PROTOCOL TITLE: BabyStrong taVNS-Paired Bottle Feeding to Improve Oral Feeding

PRINCIPAL INVESTIGATOR: Dorothea Jenkins, MD

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Medical University of South Carolina
CONSENT TO BE A RESEARCH SUBJECT

TITLE OF RESEARCH: BabyStrong taVNS-Paired BottleFeeding to Improve Oral Feeding

SUMMARY
You are being asked to enroll your infant in a research study. Research studies are voluntary, and your child does not have participate. The purpose of the research is to test a therapy to help infants learn to feed by mouth better. If you choose to have your child participate, we will pair feeding with stimulation of the vagus nerve through the skin, called transcutaneous auricular vagus nerve stimulation (taVNS), using a device that is Federal Drug Administration (FDA) cleared for investigational use in children. taVNS stimulates a nerve by the ear that enhances learning motor skills like feeding. We have used taVNS in over 500 sessions in newborns and infants, and we do not expect any significant side effects in this study. The potential benefit to your child from participating in this study is learning to feed faster or more effectively, but we are not sure taVNS will have any effect on your child's feeding. The alternative to this study is simply for your child to continue to receive the same feeding skills training by therapists that he or she has been receiving to learn to feed or get a tube surgically placed into the stomach, for direct feeding into the stomach(G-tube). The active part of the study lasts 17 days, but we will follow development for 2 years.

A. PURPOSE OF THE RESEARCH

Newborns who are born premature or suffer brain injury at birth are at risk for motor problems, including feeding difficulties. The most common motor skill that infants have to learn while in the nursery is the coordination of suck, swallowing and breathing. Feeding skills are practiced with an occupational therapist, who helps the infant feed safely while developing this skill. Nevertheless, it typically takes between 3-6 weeks for most infants to learn to feed, and this is the main reason infants stay in the hospital, when they are otherwise ready to go home. Some infants are not able to take all feeds by mouth and have a tube surgically placed in the stomach for direct stomach feeding, bypassing the mouth (G-tube).

You are being asked to allow your infant to join the study because he or she has not made progress with oral feeds. The usual care for infants who are failing oral feeds is to continue to try to learn to feed with therapists or receive a G-tube. The purpose of this

study is to evaluate the safety and effectiveness of taVNS to improve the motor skill of feeding. We will test whether nerve stimulation by taVNS for 10-17 days helps your infant to learn to feed better, strengthen the circuits in the brain involved with feeding on brain scan, and avoid a G-tube.

A course of 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 your child's left ear, the transcutaneous electrical nerve stimulator (TENS) device will deliver short treatments of small electric pulses while he or she is feeding. TENS 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. The device we will use is FDA-cleared for investigational use, but we intend to develop the device for FDA approval as a commercially available device. You will not share in any commercial profit.

This research study will be done at The Medical University of South Carolina and will include 20 infants receiving the taVNS treatment in this phase I trial. The Principal Investigator in charge of this study is Dr. Dorothea Jenkins. A grant from the National Institutes of Health (NIH) will sponsor this study. Portions of Dr. Jenkins and his/her research team's salaries will be paid by this grant.

Please read this consent form carefully and take your time making your decision. As your study doctor or 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 child to participate in this study, the following will happen:

1) Medical Records

The researchers will check your child's medical records to gather the following information: gestational age, ventilator support, number of drops in heart rate or pauses in breathing, bottle feeding, infection, your and your child's condition during labor and delivery, your child's treatment and condition, and developmental progress.

2) Transcutaneous Vagus Nerve Stimulation

We will randomly assign your child to either A or B treatment group (like tossing a coin), one of which receives active taVNS stimulation and the other no stimulation. You will not know which treatment your infant is getting.

The assigned treatment will be delivered twice a day with feedings for 10 days. If your infant makes good progress in daily oral feeding volumes by 10 days, he or she can simply continue the assigned treatment up to 17 days total, or less if they take full feeds by mouth. If there is little progress after 10 days of assigned treatment, your infant can get the other treatment for another 7 days. If no progress is noted by 17 days, you and the clinical team will arrange for a G- tube. You can decide to withdraw the baby from the study at any time.

To treat with taVNS, we will place an electrode just inside and outside your child's left earlobe immediately prior to an oral feeding. During the first treatment, the researcher will determine how much electrical stimulation is needed for your child to feel a slight tingle with a shoulder shrug or facial expression change. Next, the researcher will start the taVNS while your child is sucking milk from the bottle/breast twice daily. During treatment, we will deliver short microcurrent pulses, coinciding with sucking, repeated over the duration of the feed. The electrodes will be removed immediately after the feeding each day.

