

COVER PAGE**Title of project: Auricular Neurostimulation for Cyclic Vomiting Syndrome****NCT #: 03434652****Document date: 02.07.2020**

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STUDY TITLE: Efficacy of Auricular Neurostimulation for Children and Adults with Cyclic Vomiting Syndrome: A Pilot Study

A. PURPOSE OF THE STUDY

Functional gastrointestinal disorders (FGIDs) affect a large percentage of children and negatively impact quality of life.¹ Cyclic vomiting syndrome (CVS) is an FGID characterized by relentless episodes of vomiting followed by return to baseline health.² Majority (80%) of children and adults with CVS have concurrent severe abdominal pain and migraine-features, rendering them incapacitated throughout the emetic cycle.^{3,4} In many children, CVS evolves into migraine headaches during teenage years or adulthood. Although the etiology is still obscure, CVS is considered a migraine-equivalent disorder.

There are very few targeted treatment options for FGIDs including CVS. Empiric prophylactic therapy with tricyclic antidepressants is standard³ to attempt reducing the number of episodes but these drugs are fraught with side effects. The frequency of emergency department use for patients with CVS is extremely high and the syndrome has an immense impact on health-related quality of life.⁵ Therapies for FGIDs represent a considerable unmet need in modern gastroenterology (GI) practice and a recent systematic review concluded that there is no evidence to support pharmacologic therapy for FGIDs due to lack of high quality studies.⁶

Nausea, vomiting and gastrointestinal pain is modulated by the vagus nerve.⁷ The vagus nerve is an important regulator of the autonomic nervous system (ANS) and conveys visceral sensory information about the GI tract to the central nervous system (CNS). The major role of the vagal neurocircuitry in the generation of nausea and vomiting is well established.^{7,8} Many studies indicate that vagal nerve stimulation (VNS) activates CNS pain modulation mechanisms and provides analgesia.^{9,10} There is emerging consensus that CVS involves dysregulated central neural pathways and neuro-endocrine mediators involving the pathways for nausea and vomiting. CVS is also considered a migraine equivalent based on the symptom pattern, response to antimigraine therapies and evolution to migraine headaches. Although exact mechanisms of migraines remain unknown, stress-triggered sensitization of the trigeminovascular complex and autonomic imbalance with release of inflammatory neuropeptides are central.^{11,12} Calcitonin gene-related peptide (CGRP) released from trigeminal afferents during migraine attacks evokes anxiety responses in animals and is a novel, FDA-approved therapeutic agent for migraines.¹³ Transcutaneous VNS of the auricular branch of the vagal nerve in the ear has emerged as a non-invasive alternative to implantable VNS. We have recently demonstrated safety and efficacy of a newly developed *percutaneous* auricular neurostimulation device in children with pain-associated FGIDs compared to a sham device (randomized, controlled trial).¹⁴ Notably, vagal tone as measured by heart rate variability testing increased significantly in the treatment group compared to sham. Many patients had concurrent improvement in nausea and migraine symptoms. Auricular neurostimulation likely modulates the vagus via the trigeminal pathway that extends from the external ear to the brainstem, influencing trigeminal sensory complex excitation and connectivity with arousal/autonomic circuits. The aim of this project is to investigate the role of non-invasive neurostimulation in CVS with concurrent abdominal pain and correlate response with changes in vagal tone and CGRP levels. This study may provide a potential novel and non-invasive therapy for a debilitating and prevalent disorder with few established treatment options. It may also further our understanding of the mechanisms involved in auricular neurostimulation therapy.

B. SPECIFIC AIMS / HYPOTHESIS

Specific aim #1: Demonstrate that auricular neurostimulation prevents cyclic vomiting/abdominal migraine episodes when applied in the prodromal phase and/or as prophylactic therapy.

Hypothesis: Auricular neurostimulation will result in an overall reduction in the frequency of emesis, nausea and abdominal pain and a reduction in the severity of abdominal pain, emesis and nausea during episodes compared to baseline and sham therapy.

Specific aim #2: Compare measures of functional disability, quality of life and psychological health in children and adults with cyclic vomiting syndrome before and after auricular neurostimulation therapy.

Hypothesis: Auricular neurostimulation will improve overall functional disability, anxiety and quality of life by reducing emesis and pain episodes compared to baseline and sham therapy.

Specific aim #3: Compare heart rate variability measures as surrogate of vagal tone and trigeminovascular excitation via CGRP measurements before and after auricular neurostimulation therapy.

Hypothesis: Auricular neurostimulation will improve vagal tone and CGRP levels compared to baseline and sham therapy.

C. BACKGROUND, SIGNIFICANCE, AND RATIONALE

Cyclic vomiting syndrome is a functional GI disorder characterized by severe, stereotypical and disabling episodes of intense nausea and vomiting, lasting anywhere from 1 to 10 days.³ The disorder is more prevalent than commonly recognized, estimated to occur in 1.9% of children.^{15,16} While initially thought to be a pediatric disorder, it is as common in adults.¹⁷ This is more common than the prevalence of celiac disease and comparable to the prevalence of pediatric inflammatory bowel disease in the state of Wisconsin. The medical costs for the diagnosis and treatment of CVS are immense. In 1999, the costs of care for children with CVS was and estimated \$17, 035 annually per child.¹⁸ The costs of just hospitalizations due to CVS in adults is staggering and a total of \$400 million over 2 years was incurred due to hospitalizations alone.¹⁸ This did not include the cost of investigations and indirect costs from work days lost. Quality of life is markedly affected and worse in children and adults with CVS compared to those with IBS and healthy controls.¹⁹ In adulthood, one third are disabled by the disorder and suffer significant psychosocial problems including job loss and divorce.²⁰

About 80% of patients with CVS suffer from concurrent migraine headaches or abdominal migraines during the episodes.³ In fact, abdominal pain is a prominent feature of CVS episodes and precipitates vomiting in many cases. Therapies are therefore targeted both towards nausea and vomiting as well as aggressive pain control. If episodes occur frequently, both abortive (rescue) and prophylactic (preventive) therapies are considered as per standard of care and recommendations by consensus statement guidelines.³ Safe and effective treatments for children and with CVS are needed. Currently, there are no FDA approved drugs for the treatment of CVS in children and little evidence of success for any medication. Prophylactic therapies are empiric and response is often variable with numerous patients still requiring emergency room visits or hospital admissions.¹⁸ One of the most commonly used preventive treatments in the clinical setting is amitriptyline, a tricyclic antidepressant (TCA) that is used “off-label” similar to all other drugs used for CVS.³ Most patients receive a daily prophylactic medication such as a TCA but still require frequent hospital admits for severe and drug-refractory episodes. These patients receive high doses of intravenous anti-emetics along with anxiolytics, sedatives and pain-control including opiates while in the hospital. Chronic or frequent opiate use is seen in a subset of adults with CVS

and is associated with non-response to therapy along with risks of dependence and even addiction in some patients. Some even require anesthesia in the intensive care unit for drug-refractory CVS.²¹ Many of these therapies may involve serious side effects with TCAs being discontinued in 25% of adults due to intolerable side effects.

