,

followed by a slow decrease to no current for the duration of the robotic therapy session.

About the devices:

The Auricular Branch Vagus Nerve Stimulation device fabricated by the MIDI Product Development Corporation is designed to deliver low levels of current to the cymba conchae region of the ear using a pair of conductive silicone electrodes. The electrodes are designed to fit over the left ear and are adjustable in both rotation and location, relative to the rest of the housing, in order to accommodate subjects with different ear sizes. The device has a power switch and USB port for charging. The device is controlled using wireless Bluetooth technology via an application run on a PC that allows control over the amplitude of stimulation, onset, and timing parameters, including pulse width, frequency, and burst patterns.

The Roscoe Medical Transcutaneous Electrical Nerve Stimulation (TENS) 7000 device (www.roscoemedical.com) delivers a programmable electrical current, which can be adjusted for varying frequencies. The device may be modified to include an additional switch allowing the investigator to have precise control of the timing of stimulation. The modification will not change the manner in which the stimulation pulses are generated or delivered. The TENS 7000 will be connected to ear using clip electrodes available from Lhasa Ohms (<http://www.lhasaoms.com/Ear-Clip-Electrodes.html>) to transcutaneously stimulate the cymba conchae region of the ear, targeting the auricular branch of the vagus nerve (e.g. Arnold's nerve). This device does not allow for precise amplitude changes, and will thus be adjusted from its lowest setting gradually to a maximum tolerated threshold by individual patient report as described above in the study procedure. To confirm peak current at this level and ensure patient safety, a portable, battery-powered oscilloscope will be used during the initial adjustment of this device for each patient during each session.

Both the Auricular Branch Vagus Nerve Stimulation device fabricated by the MIDI Product Development Corporation and the Roscoe Medical Transcutaneous Electrical Nerve Stimulation (TENS) 7000 device are considered non-significant risk investigational devices. The Roscoe TENS 7000 was classified as a Class II device by the FDA in 2011 and is FDA cleared (K110390) for over-the-counter sale, with an indication to provide symptomatic relief of chronic intractable pain, relief of acute post-surgical pain, and post-traumatic pain. However, since it will be used on this study to provide transcutaneous electrical stimulation to the auricular branch of the vagus nerve, it is being used off-label as an investigational device for this study. For both devices, the non-significant risk determination was made since they are not intended as an implant, are not purported to be for use in supporting or sustaining life, and do not present a potential for serious risk to the health, safety, or welfare of a subject.

Moreover vagus nerve stimulation, which requires invasive implantation of a stimulator directly to the vagus nerve, has been approved by the FDA for the past two decades for the treatment of seizures, and has been demonstrated to be safe, without any related serious adverse events, and of clinical benefit across several clinical trials for the treatment of tinnitus (n=10), chronic depression (n=494), and more recently chronic, post-stroke hemiparesis (n=9) [8, 11, 21]. Transcutaneous electrical auricular stimulation in which the electrical current is delivered more safely and non-invasively via a transcutaneous route at the cymba concha of the ear, is also currently approved in Europe for the treatment of seizures. tVNS has been similarly demonstrated to be safe and without any related serious adverse events across several clinical trials in the treatment of tinnitus (n=24), treatment resistant epilepsy (n=30), and chronic post-stroke hemiparesis (n=7) [23, 34, 41]. Additionally, the tVNS device which we propose to use in this study has been approved by the Northwell IRB in an investigation involving healthy controls (IRB# HS16-0530) and patients with Lupus (IRB# HS16-0171). These investigations have also been conducted without any related serious adverse events.

Electromyography (EMG)

Electrical activity of the muscle will be differentially recorded during tVNS sessions using a bipolar electrode montage placed on the belly of the muscle. Recordings will be made from the biceps and triceps brachii, pectoralis major, rhomboideus, and/or the deltoids, which are some of the important muscles responsible for flexion and extension of the shoulder and elbow.

