PROTOCOL TITLE:

Transcutaneous Auricular Neurostimualtion (tAN) To Mitigate Withdrawal Behaviors In Neonates With Opioid Withdrawal

PRINCIPAL INVESTIGATOR:

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1.0 Objectives / Specific Aims

The overall aim of this proposed effort is to test transcutaneous auricular neurostimulation (tAN) as a therapeutic for opioid withdrawal and neonatal abstinence syndrome (NAS).
We hypothesize that tAN delivered for up to 60 minutes during peak withdrawal (1h before next morphine dose) will be safe, well tolerated and will decrease Finnegan withdrawal scores and shorten the length of morphine treatment compared with historical data.

Aim 1: Determine the safety and feasibility of auricular neurostimulation therapy in neonates with opioid withdrawal or NAS.
We hypothesize that auricular neurostimulation is safe and tolerable in both a single session, and 12-day treatment course. Furthermore, we believe target engagement can be validated by measuring stimulation-induced reductions in heart rate. **Milestone: No adverse events of bradycardia (HR < 80 bpm), worsening of swallowing or feeding, skin irritation, or elevation of Neonatal Infant Pain Scores.**

Aim 2: Demonstrate that auricular neurostimulation therapy in opioid withdrawing or NAS neonates reduces the Finnegan and/or WAT-1 scores from pre- to post-stimulation. We have used ear electrodes for taVNS in a similar stuy (#67997). However, in this prospective, open-label study we will use a novel, non-significant risk auricular neurostimulation device and ear electrodes to study 20 opioid withdrawing or NAS neonates at the Medical University of South Carolina. We aim to show a clinically-meaningful reduction in Finnegan scores, the routine assessment that includes 21 signs of withdrawal (Finnegan 1992). Alternatively, in infants who receive both opioids and benzodiazepine analgesics, we aim to show a clinically-meaningful reduction in Withdrawal Assessment Tool (WAT-1) scores, which is a validated, 11 item/12 point scale used to monitor opioid withdrawal in pediatric patients (Franck 2008). In the study, we will deliver **up to 60 minutes** of tAN **1 hour prior** to each morphine administration, up to **4 times** per day for up to **12 days**. If morphine is weaned off at or before 10 days, a weaning phase for tAN will begin on the following day for 2 days: **tAN Weaning Day 1**: deliver tAN twice **tAN Weaning Day 2:** deliver tAN once We will assess each patient with standard Finnegan scores and/or WAT-1 before and after stimulation, and monitor use of morphine throughout the study. **We expect a 25% reduction in Finnegan/WAT scores from before to after sessions of auricular neurostimulation.**

Drs. Jenkins and Badran have an IRB-approved protocol (#67997) for studying the use of transcutaneous auricular vagus nerve stimulation (taVNS) for improving oromotor function in newborns. In our taVNS protocol we use an ear clip electrode to devlier the stimuatlion, but this electrode has the disadvantage of becoming displaced with head turning, burping etc. Therefore, we propose to use Spark Biomedical company's non-invasive, auricular neurostimulation device in this study to treat opioid withdrawal symptoms of babies with NAS. This device will be placed in the ear (similar to a hearing aid) and will target trigeminal and vagal nerve branches. Stimulation will be delivered transcutaneously via a hydrogel interface similar to the standard EMG and EKG leads we currently use in #67997. This device has proven to be safe across many indications with the only side effect being skin irritation. Spark Biomedical is curenlty working on FDA clearance for adult opioid withdrawal based on predicate devices (K173861, DEN170018). This product will be regulated as a Class II medical device by the FDA.