Strong migraine features, including headaches, pallor, photophobia and nausea are characteristic of CVS episodes. CVS is considered a migraine related or migraine-equivalent disorder based on clinical similarities, a high family prevalence of migraines, effectiveness of anti-migraine therapy and the recent discovery of mitochondrial DNA polymorphisms in CVS and migraine patients.^{3,22,23} Therapies for CVS such as amitriptyline is also a standard migraine prophylaxis therapy.²⁴ The etiology of CVS is yet unclear but there is emerging consensus of altered brain-gut neurocircuitry and autonomic imbalance.²⁵ There is some evidence for an altered brain response to visceral and emotional stimuli.^{25,26} An altered hypothalamic-pituitary-adrenal (HPA) axis is one proposed mechanism based on a few studies.^{27,28} Typical CVS episodes are often triggered by stress states, whether physical or psychological. Stress may thus initiate the vomiting cascade in susceptible individuals (perhaps with underlying migraines, autonomic imbalance or mitochondrial defect). Similar triggers initiate migraine headaches and the pathophysiology of migraines is also not completely understood. The trigemino-cervical system, brainstem nuclei and pain modulation pathways are thought to play key roles.²⁹⁻³¹ Migraine is thought to be activated by excitation of trigeminal afferents that innervate the dural vasculature and converge centrally in the trigeminocervical complex (TCC).^{11,12,32} With its close connectivity to brainstem nuclei such as the nucleus tractus solitarius (NTS) and higher brain centers, TCC activation causes release of inflammatory neuropeptides and stereotypical symptoms.^{33,34} Calcitonin gene-related peptide (CGRP) is a novel therapeutic target and key neuropeptide in migraine pathophysiology.¹³ Blood levels of CGRP are elevated during migraine attacks³⁵⁻³⁸ and migraineurs as opposed to healthy controls develop migraine headache with CGRP infusion.³⁹⁻⁴¹ CGRP levels are also elevated at baseline in chronic migraine patients compared to healthy.^{42,43} Moreover, novel CGRP receptor antagonists are effective in alleviating symptoms.^{44,45} These and antimigraine drugs such as triptans modulate activity of the TCC.⁴⁶⁻⁴⁹ Triptans are one of very few drugs that may abort CVS episodes.^{50,51} Interestingly, animal data also support anxiogenic effects of CGRP released from the bed nucleus of the stria terminalis, a limbic area closely connected to the amygdala and involved in stress, anxiety and fears.⁵²⁻⁵⁵ These same neurocircuits are thought to be involved in CVS.⁵⁶⁻⁵⁹ Stress or arousal may thus trigger TCC excitation, CGRP release and the migraine/emetic cascade (Fig. 2).^{60,61}

Autonomic abnormalities are documented in both children and adults with CVS and migraines alike.^{25, 62-64} These features suggest that central mechanisms are key in CVS patients with migraine features.

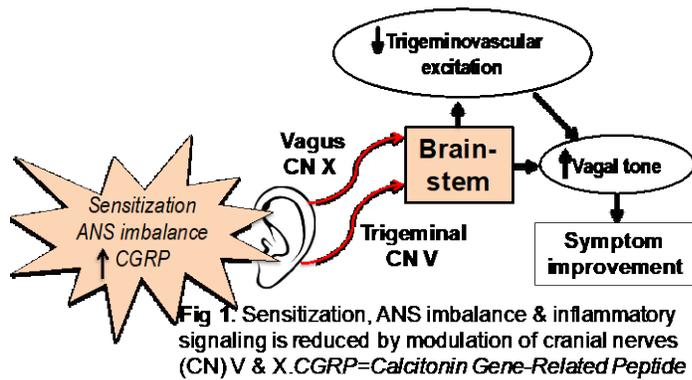


Fig 1. Sensitization, ANS imbalance & inflammatory signaling is reduced by modulation of cranial nerves (CN)V & X. CGRP=Calcitonin Gene-Related Peptide

station is the brainstem NTS. The NTS integrates afferent inputs from the vagus and trigeminal nerves and project to higher brain regions such as limbic regions (amygdala, hypothalamus) involved in arousal and *central autonomic control* (Fig 1). These regions also control the behavioral and emotional response to visceral sensations. Autonomic imbalance in adolescents is linked to reduced vagal baroreflex response and heart rate variability (HRV).⁶⁶ HRV is a measure of cardiac autonomic outflow via baroreceptors.⁶⁶ A study of adolescent FGID with nausea showed decreased HRV, suggesting low vagal modulation of the heart.⁶⁷ Low vagal (parasympathetic) tone is also demonstrated in several FGIDs including CVS.⁶⁸⁻⁷⁰ Cranial nerves IX and X may link ANS dysregulation with nausea and vomiting and the involvement of higher brain regions. The ANS hence plays a key role in both central afferent input and likely the output signals for vomiting

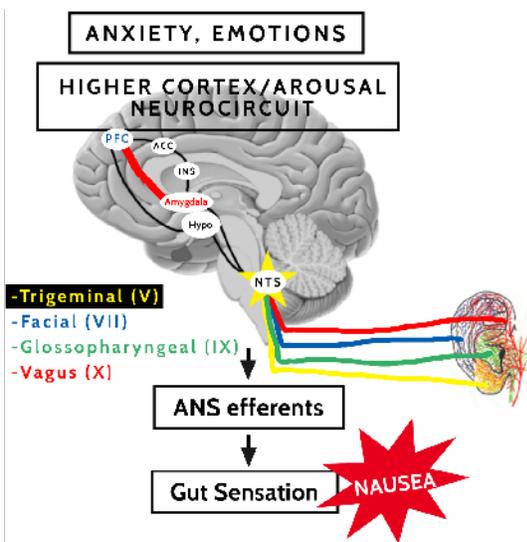


Fig 2. Central projections of 4 cranial nerves converging in brainstem NTS and modulated by auricular stimulation. Hypo=Hypothalamus; INS=Insula; ACC=Anterior Cingulate Cortex; PFC=PreFrontal Cortex

The sympathetic and parasympathetic (vagus) branches of the autonomic nervous system (ANS) connect with the enteric nervous system to modulate GI function and sensation.⁶⁵ The ANS plays an important role in the responses to various emetic stimuli. It is well known that a series of brainstem nuclei receive vagal and sympathetic afferent input during emesis.^{7,25} Output neurons then signal the stereotypical vomiting response. A central emetic relay

through vagal and sympathetic signals. There is ample data that anxiety is highly prevalent in CVS and a known trigger of episode.^{3,71,72} Stress and sympathetic nervous system activity may thus contribute to initiation of vomiting in CVS patients and therapy via vagal modulation may alter these signals and prevent episodes.