Randomization

Subjects will be stratified by established clinical impairment levels based upon admission Upper Extremity Fugl Meyer scores (low function <23 & moderate function 23-44) such that there are an equal number of low and high functioning patients in each treatment group. Subjects will then be randomized to either the active or sham tVNS group [28]. Assignment will be predetermined by a randomized assignment list, created prior to the enrollment of the first subject by an investigator from the CBEM team who is not directly involved in subject treatment. There will be concealed allocation of treatment assignment such that investigators involved in subject screening, consent, and clinical scoring will be blinded to treatment condition.

Blinding

This will be a double-blind pilot study in which subjects will be randomly assigned to either the sham or active tVNS conditions. Subjects will be told that they have a 50-50 chance of receiving either active or sham stimulation, but they will not be told which condition they receive. Additionally, the assigned clinical evaluators will remain blinded to condition. For each study session, stimulation condition will be programmed into the device by the RA or members of the CBEM team who are not performing clinical measures.

12. STATISTICAL ANALYSIS

- *Describe how your data will be used to test the hypotheses.*
- *State clearly what variables will be tested and what statistical tests will be used.*
- *Include sample size calculations.*
- *If this is a pilot study, state which variables will be examined for hypothesis generation in later studies.*

For our primary outcome measure, we will investigate whether tVNS paired in a closed loop with robotic therapy changes peak amplitude EMG activation in muscle groups along the shoulder and elbow. We hypothesize that upper extremity flexor synergy will be significantly improved when active tVNS is applied during extensor movements as compared to a sham condition, and will lead to an increase in EMG peak activation at the triceps brachii (elbow extensor muscle). This will be examined with a 2x3 ANOVA with condition (active stimulation vs. sham) and time (peak amplitude of EMG activation during extensor movements at admission, discharge, and follow-up) as factors.

For our secondary outcome measure, we will test whether active tVNS during extensor movements paired in a closed loop with intensive robotic intervention (9 sessions) significantly improves upper extremity motor function as compared to sham tVNS paired with intensity-matched robotics. This will be examined with a 2x3 Friedman ANOVA with condition (active vs. sham tVNS) and time (upper extremity fugl meyer score at admission, discharge, and 3 month FU) as factors.

Since this is a pilot study, there are presently no data from which we can derive a power calculation. However, we propose to enroll 36 subjects, in order to achieve a target of at least fifteen subjects per treatment group and also allow for a 10-15% drop out rate. In our extensive past experience with upper limb hemiparesis rehabilitation studies, 10-15 subjects per treatment group is required at minimum to capture a measurable treatment response. Additionally, two other early pilot studies investigating post-stroke upper limb motor rehabilitation combined with VNS found a significant improvement in motor performance with nine and fourteen subjects per treatment group (e.g. sham and active VNS), respectively [8 & 41].

13. SPECIMEN BANKING

- *If specimens will be banked for future research, describe where the specimens will be stored, how long they will be stored, how they will be accessed and who will have access to the specimens*
- *List the information that will be stored with each specimen, including how specimens are labeled/coded*
- *Describe the procedures to release the specimens, including: the process to request release, approvals required for release, who can obtain the specimens, and the information to be provided with the specimens.*

n/a

14. DATA MANAGEMENT AND CONFIDENTIALITY

- *Describe the data and specimens to be sent out or received. As applicable, describe:*
 - *What information will be included in that data or associated with the specimens?*
 - *Where and how data and specimens will be stored?*
 - *How long the data will be stored?*
 - *Who will have access to the data?*
 - *Who is responsible for receipt or transmission of data and specimens?*
- *Describe the steps that will be taken to secure the data during storage, use and transmission.*

The information collected on participants will be derived from self-report, brain MRI/CT scans, and data from study procedures. Brain MRI/CT scans will be obtained either directly from the subject, from the subject's treating physician, or from the subject's file in the health system EMR database with verbal consent from the subject/LAR. After an individual is enrolled into the study, the signed consent form and case report forms will be securely maintained in password protected databases behind the health system firewall and/or in a locked drawer within the locked Feinstein robotics suite, which is only accessible to study investigators. Study data and participant PHI (e.g. demographics, contact info, medical history) will be collected and stored in the HIPAA-compliant system, REDCap. To protect subjects' confidentiality, each subject will be assigned an ID number, and all data will be stored with the subject ID number only and not the subject's name. Any study data containing PHI that is transferred between investigators at Feinstein will be shared via encrypted email, through Syncplicity (health system approved encrypted cloud system server), or through encrypted storage drives. All study data will be stored for at least seven years following closure.

