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**MEDICAL DEVICE PROTOCOL**

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**Developing a Method to Objectively Measure Opioid Analgesia: A Pilot Study**

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**Medical Device:** AlgometRx Device

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**Confidentiality Statement**

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## RESEARCH PLAN

This pilot study utilizes pupillary reflexes to characterize opioid analgesia with the purpose of synthesizing the data into algorithms that detect specific conditions and provide decision support.

### A. Specific Aims

1. To develop opioid profiles based on the pupillary light reflex (PLR) using IR video pupillometry.  
Hypothesis 1a: There will be a repeatable and consistent impact, PLR signature profile, that is drug-specific and dose-dependent on pupil diameter, amplitude of constriction and constriction velocity within and between individuals.
2. To develop analgesic response profiles that assess the fiber-specific dose-dependent impact of opioids on pupillary reflex dilation (PRD).  
Hypothesis 2a: The PRD effect is more pronounced at the 5Hz stimulus than at higher frequency stimuli and leads to a characteristic sensory detection threshold (SDT) response per drug and dose.
3. Explore the evidence that the PLR profile and the PRD SDT can be used to detect drug tolerance and hyperalgesia to improve clinical decision-making for pain management
4. While we believe numbers of cases of tolerance and hyperalgesia are not rare, there are no reliable estimates of these events. Therefore, this research is designed to fill that gap so that such estimates can be used to adequately power future research. We will however use the available numbers to begin to accumulate evidence that Tolerance to the analgesic effect of an opioid, declining effect at constant dose, can be detected by a constant PLR and increasing PRD.  
Opioid induced hyperalgesia (OIH), poor responsiveness, can be detected by a PLR decline with increasing PRD.

### B. Background and Significance

The Center for Disease Control found that in 2012, healthcare providers wrote 259 million prescriptions for opioid painkillers. In addition to being concerning due to the sheer volume this is also concerning given the difficulty with which prescribers have monitoring opioid analgesia<sup>1</sup>. Furthermore, it is generally recognized that pain assessment and management especially in newborns, children and other nonverbal populations is an unmet need<sup>2</sup>. According to the American Medical Association, “The pediatric population is at risk of inadequate pain management, with age-related factors affecting pain management in children. Children are often given minimal or no analgesia for procedures that would routinely be treated aggressively in

adults. Although much is now known about pain management in children, it has not been widely or effectively translated into routine clinical practice<sup>3</sup>.” These two factors combine to emphasize the necessity for an objective tool to quantify pain and monitor the effectiveness of analgesia, especially during treatments. This protocol proposes the use of infrared pupillometry in conjunction with selective neurostimulation as a method of measuring and monitoring pain and subsequently analgesia.

Pupillometry is a useful, non-invasive clinical and research tool that can provide valuable insights into the autonomic nervous system. Pupillary tests provide a convenient and simple method for evaluation of autonomic function<sup>4</sup>. In normal pupillary responsiveness, pupils should be equal in size, approximately 3-4mm in size under average light conditions, and reactive to light at >1mm of movement. The sympathetic nervous system is activated during periods of pain and stress and creates relaxation of the ciliary muscles resulting in pupillary dilation, or mydriasis. In accommodation, the parasympathetic axons that innervate the iris muscle produce constriction, or miosis. This reflex is known as the pupillary reflex dilation (PRD) and has been shown in previous studies to occur in both awake and anesthetized participants following a noxious stimulus<sup>5</sup>. This protocol will utilize these known reactions to track the response to specific neurostimulation in participants receiving opioids to determine the effect and effectiveness of the treatment.

All mu opioid agonists cause miosis (constriction of the pupil) thus reducing the constriction amplitude and constriction velocity of the PLR. This is the one opioid side effect to which tolerance does not occur. However, the pharmacologic impact is not consistent and will vary with different drugs in the class and duration of exposure. For example, morphine and Dilaudid (hydromorphone) each produce a neuro-excitatory metabolite that causes mydriasis or dilation of the pupil and also antagonizes the parent drug, producing the clinical appearance of tolerance, requiring more drug to achieve the same effect. With other drugs of this class such as fentanyl, which is commonly administered in ICUs, mydriasis may occur due to a phenomenon called opioid induced hyperalgesia (OIH) where there is an increased sensitivity to pain, often leading to an increased dose of drug. Increasing the dosing in this situation can potentially exacerbate the issue, having a method to monitor for OIH would provide decision support to physicians and allow them to recognize and properly reconcile this issue. Evaluation of PRD in response to a 5Hz neuro-stimulus can differentiate between these drug-related issues and disease progression. This works because opioid receptors populate the C fibers, which are stimulated with a 5Hz frequency<sup>6,7</sup>, allowing us to determine dose response relationships as well as the optimized analgesic dose and precisely determine dosing with opioid rotation. This occurs empirically during standard of care based on a trial and error approach that risks under or overdosing patients and having tolerance, dependence and OIH occur.

This pilot study is part of an ongoing effort to develop a method to objectively assess pain and its response to specific interventions. It specifically aims to develop profiles of the impact of a variety of opioids under a variety of conditions in a diverse patient population. It will allow researchers to understand better the specific impact of drugs in this class on the PLR and PRD. Data collected herein will help will evaluate the feasibility of using this approach to detect and monitor opioid analgesia and open new avenues for future research in this area.

