Medical University of South Carolina
CONSENT TO BE A RESEARCH SUBJECT

TITLE OF RESEARCH: Extending taVNS Paired with Infant CIMT into a Home-Based Setting: Technology Development Requisite for a Randomized Trial

SUMMARY

You are being asked to enroll your infant in a research study. Research studies are voluntary and include only people who choose to take part. The purpose of the research is to test an experimental therapy to help infants who have weak arm movements on one side of the body due to brain injury to improve their motor skills with the weaker arm.

If you choose to have your infant participate, they will complete an intensive therapy program with an occupational or physical therapist for 4 weeks with a non-invasive form of nerve stimulation using a device that is cleared by the US Food and Drug Administration (FDA) for children. Transcutaneous auricular vagus nerve stimulation (taVNS) stimulates a nerve by the ear that may enhance learning motor skills. The intensive therapy is called Constraint Induced Movement Therapy (CIMT). CIMT involves placing a mitt constraint on the stronger hand while encouraging your infant to use the weaker arm and hand during therapy sessions. Pairing CIMT and taVNS may improve your infant's motor skills more in play than with therapy alone. The sessions in this study will take 2 hours a day, 5 days a week for 4 weeks (40 hours total CIMT) for a total of 1 month study participation. There will also be 3 assessment sessions (one before therapy, 1 immediately after the month of therapy and another session 3 months later). The assessment sessions will take about an hour each.
While your infant may become distracted or tired during these therapy sessions, we do not expect any other risks or discomfort. We have used taVNS safely in over 500 sessions in newborns and infants. The taVNS system we are using is cleared for use but is not yet FDA approved in this patient population. The alternative to this study is for your infant to continue to receive the same skills training they are currently receiving by therapists. If you are interested in learning more about this study, please continue to read below.

A. PURPOSE OF THE RESEARCH

The purpose of this study is to see if we can improve your infant's ability to use their weaker arm/hand by pairing a non-invasive brain stimulation technique, called Transcutaneous auricular Vagus Nerve Stimulation (taVNS) with CIMT. CIMT is considered the gold standard therapy treatment for children with 1 sided weakness to help them learn to use their impacted arm or hand. In this study we are specifically

investigating if we can use sensors on the skin that recognize muscle activity to turn on the taVNS stimulation. We want to do this because the non-invasive brain stimulation is thought to be most effective in helping people learn movement skills when it is used at the same time as active muscle movements.

You are being asked to allow your infant to join the study because he or she has motor problems with one arm and or hand and is 6 to 24 months of age, a time when we think we can improve brain circuits for better motor functioning.

Explanation of technology:

- **Electromyography (EMG) Sensors:** EMG sensors are adhesive electrode sensors that detect electrical activity in a muscle, in other words sensors that detect if a muscle is "on or off". In this study we will place EMG sensors over key muscles in the shoulders and trunk to automatically detect when an infant is reaching or using their trunk to work on activities like sitting or rolling in therapy. When muscles are active, it will turn on taVNS stimulation. Pairing nerve stimulation with movement may improve motor outcomes when paired with movement activities in infants and adults post stroke or brain injury.

- **Transcutaneous auricular Vagus Nerve Stimulation (taVNS):** taVNS, provides low level electrical stimulation (<2.0 mA) to the vagal nerve using an electrode placed on the ear. Daily vagal nerve stimulation has been shown to be safe and to help the brain learn motor tasks in adults and in our study of infants with brain injury or prematurity, without side effects.
  Nerve stimulation has also been used in neonates to decrease pain and improve motor function after nerve injury at birth. With electrodes on the infant's left ear, the nerve stimulator device will deliver short small electric pulses while he or she is engaging in therapy activities (reaching for toy, working on sitting balance on a swing, etc). These devices are FDA approved for pain management on muscles, and FDA-cleared and widely available for purchase online without a prescription for home use in adults and children. We will use this FDA-approved technology to stimulate the vagus nerve and brain pathways involved in motor control using an electrode placed on the ear.
  The FDA has approved transcutaneous electrical nerve stimulation (TENS) therapy for pain management. TENS requires placing electrodes directly on the skin of a specific part of your body. Small pulsed electrical currents are then delivered to these electrodes, which stimulate the underlying muscles and nerves. taVNS is a specific use of this FDA approved therapy, and is just another name for TENS therapy on the ear. *We think it may have different effects than TENS on*