The implantable vagal nerve stimulator (VNS) is approved for epilepsy and depression. It also has demonstrated anti-nociceptive effects by inhibition of sensory neurons in the brainstem based on animal models.^{73,74} In humans, VNS also reduces anxiety, improves pain and migraine headaches and has mood and memory-enhancing properties.⁷⁵⁻⁸⁰ Unfortunately, the implantable VNS is highly invasive. Our group has recently demonstrated efficacy of percutaneous auricular neurostimulation with a novel, non-invasive device [Electroauricular device (EAD), Innovative

Health Solutions, IN, USA] in adolescent FGIDs.¹⁴ This randomized, double blind, sham-controlled trial of 115 adolescents with FGIDs showed significant reduction in weekly pain scores ($p=0.003$), global symptoms ($p\leq 0.001$) and disability ($p=0.01$) compared to sham after only three weeks of therapy with sustained effects several months later ($p=0.018$). Effects are likely improved by a field stimulation effects (aka percutaneous electrical nerve field stimulator=PENFS) of the entire ear with resulting stimulation of several cranial nerves (V, VII, IX) in addition to the vagus (X). The cyma concha region of the external ear receives 100% of the afferent auricular vagal nerve distribution.⁸¹ HRV measures showed improvement in vagal tone as measured by RMSSD (root mean square of successive differences) (mean \pm SD) from pre (40.9 ± 25.9) to post (68.1 ± 47.9) in standing position ($p<0.0001$) with no change in sham (Fig 3). The standing heart rate in the treatment group was also significantly reduced from pre (83 ± 15) to post (76 ± 13) ($p=0.011$) in the treatment group which was not seen in sham. This suggests strengthening of the

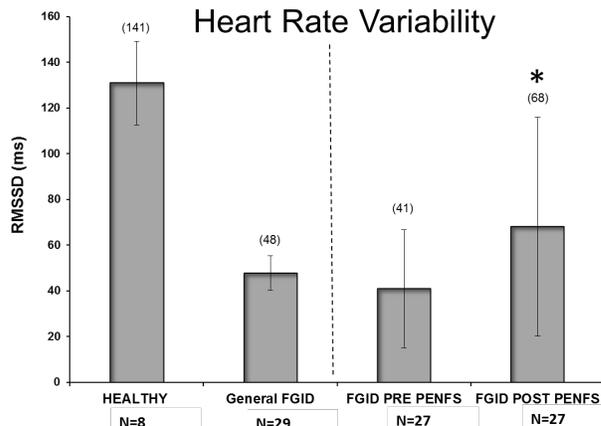


Fig 3. Left: RMSSD (vagal tone) value in healthy control vs general FGIDs. Right: PENFS (percutaneous electrical nerve field stimulation) therapy in FGID subset shows increase in vagal tone from baseline (pre) after only 3 weeks of therapy (post) ($p \leq 0.0001$).

baroreceptor stress response and vagal nerve stimulation effects with this therapy. Many had improvement in concurrent nausea, vomiting and migraine symptoms but their exact phenotype is unclear. In a small subset with improved nausea, three weeks of therapy increased vagal tone compared to baseline ($p \leq 0.01$). Further, in a rat model of post-inflammatory hyperalgesia our group has shown that this device reduces firing of amygdala and spinal neurons by approximately 50% and attenuates visceral hyperalgesia.⁸² A recent study also demonstrated that the same device

reduces symptoms of opioid withdrawal up to 97% after only 5 days of therapy.⁸³ Alterations in limbic pathways and ANS balance appears to be a common link between the state of chronic pain and opioid dependence and could explain these effects.⁸⁴ Auricular neurostimulation may thus modulate ANS balance and improve symptoms in CVS and abdominal migraines by strengthening vagal tone.



The ear is an ideal target for non-invasive vagal neurostimulation for patients with centrally mediated nausea, vomiting and pain due to the presumed sympathovagal imbalance. **We therefore propose a pilot study to investigate the effects of auricular neurostimulation in children and adults with cyclic vomiting syndrome and abdominal pain/abdominal migraines.** We will investigate the effects of auricular neurostimulation on emesis frequency, pain, functioning and quality of life in patients migraine-associated CVS.

Fig 4. Auricular neurostimulation with EAD.

D. DESIGN AND METHODS

Experimental design

This is a prospective trial to evaluate:

1. The efficacy of percutaneous auricular neurostimulation in reducing emesis episodes in children and adults with CVS.
2. Improvement in pain, nausea, daily functioning, anxiety and quality of life in patients with migraine-related CVS pre vs. post auricular neurostimulation.

Equitable subject selection, inclusion and exclusion criteria

- Children aged 6-17 years, presenting to the Pediatric Gastroenterology Clinic at the Children's Hospital of Wisconsin (CHW) and who meet criteria for CVS based on the 2016 Pediatric Rome IV Criteria for FGIDs²
- Adults ages 18-65, presenting to the Gastroenterology Clinic at Froedtert Hospital and who meet criteria for CVS based on adult Rome IV criteria.

- All patients in the rescue therapy arm will meet the following inclusion criteria: 1) suffer from concurrent episodic abdominal pain, 2) either suffer from “calendar-timed” CVS with predictable episodes every few weeks and/or have prodromal signs (nausea, pallor, pain, fatigue, irritability etc) for minimum 12-24 hours prior to symptom onset that is predictive of episode, 3) English-speaking, 4) lack other explanation for vomiting; and 5) willing to participate and consent to this study (for children, have a parent willing to participate).

In addition to above inclusion criteria, all patients in the prophylactic therapy arm will meet the following criteria: 1) child ages 6-18 years, 2) suffer from recurrent vomiting and pain episodes minimum every 4-5 weeks, 3) no need for predictable episodes and/or 12-24 hours of prodromal signs.

- A subset of 10-15 children or adult subjects in the rescue arm who consent to it will be enrolled in a sub-study to measure serum samples for CGRP (calcitonin gene-related peptide).

Medically complex children or those who take a medication or suffer from a disease that can explain symptoms will be excluded from participation in the study. Adult subjects, children or their parents who have significant developmental delay, will be excluded due to difficulties in accurately completing the questionnaires and assessing symptoms. By definition, all participants in this study will have no clear explanation for their symptoms after undergoing medical workup per standard of care. Patients with findings of organic disease such as intestinal malrotation, peptic ulcer disease, H.pylori gastritis, celiac disease, inflammatory bowel disease, allergic disorders, hydronephrosis, metabolic disorder or any other chronic condition or medication that may cause episodic pain and/or vomiting will be excluded from the study. Patients who are treated with a new drug affecting the central nervous system in the week prior to enrollment will also be excluded. Patients must have an intact external ear that is free of infection or severe dermatological conditions, have stable vital signs for their respective age and no currently implanted electrical device. Other exclusion criteria in adults (adolescents as applicable) will include: 1) pregnancy (evaluating MD screens patients as they normally would during a clinic visit (by questioning) and would only perform urine pregnancy test if clinically indicated (absence of menstrual period or other symptoms concerning for pregnancy) 2) severe cardiopulmonary diseases such as chronic obstructive pulmonary disease (COPD) or coronary artery disease and 3) current chronic marijuana use defined as marijuana use > 4 times a week over the last 6 months prior to study enrollment.

The research team will not be surveying marijuana use. Most GI physicians will ask about marijuana use when evaluating teenagers and adults with CVS as the reported use in adult CVS patients is very high. If regular marijuana use is disclosed at the time of clinic visit, that patient would not be approached for inclusion in the study per study exclusion criteria.

Subjects with a diagnosis of a concurrent anxiety or autonomic disorder will not be excluded.

Subject recruitment and enrollment

Subjects presenting to the GI clinics at CHW and Froedtert Hospital with complaints concerning for cyclic vomiting syndrome and concurrent abdominal pain will be identified by evaluating GI physician and will be approached for inclusion in the study if they meet criteria for CVS. The Principal investigator, a co-investigator or research coordinator will introduce the study to patients seen in the CHW or Froedtert GI Clinic during their regularly scheduled clinic visit. Research coordinators, the Principal investigator or a co-investigator will explain the details and purpose of the study during an informed consent discussion and obtain consent and assent. Once the patient and caregivers had enough time to consider participation, understand all of the risks and benefits and would like to participate, they will sign informed consent and HIPAA documents. With several potential participants traveling from across the country, the study team would also like the option to consent patients over the phone.

