Protocol Summary/Submission Application

Instructions

- Providing a well-written and complete submission is a critical step toward ensuring an efficient IRB review and approval process. If you have any questions, contact the CW HRPP office at 414.337.7133 or CHWIRB@chw.org for assistance early in the submission process; however, the HRPP office is not able to offer consultation for protocol design issues.
- This document should be in your own words (NOT copy/pasted from the sponsor protocol) and must be understandable to individuals who do not have clinical expertise in the area being studied.
- Summarize the proposed study without substituting references to attached material, such as grant applications, multi-center or industry-sponsored protocols. The protocol summary should not read like a grant application.
- Reference GUIDANCE – Submission Documents Checklist (found under Forms and Templates in IRBNe or on the HRPP web site under Guidances) to determine what additional documents are required to be included in the submission package.
- If this is an update to a previous version, please track the changes made using the Review tab in Word.

Version date of this document (initial or revision): 5/6/2024
Study Title: Percutaneous neurostimulation for treatment of paroxysmal sympathetic hyperactivity in children with acute severe brain injury
Principal Investigator: Binod Balakrishnan M.D.
Sponsor (if not sponsored, indicate that study is investigator-initiated): Investigator initiated

Section 1 Regulatory Criterion for Approval: Risks are Minimized

Risks to subjects are minimized: (i) by using procedures that are consistent with sound research design and that do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

- Risks must be identified and classified as risks that would only be present if the subject participates in the research versus those risks that would happen as part of routine care or regardless of the subject's participation.
- ONLY evaluate the **research** risks and consider how to minimize those risks:
  - Is the question important scientifically/scholarly to answer?
  - Is the study designed so the question can be answered?
  - Can less risky procedures answer the question?
  - Can fewer procedures answer the question?
  - Are the procedures needed at all?
  - Can additional procedures reduce risk?
  - Can different eligibility criteria reduce risk?
  - Are investigators and key personnel adequately qualified relative to the activities being performed and are the activities within each individual's scope of practice?
  - Are procedures that will answer the scientific question being done anyway? If so, can the data from these procedures be used to reduce the likelihood or magnitude of harm?

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Study Design

A. Has this proposal undergone separate formal review to determine appropriateness of study design (i.e. formal Scientific Review Committee)?

☐**No** If NO, the IRB is responsible for determining that scientific design is appropriate

☒**Yes** If YES, describe the entity and outcome of the review (provide minutes or supporting documents in the submission package, if available): Critical Care Research Operations Committee

B. Purpose of the study:

Evaluate the feasibility of using a percutaneous electrical nerve field stimulator (PENFS) for treatment of paroxysmal sympathetic hyperactivity (PSH) in children 2-17 years of age with acute severe brain injury (ASBI).

C. Hypothesis/specific aims:

Aim 1: Demonstrate the feasibility of use of PENFS to treat PSH, and tolerability of the device.
Hypothesis: The PENFS device will be well tolerated, defined as < 10% early termination from the study. We will recruit 20 patients with ASBI and PSH who will receive PENFS therapy.
Aim 2a: Evaluate the feasibility of capturing pediatric PSH symptoms using the CFS scoring tool.
Hypothesis: It is feasible to monitor the severity of PSH using a CFS scoring tool (Table 1a,1b). The scoring tool will be adapted for the appropriate age range of the patient (Table 2). We aim for at least 80% scoring (≥ 8/10 scheduled scoring per protocol while the device is worn).
Aim 2b: Evaluate the effectiveness of the PENFS device in reducing PSH symptoms using change in CFS score.
Hypothesis: A decrease in CFS severity score with use of PENFS will be associated with a lower number and/or doses of maintenance and rescue medications for control of PSH symptoms.
Aim 3a: Evaluate the change in autonomic balance with use of PENFS device
Hypothesis: Heart Rate Variability (HRV) and pupillometry parameters that correspond to sympathetic and parasympathetic activity will be different after PENFS device placement compared to before, reflecting an increase in parasympathetic tone. All patients will be on routine continuous EKG monitoring in the PICU during the study period of interest. Similarly, pupillometry is routinely performed in patients with ASBI in the PICU.
Aim3b: Evaluate feasibility of measuring PENFS effectiveness in treating PSH by a decrease in medication use.
Hypothesis: It would be feasible to use the maintenance and rescue medication dosing and frequency as a marker of severity of PSH. PENFS device use will result in lesser number and/or doses of maintenance and rescue medications for control of PSH symptoms. We will compare the pilot sample to a historical cohort to allow power analysis and sample size calculation for a future larger efficacy trial, recognizing that this pilot study is not powered for efficacy.

D. Background, significance, and rationale (including description of preliminary studies and any results):

Paroxysmal sympathetic hyperactivity – incidence, pathophysiology, diagnosis, treatment, prognosis and implications for treatment
Paroxysmal sympathetic hyperactivity is frequently seen in survivors of acute severe brain injury (ASBI). It is most commonly associated with severe traumatic brain injury (sTBI) with a reported incidence of 10-20% among survivors of sTBI (1-4,6-9). Survivors of anoxic brain injury have a higher incidence of PSH (approximately 30%) (5). The pathophysiology of PSH is incompletely understood. Current consensus is that it the result of disconnection between with neuroinhibitory higher centers in the diencephalon and the

excitatory pathways in the brainstem and spinal cord (10). PSH is characterized by a constellation of symptoms such as tachycardia, tachypnea, hypertension, hyperthermia, rigidity, tremors, sweating, and pupillary dilation as a result of sympathetic hyperactivity due to the brain injury (1,5,7,8). Research on PSH has been hampered by lack of a uniform definition and use of various terms such as neurostorming, dysautonomia. Consensus diagnostic criteria and a scoring algorithm (CFS) were developed in 2014 (1) (Table 1a,1b). PSH increases the risk for secondary brain injury and is associated with worse functional outcomes, longer hospitalization and higher healthcare costs (2,3,7,11). Appropriate treatment of PSH is important for patient comfort and to prevent secondary brain damage (12,13). Currently, PSH is treated using a combination of multiple neurotropic medications (narcotics, benzodiazepines, sympatholytics, gabapentin, muscle relaxants etc.) that can result in complications due to their side effects such as excessive sedation, respiratory depression, drug dependence, and constipation. Some of these medications necessitate longer ICU stays due to their CNS depressant effects thus potentially increasing healthcare costs (3). There has been very little research into novel ways of treating PSH other than the use of various neurotropic medications (14,15).