muscles, because we can stimulate a large nerve, called the vagus nerve, in the ear. This nerve connects to the brain and is important in many functions. In animals with brain injury, stimulation of the vagus nerve combined with motor training helps repair the motor areas of the brain. In adults and infants, taVNS improves motor function, when paired with a motor task. Using taVNS in infants to improve motor skills is experimental, even though the TENS device is cleared by the FDA. Again, the taVNS system we will use for this study is cleared for use but is not yet FDA approved for use in this patient population for recovery of motor function- this is why we say it is experimental.

Rationale for Pairing EMG triggered taVNS with CIMT.

Newborns who are born premature or suffer brain injury at birth are at risk for motor problems. The common motor skills of reaching and grasping that infants have to learn can be weaker on one side of the body, depending on the site of the brain injury. These skills are practiced with an occupational or physical therapist, to help the infant strengthen these skills.

Constraint Induced Movement Therapy (CIMT) is the gold-standard in pediatric therapy, but it is time intensive (2-5 hours per day) and unfeasible for many families if delivered in a clinic setting. Therefore, we want to improve the benefits received by doing the therapy.

We will test whether EMG muscle sensors placed on the skin can be used to pair taVNS with active movement while the infant participates in 40 hours of CIMT therapy treatment. In other words can the muscle sensors help us to match the nerve stimulation with the movements an infant does during therapy.

A course of daily vagal nerve stimulation has been shown to be safe and to help the brain learn motor tasks in adults. In our previous studies with infants in the hospital it has also been shown to help infants improve motor skills important for bottle feeding of infants with brain injury or prematurity, without side effects.

This research study will be done at The Medical University of South Carolina and will include up to 5 infants. The person in charge of overseeing this study is Dr. Kelly McGloon. The costs of this study are being paid from a grant from the National Institutes of Health (NIH). The grant will help pay for supplies as well as portions of the salaries of the therapists who will provide the treatment and the engineer who is helping set up the equipment.

Please read this consent form carefully and take your time making your decision. As your study staff discusses this consent form with you, please ask him/her to explain any words or information that you do not clearly understand.

B. PROCEDURES

If you agree for your infant to participate in this study, the following will happen:

1) Medical Records

The researchers will check your medical records to gather the following information: gestational age at birth (gestational age tells is age corrected if your infant was born early), ventilator (breathing) support, head ultrasound and imaging results (if available), bottle feeding, infection, your and your infants's condition during labor and delivery, your infant's treatment and conditions, and developmental progress.

2) Pre-assessment Session

The pre-assessment session will take about 1.5 hours. In this session you will come to the pediatric therapy lab in the College of Health Professions. You can park in the garage attached to the building and parking will be paid. In this session, we will do 3 assessments with your infant. One assessment looks at your infant's overall physical development and if they have the skills expected of an infant at their age. The other 2 assessments are for infants with weakness on 1 side of the body. For these assessments we will engage your infant in play and look at the way they use their arm and hand for things like reaching for toys and crawling. We will also be looking at the balance and the ways they try to move around (crawling, rolling, sitting up, etc). These assessments should take less than 45 minutes and you can help engage your infant during play. At the end we will make a splint for your infant to wear duing the therapy sessions. We will mold a splint to be worn on your infant's stronger hand. This will take about 15 minutes. The splint will cover the palm side of the hand and can be taken on and off with Velcro straps. Pre- assessment can take place anytime the week before treatement begins.