We will provide taVNS up to a maximum of 30 minutes or the length of the feed up to 2 times per day. We will monitor your child's vital signs and discomfort level using standard infant behavior response scales. If discomfort scores increase, we will hold treatments until the discomfort subsides. We will decrease stimulation level if discomfort recurs. We will collect information about the feeding volume, the length of the feed, the number of pauses and the length of time to full feeds, as well as medical conditions that may affect feeding. The maximum duration of the taVNS treatments is 17 days.

The US Food and Drug Administration (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 TENS 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 and in adults with brain injury, stimulation of the vagus nerve combined with specific motor training helps repair the motor areas of the brain. In adults and infants, taVNS improves motor function, when delivered with a motor task. Using taVNS in infants to improve motor skills is experimental, even though the TENS device is cleared by the FDA.

3) Modified Barium Swallow (MBSS)

In some infants with feeding problems, a modified barium swallow is ordered to if the infant has problems protecting his or her airway and milk might be entering into the windpipe. If not ordered by the clinical team, we will perform a MBSS as part of the study, and test taVNS with thin and thick barium feeds, to see if the stimulation improves any swallowing problems, and does not make them any worse. We will also perform a MBSS at the end of the treatment period to follow up on your infant's feeding problems, and see if they are improving or not getting better. This will add a short time of radiation exposure to the usual clinical study (<30 seconds) to assess the effects of taVNS on swallowing.

4) Magnetic resonance imaging (MRI)

We will perform a short MRI scan of your child's brain: before starting treatment and after 10 days of taVNS, to track changes in brain regions with the different treatments. We will also perform a short MRI after 7 more days if your child continues either treatment. MRI does not involve radiation, is safe in newborns, and is routinely obtained in infants after significant brain injury. MRI uses a magnet and radio waves to make diagnostic medical images of the body. Your child will be swaddled after a feeding so that they will sleep, then they will be placed on a narrow bed in a FDA-cleared vacuum swaddle device, used for clinical MRIs in infants and slid into a small tunnel approximately 6 feet in length and 25 inches in diameter. Earmuffs will be placed to block out the loud machine-like noise. We do not use sedation for infant MRI. We will have brain experts read the MRIs and share this information with you and your child's doctors if we detect injury that was not already reported.

5) Development

We will perform a short motor developmental test along with the MRI scans for research before and after taVNS treatment while your child is still in the nursery, which will take 10 minutes each. Preterm infants and neonates with brain injury routinely have assessments of development in the nursery and may have the motor test performed clinically, but we would like to match this test of development at the time of the MRI scan. We will also collect the data from standard developmental testing in your child after discharge from

the hospital every 3 months up to 18-24 months in the NICU follow-up clinic at MUSC or perform developmental testing in your home or other location if you prefer.

C. DURATION

This study consists of the treatment period and the follow-up period. Each treatment session will last up to the 30 minutes allowed for a bottle feed, twice a day for up to 17 days. If your child is ready for discharge before the sessions are complete, we will stop treatments at discharge. Participation in this study will not interfere with discharge plans. Developmental follow-up will be complete after 18-24 months.

D. RISKS AND DISCOMFORTS

Potential Risks of taVNS

Potential skin discomfort, irritation. Electrical stimulation of peripheral nerves can cause temporary, local discomfort under the electrodes. In recent studies at MUSC in infants using taVNS there were no episodes of transient redness of the ear, and no 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 persists, we will switch ears (use the right ear) during the next session with lower stimulation.
We will monitor your child for discomfort with our standard infant behavior response scales (scale 1-7), recorded by nurses several times a day. Scores greater than 3 indicate mild discomfort. We will hold the treatment until scores are less than or equal to 3. If scores are repeated greater than 3, we will decrease the taVNS stimulation. This level of discomfort is much less than with an intravenous line, and similar to a heel stick to obtain blood.

Potential decrease in heart rate: Stimulation of the vagus nerve increases parasympathetic nervous system activity, that provides for calm rest and digestion, the opposite of the 'fight-or-flight' response. This will result in a brief decrease in your child's heart rate that quickly rebounds within a minute. With taVNS during feeding, we expect no big change in heart rate, but we will monitor these vital signs throughout the study to ensure safety.