Measurement of autonomic function – HRV and Pupillometry Autonomic function can be evaluated clinically and is most commonly measured using heart rate variability (HRV) (16). Established standards for measurement of HRV are available (17). HRV has been studied in various disease states in the intensive care environment such as post-acute MI, sepsis, multi-organ dysfunction, brain injury, and brain death (18,19). HRV is decreased or lost in severe disease and has been shown to be associated with increased mortality in the ICU (18,19). Higher sympathetic activity in severe disease states is associated with decreased HRV (18). HRV was shown to be significantly different between children and adults with ASBI and controls (20,21). Similarly, pupillary reactivity is also under autonomic control. Recently, pupillometry has also been used to measure autonomic activity. A pupillometer quantitatively measures pupil size (size, minimum size with light stimulus, % change in pupil size) and reactivity (constriction velocity, max constriction velocity, latency, dilation velocity) that can be compared to established norms and trended over time (22,23). These parameters have been shown to reflect

Table 1a Clinical Feature Scale (CFS) – used for scoring[1]

Clinical Feature Scale (CFS)

	0	1	2	3	Score
Heart rate	< 100	100–119	120–139	≥ 140	
Respiratory rate	< 18	18–23	24–29	≥ 30	
Systolic blood pressure	< 140	140–159	160–179	≥ 180	
Temperature	< 37	37–37.9	38–38.9	≥ 39.0	
Sweating	Nil	Mild	Moderate	Severe	
Posturing during episodes	Nil	Mild	Moderate	Severe	
			CFS subtotal		

Severity of clinical features	Nil	0	
	Mild	1–6	
	Moderate	7–12	
	Severe	≥ 13	

Table 2 PSH scoring modified for pediatric population[34]

	0	1	2	3
Heart rate	1–4 years: <110 5–15 years: <100	1–4 years: 110–124 5–15 years: 100–119	1–4 years: 125–139 5–15 years: 120–139	1–4 years: ≥140 5–15 years: ≥140
Respiratory rate	1–4 years: <30 5–15 years: <25	1–4 years: 30–34 5–15 years: 25–29	1–4 years: 35–39 5–15 years: 30–34	1–4 years: ≥40 5–15 years: ≥35
Systolic blood pressure	1–4 years: <100 5–15 years: <120	1–4 years: 100–109 5–15 years: 120–129	1–4 years: 110–119 5–15 years: 130–139	1–4 years: ≥120 5–15 years: ≥140
Diastolic blood pressure	1–4 years: <65 5–15 years: <75	1–4 years: 65–72 5–15 years: 75–82	1–4 years: 73–79 5–15 years: 83–89	1–4 years: ≥80 5–15 years: ≥90
Temperature	<37°C	37–37.9°C	38–38.9°C	≥39°C
Sweating	Normal	Increased sweating	Localized diaphoresis	Generalized diaphoresis
Muscle tone increase	Absent	Mild increase	Neat increase	Generalized spasticity or opisthotonus

sympathetic (dilation velocity) and parasympathetic system (% change in pupil size, latency, constriction velocity) activity and sympatho-parasympathetic balance (baseline pupil size) (24). PSH, as the name implies, is associated with uncontrolled paroxysms of sympathetic activity that results in pupillary dilation among other symptoms. It is conceivable that an increase in parasympathetic activity would alter these parameters that could be compared using the patient as his/her own control

PENFS device – description, mechanism of action, and applications The PENFS (auricular neurostimulator) device is a novel, non-pharmacological therapy that has been effectively used for various conditions such as functional abdominal pain, chronic pain, and narcotic withdrawal (25-27). Recent data from CW also demonstrates efficacy in a pilot study for children with cyclic vomiting syndrome, with improvement in episode severity and frequency lasting an average 5 months (unpublished data). Cyclic vomiting syndrome (CVS) is a disorder of autonomic imbalance manifested by severe sympathetic hyperactivity. Symptoms of nausea/vomiting, pallor, diaphoresis, and tachycardia are similar to PSH. Many of the symptoms of narcotic withdrawal are also very similar to those of PSH including tachycardia, tachypnea, hypertension, fever, tremors, sweating (28). Clonidine, an alpha-2 agonist with sympatholytic properties is commonly used as an adjunct in the treatment of narcotic withdrawal syndrome (29). Clonidine is also one of the first-line medications used for treatment of PSH (12,13). Thus, it is plausible that PENFS could be effective in treatment of PSH.

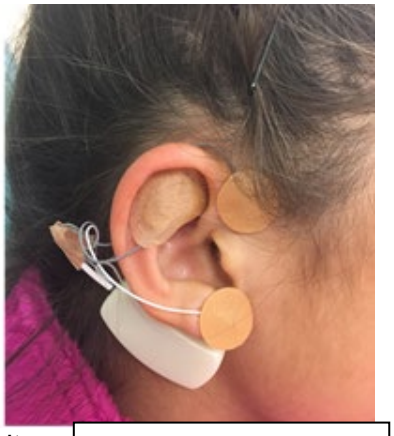

Figure 1. PENFS device

The PENFS device is applied over the external ear (Fig.1) and is continuously worn for 120 hours at a time. The electrical current stimulates the auricular branch of the vagus nerve (ABVN) and auricular branches of cranial nerves V, VII and IX. The nerves project to the various parts of the brain, including the brainstem nucleus tractus solitarius. fMRI scans in healthy human volunteers have shown significant activation of the central vagal projections by stimulating ABVN (30). Sympathoinhibition has been shown to be one of the primary mechanisms of actions of the device in the various conditions for which it is used (31-33). The study by Mahadi et al., showed that electrical stimulation of the tragus in rats resulted in central sympathoinhibition by up to 36% within 5 minutes of stimulation (31). This central sympathoinhibition by the PENFS device could improve the symptoms of PSH.

One of the advantages of PENFS in the treatment of PSH is that it is continuously active while it is worn thus providing symptomatic treatment throughout that period. This could help prevent or ameliorate the paroxysmal symptoms classically seen in PSH and thus reduce the need for rescue medications. The device also has been shown to have a relatively rapid onset of action. A recent study showed that the onset of action was rapid with 63% reduction in narcotic withdrawal score within 20 minutes of activation of the device and 85% reduction within 60 minutes (26). Thus, PENFS could offer a non-pharmacological tool for managing PSH, helping to decrease the need for maintenance and rescue medications and thus limiting the side effects of some of these medications. Decreased need for neurosedative medications could further decrease the length of ICU stay for these patients thus decreasing healthcare costs. The device is also well-tolerated without any serious adverse effects (25).

Innovation:

The treatment of PSH has been limited to various combinations of neurotropic medications. We explore the novel use of an auricular neurostimulator (PENFS) device for PSH treatment. We hypothesize that the PENFS device, by stimulating the parasympathetic AVBN will inhibit the sympathetic hyperactivity due to PSH. If this approach proves to be efficacious, it will help to decrease the need for neurotropic medications thus decreasing some of the serious adverse effects of these medications (drug dependence, acute cardiorespiratory compromise due to neurodepressant effects, constipation and feeding intolerance due to bowel dysmotility). The PENFS device is worn continuously for 120 hours thus providing continuous treatment of PSH symptoms which would potentially decrease the need for rescue medications. Limiting the need for neurodepressant medications would reduce the need for close monitoring in the ICU resulting in decreased healthcare costs. The use of objective measures of autonomic function - HRV and pupillometry – is also a novel way of evaluating response to treatment using the PENFS device. Further, the application of the CFS score in pediatrics will potentially provide a simple, instantaneous mode of tracking symptoms severity and response to treatment.