15. DATA AND SAFETY MONITORING PLAN

A specific data and safety monitoring plan is only required for greater than minimal risk research. For guidance on creating this plan, please see the [Guidance Document](#) on the HRPP website.

*Part I – this part should be completed for all studies that require a DSMP.
Part II – This part should be completed when your study needs a Data and Safety Monitoring Board or Committee (DSMB/C) as part of your Data and Safety Monitoring Plan.*

Part I: Elements of the Data and Safety Monitoring Plan

- *Indicate who will perform the data and safety monitoring for this study.*
- *Justify your choice of monitor, in terms of assessed risk to the research subject's health and well being. In studies where the monitor is independent of the study staff, indicate the individual's credentials, relationship to the PI, and rationale for selection*
- *List the specific items that will be monitored for safety (e.g. adverse events, protocol compliance, etc)*
- *Indicate the frequency at which accumulated safety and data information (items listed in # above) will be reviewed by the monitor (s) or the DSMB/C.*
- *Where applicable, describe rules which will guide interruption or alteration of the study design.*
- *Where applicable, indicate dose selection procedures that will be used to minimize toxicity.*
- *Should a temporary or permanent suspension of your study occur, in addition to the IRB, indicate to whom will you report the occurrence.*

Although this is a minimal risk study, to protect both the integrity of the data and the safety of all study participants, study data review in aggregate will occur every 4 months by the Principal Investigator. Additionally, if a subject experiences an adverse event during the course of the study, the PI will be notified immediately and the IRB will be contacted within 5 days if the PI determines that the event is or may be related to the study intervention. If it is determined that the study intervention caused or may have caused the adverse event, the participant may be removed from the study and the study protocol will either be modified or ceased. However serious adverse events are unanticipated as tVNS is a nonsignificant risk device. Additionally, there were no serious adverse device effects of implanted VNS or tVNS in individuals with stroke [8, 41].

Part II: Data and Safety Monitoring Board or Committee

- *When appropriate, attach a description of the DSMB.*
- *Provide the number of members and area of professional expertise.*
- *Provide confirmation that the members of the board are all independent of the study.*

n/a

16. WITHDRAWAL OF SUBJECTS

- *Describe anticipated circumstances under which subjects will be withdrawn from the research without their consent*
- *Describe procedures for orderly termination*
- *Describe procedures that will be followed when subjects withdraw from the research, including partial withdrawal from procedures with continued data collection.*

Study participation is voluntary, and a subject can withdraw at any time by notifying a member of the research team. It is also possible that a subject may be withdrawn from a study without his or her consent. Reasons for such withdrawal may include failure to keep study appointments, changes in medications or medical history such that the subject no longer meets inclusion criteria, experiencing an adverse event that is related or potentially related to the study intervention, or study cessation. Once a subject is withdrawn from the study, no new data will be collected, but previously collected data will be kept and may be used.

17. RISKS TO SUBJECTS

- *Describe any potential risks and discomforts to the subject (physical, psychological, social, legal, or other) and assess their likelihood and seriousness and whether side effects are reversible. Where appropriate, describe alternative treatments and procedures that might be advantageous to the subjects.*
- *Include risks to others, like sexual partners (if appropriate)*
- *Discuss why the risks to subjects are reasonable in relation to the anticipated benefits and in relation to the importance of the knowledge that may reasonably be expected to result.*
- *Describe the procedures for protecting against or minimizing any potential risks, including risks to confidentiality, and assess their likely effectiveness.*

Transcutaneous vagus nerve stimulation by the ear has the potential to cause temporary changes in hearing, pain at the site of stimulation, skin irritation or burns, and in rare occurrences, increases or decreases in heart rate as a result of activating the cervical vagus nerve via transcutaneous electrical stimulation of the ear. However, serious adverse events are unanticipated with tVNS, as there were no serious adverse device effects of implanted VNS or transcutaneous VNS in individuals with chronic stroke [8, 41].