2.0 Background

NAS is a condition in which infants undergo withdrawal after exposure to prescription or non-prescription opioids such as morphine, methadone or heroin in utero (Finnegan 1992). The withdrawal is characterized by hyperirritability of the central nervous system and respiratory, gastrointestinal, and autonomic symptoms (Finnegan 1992). These symptoms usually appear within 24 to 72 hours after birth. Opioid withdrawal is characterized by CNS dysfunction with loss of glutamate homeostasis, glutathione dysregulation and oxidative stress(McCLure EA e tal, 2014) leading to poor neuronal health and clinical symptoms of hyperirritability, hypertonicity, tremors, high-pitched crying, tachypnea, gastrointestinal symptoms, sweating, temperature elevation, sneezing and nasal congestion, and poor feeding, emesis, and loose stools.

From 2000 to 2012 there was a five-fold increase in the number of babies born with opioid withdrawal due to Neonatal Abstinence Syndrome (NAS, Patrick SW, et al., 2015). It is estimated that one baby is born every 25 minutes addicted to opiates (Patrick, et al. 2012). In 2012, term infants being treated for NAS stayed on average 16.9 days (compared to 2.1 days for other newborns), often in a neonatal intensive care unit (NICU). The length of stay has increased to 25 days in a neonatal intensive care unit (NICU) at an average treatment cost of $66K (Barlow 2017, Sanlorenzo 2018). Hospital costs totaled $1.5 billion, with 81% paid by state Medicaid programs (Patrick, et al. 2015). Despite improved recognition of NAS and early implementation of treatment (both pharmacologic and non-pharmacologic), One of the most important reasons for the difficulty in managing slow withdrawal in neonates is polydrug dependency of the mother, as opiates plus another substance of abuse has become increasingly common (Grim, 2013).

Currently, treatment consists of either morphine or methadone, occasionally in combination with clonidine or phenobarbital, but with inability to truly tailor treatment to the mothers substance(s) of abuse (Bio, et al. 2011; Hudak, et al. 2012). In addition, oral morphine or methadone have unwanted and harmful side effects in the infant (Sublett 2013). Other drugs including clonidine and phenobarbital are also used as adjuncts when needed (Sublett 2013). Iatrogenic opioid dependence is also a problem in sick neonates and infants, 90% of whom require prolonged analgesics for sedation for mechanical ventilation, cardiac procedures, and conditions such as sepsis and pulmonary hypertension (Franck, et al., Pain, 2013). **As opioid withdrawing or NAS babies are already under oxidative stress from opioid withdrawal and/or their undelying condition, a non-pharmacological treatment protocol would greatly benefit these vulnerable patients, potentially decreasing the need for additional drugs and shortening their hospital stay.**

Alternative non-pharmacologic approaches

Auricular acupuncture (Filipelli 2012; Raith 2014) has recently been studied as an adjunctive therapy for NAS newborns. Non-insertive acupuncture (NIA) using traditional needles (Filipelli 2012) or a handheld laser (Raith 2014) was applied to the ear of newborns with NAS resulting in some of the babies becoming more relaxed during their course of treatment. While more in-depth studies are needed to evaluate NIA as an effective adjunct therapy for NAS newborns, the early results show promise of tapping into the auricular neural pathways for treating NAS.

A more controlled, repeatable method of neurostimulation may provide effective treatment for opioid withdrawal in neonates.

Neurostimulation and Opioid Withdrawal. Transcutaneous neural stimulation to treat opioid withdrawal in adults has been studied with promising results (Miranda 2017). In the study, **an FDA-cleared auricular stimulation device** was used to stimulate the areas in the brain involved in fear, pain, and nociception. Clinical opioid withdrawal scale (COWS) scores, which measure the severity of opioid withdrawal (Wesson 2003), were recorded before and after auricular neurostimulation. ***After just 20 minutes of stimulation, the COWS scores were reduced by 60% and by 85% after 60 minutes of stimulation.*** No rescue medications were required. *After 5 days on neurostimulation therapy, patients exhibited 97% reduction in COWS scores.* As a result of this study, the authors concluded that **auricular stimulation is associated with a reduction in opioid withdrawal scores.**