E. Design and methods (including experimental design, technical details and laboratory methodology):

Design & Methods

In this prospective unblinded pilot study we will enroll eligible patients until 20 parent/child dyads complete the study. It is expected many of the consented patients will not meet the eligibility criteria of CFS score > 6 (moderate severity of PSH. Those children will be considered Screen Failures and their parents/LAR told they are ineligible to continue in the study. Children admitted to the PICU at CW aged 2-17 years with ASBI and symptoms of PSH with a CFS score > 6 (moderate severity of PSH) will be eligible for inclusion. Exclusion criteria include age < 2 years (small ears thus less surface area to apply the leads), ear deformity or severe dermatitis of ear lobes, intractable seizures, heart block, patients with other implantable devices (cardiac pacemaker, vagal nerve stimulator, etc.) or known pregnancy.

Study treatment

Patients with ASBI are routinely co-managed by the ICU Neurology team who have extensive experience diagnosing and treating PSH. Potentially eligible patients will be identified by the ICU Neurologists (Co-I). Once enrolled, the PENFS device will be placed over the external ear and will remain continuously active for 120 hours. CFS scores will be calculated before and after initiation of PENFS as per study protocol.

Medication detail during study treatment:

No additional maintenance medications (propranolol, bromocriptine, dantrolene, gabapentin, baclofen) will be allowed to be initiated for the first 12 hours after initiation of PENFS. Patients could continue to receive rescue medications (morphine, benzodiazepines such as lorazepam, midazolam, diazepam, clonidine) during this period for break through symptoms or remain on maintenance medications that were already in

place that would normally be used to treat PSH. Additional maintenance medications could be instituted beyond the initial 12-hour period if PSH symptoms are not adequately controlled. Initiation of maintenance medications before placement of PENFS will not be a contraindication to enrollment, but once enrolled, no new maintenance medications would be allowed for the initial 12 hours after device placement.

Aim 1: Identify and enroll 20 pediatric patients with ASBI and PSH.

Methods: Parent(s)/legal guardians, 18 years or older, will be approached for informed consent if their child has ASBI and is exhibiting clinical signs and symptoms of PSH. Once consented, the CFS scoring tool (Table 1a,) will be used to evaluate patients felt to be exhibiting symptoms of PSH to identify eligible ASBI patients. Patients with CFS score > 6 will be eligible for enrollment in the study.
Families of patients who do not meet the CFS score criteria > 6 will be told their child did not meet scoring criteria of study and will be considered consented but not enrolled in study.
Study Enrollment is defined as meeting CFS criteria of > 6 after consent. If CFS scores are already being collected for subject prior to subject consent as a standard of care, we can use already available CFS scores from medical record. The PENFS device will be placed over the external ear by study investigator or one of trained nurses (RNs) from the Pediatric Translational Research Unit (P-TRU) within 24 hours of meeting CFS > 6 score criteria..
There are 380-400 PICU admissions/year that are seen by ICU Neurology. Using a conservative estimate of 8-10% incidence of PSH, we expect to have 35-40 patients with PSH. At a conservative 60% enrollment rate, we expect to be able to successfully enroll 20 patients in this pilot study. Previous studies using the device has shown it to be well-tolerated with minimal side effects (25,26). In a large, randomized sham-controlled trial Kovacic et al showed a very low rate of discontinuation of the device due to side effects. We hypothesize that the dropout rate will be ≤ 10%. Tolerability of the device will be assessed by subjective assessments of device tolerance by the bedside nurse, the CFS score (increasing score after device placement would suggest worsening PSH symptoms) and skin integrity (bedside nurses will perform routine skin evaluation and care while the device is in place.). To evaluate safety, we will monitor for serious adverse effects such as cardiac dysrhythmia (EKG monitoring), and new-onset seizures.

Aim 2a: Evaluate feasibility of scoring PSH symptoms using the PSH scoring tool

Methods: The CFS (Table 1a) will be used to score the severity of PSH using the pediatric adaptation for the appropriate age range (Table 2 – diastolic blood pressure will not be used for scoring)[34]. CFS scoring will be performed by the bedside nurse who will be trained in using the scoring tool. PSH severity for the 12-hour period prior to placement of the device will be calculated retrospectively based on the features of CFS. After placement of the device, patients will be scored prospectively every 12 hours while the device is worn. The device will be discontinued after 120 hours of wear (usual duration of wear of a device). Scoring will be continued every 12 hours until 120 hours of device placement and then for another 72 hours(total of 192 hours for complete study duration). Every CFS score will be based on the severity of PSH symptoms in the preceding 12 hours.

Aim 2b: Evaluate the effectiveness of the device in reducing PSH symptoms using the change in CFS score

Methods: We will analyze the within-patient change in the modified CFS score with use of the device (before and after device placement and trend in score over time). No maintenance medications will be allowed

during the initial 12 hours of use of the device; however, rescue medications will be allowed during this period. Maintenance medications would be allowed after 12 hours of device use. We will also compare the trend in scores while using the device to the trend once the device is discontinued after 120 hours of use as we will be following the trend in the CFS scores every 12 hours for an additional 72 hours after removal of the device. This will be impactful as the patient will be his/her own control. However, we recognize that this could be confounded by the initiation of maintenance medications.

Aim 3a: Evaluate the change in autonomic balance with use of PENFS device

Methods: We will use two separate validated modalities to evaluate the autonomic activity/balance in response to use of the device – HRV and Pupillometry. HRV denotes the beat-to-beat variability in the R-R interval on the EKG. Cardiac pacemaker automaticity is continuously altered and regulated by the autonomic nervous system (ANS). The parasympathetic system regulates HR on a beat-to-beat basis whereas the sympathetic system has slower onset but longer duration of action (16-18). Decreased HRV parameters has been shown to be associated with increased 30-day mortality in critically ill patients (19). Children with PSH were shown to have significant differences in HRV parameters compared to controls (20). We will calculate time-domain (mean heart rate, standard deviation of all average R-R intervals (SDNN), root mean square of the successive differences (RMSSD), physical stress index (PSI), approximate entropy (ApEn); successive R-R interval difference (SRD)) and frequency-domain indices (total power (TP), high frequency (HF), low frequency (LF), normalized HF, normalized LF, and LF/HF ratio) and compare the 12-hour period before and after placement of the PENFS device. Three separate 5-minute segments of continuous EKG tracings at rest (lying in bed) and body temperature 36-37.5C will be identified for both periods for comparison. Similarly, we will compare the pupillometry parameters along with direction of change before and after device placement.

Aim 3b: Evaluate feasibility of measuring PENFS effectiveness in treating PSH by a decrease in medication use

Methods: The maintenance medications and the number of doses and type of rescue medications administered will be collected for every 24 hours (0-24h, 25-48h, 49-72h, 73-96h, 97-120h, 121-144h, 145-168h, 169- 192h) for the enrolled patients. These will be compared to a historical cohort of PSH patients. The historical cohort will consist of PSH patients (2-17 years old) identified using the ICU Neurology administrative dataset from January 2018 – August 2021. This dataset will be used to identify ASBI patients who likely developed PSH. Eligible patients with PSH will be identified and relevant data collected by individual chart review. During this period all the PSH patients were followed by ICU Neurology thus ensuring a uniform approach to their treatment. We have also developed a practice guideline for treatment of PSH that will ensure uniform treatment of these patients during the study period. Similar to Aim 2a, we will examine the need for additional maintenance medications or change in frequency of rescue medications with discontinuation of the device. We hypothesize that, with discontinuation of the device, the patients may experience worse PSH symptoms as demonstrated by increasing CFS score and need for additional maintenance and/or rescue medications.