Subjects will undergo medical workup per standard of care. Subjects refractory to current medical therapy may be enrolled without changes to their current medical treatment within the past two weeks. No new pharmacological agents will be added during the study period unless clinically indicated and no changes in dosing or scheduling of current therapy will be allowed during the study period. Subjects will be asked to not use any as needed anti-emetic or pain medications during the study. To participate in the study, patients must be able to verbalize their condition and concerns about nausea, vomiting, pain and other symptoms. Subjects will be screened by RNs from the Pediatric Translation Unit (pTRU) at all visits for any side effects. Subjects will be asked to notify the PI or research team with any worsening in symptoms or side effects of therapy. Any subject without improvement in symptoms during the study will be able to discontinue the study. If symptoms worsen or fail to improve during the study or if their clinical presentation changes in any way, subjects will have the option to drop out any time, receive standard medical therapy and appropriate referrals. If per standard of care, a subject requires a change in one or several of their regular medications during the study, they will be asked to notify the research team. To monitor this, the subjects will be inquired about their medication list and doses at each visit. Their medical record at CHW or Froedtert Hospital will be reviewed as well. If the medication change is determined to potentially affect the study results, the subject may be excluded from further study as determined by the PI. Subjects will also be asked if they wore the device for all five days.

Subjects will undergo diagnostic testing as clinically indicated per standard of care. This may include but is not limited to upper endoscopy, upper GI contrast study, renal ultrasound, brain imaging, 4-hour solid-phase gastric emptying scan, metabolic workup, stool studies and screening blood work. Subjects with positive testing for any organic condition will be excluded from further study and treated per standard of care.

After consent and assent is obtained, the standard-of-care clinic procedures and research questionnaires will be performed. Information on demographics, medical history, symptoms, treatment and diagnostic workup will be collected by physician as part of the initial clinic visit. Participants in the rescue arm will complete the attached baseline questionnaires (see Table 1). These will take about 15 minutes to complete (see attached and explanations below). Patients in the rescue arm will return to the pTRU on a separate day during the prodromal phase prior to episode onset or 1-3 days prior to predicted CVS episode if “calendar-timed” for placement of the ear neurostimulator (Table 1; Visit #1). Patients with “calendar-timed” CVS will be primary targets for the study as their episodes occur on same day each month (many triggered by menstrual periods). Patients in the prophylactic arm will be return to the pTRU to start therapy within a few weeks of enrollment. They will complete most of the same instruments in addition to the Abdominal Pain Index (API) and Nausea Severity Scale (NSS) on a weekly basis (see Table 2 for instruments and timing of completion).

During each week of neurostimulation therapy, subjects will complete daily vomiting, nausea and pain surveys (INVR, BARF and numeric pain scale; attached). These questionnaires would either be answered on paper or iPad in a REDCap database. At the end of the week (day 5 +/- 2 days due to possible coinciding with weekend), subjects in the rescue arm will return to the pTRU for HRV measurement (Visit #2) and completion of questionnaires (per Table 1). Paper copies of the Daily Diaries will be sent home with participants or participants can opt to have the REDCap link emailed to them. These emails do not contain any PHI. If patients received paper measures, then they are asked to mail them back to the study team or bring them back to their next study visit. When subjects in the rescue arm return for the second week of therapy (Visit #3), they will complete questionnaires as outlined in Table 1. Each week, the subject will wear the neurostimulator for 5 days and then remove it in the home setting or in the pTRU if they return on day 5. At Visits #2 and #4, patients in the rescue arm will be asked if they had to use their rescue

medication during the previous placement and if they believe they have a real or sham device.

Technical details

Subjects will prospectively complete the following questionnaires at different time points during the study (see Tables 1 and 2 for timeline):

1. Demographics: a brief demographic questionnaire will be completed by a member of the research team (see attached).
2. Rome IV Diagnostic Questionnaire on Pediatric and Adult Functional Gastrointestinal Disorders: clinical classification into Rome IV CVS criteria (pediatric and adult)⁸⁴
3. Rhodes Index of Nausea, Vomiting and Retching (INVR): validated short, 8-item scale to assess severity of nausea, vomiting and retching symptoms daily (assessed daily during treatment in both rescue and prophylactic arms).⁸⁵
4. Baxter Retching Faces (BARF): pictorial nausea scale (0-10) validated in children (assessed daily during treatment).⁸⁶
5. Numeric pain rating scales (0-10). Subjects will be asked to grade the severity of any abdominal and headache pain (average and worst) that was significant enough to distract from their usual activities (daily).
6. Assessment of rescue medicine. Participants will be asked if they had to use rescue medication during the 5 days they wore the neurostimulation device.
7. Effectiveness of test blinding. Subjects will be asked if they believe they have a treatment or sham device at Treatment 1 and 2.
8. State-Trait Anxiety Inventory for Children (STAI-C) and Adults (STAI-AD). Subjects will be assessed for symptoms of state anxiety by this validated measure.⁸⁷ State and trait anxiety is measured with a two-page (40-item) questionnaire at baseline. Repeat measurements will assess state anxiety only. A Research Psychologist (PhD) will assist with interpretation of the psychometric data. Children <8 will not be assessed on this measure.
9. Patient Reported Outcome Measurement Information System (PROMIS): A newly developed and validated global health/quality of life outcome measure that efficiently measures physical, emotional, psychosocial functioning in children ages 8-17 years (PROMIS Pediatric Profile-37); for children <8, parents will complete the identical questions of the PROMIS Parent Proxy Profile v2.0 – Profile-49. Adults in the rescue arm will complete the comparable adult PROMIS-27 Profile.⁸⁸
10. Functional Disability Inventory (FDI): Symptoms of disability and reduced quality of life in children will be assessed with the FDI.⁸⁹ This is a one page, self-report (ages 8+) or parent report (ages <8) measure of the degree that children experience difficulty in physical and psychosocial functioning due to impaired physical health. Patients rate each of the 15-items on a five-point Likert scale indicating how much difficulty they have doing common childhood activities because of their physical health.
11. Adult and children will complete the short, 5-item validated Sheehan Disability Scale, assessing functional impairment in work/school, social and family life.⁹⁰
12. Pittsburgh Sleep Quality Index: A 9-item questionnaire for children and adults to measure quality and patterns of sleep.⁹¹
13. Subjects will also fill out a short validated overall symptom response scale.⁹² Subjects will rate their symptoms as better, worse or no change based on a 15 point scale: -7 to -1= worse; 0 = no change; +1 to +7 = better). Specific symptoms that improved (or worsened) will be checked if applicable.
14. Abdominal Pain Index (API). The API is a short, one-page instrument validated in children with functional abdominal pain.⁹³ A revised, recently validated form of this scale will be used to assess nausea (Nausea Severity Scale; NSS).⁹⁴

15. A short follow-up questionnaire inquiring about symptom improvement and patient satisfaction will be completed at the follow-up clinic visit.