2) Intervention

For the intervention part of the study your infant will receive therapy for 2 hours, 5 sessions per week for 4 consecutive weeks (40 hours total). The therapy will be provided by a pediatric therapist specifically trained in Constraint Induced Movement Therapy (CIMT). During the therapy sessions your infant will wear the custom-made hand splint (this is the constraint) on the stronger hand to encourage them to work on using the weaker arm/hand- this type of therapy focused on using the weaker side is called CIMT.

CIMT is used with infants, children, and adults who have weakness on 1 side of the body due to brain injury to help improve their ability to use the weaker side.

The therapist will keep daily therapy logs and ask you if you are noticing any changes at home (for example, have you seen your infant use the weaker hand in any new ways). The therapist will review targeted therapy goals at each session with you.

During the last week of therapy, the therapist will create a take-home packet for you. This will include pictures and a written plan explaining things we have been doing in therapy and what would be good next steps if you wanted to continue working with your infant on their movement goals once treatment ends. For example, the therapist may explain how they hold food items so your infant can work on feeding themselves independently with the weaker hand.

We will videotape therapy sessions then randomly select 1 session a week (20% sessions) and score how well the therapist provides the CIMT treatment while delivering taVNS. We will store these videotapes for teaching purposes and future research.

During the therapy sessions your infant will also receive non-invasive nerve stimulation Transcutaneous auricular Vagus Nerve Stimulation (taVNS). This stimulation will be provided using stick on electrodes just inside and outside your infant's left ear. At the beginning of each session the researcher will determine how much electrical stimulation is needed for your infant to feel a slight tingle. We look for signs like the infant turning their head, making a sound, bringing their hand to the ear, flintching, etc as signs that the infant has felt a slight tingle. We ask the parents/caregivers to watch too and if you notice anything you can tell us. If we see your infant demonstrate the same behavior 2 times when we turn the stimulation on then we take that as an indicator your infant felt the tingle. Then we turn the stimulation down 1 level (0.1mA) so that the infant will not feel the stimulation. If at any point during the session it seems like the infant is noticing the stimulation we will take a short break and then re-test the levels to check when the infant notices a tingle. We will adjust stimulation as needed during the session. We document all stimulation changes, the reason, and what behavior we used as a cue the infant felt a tingle (for example, the infant brought his hand to his ear).

We will also place sensors on key muscles in the infants shoulder and back. These sensors will tell us when muscles are being used or at rest. When the sensors detect that a muscle is being used it will start the low level taVNS stimulation. For example stimulation will be turned on when your infant uses muscles in the arm to reach towards a toy. The nerve stimulation will turn off when the muscle relaxes (stops moving) or after 2 minutes, whichever is shorter.

We will monitor your infant's behavior throughout the session. We will stop stimulation if needed (if the infant becomes fussy and stops participating). The electrodes and splint

will be removed immediately after the CIMT therapy session. Each day we will ask you a series of questions to see if your infant has experienced any side effects from the stimulation. These questions will include 1) was your infant's ear red after treatment and if so for how long? 2) Did you notice any changes in sleep? 3) Did you notice any increase in reflux? 4) Did you notice any other changes in your infant?

If the ear shows any signs of irritation after 24 hours we may switch stimulation to the right ear. If skin irritation does not resolve or worsens we will discontinue stimulation and may end treatment. This has not happened with any of the infants in our previous studies.

***Intervention Location*:** The first 2 infants enrolled will complete therapy in the pediatric therapy lab in the College of Health Professions at MUSC. This will allow for minor modifications to be made to the set-up if needed. For example, we may want to add tape or Velcro to help keep wires out of the way when your infant is crawling or rolling. If we can successfully use EMG muscle sensors to turn on taVNS stimulation for 75% of movements with the first two infants then the remaining 3 infants will complete the intervention in their home. If we are not able to use EMG sensors with 75% accuracy then we will complete all intervention session in the lab so that we can better track the percentage accuracy of using the EMG sensors. The study staff can tell you now if your infant will be receiving the 40 hours of therapy intervention in the lab or in your home. We realize that the intervention location may influence your willingness to participate in the study so please feel free to ask any question you may have. We will do our best to accommodate to a time schedule that works best for you and all therapy supplies will be provided by the treating therapist regardless of location.