Data collection & Management

Screening & Consent:

We will screen all ASBI patients who appear to have symptoms of PSH during their PICU stay. If they meet study eligibility, we will approach the parents/LAR for informed consent. The PI will verify the status of who has been appointed the subject's guardian or LAR. Due to the nature of ASBI, we assume all children will be incapable of assenting to this study. Once the parent(s) / LAR have consented for their child to participate in the study, the CFS scores will be calculated to confirm study eligiblity. The families will be told that their child does not qualify for the study if they do not meet the CFS scoringcriteria. We expect 20 parent/child dyads to

complete the study. If the patient does meet CFS scoring criteria for study enrollment, we will collect the CFS score for a 12-hour period before placement of the device followed by every 12 hours while the device is in place and for an additional 72 hours after removal of the device.
Data collection & Management: We will collect demographics, cause of ASBI, imaging findings, sedative, pain and other neurotropic medications, and maintenance and rescue medications for PSH including their number and doses for every 24-hour period from placement of the device. We will also collect all the HRV and pupillometry parameters for the 12-hour period before and after placement of the device. For the historical cohort, we will collect demographics, cause of ASBI, imaging findings, maintenance and rescue medications used in each 24 hour period for the first 120 hours and then additional 72 hours from the time of meeting CFS score > 6 criteria. . The REDCap database for this study will be developed and managed by Quantitative Health Sciences on MCW-secure servers

Table 3: Data collection plan

	-24 to -12 h	-12 to 0h	Device placement **0 h**		**6h**	**12h**	**24h**	**24-48h**	**48-72h**	**72-96h**	**96-120h**	120-144h	144-168h	168-192h
Consent	x													
CFS score		x	x			x	X 12 hourly	x 12 hrly	x 12 hrly	x 12 hrly	x 12 hrly	x 12 hrly	x 12 hrly	x 12 hrly
Pupillometry		x	x		x	x								
HRV using EKG		x	x		x	x								
Maintenance meds[1]		x				x	x	x	x	x	x	x	x	x
Rescue Meds[2]		x				x	x	x	x	x	x	x	x	X
Adverse Events						x	x	x	x	x	x	x	x	X

1 No additional new Maintenance Medications are allowed for the first 12 hours after device placement. Patients may remain on Maintenance Medications they are already taking. Additional Maintenance Medication are allowed after the first 12 hours of device placement.

2 Patients may continue Rescue Medications during the first 12 hours of device placement.

Data analysis & interpretation (Overview)
Missing data: In general, the assumption of missing at random (MAR) will be assumed. Under this assumption, we will impute or use mixed models. A sensitivity analysis, using clinical and biological expertise will be included. Exploratory data analysis will include exploration of distributions and relationships of the variables, using summaries, such as correlation, plots such as Loess smooth plots, and Classification and Regression Trees (CART). To satisfy parametric assumptions, transformation of variables will be used or non-parametric tests when necessary. Continuous data: we will use mixed models to describe changes over time, the variance covariance matrix will be chosen to be parsimonious but to fit the data and will likely be an autocorrelation matrix. Design justification: Although it would be better as a pilot to randomize patients to a sham and active PENFS, the numbers would be so small (and heterogeneous) that the study would have limited information. The next step would be to evaluate the acceptability of randomization in this group of patients.

Hypothesis 1: The number approached and consented will be tracked. Reactions/ adverse events will be summarized and reasons for early termination, if any, evaluated.
Hypothesis 2a, 2b: The scoring tool will be adapted for the appropriate age range of the patient (Table 2). We aim for at least 80% scoring (≥ 8/10 scheduled scoring per protocol while the device is worn). The association of the score and the number of doses of maintenance and rescue medications will be summarized with a spearman correlation and exact 95% Confidence intervals (CI).
Hypothesis 3a: HRV and Pupillometry measures will be tracked over time with any loss of data recorded with reasons. Wilcoxon Rank Sum test will be used to compare the mean ±SD for the parameters for the 12-hour periods before and after device placement.
Hypothesis 3b: The number of doses of maintenance and rescue medications for control of PSH symptoms will be compared to historic data using a t-test or non-parametric Mann Whitney. Further a classification tree will be used to evaluate the effect of demographics, clinical history and use of PENFS.

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F. **Research procedures such as lab draws (including volume of samples), ECG, imaging, clinical procedures, genetic testing, surveys (may attach activity table if available):**

Describe what will happen to the subject solely for the purpose of this research study:

1) Placement of PENFS device on the external ear of the enrolled patient by study investigator or one of trained P-TRU nurses (RNs) that will remain in place for 120 hours.
2) CFS scoring per protocol by the bedside nurse
3) Evaluation of heart rate variability using EKG data obtained from the bedside monitor during the 12 hour period before and after placement of PENFS device.
4) *The bedside RN, TRU RN, or physician will remove the device and dispose of properly in a sharps container. The devices are easily removed by removing the tape and adhesives.*
5) Parental survey of their perceptions about the use of the device at the end of the study.

Describe what is happening per protocol but is considered part of routine care (would happen even if the individual did not participate):

1) Pupillometry
2) Medical management of PSH

Clinical Trial

A. Is this study a Clinical Trial/Clinical Investigation?

Clinical Trial *means a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of the interventions on biomedical or behavioral health-related outcomes.* [45 CFR 46.102(b)]

Clinical Investigation *means any experiment that involves a test article and one or more human subjects, and that either must meet the requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the act, or need not meet the requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be later submitted to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The term does not include experiments that must meet the provisions of part 58, regarding nonclinical laboratory studies. The terms research, clinical research, clinical study, study, and clinical investigation are deemed to be synonymous for purposes of this part.* [21 CFR 56.102(c)]. Note: this also include biospecimens.

☐**No** If NO, skip questions B-H ☒ **Yes** If YES, answer the following questions B-H:

B. **What** phase of clinical trial **best describes this research?**

☐**Phase I** ☐ **Phase I/II** ☐ **Phase II** ☐ **Phase II/III** ☐ **Phase III** ☒ **Phase IV**
☒**Feasibility** ☐ **Pivotal (Feasibility vs Pivotal device studies)**

C. Is this trial "first-in-human" (in clinical trials, the first Phase-1 study in which a test product is administered to human beings)?

☒**No** ☐ **Yes**

If YES, the protocol must contain an adequate description of the pre-clinical research and/or other relevant data that supports the performance of the study.

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D. Is this trial the first in a population (e.g., children)?

☒**No** ☐**Yes**

If YES, the protocol must contain an adequate description of the pre-clinical research and/or other relevant data that supports the performance of the study in the new population.