Table 1. Summary of Study Procedures for Rescue arm

	Baseline	Visit 1	Visit 2	Visit 3	Visit 4	Follow-up
Screening Consent	X					
Neurostimulator (EAD)		x		x		
HRV	x	x*	x**	x*	x**	x
Demographics	x					
Rome IV questionnaire ^o	x					
INVR (daily during therapy) ^l	x	x		x		x
BARF (daily during therapy) ^l	x	x		x		x
Pain scale (daily during therapy) ^l	x	x		x		x
STAI-C/STAI [^]	x	x	x	x	x	x
PROMIS ^l	x	x	x	x	x	x
FDI ^l	x	x	x	x	x	x
Sheehan Disability Scale ^l	x	x	x	x	x	x
Pittsburgh Sleep Index ^l	x	x	x	x	x	x
Symptom response scale (SRS) ^l			x	x	x	x
Follow-up questionnaire						x
CGRP Blood Draw (Optional) ^{***}	x	x		x		

*Before and after neurostimulator placement

** To occur 5-7 days following the nerve stimulator placement

STAI-C= State-Trait Anxiety Inventory for Children; PROMIS= Patient Reported Outcome Measurement Information; FDI=Functional Disability Inventory

*** There will be 5 total CGRP draws at both visits 1 and 3. Each patient will provide up to 11 samples/subject throughout the whole study..

^o Self-reported for ages 10+; Parent-reported for ages <10

^l Self-reported for ages 8+; Parent-reported for ages <8

[^] Self-reported for ages 8+ only (no data to be collected on ages <8)

Table 2. Summary of Study Procedures for Prophylactic arm

	Baseline	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Follow-up
Screening Consent	X							
Neurostimulator (EAD)		X	X	X	X	X	X	
HRV	X	X*					X*	x
Demographics	X							
Rome IV questionnaire ^o	X							
INRV (daily during therapy) ^l	x	x	x	x	x	x	x	
BARF (daily during therapy) ^l	X	X	X	X	X	X	X	
Pain scale (daily during therapy) ^l	X	X	X	X	X	X	X	
STAI-C/STAI [^]	X						X	X
PROMIS ^l	X	(X)	X	X	X	X	X	X
FDI ^l	X						X	X
Sheehan Disability Scale ^l	X	X	X	X	X	X	X	X
Pittsburgh Sleep Index ^l	X						X	X
Symptom response scale (SRS) ^l	X		X	X	X	X	X	X
Abdominal Pain Index (API) ^l	X	(X)	X	X	X	X	X	X

Nausea Severity Scale (NSS) ⁱ	X	(X)	X	X	X	X	X	X
Follow-up questionnaire								X

* Patients in the prophylactic arm will only complete HRV before the device placement at week 1 and week 6.

^o Self-reported for ages 10+; Parent-reported for ages <10

ⁱ Self-reported for ages 8+; Parent-reported for ages <8

[^]Self-reported for ages 8+ only (no data to be collected on ages <8)

Statistical Analysis

Data Management

The data gathered will be entered into REDCap data system with each ID having a unique identifier for each participant. REDCap is a secure, web-based application for building and managing online databases. All data will be de-identified and samples will only have a unique identifier that will link the unique identifier with the patient's name.

The REDCap clinical database will be maintained by the Department of Quantitative Health Sciences, at the Children's Research Institute under the direction of Pippa Simpson, PhD.

Questionnaires may be emailed to the patient when feasible through the RedCap secure survey link, otherwise paper forms will be used in the event that the patient does not have access to a computer.

Statistical Analysis

Missing Data Handling

Every effort will be made to avoid missing data. Using logistic regression (LR), the assumption of missing at random data will be explored. If the data appear missing at random (MAR), multiple imputations for items and longitudinally random effects models will be used. If missing data appear not random, a sensitivity analysis will be employed, using clinical information and different assumptions to substitute values and see how results are affected.

Data analysis overview: Summary statistics, such as mean, median, standard deviation, range and correlation will be used as a first step to examine data. To satisfy parametric assumptions, we may perform transformations with justifications if possible and otherwise use non-parametric tests. We will use CART and biological and physiological information to identify interactions when formulating regression models. Statistical software employed for data analysis will be: Cytel StatXact, SAS version 9.4, Salford System CART for trees, SPSS Version 24. The power calculation was made using PASS 15.

Specific aim #1: Demonstrate that auricular neurostimulation prevents cyclic vomiting/abdominal migraine episodes when applied in the prodromal phase. **Hypothesis:** *Auricular neurostimulation will result in a reduction in the frequency of emesis and severity of abdominal pain and nausea during episodes.* The primary outcome will be number of emesis episodes during the 4 visits. We will compare these using a two-sample two-sided t-test at an alpha of 0.049 to allow for an interim analysis. Power: With 50 in each group allowing for 20% drop out we will have 40 in each group. We will have at least 80% power to detect a difference between groups of at least 0.64 standard deviations. Further we will use a generalized linear model with a negative binomial link function to examine covariates such as demographics and clinical variables. We will examine secondary outcomes similarly but the link function may differ.

Specific aim #2: Compare measures of functional disability, in children and adults with cyclic vomiting syndrome before and after auricular neurostimulation therapy. **Hypothesis:** Auricular

neurostimulation will improve overall functional disability, anxiety and quality of life by reducing emesis and pain episodes. The primary outcome will be the change from baseline to week 4 of functional disability. We will use a generalized linear model with a contrast to compare the group and subject random. An autocorrelation structure will be considered for the variance covariance model but we will also consider other structures. Power. For simplicity, we use a two-sided two sample t-test of the change from baseline at an alpha of 0.049 to allow for an interim analysis. With 50 in each group allowing for 20% drop out we will have 40 in each group. We will have at least 80% power to detect a difference between groups of at least 0.64 standard deviations. In the generalized model, we will include covariates such as demographics and clinical variables. Other secondary outcomes such as quality of life, psychological health and heart rate variability changes will be analyzed similarly.

Safety Data

All safety variables (e.g., adverse events will be summarized for each assessment time (including follow-up) using descriptive statistics. Incidence of adverse events will be summarized by treatment.

E. TOTAL NUMBER OF HUMAN RESEARCH PARTICIPANTS PROPOSED FOR THIS STUDY AT THIS SITE AND GLOBALLY. WHAT ARE THESE NUMBERS BASED ON?

We expect to enroll up to 90 subjects total (rescue arm + prophylactic arm). The rescue arm of the study will consist of 25 children from Children's Hospital of Wisconsin, 6-17 years of age, and about 25 adults, recruited from Froedtert Hospital, 18-65 years of age. Also, a subset of 10-15 patients already enrolled will be asked to provide blood to measure calcitonin gene-related peptide (CRGP) levels.

In order to effectively assess the prophylactic therapy, up to 40 children ages 6-18 will be asked to participate in a prophylactic group arm. This number was chosen to account for potential subject dropouts and screen failures.

The pediatric GI clinic evaluates at least 4-6 patients with cyclic vomiting syndrome each week. The CVS program at CHW (run by Dr. Kovacic) has several hundred established patients. The CVS program at Froedtert (run by Dr. Venkatesan), evaluates at least 12-16 per week and has > 1000 established patients enrolled in a clinical registry who receive ongoing care at the CVS clinic at Froedtert hospital.