3) Post Assessment

After the 40 hours of treatment we will do a post assessment session. Post assessments may be completed in the pediatric research lab at MUSC or in your home depending on what works best for your scheduling. We will do the same 3 assessments as in the pre-assessment session. This will include 1 assessment of overall physical development and 2 assessments specifically looking at how well your infant can perform various types of movements like reaching for a toy, crawling, etc. This session should take no more than 1 hour. This session is shorter than the first session because we will be more familiar with how your infant moves and we will not have to make the hand splint. Post- assessment can take place anytime the week after treatement ends.

4) 3 month follow-up

Three months after the post assessment you will come back to the pediatric lab and we will do the same 3 assessments again. This session should again take no more than 1 hour. Assessments may be completed in the pediatric research lab at MUSC or in your home depending on what works best for your scheduling.

C. DURATION

The pre-assessment session will take about 1.5 hours. Treatment will be provided for 40 hours (2 hours a day, 5 days a week for 1 month). Post assessments will take no more than 1 hour once treatment is completed. The three month follow-up will take no more than 1 hour. In total this study will require approximately 43.5 hours over the course of 3.5 months.

Pre-assement	Treatment	Post-assessment	3 month follow-up
One session lasting 1.5 hours the week before treatment starts	CIMT &taVNS treatment 2 hours per day 5 day a week for 1 month.	One session lasting 1 hour within 1 week after treatment ends	One session lasting 1 hour 3 months after treatment ends

Participation in this study will not interfere with routine therapy plans. In other words, if your infant has private physical therapy once a week they can continue to receive these regular services.

D. RISKS AND DISCOMFORTS

Potential Risks of taVNS

Potential skin discomfort or irritation. Electrical stimulation of nerves can cause short term, discomfort under the electrodes. In recent studies at MUSC in infants using taVNS there were no problems seen with short term redness of the ear or other skin problems. We will monitor the skin for any redness or irritation, which should resolve quickly. If the skin under the probe shows redness that does not go away, we will switch ears (use the right ear) during the next session with lower stimulation. We will watch your infant to see if there are signs of discomfort. If we are unsure if the stimulation is bothering your infant we will take a short break and then test stimulation levels again to make sure that it is low enough that the baby does not notice it. If it seems like your infant is tired or fussy we can stop to take a break or end the session early. We will write down any times we take breaks or lower stimulation level in our notes.

Potential decrease in heart rate: We expect stimulation of the vagus nerve may result in a brief decrease in your infant's heart rate that quickly rebounds within a minute. With this brief heart rate change we know the electrodes are in good position. The slight decrease should stay within normal range we would expect for an infant.

Loss of confidentiality: There is a risk of a loss of confidentiality of your infant's personal information and your labor and delivery personal information as a result of participation in this study. To keep this risk small, we will not have names on research documents. Instead we will use a code to identify your infant's records, and keep them in a locked cabinet and office. Your infant will not be identified directly in any publication or presentation of this research.

Unknown Risks: We are using a type of nerve stimulation called Transcutaneous auricular Vagus Nerve Stimulation (taVNS). It is essentially Transcutaneous electrical nerve stimulation (TENS) on your infant's ear. TENS stimulation of peripheral nerves is FDA approved and is considered very safe. You can buy TENS devices without a prescription at most local pharamcies. Although taVNS is essentially TENS on your infant's ear, it is still an experimental procedure that has not been approved by the FDA to improve motor function. Therefore, there may be risks and discomforts that we are not aware of. The Principal Investigator will let you know if she learns anything that might make you change your mind about participating in the study.

E. MEDICAL RECORDS

Information about your study participation will not be in your medical record. This means that neither your research participation nor any of your research results will be included in any MUSC medical record.

F. BENEFITS

The potential benefit to your infant from participating in this study is learning to move their arm and hand faster or more effectively, but we cannot quarantee that your infant will show these improvements. However, the information gained from the study may help researchers learn about if nerve stimulation can show greater benefits in the way your infant moves as a result of therapy compared to therapy by itself.