3.0 Intervention to be studied

The Auricular Branch of the Vagus Nerve. The vagus nerve efferently projects to the esophagus, trachea, lungs, heart, pancreas, stomach, intestines; and afferently projects to the nucleus tractus solitarius (NTS) and other brain regions (Frangos 2015). Activation of the NTS plays an important role in modulating cardiopulmonary function (Groves 2005, Sluka 2003, Lilei 2013), neuroplasticity (Porter 2011, Engineer 2011), systemic inflammation (Koopman 2016), and epilepsy (Cutsforth 2017). Recently, several studies examined the function of the auricular branch of the vagus nerve (ABVN), as potential non-invasive method to stimulate the NTS and associated structures. The ABVN is a sensory branch of the vagus nerve and exclusively innervates the outer ear cymba concha region (**Figure 1**). Through anatomical cadaver studies (Peuker 2002), and animal (Gao 2010, Nomura 1984)/human (Frangos 2015) physiological studies, there is clear evidence that the ABVN has direct modulatory projections to the NTS. Thus, the ABVN serves as a non-invasive access point to the brain and central nervous system to deliver information, as similar to the cervical vagus nerve.

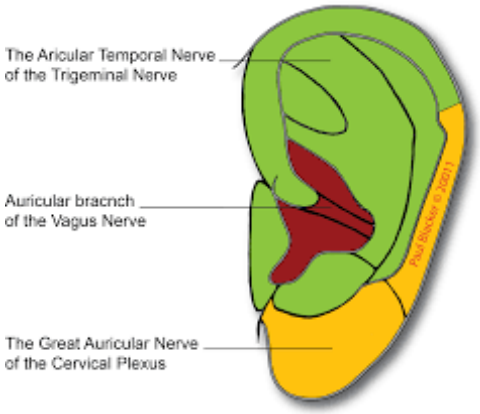


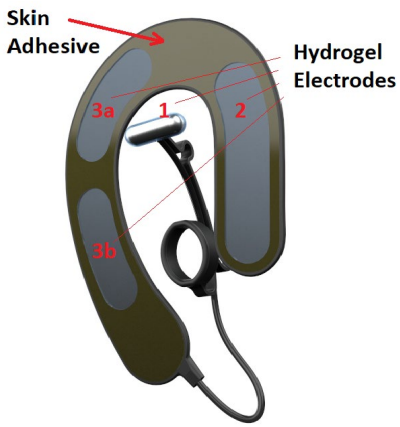
Figure 1: Dermatome representations of sensory nerve innervations of the outer ear. The auricular branch of the vagus nerve innervates 100% of the cymba concha (red region).

Dual nerve stimulation. Sensation of pain is transcended throughout both vagus (Page 2008) and trigenimal (Pecikoza 2018) nerve pathways. While vagus nerve stimulation has been the subject of many studies, trigeminal nerve stimulation is a newer target, particularly for pain treatment and blocking opioid receptors (Abd-Elsayed 2015, Sayegh 2016). Electrical stimulation has been shown to successfully treat adults for opioid withdrawal (Meade 2010, Han 1992) by blocking opioid receptors. We hypothesize that having the ability to stimulate both the vagus nerve and trigeminal nerve, we will be able to saturate opioid receptors and block the effects of withdrawal from opioids such as morphine. **By blocking a significant amount of opioid receptors through stimulating both the vagus and trigeminal nerves, we postulate that transcutaneous auricular neurostimulation (tAN) will enable non-pharmacological treatment of opioid withdrawal.**

Based on evidence that auricular neurostimulation reduces opioid withdrawal severity in adults, our team's experience in an ongoing clinical study of auricular neurostimulation to improve oromotor function in newborns (#67997), we propose to use an auricular neurostimulation device, specifically to fit newborns, to treat opioid withdrawal and NAS patients.