Ear pain/discomfort occurs from stimulation of the sensory nerves innervating the ear. Activation of the sensory nerves correlates with the peak charge density applied to the innervated area. Consequently, during the stimulation period, we will monitor for discomfort and can adjust the charge intensity in real time to rapidly reduce the stimulation intensity and reduce the physical discomfort. This physical discomfort is not serious and the side effects are reversible.

Thermal burns at the stimulation site are due to excess power density through the electrode area. The FDA guidance for document for powered muscle stimulators (FDA document 2246) specifies a maximum power density at the electrode site of 250 mW/cm². The MIDI fabricated stimulator has a maximum power density of less than 100 mW/cm², which falls well below the guidance limit for thermal burns. A portable, battery-powered oscilloscope will be used to confirm peak current for the Roscoe device, and ensure that power density does not exceed this level.

Given the rare risk of heart rate changes occurring with tVNS, patients with known cardiac arrhythmias have been excluded from this study. Additionally, subjects will be continuously monitored during therapy. Any patient report of dizziness, lightheadedness, or nausea, which are associated symptoms with arrhythmia will result in immediate reduction in the stimulation intensity and/or cessation of stimulation and robotic intervention. A medical professional trained in basic life support (BLS) and will be present at the time of stimulation and afterwards. Additionally, appropriate medical equipment is available on site and the PI and other trained physicians are available on-call in the case of an emergency to further safeguard against risks.

There are no known risks associated with the use of robotic training for stroke rehabilitation. Some patients have pain in the shoulder after a stroke. Our experience has demonstrated a comparable incidence of shoulder pain in groups that were or were not treated by the robot.

There is also a risk of a breach of confidentiality if unauthorized individuals obtain access to protected health information. This risk will be minimized by securely storing all collected information and limiting access to study investigators only.

18. RESEARCH RELATED HARM/INJURY

- *Describe the availability of medical or psychological resources that subjects might need as a result of anticipated problems that may be known to be associated with the research.*
- *If the research is greater than minimal risk, explain any medical treatments that are available if research-related injury occurs, who will provide it, what will be provided, and who will pay for it.*

Since this study is considered minimal risk, physical injuries are not expected. However, if participants are injured from study participation, they will be provided treatment by Northwell Health. However, they or their insurance company will be responsible for the associated costs. No money will be given to participants.

Subjects will be continually monitored during the stimulation period, and will be in constant contact with a member of the research staff. The study can be immediately stopped at the subject's request.

In the case of a medical emergency, the PI and or other licensed physicians on site will be immediately summoned, and EMS may be contacted. Additionally, the Feinstein is equipped with necessary resuscitation equipment, including a code box, cardiac defibrillator, intravenous fluids, and supplemental oxygen. An EKG machine is also available at the CRC if needed. The PI or other licensed medical professional will be available to provide any and all medical treatments deemed necessary.

19. POTENTIAL BENEFIT TO SUBJECTS

- *Explain what benefits might be derived from participation in the study, noting in particular the benefit over standard treatment (e.g. a once-a-day administration instead of four times a day, an oral formulation over an IV administration).*
- *Also state if there are no known benefits to subjects, but detail the value of knowledge to be gained*

The potential benefit of the proposed study is to develop a tool to augment conventional rehabilitation methods and improve motor recovery after stroke.

20. PROVISIONS TO PROTECT PRIVACY INTERESTS OF SUBJECTS

- *Describe the methods used to identify potential research subjects, obtain consent and gather information about subjects to ensure that their privacy is not invaded.*
- *In addition consider privacy protections that may be needed due to communications with subjects (such as phone messages or mail).*

Eligible participants will be recruited by Northwell Health clinician's in the Departments of Physical Medicine and Rehabilitation, Neurology, and Outpatient Stroke Rehabilitation at NSUH, LIJMC, GCH, SSH, Transitions of Long Island, and STARs Outpatient Rehabilitation Center. These clinicians will identify potential study participants, and either: 1.) provide the patient with the study coordinator's contact information or 2.) provide the patient's contact information to study personnel.