E. **Does this trial evaluate one or more** FDA-regulated products?

Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/P's) may be classified as drugs, devices, and/or biologics. Information on the classification of HCT/P's is available on this FDA website.

The 21st Century Cures Act excludes certain medical and decision support software from the definition of medical device meaning that such software is not subject to FDA regulations. Information regarding these exclusions is available on FDA's website for digital health. If uncertain whether a product under investigation is a medical device, contact the CW HRPP office.

☐**No** ☒ **Yes** If YES, indicate the following:

Product Type(s): Percutaneous electrical nerve field stimulator

Product Name(s): IB Stim

If YES, also include in the submission package **IRB – Supplement Form – Drugs and Biologics** for studies of drugs and biologics and/or **IRB – Supplement Form – Devices** for medical device studies. These forms are found in IRBNet under Forms and Templates.

F. Will this trial enroll pregnant women or minors/women who are of child-bearing potential?

☒ **No** ☐ **Yes**

If YES, the protocol and consent must contain an adequate description of any known or anticipatable risks to pregnant women and fetuses and any measures to mitigate those risks. Birth control requirements, if applicable, must also be described. CW template pregnancy test language regarding disclosure of results must be included in parental permission/assent documents.

G. Does the sponsor intend to collect data on "pregnant partners" (sexual partners of clinical trial subjects who become pregnant while the subject is receiving investigational agents)?

☒**No** ☐**Yes**

If YES, review Children's Wisconsin IRB Position Statement Pregnant Subjects and Pregnant Partners found in IRBNet under Forms and Templates and on the HRPP web pages.

H. **Is this trial registered in** ClinicalTrials.gov?

Contact MCW CTSI if there are questions about what needs to be registered or visit their website for registration instructions.

☐**N/A, registration is not required for this trial (confirm with CTSI if uncertain)**

☐**No, but trial will be registered prior to enrolling any subjects**

☒**Yes, ClinicalTrials.gov #:** NCT05343988

For FDA-regulated and NIH funded clinical trials that are or will be registered in ClinicalTrials.gov, the following statement must be included verbatim in the consent/parental permission forms:

FDA: "A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time."

NIH: "A description of this clinical trial will be available on http://www.ClinicalTrials.gov. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time."

Risks

A. Describe potential research-related risks and discomforts (consider physical, psychological, legal, social/economic/financial, loss of confidentiality, group harms); describe the probability, magnitude, and duration of the potential risks; do not address risks that would be present if the individual did not participate:

Local discomfort/pain, skin irritation. Theoretical risks include cardiac dysrhythmia and new-onset seizures neither of which have been reported in previous studies. In a randomized sham-controlled trial of the use of the device for 115 children with functional abdominal pain, only 1 patient among 60 with active device discontinued treatment due to discomfort, whereas 6 patients in the sham-group discontinued the device one being adhesive allergy. Patients will be monitored (including EKG monitoring at least in the initial 48 hours of the device) as inpatient during the time the device is in place. Other studies[35,36] have also reported minimal to no side-effects using the device for other indications.

Other risks include remote possibility of loss of confidentiality if there is any breach of study data.

B. Describe steps taken to minimize risks:

Patient comfort will be monitored to assess tolerability, skin will be monitored for contact dermatitis. EKG/Heart rate monitoring for dysrhythmia and monitoring for new onset clinical seizures. To minimize the remote possibility of a breach in confidentiality, patient data including PHI will be assigned a study ID and stored in a password-protected Excel file on MCW's secured drive: and be only accessible to limited members of the study team. Only coded data with a Study ID will be entered into the password-protected REDCap database.

Section 2 Regulatory Criterion for Approval: Benefits

Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research).

- If there is no benefit and no knowledge to be gained, there is no justification to expose subjects to risk.

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A. Describe the potential benefits to science and/or society which may accrue as a result of this research:

If found to be effective in treatment of PSH, the PENFS device will offer a non-medication modality for treatment of PSH thus helping to decrease the need for neurosedative medications and decreasing the adverse effects of the medications.

The natural history of PSH is that the symptoms are worse initially requiring multiple medications to ameliorate the symptoms. Over time, the PSH symptoms decrease allowing weaning of some of the medications. Thus, the PENFS device might offer significant benefit in the initial period helping to limit the number of medications needed to control the symptoms of PSH.

B. Are there any benefits which may accrue to the individual subjects in this research (compensation is not considered a benefit)?

☐**No** ☒ **Yes**

If YES, describe: Improvement in PSH symptoms and reduction in need for medications to treat PSH could potentially decrease the adverse effects associated with use of these medications.

Section 3 Regulatory Criterion for Approval: Equitable Selection

Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted. The IRB should be particularly cognizant of the special problems of research that involves a category of subjects who are vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons.

- No population is unfairly targeted
- No population is unfairly excluded
- Burdens are distributed fairly
- Benefits are distributed fairly

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The research population includes the following:	Check all that apply:
Normal adults/health volunteers	☒
Inpatient population	☒
Outpatient population	☐
CW or MCW Employees/Staff	☐
Students of *(describe)* Click here to enter text.	☐
Residents/Fellows	☐
Prisoners	☐
Children	☒
Pregnant Women, Fetuses, Neonates (of uncertain viability or nonviable), after delivery, placenta, dead fetus, or fetal material	☐
Adults with Impaired Decision-Making Capacity (enrolled by legally authorized representative)	☐
Individuals with limited English proficiency *(specify anticipated primary language)*: Click here to enter text.	☐
Economically disadvantaged persons	☐
Educationally disadvantaged persons	☐
Other *(describe)*: Click here to enter text.	☐

A. Total number of human research subjects proposed:

Locally: 20 parent/child dyads who complete the study **/** Study-wide (if applicable): N/A

Describe what are these numbers are based on: There are 380-400 PICU admissions/year that are seen by ICU Neurology. Using a conservative estimate of 8-10% incidence of PSH, we expect to have 35-40 patients with PSH. At a conservative 60% enrollment rate, we expect to be able to successfully enroll 20 patients in this pilot study who complete the study and 20parents/legal guardians to take the parental questionnaire.

B. How do you plan to identify subjects for recruitment or records for inclusion in the study?

All of the eligible patients (those with acute severe brain injury) would already have had an ICU Neurology consult. If they exhibit symptoms of PSH per Neurology and Critical Care teams routine assessment, a member of treatment team will evaluate their interest to hear about a research study. If they agree to hear about a research study, one of research team members will approach the family for consent..

For the historical controls, the Neurology ICU Billing administrative dataset will be used to collect the MRNs of patients who meet the broad criteria of TBI.

C. Eligibility Criteria (inclusion/exclusion criteria):

Inclusion criteria:

1) Children admitted to the PICU aged 2-17 years
2) Acute severe brain injury (ASBI) and symptoms of PSH- defined as CFS score > 6 (moderate severity of PSH)

Exclusion criteria:
1) age < 2 years (small ears thus less surface area to apply the leads)
2) ear deformity
3) severe dermatitis of ear lobes
4) intractable seizures
5) heart block
6) other implantable devices (cardiac pacemaker, vagal nerve stimulator, etc.)
7) known pregnancy
8) Parent or LAR under the age of 18.