Device Description. The "Roo" (**Figure 2C**) is a non-invasive, battery-operated, prescription device designed to transcutaneously stimulate nerves on and/or around the auricle. Electrical stimulation is delivered through an ergonomically designed Earpiece (**Figure 2A**). The Earpiece is a disposable component that includes a single flexible circuit board with over molded silicone. The Earpiece contains four embedded hydrogel electrodes (**Figure 2B**), for stimulation of the ABVN and auricular temporal branch of trigeminal nerve nerve (ATN). To ensure sufficient skin-contact, the surface surrounding the hydrogel electrodes is covered with a medical grade adhesive. The system includes an External Pulse Generator (EPG, **Figure 2A**) that produces a current-controlled, biphasic stimulation output. The EPG and the Earpiece are connected to each other via a cable. The Roo device is based on the adult Phoenix System, but will fit neoantes and infants.

A



B

C

Figure 2. (A) Phoenix System (adult), External Pulse Generator and Earpiece. (B) Phoenix System, Patient contacting side of the Earpiece. (C) Roo device, fit for infant use.

The earpiece is worn around and inside the ear. The four electrodes are positioned to stimulate three key dermatome regions (Figure 3, below). These regions are adjacent to several cranial nerves (V, VII, IX, X) and occipital nerves. In particular, the electrodes are located in the concha cymba (Figure 3, *Region 1*), on the temporomandibular join region, just anterior to the tragus (Figure 3, *Region 2*), and behind the auricle (Figure 3, *Region 3*).

Initial use. During first use, Dr. Badran will program the device with the study team and set the stimulation intensity to just below the perceptual threshold.

4.0 Study Endpoints

Safety Outcomes: 1) Skin irritation, assessed by staff daily. 2) NIPS pain scores recorded during treatment.
Efficacy Outcomes: 1) Finnegan scores before and after tAN will be recorded at each session or WAT-1 scores will be recorded with hands on care . 2) Duration of morphine weaning. 3) Length of stay
We will also collect data on developmental outcomes from a short motor test in the nursery and from routine clinic visits to the NICU high-risk follow-up clinic up to 24months.

5.0 Inclusion and Exclusion Criteria/ Study Population

Inclusion criteria: Neonates or infants with opioid withdrawal or NAS who have withdrawal scores requiring morphine replacement therapy. They must be clinically stable, on minimal respiratory support (Continuous positive airway pressure (CPAP), nasal cannula, or room air), >33 weeks gestational age at enrollment, and currently receiving replacement therapy for opioid dependence.

Exclusion criteria:

1) Unstable infants or those requiring significant respiratory support.
2) Repeated episodes of autonomic instability (apnea or bradycardia) which are not self-resolving *
3) Infants <33weeks gestation at enrollment.
4) Major unrepaired congenital anomalies
5) Cardiomyopathy

*Preterm infants commonly have short periods of shallow or absent breathing or lower heart rate termed apnea and bradycardia, respectively, and most are being treated for these physiologic manifestations of prematurity with caffeine, an effective central stimulant. Infants are on cardiorespiratory monitors through the nursery stay with recording devices to capture events and play them back. However, nearly all of these events are self resolving, meaning the infant resolves the breathing pause or bradycardia on their own. Infants who require repeated episodes of stimulation to come out of these events are defined as *unstable*. Similarly, infants on significant respiratory support are not stable, and will not be eligible.

Stable neonates who are dependent on opioids, such as after ECMO, severe illness or brain injury, will be included in this study, as these neonates represent a population in which tAN could minimize withdrawal while not adding to burden of pharmacotherapies. Congenital syndromes may be included if the infants do not have major, unrepaired anomalies.

6.0 Number of Subjects

Total Planned Enrollment: 20

Up to twenty neonates will be enrolled in this prospective, open-label safety and feasibility trial. The experimental paradigm consists of up to 60 minutes of tAN at the peak withdrawal time 1 hour before usual morphine dose every 3h, before feeding, up to 4 times per day, and up to 12 days or until morphine is weaned off. If morphine is weaned off at or before 10 days, a weaning phase for tAN will begin on the following day for 2 days:

- tAN Weaning Day 1: deliver tAN twice
- tAN Weaning Day 2: deliver tAN once

All consented participants will receive the active stimulation condition.