Investigators may contact (or be contacted by) a potential subject or subject's LAR/next-of-kin by telephone or email to discuss participation in this research protocol. The investigator will explain the goals and the risks of participating in this research study and the requirements of participation. If the subject/LAR/next-of-kin expresses interest in the study, the investigator will also review a pre-screening checklist, and schedule a meeting with the patient-subject. We will inform the patient that it is possible if they come in for the meeting, s/he may not be eligible for this study. If the subject is interested in participating in the study and has obtained a brain scan within the health system that is accessible through EMR, we can review that scan prior to the meeting if the subject provides verbal consent. Review of brain scans will occur in the interest of expediting determination of study candidacy, as many of our study participants have significant mobility impairments and prescreening brain scans may prevent excess hardship/travel to study site for ineligible subjects.

During the initial evaluation or screening visit, the investigator will verify the patient's candidacy and provide the subject/LAR/next-of-kin with all the

information contained in the written consent form, including a discussion of the risks/benefits of the study and the study schedule. The investigator will answer any questions regarding the research and give the subject/LAR/next-of-kin ample time to consider participation in the study. Following this discussion, the potential participant and/or their LAR/next-of-kin will be asked to provide consent to participation. Upon signing, the subject/LAR/next-of-kin will be provided with a copy of the consent.

In the event that a subject and/or LAR/next of kin arrives for the first evaluation and then requests to take the consent form home for review prior to signing it, minimal risk clinical measures of the subject's upper extremity function may still be collected during the initial study visit, prior to the signing of the consent, in order to reduce the burden on the disabled subject and their family who would otherwise be required to come for an additional study visit. If that subject and/or their LAR/next of kin then decline further participation in the study, the data for that subject's first evaluation will be destroyed.

In order to protect their confidentiality, subjects will be assigned a study ID number. The participant will then be referenced by that number. This identifiable information will be located on the HIPAA-compliant database, REDCap, and in hard-copy paper charts, which will be stored in a locked file cabinet. The study's de-identified data may be shared to facilitate study conduct such as data analysis. In addition, all study data will be securely maintained with access limited to investigators and authorized individuals only.

21. COSTS TO SUBJECTS

- *Describe any foreseeable costs that subjects may incur through participation in the research*
- *Indicate whether research procedures will be billed to insurance or paid for by the research study.*

There will be no direct costs to the subject for any study procedures or rehabilitation interventions. However, subjects are required to provide their own transportation.

22. PAYMENT TO SUBJECTS

- *Describe the amount of payment to subjects, in what form payment will be received and the timing of the payments.*

Subjects will receive no payment for participation in this study.

23. CONSENT PROCESS

If obtaining consent for this study, describe:

- *Who will be obtaining consent*
- *Where consent will be obtained*
- *Any waiting period available between informing the prospective participant and obtaining consent*
- *Steps that will be taken to assure the participants' understanding*
- *Any tools that will be utilized during the consent process*
- *Information about how the consent will be documented in writing. If using a standard consent form, indicate such.*
- *Procedures for maintaining informed consent.*

The consent process will take place in the robotics suite at the Feinstein. The investigator will provide the subject/LAR/next-of-kin with all the information contained in the written consent form. The investigator will then encourage the subject/LAR/next-of-kin to “teach back” the risks and benefits of the study to ensure their comprehension. The investigator will answer any questions regarding the research and give the subject/LAR/next-of-kin ample time to consider participation in the study. If so desired, those interested will be given a copy of the consent form so that they may have the opportunity to discuss participation further with family and/or advisors. If an individual joins the study by providing informed consent, the subject will receive a signed copy of the consent form.