G. COSTS

You will not be charged for the study assessments, splint fabrication, or therapy provided in the study. If you receive other care or therapy outside of this study the usual costs of your infant's care will be billed to your insurance.

H. Payment to Participants

You will not be paid for participating in this study. If you park in the MUSC garage when you come to the research lab we will give you a sticker so you do not have to pay for parking during the time you spend at MUSC for the study.

I. ALTERNATIVES

If you choose not to participate in this study, your infant will receive the usual care. Your infant can still receive standard therapy services outside of this study (usually 1 hour a week). Transcutaneous auricular Vagus Nerve Stimulation (taVNS), nerve stimulation, is not available other than in this research study. Constraint Induced Movement Therapy is not readily available for young infants but may be available with a local therapist. There are also CIMT camps in the region but many of them start at age 3. If you are interested in these programs we can share information with you. At this time, there are no other therapies to combine with CIMT to help an infant learn to move more effectively.

J. DATA SHARING

Information about your infant will have all of your infant's identifiers removed and may be used for future research studies or distributed to other researchers for future research without additional informed consent from you or your legally authorized representative.

The CIMT videotapes will be stored for future use and may include identifiable information. Your infants face will be shown in the videos. Additionally therapists frequently say your infants first name as they engage with your infant. This is the identifiable information that may be included in the videos. Sessions need to be recorded for infants to participate. As part of this study we will be regularly assessing the quality of the treatment provided by the therapist. After we score the videotapes to assess the quality of treatment provided by the therapist, if you do not wish for them to be used for teaching purposes, in presentations of this research, or for future research, you may have them destroyed by written request to Dr. McGloon. Written requests for destruction of videos can be sent via email to Dr.McGloon at mcgloon@musc.edu. You can send the request to

Dr. Kelly McGloon
College of Health Professions
Medical University of South Carolina (MUSC)
151-B Rutledge Avenue, MSC 960
Charleston, SC 29425

K. DISCLOSURE OF RESULTS

Results of the overall research study will be disclosed to you at the end of the study by email.

L. AUTHORIZATION TO USE AND DISCLOSE (RELEASE) MEDICAL INFORMATION

As part of this research study, your study research team will keep records of your participation in this study.

The health information MUSC may use or disclose (release) for this research study includes information in your medical record, results of physical exams, medical history, lab tests or certain health information indicating or relating to your condition.

Your study research team will use and disclose (release) your health information to conduct this study. The health information listed above may be used by and/or disclosed (released) to the following, as applicable:

- The sponsor of the study including its agents such as data repositories or contract research organizations monitoring the study;
- Other institutions and investigators participating in the study;
- Data Safety Monitoring Boards;
- Accrediting agencies;
- Clinical staff not involved in the study whom may become involved if it is relevant;
- Parents of minor children if less than 16 years old. Parents of children 16 years old or older require authorization from the child; or
- Health insurer or payer in order to secure payment for covered treatment;
- Federal and state agencies and MUSC committees having authority over the study such as:

    - The Institutional Review Board (IRB) overseeing this study; Committees with quality improvement responsibilities; Office of Human Research Protections; Food and Drug Administration; National Institutes of Health or Other governmental offices, such as a public health agency or as required by law.

Those persons who receive your health information may not be required by Federal privacy laws (such as the Privacy Rule) to protect it and may share your information with others without your permission, if permitted by laws governing them. You do not have to

sign this consent form. If you choose not to sign, it will not affect your treatment, payment or enrollment in any health plan or affect your eligibility for benefits. However, you will not be allowed to be a participant in this research study.

You will be given a copy of this consent form. Your authorization will expire at the conclusion of this study or, if you are participating in a study designed for the development of a drug or device, your authorization will remain in effect until the drug or device is approved by the FDA or until the company's application to study the drug/device is withdrawn. You have the right to withdraw your agreement at any time. You can do this by giving written notice to your study doctor. If you withdraw your agreement, you will not be allowed to continue participation in this research study. However, the information that has already been collected will still be used and released as described above. You have the right to review your health information that is created during your participation in this study. After the study is completed, you may request this information.