D. Who will be responsible for determining whether potential subjects satisfy eligibility criteria and how will they do so?

Note: if the analysis of health information is necessary to determine eligibility, a medically-qualified person must be involved in the determination.

Eligibility will be determined by either the Principal Investigator or Sub-Investigator. A checklist of the Inclusion/Exclusion criteria will be followed to determine eligibility.

E. Will recruitment materials be used?

☒**No** ☐ **Yes**

If YES, describe how and where materials will be posted/distributed: Click here to enter text.

Documents containing exact language to be used must be included in submission package for review and approval by the IRB. Review **Guidance – Recruitment for Human Subject Research** (found in IRBNet under Forms and Templates) for more information and instructions for logo use.

Section 4 Regulatory Criterion for Approval: Informed Consent Process

Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by, §46.116./50.20.

- Circumstances of the consent process will provide the subject sufficient opportunity to consider whether to participate (this is an ongoing process and should be confirmed at the time of each interaction)
- Circumstances of the consent process will minimize the possibility of coercion or undue influence
- Information will be given in an understandable language
- Special issues that could present undue influence and need additional consideration: advertisements, payment for participation

Description of Process to Obtain Consent

Information regarding parental permission and assent is captured in Section 8: Vulnerable Populations.

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A. WHO: List appropriately trained personnel *by role* rather than individual name (i.e., Investigators, Study Coordinators, etc.) who have been delegated authority by the PI to conduct the consent process, and indicate whether those individuals have an existing treating relationship with the potential subject:

Members of study team including research coordinators will conduct the consent process. None of these will have an existing relationship with the potential subject.

B. WHEN: Describe when subjects are being informed of the research opportunity and how much time they are given to consider whether to participate:

The local research team will screen all admitted PICU patients to determine the eligibility for study. Once eligibility is confirmed, the study team will reach out to attending physician and clinical team to obtain their permission to approach the subject and family. If the clinical team is ok for the subject to participate in the study, someone who has a treating relationship with the subject will make the initial contact, introducing the research study and study team to the subject and their family. It is expected that ample time will be provided to subject's family so they can think about participation and receive answers to any questions they may have.

Parent as Participant: After the main study consent is signed, parent(s)/guardians will be given the "CHW Minimal Risk template" to read and discuss. All of their questions regarding this consent, which pertains to completing a brief questionnaire about their perceptions of their child's involvement in this device study will be answered. It is expected this consent process will take approximately 15 minutes.

After the consents are signed, the CFS assessment will be made to ascertain study eligibility. If the child does not meet eligibility criteria based on their CFS scores, the family will be told their child is not eligible for the study as they did not meet study defined CFS scoring criteria. Study Enrollment is defined as meeting CFS criteria of > 6 after consent. If CFS scores are already being collected for subject prior to subject consent as a standard of care, we can use already available CFS scores from medical record. The PENFS device will be placed over the external ear by study investigator or one of trained nurses (RNs) from the Pediatric Translational Research Unit (P-TRU) within 24 hours of meeting CFS > 6 score criteria

C. WHERE and HOW: Describe the physical location of the consent discussion and how it will be conducted:

Someone who has a treating relationship with the potential subject will make initial contact with the patient, obtain permission for the study team to approach, study team will then approach the patient and family for consent discussion in private setting in PICU.

D. SPECIAL CONSIDERATIONS: Describe any subject compensation (reimbursement for expenses; compensation for time and effort):

No subject compensation is offered in this study.

E. If you are requesting to waive consent for some or all subjects, provide rationale:

We are requesting a full waiver of assent for this study as we do not anticipate any of the subjects will be able to assent because of their severe brain injury. These patients will either have reduced consciousness or will cognitively not be able to understand what they are consenting/assenting to.

Include **IRB – Request form for Alteration or Waiver of Assent, Consent, Parental Permission** (found in IRBNet under Forms and Templates) in the submission package.

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Section 5 Regulatory Criterion for Approval: Documentation of Informed Consent

Informed consent will be appropriately documented or appropriately waived in accordance with §46.117/50.27.

A. Describe the plan for documentation of consent and process that is specific to the protocol and consistent with local requirements:

If you are requesting to waive documentation of consent/assent/parental permission, include **IRB – Request form for Alteration or Waiver of Assent, Consent, Parental Permission** (found in IRBNet under Forms and Templates) in the submission package.

The study team anticipates an adequate number of qualifying patients to be available within the PICU. These patients will be identified during their PICU stay and approached if they meet the study inclusion criteria and do not meet any of the exclusion criteria. The research coordinator or other members of research team will approach the family for consent after receiving permission from the clinical team. If the principal investigator is part of the potential subject's care team he/she will not approach the family and one of the sub-investigators or research coordinators will participate in the consent conversation instead. Someone who has a treating relationship with the potential subjects will make the initial contact with the patient, obtaining permission for the study team to approach, and a member of study team will then approach the patient and family for research study participation. The research team will meet with the patient and their parent(s)/ legal guardian to discuss the study and obtain consent. A copy of the consent signed by the parent(s)/ legal guardian will be uploaded into the patient's medical record. A signed copy of the consent will be given to the patient's parent(s) or legal guardian.

Parent as Participant: The original consent and documentation will not be scanned into the child's medical record, but will be secured in the subject's study file in a locked cabinet along with other study documents. The parent(s)/guardian will be given a signed copy of the Minimal Risk template.

Section 6 Regulatory Criterion for Approval: Safety Monitoring

When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

Considerations applicable to research that is deemed greater than minimal risk include:

- Who reviews safety data?
- What data are reviewed (safety and efficacy)?
- When/how often are data reviewed?

A. Is a Data Safety Monitoring Board (DSMB)/Data Monitoring Committee (DMC) in Place?

☒No ☐ Yes ☐ N/A (study is not greater than minimal risk)

If YES, describe its members and how often they meet (you may include any DSMB/DMC charters in the submission package; once the study has been opened locally any DSMB/DMC reports should be submitted for review as reportable new information):

B. If there is no formal DSMB/DMC, describe the monitoring plan or indicate that the study involves no more than minimal risk (if the IRB disagrees and determines the study to be greater than minimal risk, the study will be deferred until an appropriate monitoring plan has been developed):

Members from the division of critical care (MD, APP) will meet every 2 months to review data on device safety. Any serious adverse event deemed related to study will be notified immediately for adjudication.

C. Have stopping rules been established for the study (to evaluate whether the objectives have been met, or that the objectives cannot be met, or that the accumulated data indicates that the risks exceed the benefits of the study)?

☐**No** ☒ **Yes** ☐ **N/A (study is not greater than minimal risk)**

If YES, describe the stopping rules:
Any symptomatic cardiac dysrhythmia or new-onset seizure deemed to be as a result of the device use.
5 consecutive patients showing device intolerance i.e worse comfort scores, worse CFS score,

D. Describe procedures to be employed in analyzing data (including a power analysis):

This is a pilot feasibility study of use of the device. A convenience sample of 20 patients was chosen.