Written consents will be maintained in a locked file cabinet within the locked Feinstein robotics suite for up to 7 years.

In the state of NY, any participants under the age of 18 are considered children. If your study involves children, additional information should be provided to describe:

- *How parental permission will be obtained*
- *From how many parents will parental permission be obtained*
- *Whether permission will be obtained from individuals other than parents, and if so, who will be allowed to provide permission. The process used to determine these individual's authority to consent for the child should be provided*
- *Whether or not assent will be obtained from the child*
- *How will assent be documented*
- *Whether child subjects may be expected to attain legal age to consent to the procedures for research prior to the completion of their participation in the research. If so, describe the process that will be used to obtain their legal consent to continue participation in the study. Indicate what will occur if consent is not obtained from the now-adult subjects.*

n/a

If the study involves cognitively impaired adults, additional information should be provided to describe:

- *The process to determine whether an individual is capable of consent*
- *Indicate who will make this assessment*
- *The plan should indicate that documentation of the determination and assessment will be placed in the medical record, when applicable, in addition to the research record.*
- *If permission of a legally authorized representative will be obtained,*
 - *list the individuals from who permission will be obtained in order of priority*
 - *Describe the process for assent of subjects; indicate whether assent will be required of all, some or none of the subjects. If some, which subjects will be required to assent and which will not.*
 - *If assent will not be obtained from some or all subjects, provide an explanation as to why not*
 - *Describe whether assent will be documented and the process to document assent*
 - *Indicate if the subject could regain capacity and at what point you would obtain their consent for continued participation in the study*

If the patient is awake, alert, and oriented to person, place, and time, and demonstrates appropriate cognitive and communicative abilities as determined by the study coordinator or PI, the patient will be deemed to have the appropriate capacity to consent; however, given that borderline cognitive dysfunction and/or aphasia may not be easily distinguishable, the patient's LAR/next of kin will be routinely included when consent to participate is being obtained for all subjects.

If it is determined that a patient is unable to consent for him/herself, due to a lack of capacity or lack of comprehension, consent will be sought from the patient's LAR/next of kin. Assent of the adult subject with LAR/next-of-kin will be obtained as appropriate. If such a subject regains his/her ability to make healthcare decisions, he/she will be given the opportunity to provide consent. This consent will be documented using the Addendum to Consent by Research Proxy for Continuing Participation in a Research Study form.

If the patient provides the consent delegate with assent to participate in the research but, due to a physical disability, is unable to sign the consent form, the patient will provide verbal consent and one witness/a and the patient's LAR/next of kin will sign the document affirming their presence during the consent process and the patient's physical disability as reason for an absent signature.

If the study will enroll non-English speaking subjects:

- *Indicate what language(s) other than English are understood by prospective subjects or representatives*
- *Indicate whether or not consent forms will be translated into a language other than English*
- *Describe the process to ensure that the oral and written information provided to those subjects will be in that language*
- *If non-English speaking subjects will be excluded, provide a justification for doing so*

Subjects with limited English proficiency are not the target of this study, but it is possible that subject's with LEP may qualify for the study and seek enrollment. In such cases, the study will seek consent as per Northwell Health policy.

24. WAIVER OR ALTERATION OF THE CONSENT PROCESS n N/A

Complete this section if you are seeking an alteration or complete waiver of the consent process.

- *Describe the possible risks of harm to the subjects involved in this study and explain why the study involves no more than minimal risk to the subject:*
- *Explain why the waiver/ alteration will not adversely affect the rights and welfare of subjects*
- *Explain why it is impracticable to conduct this research if informed consent is required*
- *If appropriate, explain how the subjects will be provided with additional pertinent information after participation. If not appropriate to do so, explain why.*

n/a

*Complete this section if you are obtaining informed consent but you are requesting a waiver of the documentation of consent (i.e., verbal consent will be obtained). To proceed with a waiver based on these criteria, each subject must be asked whether they wish to have documentation linking them to this study. **Only complete subsection 1 OR subsection 2.***