F. DRUGS OR PROCEDURES

Auricular Neurostimulation treatment protocol

Subjects in the rescue arm will enter a two-week, prospective randomized-controlled, cross-over treatment trial with the FDA-approved and commercially available device Neuro-Stim manufactured by Key Electronics (Jeffersonville, IN, USA) and distributed by Innovative Health Solutions (Versailles, IN, USA). This is an ambulatory, neurological device which consists of a battery powered, externally affixed generator with 4 wire leads attached to 3 electrode/ needle arrays and one single point needle. The device delivers low voltage (3.2V) stimulation in alternating frequencies for a total of 5 days (around the clock). The arrays are designed to produce a field effect similar to surgically implanted peripheral neurostimulators. Study Investigators (MDs) or trained pediatric TRU RNs will place the electrodes percutaneously in the external ear with the help of a transilluminator to visualize the neurovascular bundles. Three electrodes will be

placed on the ventral and one on the dorsal aspect of the ear. The electrodes will be taped and secured behind the ear next to the generator itself which is secured to the skin with adhesive. The entire device may be covered by longer hair. The placement of the devices is within standard of care by properly trained medical doctors or registered nurses as already performed as part of separate, ongoing IRB-approved trial. Training of MDs (Dr. Kovacic and Krasaelap) has already been performed by Dr. Chris Brown or Dr. Brian Carrico as representatives of Innovative Health Solutions. Device application by pediatric TRU RN's has been approved by CHW regulatory and compliance. The placement protocol is the same as prior IRB approved study (#689519) recently completed at CHW. All subjects will receive the device in their prodromal/warning phase of their cyclic vomiting cycle or in case of calendar-timed CVS, within 1-3 days prior to expected start of vomiting cycle.

Subjects in the rescue arm will be randomized in a 1:1 ratio to either treatment or sham group for their first week of treatment. They will subsequently cross over to the other group for the second week of treatment. Randomization will be stratified by age (child vs adult) and gender and determined using a computer program based on random number generation in blocks of 10 subjects at a time and subjects will be stratified by gender and age (child vs adult). The manufacturer will provide the researchers with 2 devices per package (2 treatments per patient). Each package will have a serial number and only one research coordinator will have the key to which serial numbers represent active devices and which represent inactive ones. This research coordinator will keep the data in a secure database and will not be involved in any of the patient recruitment or study procedures. All other research coordinators, investigators, statistician and nurses involved will be blinded to group allocation.

Subjects enrolled in the prophylactic therapy arm will undergo exact same device placements but will receive 6 consecutive weeks of active neurostimulation therapy (no sham group). There will be no randomization process for this group as only active therapy will be provided. Subjects in this arm will undergo the exact same placement procedures and fill out the same questionnaires (only on at slightly different time points as noted in Table 2). They will also undergo HRV measurements although this will only occur before and at the end of the 6 weeks of therapy.

Devices will be delivered by Innovative Health Solutions. Research coordinators within the division of gastroenterology will store the devices as pre-packaged by manufacturer. A coded folder for each patient with all questionnaires needed for the entire study will also be kept with each subject package. The devices and folders will be stored in a locked office in the pediatric gastroenterology division, only accessible by the research team. A research coordinator will meet the patient in the TRU for device placement by one of the certified doctors or pTRU RN.

The inactive devices will be custom made by the physical manufacturer, Key Electronics, Jeffersonville, IN. This control device will be identical in every way to the active device except it will lack the battery. The devices will be "made to order" when requested by the PI and will be shipped packaged as above. Both the subjects and the doctors placing the devices will be blinded, as the treatment and inactive devices will look identical with identical packaging and placement procedures. All patients will be told that they may or may not feel a flushing sensation after device placement. Blinding will be tested by asking the subjects and caregivers to guess their group assignment (active vs control) at the end of the study (Visit #4).

The electrode/needle arrays are placed according to the individual's arterial and cranial nerve anatomy. The exact location of the placement may vary slightly from person to person but is determined by both knowledge of auricular neuro-anatomy and visualization of the neurovascular bundles by transillumination (IHS, Versailles, IN, USA). The points will be targeted by four-point electrical stimulation using the EAD after carefully disinfecting the ear. The small device will be



positioned and secured behind the ear similar to a hearing aid, which may be covered by hair. Neurostimulation will be delivered below sensation threshold for 5 consecutive days. The device will be applied by a trained MD. A second week of neurostimulation will be performed at the expected next calendar-times CVS onset unless the patient is symptom free. If so, the treatment trial but may be stopped after one week if there is complete symptom resolution. If there is evidence of symptoms or emesis after the first 5 days of therapy, subjects may resume their usual abortive medicines as clinically indicated. They will remove the device independently at home and will be asked to return the used device for proper disposal when they return the following week. (or to their follow-up medical appointment if last treatment week)."

Each week when subjects return to the hospital, they will be asked if they wore the device for the whole 5 days and this will be documented by pTRU RN. The devices are easily removed by removing the tapes and adhesives. Subjects will complete questionnaires at different time points as shown in Table 1.

The EAD Surgical kit consists of:

- (1) An alcohol swab
- (2) prep and stay swab
- (3) round fixation plasters
- (4) fixation plasters to fasten the generator
- (5) Steri-strip adhesive vial
- (6) Sterile wire harness pack
- (7) Generator
- (8) Tweezers
- (9) Surgical marker
- (10) Transilluminator

EAD placement details:

1. A research coordinator in the GI office will document the patient ID, name and the device serial number in the study database.
2. Patient will return to the CHW pTRU where the research coordinator will give a labeled device package (with patient ID and serial number only) to the doctor to attach to the subject.
3. The research coordinator or RN will administer the above questionnaires to the subjects and perform a medication and side effects check at all visits. At the initial visit, the baseline questionnaires will be administered by the research coordinator at the time of the clinic visit.
4. The pTRU RN will document the patient's vital signs (temperature, heart rate and blood pressure).
5. The neurostimulator placement will be performed as directed and per EAD training protocol instructions identically to per our prior IRB approved protocol (#689519).
6. Before neurostimulator placement, the subject should be advised that some discomfort is normal at first but should report if the discomfort persists or gets worse after a few minutes. The patients should be advised that they may feel a slight pulsing sensation and perhaps a warming sensation in the ear to which the electrodes are affixed. The pulsing and warming sensation may disappear after approximately 5 minutes. If the discomfort level increases the offending array can be slightly repositioned until the patient's discomfort level decreases to an acceptable level.
7. The patient will remain at rest for the next 10 minutes.
8. Subjects will be advised not to immerse the device in water as the device is water resistant but not water proof. If showering or washing their hair, place a dry wash cloth over the area to help protect the device. Subjects will be given a contact person (Principal investigator and research coordinator) to call if they are having any problems with the device or if it falls off.

9. The patient will be instructed on removing the device after 5 days. If not comfortable doing so or unable to carry out the instructions, the patient will be seen on that day for removal by one of the investigators.
10. The patient will be asked to return the used device for proper disposal when they return the following week (or to their follow-up medical appointment if last treatment week).
11. Subjects will be given a handout with short, daily symptoms surveys and reminded to complete them every night and bring them back the following week.
12. The subject will be given a handout with information (attached) on device handling, exact date and time of device removal and date and time to return.
13. The subject will be advised to refrain from using any as new or as needed anti-emetic or pain medications during the time of study period.
14. The research coordinator will ensure a follow up visit has been scheduled in GI clinic within 1-2 months of study completion.
15. The subject is dismissed.

Heart rate variability (HRV)

The evaluation of heart rate variability (HRV) provides a functional assessment of the relation between the sympathetic and parasympathetic tone. The high-frequency power of the heart rate variability and the root mean square of successive differences (RMSSD) reflects the vagal modulation of the heart. This can be evaluated by analyzing the HRV at rest and in standing position to assess the baroreflex response.