7.0 Setting

This study will be conducted in the neonatal intensive care nurseries at MUSC.

8.0 Recruitment Methods

Prospective participants will be identified by Dr. Jenkins at the neonatal intensive care units (Level II and III), and checked for potential inclusion. Clinical teams will mention the study to parents and refer them to Dr. Jenkins if they are interested in participating.

9.0 Consent Process

Dr. Jenkins will approach parents of stable infants in the nursery who meet inclusion criteria, for participation in the study, using the IRB approved consent form. Electronic Consent will be used for situations when the parent (or Legally Authorized Representative) is at another hospital and cannot travel to MUSC to provide consent in person. We will use the approved REDcap system to obtain consent. Dr. Jenkins or other approved study personnel will go over the entire consent document on the phone with

the parent to ensure comprehension and to confirm identity. Parent will be given a copy of the completed, signed consent form in person or by email or fax.

10.0 Study Design / Methods

After obtaining consent and describing this procedure to the parents and all members of the baby's care team, we will first deliver stimulation per our protocol in #67997 to determine the perceptual threshold. We will use the identical method for determining the intensity for PT, which has proven to be safe as in our taVNS study in infant feeding. We will start with 0.2mA with a 250μs, 5Hz in vagus and 100Hz in trigeminal nerve area, and gradually increase the intensity of the TENS unit until the baby can first feel something in their ear. We will use the facial expression change, fidgety movements to determine when the infants feel the stimulation, as in the taVNS study. This intensity will be recorded as the **perceptual sensory threshold (PT)**. The procedure is detailed below.

Determination of Perceptual Threshold

1. Electrode clip will be placed on the left tragus in an enrolled infant at rest. Starting at 0.2mA at 5Hz in vagus and 100Hz in trigeminal nerve area, we will deliver 5 seconds of pulses, and increase by 0.1mA until the perceptual threshold is achieved by observation of the infant's facial expression, fidgety movements. This will be termed the perceptual threshold.
2. We will decrease the microcurrent by ~0.1mA *below the perceptual threshold* and administer this as the taVNS treatment dose 1h before the morphine dose and before the infant is feeding, every 3h, for 60 minutes, up to 4 times per day. Current will then be held constant while pulse width and frequency will be set at 250μs and 5Hz in vagus area and 100Hz in trigeminal nerve area, respectively.
3. Finnegan scores will be rated before and immediately after the taVNS treatment, and per usual clinical protocol. WAT-1 scores will also be rated during tAN treatment per usual clinical protocol.
4. Physiological data will be monitored continuously as measured by the echocardiogram (ECG).
5. Neonatal Infant Pain Scale (NIPS) data collected at beginning and the end of treatment session. The NIPS rating scale currently in use in the nursery is included in this submission.

taVNS Protocol

These studies will be conducted in the Shawn Jenkins Children's Hospital's Neonatal Intensive Care Unit (NICU).

Participants will receive tAN stimulation to their left ear via electrodes attached to the ear. The stimulation intensity we will use for tAN will be ~0.1mA less than PT or each infant. We will recalibrate the PT daily, and then deliver that current intensity for each session that day administered every 3h, starting 1h before the morphine dose. The current will be on for 5 minutes, off for 10 seconds, for up to 60 minutes total each session, up to 4 times per day, for up to 12 days or until morphine is weaned off. If morphine is weaned off at or before 10 days, a weaning phase for tAN will begin on the following day for 2 days. tAN Weaning Day 1: deliver tAN twice. tAN Weaning Day 2: deliver tAN once.

The nurses will score the NAS using the Finnegan scale before and after the treatment. The Withdrawal Assessment Tool (WAT-1) will also be used to assess infant withdrawal symptoms before and after treatment in infants receiving benzodiazepines and opioids (Franck 2008, 2013). The WAT-1 is an 11 item/12 point scale to monitor withdrawal and is routinely performed by nurses 3 times per 12 hour shift with hands on care.