Risks of MRI: There have been no ill effects reported from exposure to the magnetism or radio waves used in this test, which is standard of care in infants with brain injury. A known risk is that the magnet could attract certain kinds of metal, which babies do not routinely have implanted. However, if your child has MRI incompatible clips, we will not

perform the MRI scan, and they cannot participate in the study. Therefore, we will ask you about metal within your child's body. We will also keep the examining room closed so that no one carrying metal objects enters while your child is in the scanner. The MRI may show abnormalities not detected by head ultrasound. If the research team finds new abnormalities, Dr. Jenkins or the pediatric neurologists will discuss these with you and your care team.

Risk of Modified Barium Swallow (MBSS):
The MBSS is designed to safely assess whether milk touches the vocal cords or enters the windpipe during feeding. The pediatric speech pathologists are very skilled at performing this study, and serious aspiration requiring suctioning or resuscitation have not occurred using this procedure. Short gagging or brief choking can occur during the feed, as with any feed, and is handled per usual clinical practice of pausing feeding, allowing infant to clear his or her airway, and close monitoring of vital signs. The speech pathologist will screen the infant for gag reflex and safe feeding prior to any MBSS. Increased radiation exposure for the taVNS study procedures will be less than 30 additional seconds for each clinical MBSS study, or if performed only for research, less than 1 minute radiation exposure. We will discuss the findings on these studies with you and the clinical team taking care of your infant.

Loss of confidentiality:
There is a risk of a loss of confidentiality of your child'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 use a code to identify your child's records, and keep them in a locked cabinet and office. Your child will not be identified directly in any publication or presentation of this research.

Unknown Risks: Although taVNS is essentially TENS on your child's ear, it is still an experimental procedure that has not been approved by the FDA to improve motor function during feeding. 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

Your infant is an MUSC patient and they have an MUSC medical record. Participation in this research study and results of research tests or procedures will be included in your infant's MUSC medical record. All information within your infant's medical record can be viewed by individuals authorized to access the record. We will make every effort to keep

confidential all research information in the medical record that identify your infant to the extent allowed by law.

F. BENEFITS

The potential benefit to your child from participating in this study is learning to feed faster or more effectively, but we are not sure taVNS will have any effect on your child's feeding. However, the information gained from the study may help researchers learn about how to better stimulate brain function in infants and also whether and how to use taVNS to help with recovery from preterm birth or brain injury.

G. COSTS

There will be no additional cost to you for procedures required in this research study. All routine clinical care that your child would have undergone without participation in the study, including testing and procedures, will be billed to you/your insurance company. All study-related tests and procedures will be paid for by the Sponsor.

Some insurance plans will not pay for these services for people taking part in research studies. You will be responsible for any charges that you insurance does not cover including co-payments and deductibles.

H. PAYMENT TO PARTICIPANTS

You will not be paid for participating in this study.

I. ALTERNATIVES

If you choose not to participate in this study, your child will receive the usual feeding training or a G-tube. Other than practicing feeding, there are no other ways to help an infant learn to feed more effectively.

J. DATA SHARING

Information about your infant (including their identifiable private information and/or any identifiable biospecimens) may have all of your infant's identifiers removed and used for future research studies or distributed to other researchers for future research without additional informed consent from you or your legally authorized representative.

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 doctor and his/her 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 doctor and his/her 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 Web 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 child will not be identified. Information that is obtained concerning this research that can be identified with your child will 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 child is injured as a result of participation in this study, you should immediately take your child 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 child is in a research study. They will call your child's study doctor who will make arrangements for your child's treatment. If the study sponsor does not pay for your child's treatment, the Medical University Hospital and the physicians who render treatment to your child 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 child.

Your child's participation in this study is voluntary. You may refuse for your child 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 you decide to do this. Your decision for your child not to take part in the study will not affect your child's current or future medical care or any benefits to which your child is entitled.

The investigators and/or the sponsor may stop your child's participation in this study at any time if they decide it is in your child's best interest. They may also do this if your child 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 child's participation in this study or study related injury, I may contact Dr Jenkins (843- 792-2112). I may contact the Medical University of SC Hospital Medical Director (843-792-9537) concerning medical treatment.

If I have any questions, problems, or concerns, desire further information or wish to offer input about my child'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 child 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 if consenting on paper and if you are consenting electronically you should scroll to the next screen to sign.

_____

**Printed Name of Participant Date*

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Signature of Person Obtaining Consent Date

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Signature of Parent/Legal Guardian Date