Section 7 Regulatory Criterion for Approval: Privacy and Confidentiality

When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

- Privacy refers to persons and their interest in controlling access to themselves
- Confidentiality refers to agreements with the subject about how data are to be handled

A. Provisions for the protection of privacy of subjects (having control over the extent, timing, and circumstances of sharing oneself [physically, behaviorally, or intellectually] with others):

Every effort will be maintained to protect the privacy of subjects. Potential patients and their families will be approached in a private room in the PICU to discuss the study. If they agree, the consent process will also take place in this private room without interference from others. In addition, during the consenting process the subject of privacy surrounding the subject's data will be discussed.
Individuals will not be identified in scientific presentation of findings or in publications. The subject will have right to withdraw from study anytime by writing to study PI and any further data collection will be stopped beyond that point.

B. Provisions to maintain the confidentiality of data (the treatment of information that an individual has disclosed in a relationship of trust and with the expectation that it will not be divulged to others in ways that are inconsistent with the understanding of the original disclosure, without permission):

Every effort will be made to protect the confidentiality of patient's data. Their coded data, including a Study ID, will be entered into a password protected REDCap database for study analysis. A separate password protected Excel file will exist as a key to the coded data. It will contain the Study ID number along with some PHI such as MRNs. The MRN in this file is the PHI which serves as the key to the code. Both password protected files will be stored on the secured MCW secured servers and are only accessible by the study team.

All research team members will be trained regarding human subject research and the confidentiality of data using the institution's standard, web-based CITI training modules and will possess appropriate CITI certification.

C. If paper records are being maintained, indicate where paper documents will be kept and how secured (This includes hard copies of signed consent forms, as well as any other documents containing subject PHI):

Any hard copy data forms will be assigned the appropriate Study ID. The data will be entered into the REDCap study database. The hard copies will be stored in a locked cabinet accessible only to the study team. A copy of the signed consent with HIPPA authorization will be maintained in patient's medical records at Children's Wisconsin.

D. **Describe whether data will be shared outside MCW/CW, with whom (include outside collaborators and their institutions), and how (anonymous, identifiable, coded, de-identified [review OHRP guidance if uncertain]):**

If an investigator leaves MCW/CW during the study and the PI intends for the individual to continue to work on the study as a collaborator, this section must be updated and submitted as amendment package for IRB review. The CW HRPP will need to consider whether the investigator is conducting human subject research, whether data are appropriately protected, and whether a reliance agreement will need to be executed with the investigator's new institution.

The only people allowed to handle subject's health information are those on the research team at CHW/MCW and those who check on research activities to make sure the hospital rules are followed.

E. Will a Certificate of Confidentiality (CoC) be obtained for this research or is one already in place?

Certificates of Confidentiality are issued automatically when:

- *Research is conducted or supported by NIH and falls within the scope of the NIH policy.*
- *Research is conducted or supported by the CDC and involves the collection of identifiable, sensitive information.*
- *Research is funded by the FDA in whole or in part and involves the collection or use of identifiable, sensitive information as defined in 42 U.S.C. 241(d).*

If you need help in making the determination, contact the HRPP office at 414.337.7133.

☒ No ☐Yes ☐ N/A (study is not conducted, supported or funded by NIH/CDC/FDA)

If YES, the required disclosure language must be included in the consent form(s) (see NIH website for suggested consent language).

Data Security Provisions

All research projects that collect electronic data must use appropriate security measures to ensure that data are protected from theft or loss in order to prevent breaches of confidentiality. You must indicate what encryption tools will be used from the options below, or indicate further below why they are not necessary.

The IRB will not review this protocol unless you indicate the encryption tools being used to secure your research data. If you do not have encryption in place on your systems, contact your Information Management Systems support team to arrange for one of the encryptions options listed below.

The following encryption products employ cryptographic modules that the National Institute of Standards and Technology has certified as meeting FIPS 140-2 requirements. Children's Hospital and Health System endorsed the use of these products made to encrypt hard drives and removable media. All electronic research data must be encrypted using one or more of these products.

This protocol summary/submission application must be kept current and revised via the amendment process for IRB approval if any security measures change during the course of the research study.

Indicate which encryption tools you are using to secure your research data:

Key: HD = Hard Drive; RS = Removable Storage (USB flash drive, CD, etc.); PD = Portable Device (iPod, iPhone, PDA, etc.)

☐	**Credent Mobile Guardian (RS, PD)**	☐	**McAfee Endpoint Encryption (HD, RS)**
☐	**GuardianEdge Hard Disk and GuardianEdge Removable Storage Encryption (HD, RS, PD)**	☐	**Seagate Secure Self-Encrypting Drives (HD when encryption option is enabled)**
☐	**IronKey encrypted flash drives (RS)**	☒	**Symantec Endpoint Encryption (HD, RS, PD)**
☐	**SafeNet Protect Disk and SafeNet Protect File (HD, RS)**	☐	**WinMagic SecureDoc encryption (HD) (for MCW owned computers)**
☐	**Microsoft Bitlocker (HD, RS when used with Windows 7 and FIPS compliant algorithms are enabled)**	☐	**PGP Whole Disk Encryption and PGP Portable (HD, RS)**
☐	**OTHER (describe):** Click here to enter text.		
NOTE: BOX is not a CW-approved tool for securing protected health information and cannot be used for research.			

Does not apply because:

☐	**Data are de-identified – no PHI collected (provide detailed information on data elements in the protocol summary/submission application)**	☐	**Data are stored on BOTH CW and MCW secured shared drives**
☐	**Data are stored on CW secured shared drives**	☐	**Data are stored on paper only**
☒	**Data are stored on MCW secured shared drives**	☒	**OTHER (describe):** Password protected REDCap Database managed by QHS

Section 8 Regulatory Criterion for Approval: Vulnerable Populations

When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

Additional steps to minimize coercion and undue influence:

- Assessment of capacity
- Permission of a representative
- Assent
- Witness to the consent process

Subpart D—Additional Protections for Children Involved as Subjects in Research (FDA: In order to approve research in which some or all of the subjects are children, an IRB must determine that all research is in compliance with 21 CFR part 50, subpart D.)

A. Do you intend to enroll children as subjects?
Yes
B. What is the age range of the children in this research?
2-17 years

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C. Where will the children participate? (Check all that apply):

☒ **CW Hospital/Facility:** PICU

☐ **CW Outpatient Clinic/Facility:** Click here to enter text.

☐ **Froedtert Facility:** Click here to enter text.

☐ **MCW lab/office:** Click here to enter text.

☐ **Home**

☐ **School**

If School is checked, have you obtained the necessary permission from the school district?

☐**No** ☐ **Yes** (if YES, include documentation of permission in submission package)

☐ **Other - Specify:** Click here to enter text.

If Other is checked, have you obtained the necessary permission?

☐**No** ☐ **Yes** (if YES, include documentation of permission in submission package)

D. Are any of the children Wards (46.409) of the State or any other agency, institution, or entity?

☒**No** ☐ **Yes**

If YES, contact the HRPP office prior to submission and provide protocol-specific details:

E. Risk Levels For Studies Involving Children

Check the category below that best represents the degree of risk and benefit to which the children in this study will be exposed.