Prior to beginning the study, Drs. Jenkins and Badran will perform an in-depth in service with the charge nurses of the neonatal nurseries, a limited pool of 10 nurses. They will also in-service the neonatal nurses at their staff meetings to introduce them to the study, the rationale, the protocol and the equipment. Most nurses are familiar with ear electrode stimulation from the taVNS-paired feeding study conducted over the past 18 months.

A short developmental test, the STEP, will be performed while the infant is stil in the nursery and at the first neonatal high-risk developmental clinic (outpatient) follow-up visit.

Safety Monitoring

Prior to determination of the daily sensory threshold of the infant by the study coordinator or research assistant, an initial pain level will be recorded using the NIPS. The nurse or other staff may decrease the current intensity or stop stimulation entirely if the infant shows signs of distress or an increase in NIPS score >3 above baseline. As opioid withdrawing infants frequently have higher NIPS, we will only halt or adjust stimulation if the NIPS is 3 greater than their baseline. The nursing staff routinely measure and record the NIPS throughout the day. We will monitor the relationship of increased NIPS scores to the up to 60 minute stimulation period daily.

Switching from left to right ear in case of left ear difficulties
Skin redness at the site of tAN attachment to the ear is possible after treatment, but is expected to be transient. In order to prevent injury to the skin in contact with the device, each day the left ear will be first examined for redness or other medical device placement prior to attaching the tAN earpiece. If there is skin redness or any emergent medical needs at the site of attachment to the ear prior to each day's treatment, we will switch the site of stimulation to the right ear until redness or emergent medical needs on left ear are resolved.

Estimated Difficulties, Limitations and Time Frames

Estimated Difficulties: Many of the initial difficulties surrounding taVNS in humans, such as feasibility, were accomplished in the taVNS-feeding pilot trial at MUSC by Jenkins and Badran that were approved by IRB 1. Electrode placement: The ear electrode is easy to fit to the infant's ear and much less likely to become dislodged due to head movement than the ear electrodes used in our taVNS infant feeding study. However, we will make sure the staff feel comfortable placing the electrodes and be on call to assist with electrode placement as needed for night shift nurses. The program will be either on or off switch for nurses to activate, but will have ability to decrease stimulation current as needed.

Limitations: Finnegan scores may not show a difference acutely with tAN treatment, but may lead to faster morphine weaning. However, this is not a randomized study, and we will not be able to determine if this is significant, as it will have to be compared with historical control data already collected and analyzed in Pro # 63667. Nevertheless, we will show feasibility and safety, and gather data for a larger randomized study.
Estimated Time Frames. We plan on completing enrollment in this study over a 6-12 month period.

12.0 Data Management

Limited demographic and personal health history data will be collected for the study. All screening data will be identified only by study number except for the consent form and a master enrollment file, which will be kept in a binder a the locked office, and password protected, respectively, per the requirements of the IRB.

All infants will be withdrawing from opioids, and will have had urine or meconium drug screens per clinical protocol. Also all fetal drug exposures will be a matter of clinical record, and not obtained for this study. We will not be doing any drug screening for this study. Study records will be kept confidential. However, as we will only have substance use information which is included in the clinical record and already known/reported to social services, we will not obtain a certificate of confidentiality.

Power Calculation: N/A. This is a convenience sample. We estimate we can enroll up to 20 patients within 12 months.
Statstical Analysis: tAN Finnegan scores obtained before and after will be compared within subjects by paired test.

13.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

Drs. Jenkins and Badran will ensure confidentiality of the subject data, monitor and review adverse events, and minimize possible risks associated with tAN procedures.

Regarding informed consent, participants are fully advised on the research procedures to be used, the amount of time required of them, the possible risks and benefits of the procedures, their right to refuse participation in the study without prejudice, their right to terminate participation at any moment without prejudice, and the name and telephone number of the principal investigator. All subjects will be required to have capacity to consent.