Subjects will undergo HRV measurements before and after each week of neurostimulation therapy (day 1 and also once when return after therapy on day 5-7 of both treatment weeks). The HRV measurements will also be repeated immediately after each neurostimulator placement. After a 10-minute period of rest in sitting position, the subject will sit upright for 3 minutes for HRV recordings followed by 3 minutes of recording while standing and 3 minutes while sitting (total of 19 minute per session). We will use the Actiwave EKG recorder by CamNTEch to measure HRV. This device is a single channel recorder, where two electrodes are placed on the patient's chest by an RN who then completes the recording according to our standard protocol. The HRV evaluation will take place at the baseline visit and before and after both neurostimulator placements (visits #1 and 3) and at the end of each therapy (day 5-7; visits #2 and 4) and at the post-study follow-up clinic visit for patients in the rescue arm. For patients in the prophylactic arm, it will take place at baseline (clinic visit or before first device placement), after therapy (week 6) and at follow-up clinic visit.

The HRV data will be analyzed using Kubios program or a similar computer program. Dr. Stephen Porges and Dr. Gregory Lewis of Indiana University will be interpreting the HRV data from this study. However, they will only be reviewing de-identified data and will not be receiving any PHI.

Calcitonin Gene-Related Peptide (CGRP) measurements

CGRP is a novel neuropeptide found elevated in patients with acute migraine attacks. CGRP antagonist drugs have recently been found effective and recently approved for the treatment of migraines.⁶⁰ Due to the close relationship between cyclic vomiting syndrome and migraines, CGRP data may provide further mechanistic understanding if the pathophysiology of CVS. We will measure CGRP levels as follows:

1. At baseline (fasting am level when well) x1
2. During a CVS attack: at onset + at 30, 60, 90 and 120 min following neurostimulation and sham therapy for a total of 11 samples/subject.

All blood levels will be drawn in the pediatric TRU. Minimum of 3 ml blood/sample will be collected into standard microcentrifuge polypropylene tubes. A minimum of 1ml of serum will be generated in 0.3ml aliquots. Aliquots will be stored at -20C until assayed. A commercial enzyme immunoassay kit will be used to measure CGRP levels according to manufacturer protocol. CGRP assays will be performed by Dr. Hershel Raff in the Endocrine Research Laboratory at Aurora St. Luke's Medical Center.

We request permission to store the remaining processed serum. These samples will be coded and stored at Dr. Raff's Lab in the Endocrine Research Laboratory at Aurora St. Luke's Medical Center for future research, including possible other biochemical markers. Participants who agree to this will initial the corresponding option on the consent form.

Data to be collected:

Consent from participants for use of these materials for research will be obtained.

Demographic Information

Data will be collected as part of the clinic visit and at enrollment. This includes subject's date of birth, age, sex and ethnicity. The physician assessment will also include questions about prior medical diagnoses, co-morbid symptoms and the characteristics of vomiting, pain and nausea such as timing and triggers.

Symptom Information

Patients will complete the questionnaires as outlined above before application of the neurostimulator, after the first week of therapy and at the follow up clinic visit. They will also complete daily surveys. These instruments have demonstrated reliability and validity and have been used for both clinical and research purposes in both adult and pediatric populations. Up to one year after study completion, the investigators may conduct brief follow-up phone calls to subjects to assess long-term effects.

Medical Information

Information recorded for patients is part of clinical care and includes weight, height, vital signs, medications, gastrointestinal symptoms, early life events, family history, surgeries and other medical co-morbidities.

G. RISK CATEGORY:

(2) [45 CFR 46.405](#) - Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual child subjects involved in the research.

Overall risks/ discomforts involved are very minimal – Rare (event rate 1% - < 5%)

Possible risks/discomforts may involve:

- a. Discomfort upon insertion of the electrodes for < 5 minutes - Rare (event rate 1% - < 5%)
- b. Discomfort at the lead placement site > 5 minutes – Rare (1 % - < 5%)
- c. Bleeding at the electrode site if the neurovascular bundle is penetrated - Rare (event rate 1% - < 5%)
- d. Localized discomfort if the electrodes should become dislodged during the wearing of the device - Rare (event rate 1% - < 5%)
- e. Localized dermatitis - Rare (event rate 1% - < 5%)
- f. Drop in blood pressure - Rare (event rate 1% - < 5%)
- g. Syncope (fainting) - Rare (event rate 1% - < 5%)

Adverse effects to supporting personnel

a. Skin piercing with percutaneous needles - Rare (event rate 1 % - < 5%)

Of note, in the recently completed neurostimulation trial for functional abdominal pain disorders, there were no serious adverse events. The rate of reported side effects were no different between the treatment and placebo groups. Of 115 subjects, n=10 (9%) reported the following side effects: ear discomfort (n=6; three treatment/three placebo), adhesive allergy (n=3; one treatment/two placebo) and syncope due to needle phobia (n=1; placebo).

H. RISKS AND THE PRECAUTIONS WHICH WILL BE TAKEN TO MINIMIZE RISK EXPOSURE

Safety Monitoring Plan

All procedures will be performed by trained professionals within the standard of care under continuous medical supervision in the hospital setting (research unit). Side effects will be inquired about and documented every week during the study they have the device placed and at the post-study follow-up visit. Daily vomiting, pain and nausea ratings will be filled out by patients, so this will be carefully monitored. If any serious harm or discomfort is identified by the subjects or the study personnel, the treatment will be discontinued. Any patient with worsening or no improvement in symptoms during the study will be able to drop out at any time and receive standard of care medical therapy. The skin of the external ear will be carefully disinfected to avoid any infection risks.

Safety Analysis Plan

There are no dangerous interventions related to this study, and the short study timeline allows for discontinuation of treatment when it is proven to be ineffective. Completion of psychometric questionnaires may be associated with mild distress in some participants. Because the questionnaires include assessment of patient psychosocial functioning, clinically significant symptoms that the patient or parent were unaware of may be brought to light.

Patient distress during questionnaire completion: If children/adults become distressed during completion of study questionnaires, they are instructed in the consent and assent forms to inform the researchers or nurse. The researchers/nurse will then contact the primary investigator who will place a referral to a psychologist as necessary and as dictated by law (e.g., suspected child abuse/neglect) to ensure patient and family safety and to address psychosocial needs.

Patient/Parent report of clinically significant psychosocial or safety issues: Any child endorsing clinically significant psychological distress on questionnaire-reported screening measures will be referred to a psychologist. Regarding psychological screeners, research assistants will score the STAI-C questionnaires within a week of completion. Based on the normalized T-scores for the STAI-C S-anxiety scores (Table 2 in State-Trait Anxiety Inventory for Children Sampler Set Manual, Test Booklet and Scoring Key), any scores 2 or more standard deviations above 50⁵¹ will be reported to the PI. In turn, the PI will discuss the results with the family and provide them with a referral to a licensed clinical psychologist as necessary.