SUBSECTION 1

- *Explain how the only record linking the subject to the research would be the consent document.*
- *Explain how the principal risk of this study would be the potential harm resulting from a breach in the confidentiality*
- *Indicate whether or not subjects will be provided with a written statement regarding the research.*

n/a

SUBSECTION 2

- Describe the possible risks of harm to the subjects involved in this study and explain why the study involves no more than minimal risk.
- Confirm that the research only involves procedure for which consent is not normally required outside the research context.
- Indicate whether or not subjects will be provided with a written statement regarding the research.

n/a

25. WAIVER OF HIPAA AUTHORIZATION

N/A

Complete this section if you seek to obtain a full waiver of HIPAA authorization to use and/or disclose protected health information.

- Describe the risks to privacy involved in this study and explain why the study involves no more than minimal risk to privacy:
- Describe your plan to protect identifiers from improper use or disclosure and to destroy them at the earliest time.
- Indicate why it is not possible to seek subjects' authorization for use or disclosure of PHI.
- Indicate why it is not possible to conduct this research without use or disclosure of the PHI.
- Indicate if PHI will be disclosed outside NSLIJ Health System, and if so, to whom. Note: PHI disclosed outside NSLIJ Health System, without HIPAA authorization needs to be tracked. Please see guidance at www.nslj.com/irb for information about tracking disclosures.

n/a

Complete this section if you seek to obtain a partial waiver of the patient's authorization for screening/recruitment purposes (i.e., the researcher does not have access to patient records as s/he is not part of the covered entity)

Note: Information collected through a partial waiver for recruitment cannot be shared or disclosed to any other person or entity.

- Describe how data will be collected and used:
- Indicate why you need the PHI (e.g. PHI is required to determine eligibility, identifiers are necessary to contact the individual to discuss participation, other)
- Indicate why the research cannot practicably be conducted without the partial waiver (e.g. no access to medical records or contact information of the targeted population, no treating clinician to assist in recruitment of the study population, other)

If the subject is interested in participating in the study and has obtained a brain scan within the health system that is accessible through EMR, investigators can review that scan prior to the meeting if the subject provides verbal consent. Additionally, if a subject only has a brain scan from a health system outside of Northwell, the subject/LAR can provide investigators with a copy of that scan, if willing, prior to meeting. Review of brain scans will occur in the interest of expediting determination of study candidacy, as many of our study participants have significant mobility impairments and prescreening brain scans may prevent excess hardship/travel to study site for ineligible subjects.

26. VULNERABLE POPULATIONS:

Indicate whether you will include any of these vulnerable populations. If indicated, submit the appropriate appendix to the IRB for review:

- Children or viable neonate*
- Cognitively impaired*
- Pregnant Women, Fetuses or neonates of uncertain viability or nonviable*
- Prisoners*
- NSLIJ Employees, residents, fellows, etc*
- poor/uninsured*
- Students*
- Minorities*
- Elderly*
- Healthy Controls*

If any of these populations are included in the study, describe additional safeguards that will be used to protect their rights and welfare.

Given that the goal of this study is to treat motor impairments following stroke, it is necessary that our study enroll subjects who may have cognitive impairments from the associated neurological injury, are often elderly, and may be from minority and/or uninsured/poor populations. In all cases, the risks/benefits of the study and the commitment of the study schedule will be discussed at length with the subject. The subject's LAR/next-of-kin will also be routinely included in these discussions. Subjects will be informed that their enrollment decision will not affect their medical access/care through Northwell Health, and that they can drop out of the study at any time, though they will be encouraged to maintain good attendance while enrolled. Additionally, the consent form will clearly state that participation is voluntary.

27. MULTI-SITE HUMAN RESEARCH (COORDINATING CENTER)

If this is a multi-site study where you are the lead investigator, describe the management of information (e.g. results, new information, unanticipated problems involving risks to subjects or others, or protocol modifications) among sites to protect subjects.

n/a

28. REFERENCES/BIBIOGRAPHY

Provide a reasonable list of references directly related to the study. Any diagrams for new medical devices or brief reprints from journals might also prove useful.

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