Regarding confidentiality, subjects are informed that the information they provide will be kept strictly confidential, with access limited to the research staff. Participation in the study will be treated as confidential, as will all records. The identity of subjects will be protected with alphanumeric codes. All data will be kept in locked file cabinets or in password-protected files on secure servers with access by study team members only.

Spark biomedical personnel will receive de-identified patient data via our clinical trial agreement under the SBIR. Spark biomedical personnel may review identified patient data on site visits.

We do not anticipate any adverse events to occur in this study, however the experienced research team has a long standing record of recording and reporting unanticipated adverse events to the IRB.

14. Withdrawal of Subjects

If any parent wishes to withdraw their infant from treatment, we will immediately terminate the tAN sessions, but still continue to collect information on the morphine dosing and length of stay. If a parent wishes to withdraw from the study entirely, then no further data will be collected on the patient, but safety and treatment data up to that point will be retained under deidentified study number.

15.0 Risks to Subjects

tAN is another form of taVNS using transcutaneous electrical nerve stimulation (TENS) of the auricular branches of the vagus and trigeminal nerves that innervate the ear. Although this novel therapeutic modality is still in the development and optimization process, risks are a combination of those to be expected by both the peripheral TENS and taVNS, which has been safely used in neonates and infants at MUSC by the study team: Heart rate decrease, discomfort and skin irritation.

Theoretical risks associated with neuromodulation of the parasympathetic nervous system via taVNS would also be applicable in the administration of noninvasive tNS, including reduction of heart rate. In the taVNS study we observe a transient 10% decrease of baseline HR with onset of stimulation and rapid rebound within 60 seconds. We have seen no epsidsodes of bradycardia related to taVNS stimulation and expect none in this protocol.

TENS devices are FDA approved for pain relief and are available over the counter. The main risks associated with TENS is that stimulation may result in discomfort. The unit used in this studies is an FDA 510(k) cleared electrical stimulator that meets the rigorous electrical standards of the FDA. Skin irritation, redness, or inflammation may occur under the stimulating electrodes if TENS current is delivered for a prolonged period of time, but is not expected with up to 60 minutes of stimulation, similar to the duration of taVNS in protocol #67997.

Given the minimal risk both of these already FDA approved methods, we expect tAN like taVNS, will be a very safe procedure.

Risk of loss of confidentiality: We will assign study numbers to each participant, keep CRF and consent forms in locked cabinets in locked offices. Database files with names and contact information will be password protected and stored on the MUSC Pediatric server. All other data files related to this study will be identified by participant number only, without link to standard identifiers. We will publish the aggregate data only.

Unknown Risks: TENS stimulation of peripheral nerves is FDA approved and is considered very safe. Although tAN is essentially TENS on the ear, it is still an experimental procedure that has not been approved by the FDA to improve outcome of infants with opioid withdrawa symptoms. Therefore, there may be risks and discomforts that we are not aware of.

16.0 Potential Benefits to Subjects or Others

tAN delivered at the peak time of withdrawal between doses of morphine may decrease behavioral scores on the Finnegan scale, and enable faster weaning of morphine or adjunctive medications and possibly earlier discharge from hospital. The treatment could potentially help avoid escalation

of morphine doses. tAN may also decrease scores on the WAT-1 scale. However, there may be no direct benefit to the participant, but we will gain knowledge about tAN in infants, and this information may help develop strategies to improve treatment of opioid withdrawal and NAS.

17. Sharing of results with subjects: Individual study results will be known to parents and care providers, as this is an open label study. Overall study results will not be shared with subjects unless they request it.

18.0 Drugs or Devices

The electrode and TENS device will be stored in Dr Jenkins' office, the Research Clinical Trial lab at Shawn Jenkins Children's Hospital or the Brain Stimulation Laboratory, and brought to the bedside of enrolled subjects. Charge nurses and staff will be inserviced on use of the TENs unit, and the study team, Dr. Jenkins or Dr Badran will be available for questions about use of the device.

This non significant risk device, similar to taVNS used in Pro # 67997, 89851, 73767, and 86291.

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