I. PROVISION FOR THE PROTECTION OF PRIVACY OF SUBJECTS AND TO MAINTAIN THE CONFIDENTIALITY OF DATA

Each subject will be assigned a unique identifying number which will be the only identifier listed on the questionnaires, neurostimulator kits and data collection forms. Each subject's identifying number and related electronic data will be kept on a secured, MCW password-protected database that provides access only to the PI and research staff. Only authorized research personnel will have

access to the database. A separate secure database will have the subject identification number linked to the patient's name. The neurostimulator devices will be shipped directly from the manufacturer (Key Electronics) to the GI office research coordinator who will store the randomization scheme on a secure computer and label each package of 2 devices with a patient ID and serial number with a prepared sticker label. A subject folder will also be prepared and labeled with the same ID and kept together with the device package. The devices will be stored in a locked room in the division of gastroenterology. Only one kit at a time will be transported by a research coordinator to the pTRU. The remaining kits will be stored in the same locked room, labeled with the patient's ID. Only research coordinators within the division of gastroenterology will have access to the storage room. To track use and proper disposal of the devices, subjects will be asked to return the used device the following week (at time of the next stimulator placement or their follow-up clinic visit). The RN or research coordinator will record that device was returned and dispose it properly.

J. PROVISIONS FOR MONITORING DATA TO ENSURE THE SAFETY OF SUBJECTS; AND ADDITIONAL SAFEGUARDS TO PROTECT THE RIGHTS AND WELFARE OF SUBJECTS WHO ARE LIKELY TO BE VULNERABLE

The PI will monitor the health of all patients in the study per standard clinical practice. Dr. Kovacic will monitor protocol adherence and supervise data collection, entry, and analysis.

K. ANTICIPATED BENEFITS ASSOCIATED WITH THE PROTOCOL TO HUMAN RESEARCH PARTICIPANTS AND SOCIETY

There are numerous, possible direct and long-term benefits to the subjects in this study. Our preliminary data on the EAD in adolescents with functional GI disorders is showing safety and high efficacy over placebo. For the first time, adolescents suffering from CVS have the opportunity to benefit from a non-pharmacological and non-invasive therapy without the adverse effects of multiple pharmacological agents that CVS patients depend on. The results of this study may provide important insights to the medical field regarding a poorly characterized group of patients and the underlying mechanisms. Most importantly, this study may shed light on a new, non-pharmacologic therapy that could improve quality of life for patients suffering from a debilitating condition with very few treatment options.

L. STOPPING POINTS THAT WOULD NOT ALLOW THE STUDY TO CONTINUE AS PROPOSED

Stopping points for the study include achieving adequate information on enough of the goal subjects, unanticipated adverse events, inability to obtain enough data or patients/caregivers electing to discontinue the study.

Reporting Adverse Events and Unanticipated Problems

Expected adverse events that are not serious will be reported on the Continuing Review Progress Report. Continuing Review will be performed on a 12-month cycle, starting at time of protocol's initial approval. More frequent progress reports will be submitted at the request of the IRB.

Serious Adverse Events: The PI, within 24 hours, will report all serious adverse events occurring in any enrolled subjects to the IRB. Unexpected (but not serious) adverse events occurring in enrolled subjects which, in the opinion of the PI, are possibly related to participation in the protocol will be reported by the PI within 5 working days to the IRB.

Unanticipated problems involving risks to subjects or others will be reported to the IRB within 24 hours.

M. IS THERE A DATA SAFETY MONITORING BOARD IN PLACE? WHO ARE IT'S MEMBERS? HOW OFTEN DO THEY MEET?

As this is a low risk protocol, no data safety monitoring board will be appointed unless requested.

N. DESCRIBE HOW THE CONSENT PROCESS WILL TAKE PLACE. INCLUDE A LIST OF APPROPRIATELY TRAINED PERSONNEL WHO WILL BE INVOLVED.

Written informed consent for participation will be obtained from the adult subjects and from parents and children for their child's participation. Written assent will be obtained from youth between 6 and 13 years of age using the CHW assent form. Patients aged 6 will need to meet with Dr. Kovacic prior to enrolling in order to confirm they have the required maturity to participate. This meeting will consist of Dr. Kovacic explaining the neurostimulation therapy to them and the requirements in order to participate. If, after this conversation, Dr. Kovacic confirms they are mature enough to participate, Dr. Kovacic will obtain their written assent on the CHW assent form (similar to patients ages 7-13). Patients ages 14 and above will sign the assent line on the consent form per CHW policy. Consent will be obtained by a study investigator or member of the research team at the patients' appointment in the GI Clinic. Volunteers' consent will allow for accessing information collected for program evaluation/clinical purposes. Participating children and parents will have the option of having the consent/assent document read aloud to them to facilitate understanding. Copies of signed consent/assent documents will be given to participants.

Potential patients may be screened in clinic and given consent form however may decide at a later time to participate in the study. The study team would like the option to consent the patient over the phone and schedule first visit. These patients may potentially be sick at time of first visit, this way the consenting process is completed and the subject does not sign the consent under duress of being ill. If the patient is 7-17 years of age, the assent process will take place over the phone as well with the patient. Patients aged 6 will not be assented over the phone as they have to meet with Dr. Kovacic prior to enrolling in order to ensure they have the maturity required to participate. The subject will bring the final version back to clinic where the study member who completed the consent over the phone will sign consent and give copy back to the participant.

Patients who turn 18 years of age while participating in this study will be re-consented. The consenting process will be conducted by the PI or a member of the research team. If age of majority is reached while the participant is active and continues to receive study interventions per the study protocol, he/she will be re-consented using the most current approved IRB informed consent document and HIPAA form. If age of majority is reached after all study interventions have been completed and the participant remains in the study for purposes of data collection for outcomes only a separate "Age of Majority" informed consent will be obtained. Patients will be re-consented at 18 years of age so that their samples may continued to be stored, if they previously agreed to this option on the consent form.

O. PROCEDURES TO BE EMPLOYED IN ANALYZING DATA AND THE ANTICIPATED SIGNIFICANCE OF THE PROPOSED STUDY

Analyses will be conducted with SPSS and SAS software programs. Probability levels of < .05 will be used as cut offs for statistical significance.

The key significance of this study is the identification of a successful, non-invasive therapy for pain-related CVS that can give clues to underlying physiology and individual physiological and susceptibility factors, making the enrollment of appropriate study participants critical. We expect to be able to show if neurostimulation is effective for CVS. With this study, we hope to lay the foundation for the application of auricular neurostimulation for CVS. This is an innovative and novel treatment approach, which will enhance our knowledge on the brain-gut neural connectivity underlying functional disorders and ultimately improve patient care.

P. FINANCIAL RELATIONSHIPS

The EAD devices will be purchased by the distributing company (IHS) at the manufacture rate. The Cyclical Vomiting Syndrome Association has donated funds to provide each study participant a \$75 stipend. Each subjects who consents to provide CGRP will be provided with an additional \$25 stipend. Internal grant funds have been received from MWC Digestive Disease Center.

Q. ADVERTISEMENTS / FLIERS

Redcap will be utilized for advertisement to adult subjects in Dr. Venkatesan's established cyclic vomiting syndrome research registry.

We will use the following language:

“Dear XX,

We are recruiting adult patients ages 18-65 years with Cyclic Vomiting Syndrome for a study investigating the effectiveness of a non-invasive ear neurostimulation therapy, in collaboration with Children's Hospital of Wisconsin. This device has been shown to reduce pain, nausea and vomiting in certain medical conditions. We think that this device may help abort an episode of cyclic vomiting syndrome without the need for other medications or using less other medications. Patients who use marijuana are not eligible to participate. There is no cost to being in the study, but you will need to travel to Medical College of Wisconsin to participate. Certain other restrictions may apply. Please contact research coordinator Louis Pawela #414-266-6728 (or email lpawela@mcw.edu) if you are interested.

Dr. Venkatesan”

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