More than one category may be indicated such as when a protocol involves both an experimental and a control group. In these cases, specify which category you believe applies to which group. The IRB will consider the Principal Investigator's assessment and rationale regarding the risk level for this study but it is ultimately the IRB's responsibility to determine appropriate risk levels.

☐	**Risk Level 1 (46.404/50.51):** (Research not involving greater than minimal risk.) Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.
	Provide protocol specific rationale (for each group): Click here to enter text.
☒	**Risk Level 2 (46.405/50.52):** (Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.) More than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject's well-being.

Provide rationale for why/how:

(a) **the risk is justified by the anticipated benefit to the subjects (for each group):** PENFS device use is offered as a non-medication modality to these subjects for treatment of PSH symptoms. Improvement in PSH symptoms and reduction in need for medications to treat PSH could potentially decrease the adverse effects associated with use of these medications.

(b) **the relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches (for each group):** Reducing the need of neuro-sedative medications and decreasing the side effects of these medications is a benefit for these subjects in comparison to the discomfort of this device placement which is slight to minor. No significant side effects have been reported with the use of this device for other indications.

☐ **Risk Level 3 (46.406/50.53):** (Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.) More than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual subject, or by a monitoring procedure which is not likely to contribute to the well-being of the subject.

Which intervention(s) or procedure(s) present more than minimal risk without offering the prospect of direct benefit to individual subjects (for each group):

Provide rationale for why/how:

(a) **the risk of the intervention(s) or procedure(s) represents a minor increase over minimal risk (for each group):** Click here to enter text.

(b) **the intervention(s) or procedure(s) presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations (for each group):** Click here to enter text.

(c) **the intervention(s) or procedure(s) is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition (for each group):** Click here to enter text.

☐ **Risk Level 4 (46.407/50.54):** (Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.) The proposed research does not meet the criteria of the above categories but presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

Provide justification for why this research of this risk level should be approved (for each group):

Parental Permission (46.408/50.55)

F. What permission will be obtained from the parents?

In general, permission from both parents is required for research involving children unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child. However, for Categories 404/51 & 405/52, the IRB may find that the permission of one parent is sufficient. Permission from both parents should be obtained whenever possible regardless of risk level determination.

☐ **Permission will be obtained from both parents where possible**

☒ **Permission from only one parent is being requested**

☒ **A waiver of parental permission is being requested** (complete **IRB – Request form for Alteration or Waiver of Assent, Consent, Parental Permission** found in IRBNet under Forms and Templates) This is also for the historical controls

☐ **A waiver of DOCUMENTATION of parental permission is being requested** (complete **IRB – Request form for Alteration or Waiver of Assent, Consent, Parental Permission** found in IRBNet under Forms and Templates)

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G. If the research is being conducted in a group setting (e.g., a classroom), in which some children have permission to participation and some do not, what is the process to ensure that those children who do not have parental permission do not participate in the research.

N/A

Assent (46.408/50.55)

Adequate provisions must be made for soliciting the assent of children when in the judgment of the IRB the children are capable of providing assent and for soliciting the permission of their parents or guardians.

H. Indicate whether the children you intend to include in the research are generally capable of providing assent taking into account the ages, maturity and psychological state of the children proposed to be involved. Please be specific:

☐ **All are capable**

☒ **None are capable: Explain:** The patients being studied are survivors of acute severe brain injury and would be unable to provide assent during the enrollment period when they have symptoms of PSH and are cognitively unable to provide assent.

☐ **Some are capable: Explain:** Click here to enter text.

I. If children are capable of providing assent, are you planning to obtain assent from the children?

☐ **Yes** ☐ **No** ☒ **N/A – none are capable**

If YES, describe the proposed process for obtaining assent, including who will be involved and the setting and circumstances under which it will be sought:

If NO, a waiver of assent is being requested (complete IRB – **Request form for Alteration or Waiver of Assent, Consent, Parental Permission** found in IRBNet under Forms and Templates).

We are requesting a Waiver of Assent (see uploaded form) for all children due to the child's diminished cognitive functioning. Given the inclusion criteria of nature of brain injury causing subject to meet study criteria and associated sedation necessary as standard of care for these patients, we do not anticipate that any of subjects enrolled in study will be conscious enough to comprehend, process and understand the study, so we request a waiver of assent for all subjects who will be approached for study.
If child has already completed study before achieving the age of majority, we request a waiver of consent and HIPAA authorization for continued use of their data on reaching the age of majority.

A waiver of consent/ assent is also being requested for the historical controls.

J. If assent will be obtained, describe the process and select how assent will be documented. Include in the submission package proposed assent forms or child information sheet, if any.

Describe the process:

☐ All minors will sign the assent signature line on the parental permission form. Minors >12 years of age will be asked to sign the assent signature line on the parental permission form.

☐ All minors will sign a separate assent form

☐ Minors in the age range of seven to twelve years of age will sign a separate assent form

☐ Verbal assent will be obtained and discussion documented in research records

K. Describe the plan for obtaining legally effective informed consent and HIPAA Authorization at the age of majority [18] or describe why it is not applicable (review **Guidance – Consent for Continued Participation When a Child Reaches Age 18** found in IRBNet under Forms and Templates**):**

Age of Majority Plan:

If a subject is in PICU and reaches the age of majority, we will assess already enrolled subject for their consent capacity during the time when device is already on the subject (active study participation phase). We do not anticipate the child will be conscious enough in this period and so, re-consent will be obtained from parent or legal guardian if subject is still in PICU. If the device has already been removed from the subject and the only study participation pertains to use of already collected data, we request a waiver of re-approach, consent and HIPAA authorization for continued use of data at the age of majority.

If the subject has already left PICU and there is no active study participation, no follow up contact will be made to subject or family as they are lost to follow up. The only study activity ongoing is continued use of their collected research data and we request waiver of consent and HIPAA authorization for continued use of this data, for the reason subject is lost to follow up.

Contact the CW HRPP office to obtain appropriate supplements if you intend to enroll other vulnerable populations such as pregnant women, fetuses and neonates, prisoners (including incarcerated minors), or cognitively impaired adults.

Section 9 Potential Conflicts of Interest

Relationships of all members of the research team: Do any research personnel or any of their family members (spouse or dependent children) have an incentive or interest, **financial or otherwise**, which may appear to affect the protection of the human subjects involved in this project, the scientific objectivity of the research or its integrity?

☒**No** ☐ **Yes** If YES, for each individual provide a description of each situation (including dollar values if applicable) as a separate document in the submission package which will be shared with the CW Conflict of Interest Committee.

It is the PI's responsibility to review applicable MCW/CW policies on conflict of interest with every study team member and determine whether any member has a Significant Financial Interest related to this project.

- ***For MCW faculty or staff, refer to MCW's Research Financial Conflicts of Interest Policy.***
- ***For employees of Children's, refer to Children's Research Conflict of Interest Policy.***
- ***For subcontractors or physicians/staff who are employed outside of Children's or MCW, contact Tom Twinem at 414-266-2215 for further guidance.***

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Section 10 Bibliography

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