Your health information will be used or disclosed when required by law. Your health information may be shared with a public health authority that is authorized by law to collect or receive such information for the purpose of preventing or controlling disease, injury or disability and for conducting public health surveillance, investigations or interventions. No publication or public presentation about the research study will reveal your identity without another signed authorization from you.

If you have questions or concerns about this Authorization or your privacy rights, please contact MUSC's Privacy Officer at (843) 792-8740.

Regulations require that you be given a copy of the MUSC Notice of Privacy Practices (NPP) describing the practices of MUSC regarding your health information. One can be found at the end of this form.

M. SIGNIFICANT NEW FINDINGS

If there are significant new findings during the course of the study, you will be notified.

N. CLINICAL TRIALS.GOV

A description of this clinical trial is 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 site at any time.

O. FUTURE CONTACT

The researcher in charge of this study might like to contact you in the future about other research opportunities. If consenting on paper, please initial by your choice below, and if consenting electronically scroll to the next screen and indicate your choice by selecting 'yes' or 'no' and then initial the statement confirming your choice in the space that follows.

____Yes, I agree to be contacted

____No, I do not agree to be contacted

GENERAL INFORMATION:

Results of this research will be used for the purposes described in this study. This information may be published, but your infant will not be identified. Information that is obtained concerning this research that can be identified with your infantwill remain confidential to the extent possible within State and Federal law. The sponsor and the Food and Drug Administration (FDA) will receive copies of the research records. The investigators associated with this study, employees of the sponsor, the FDA, and the MUSC Institutional Review Board for Human Research will have access to identifying information. All records in South Carolina are subject to subpoena by a court of law.

In the event that your infantis injured as a result of participation in this study, you should immediately take your infant to the emergency room of the Medical University Hospital, or in case of an emergency go to the nearest hospital, and tell the physician on call that your infantis in a research study. They will call your infant's study doctor who will make arrangements for your infant's treatment. If the study sponsor does not pay for your infant's treatment, the Medical University Hospital and the physicians who render treatment to your infant will bill your insurance company. If your insurance company denies coverage or insurance is not available, you will be responsible for payment for all services rendered to your infant.

Your infant's participation in this study is voluntary. Your infant may refuse to take part in or stop taking part in this study at any time. You should call the investigator in charge of this study if your infant decides to do this. Your infant's decision not to take part in the study will not affect your infant's current or future medical care or any benefits to which your infant is entitled.

The investigators and/or the sponsor may stop your infant's participation in this study at any time if they decide it is in your infant's best interest. They may also do this if your infant does not follow the investigator's instructions.

Volunteers Statement

I have been given a chance to ask questions about this research study. These questions have been answered to my satisfaction. If I have any more questions about my infant's

participation in this study or study related injury, I may contact **Kelly McGloon at 843-792-6443.** I may contact the Medical University of SC Patient and Family Care Liaison (843) 792-5555 concerning medical treatment.

If I have any questions, problems, or concerns, desire further information or wish to offer input about my infant's rights as a research subject in this study, I may contact the Medical University of SC Institutional Review Board for Human Research IRB Manager or the Office of Research Integrity Director at (843) 792- 4148. This includes any questions about my rights as a research subject in this study.

I agree for my infant to participate in this study. I have been given a copy of this form for my own records.

If you wish to participate, you should sign below.

_____ _____

Signature of Person Obtaining Consent Date *Printed Name of Minor Participant

_____

Signature of Adult Participant Date

_____

Signature of Participant's Personal Representative (if applicable) Date

_____

Printed Name of Personal Representative (if applicable)

Relationship: ___ Spouse ___ Parent ___Next of Kin ___Legal Guardian* ____ DPOA for Healthcare*

**(If you are the health care agent or guardian, please provide proof of your authority to act on behalf of the patient)*