The PI for this investigation, Julia Finkel, MD, has invented a device that combines pupillometry and neuro-specific neurostimulation that has the capability of measuring these three

pupillary reflexes. The intellectual property associated with this project is the subject of three patents: US9326725B2, US2015/0116665A1, US2017/0100061A1<sup>8-10</sup>. This technology was developed at Children's National Medical Center by Dr. Julia Finkel. AlgometRx, Inc. is a spin out company from CNMC that will commercialize the technology. Dr. Julia Finkel is the founder and Chief Scientific Advisor of AlgometRx. The "AlgometRx device" is the technology that will be used to carry out this exploratory observational study, and is being developed to ultimately measure pain and drug effect.

## **Description of Devices to be used:**

### **AlgometRx Device:**

The AlgometRx device is part of a platform technology, which integrates a smartphone enabled infrared video pupillometer comprised of an attach-on Camera, Processor, and Control Module (CPCM) with a Bluetooth enabled neuro-specific Neurostimulator Module (NSM). The smartphone serves as the graphical interface and display for clinical output. All data and signal processing occur on the CPCM and data is stored on a HIPAA compliant platform. These elements are used to assess the pharmacodynamic impact of analgesics and provide an objective measure of pain and pain sensitivity by modeling pupillary reflexes. Eventually, it will be used to provide an objective measure drug effect.

The smartphone-enabled device makes use of pupillary responses to two different stimuli: the pupillary light reflex (PLR) and the pupillary reflex dilation (PRD), which have both been extensively studied and established in literature. The team utilizes low intensity, non-noxious neurospecific neurostimulation from the NSM to produce a neuro-stimulus induced pupillary reflex dilation (nPRD). This is fundamental to our observations regarding pain sensitivity and drug effect. These pupillary reflexes have been evaluated several times by the study team using the NeuroOptics pupillometer. The IR pupillometer in the CPCM collects pupillary measurements in the same way that the NeuroOptics pupillometer does.



Figure 1. AlgometRx Research Prototype

The CPCM smartphone attachment communicates through a Wi-Fi connection. An application running on the smartphone provides the graphical user interface for control and monitoring of the system. The CPCM controls lighting within the eyepiece and records video during a measurement to monitor pupil dilation in response to a controlled light source and/or neurostimulation. The NSM provides electric stimulation through electrodes attached to the patient, and is controlled via the Bluetooth connection. Video recording of the pupil, processing, and parameter calculation are all performed using electronics within the CPCM. The device works with the same purposes as the NeuroOptics pupillometer (for the pupillary measurement) and the Neurotron Neurometer (for the electric stimulation).

### Pupillometry

This device delivers a light stimulus to the eye and measures the following: the pupil diameter at time of constriction (max pupil diameter), the pupil diameter at peak constriction (minimum diameter), the constriction amplitude (max-min/max), latency of constriction, velocity of constriction, and velocity of re-dilation.

In addition to assessment of the pupillary light reflex, CPCM also allows for the assessment of the pupillary reflex dilation (PRD). The device tracks the pupillary diameter without a light stimulus, which allows the researchers to measure changes in pupillary diameter in response to stimuli a valuable tool for detection of analgesia.

#### Neurostimulator Module:

Neurostimulation is accomplished by the delivery of minute currents, the magnitude and duration of which are designed to fall well below injurious or intolerable pain. A sinusoid waveform at a specific frequency selectively depolarizes a particular nerve type because different diameter nerves have characteristic refractory periods. Each of the three major sensory nerve fibers: small unmyelinated C (slow pain, temperature, postganglionic sympathetic nervous system), small myelinated A $\delta$  mechanoreceptors (touch, fast pain), and large myelinated A $\beta$  (cutaneous touch, pressure) can be evaluated at 5 Hz, 250 Hz and 2,000 Hz, respectively<sup>6,11</sup>. The stimulus is administered through electrodes attached to a finger or toe (resembling a pulse-ox probe). This module works the same as the Neurotron NEUROMETER<sup>®</sup>, which is an FDA-approved device that the study team has employed in past studies at Children's National.

#### Neurostimulator Patient Prep and Attachment of Electrodes

The neurostimulator is attached to the patient using standard NEUROMETER<sup>®</sup> CPT disposable Goldtrode<sup>®</sup> electrodes purchased from Neurotron, Inc. (Baltimore, MD).

#### Electrode Description:

Goldtrode<sup>®</sup> electrodes consist of a pair of round, gold plated electrodes (1 cm./dia.) mounted in a clear, semi-rigid Mylar spreader separated by a distance of 1.7 cm. They are composed of materials which deliver the stimulus with minimal amount of distortion for consistent, accurate measures.

#### Attaching Electrodes:

Over flat surfaces, the standard distance between the electrodes is 1.7 cm. However, when stimulating the fingers or toes, the 1.7 cm distance only gives the maximum distance between the electrodes. For the fingers and toes the electrodes must be placed on the "medial and lateral aspect of the distal phalange (overlying the digital branches of the nerve), proximal to the cuticle and distal to the distal interphalangeal joint." (Neurometer Operating Manual Version 17.2c)

Electrodes are attached to the patient using conductive gel. Gel is hypo-allergenic, non-staining and chloride free. Only enough gel will be applied to cover a thin layer of the skin that will be in contact with the electrodes. After gel application, the electrodes are fixed to the skin

surface with SOFTAPE™ electrode tape. The tape is applied over the backs of the electrodes to hold them in place. Tape secures the electrodes so that they are in constant contact with the skin surface and not too tight as to cause significant sensation or restrict circulation.

#### Device Safety Features

- The AlgometRx device was developed to the same specifications as the predicate devices (Neurotron NEUROMETER®, NeurOptics pupillometer) used by this team in a number of prior trials
- Several systems work in tandem to absolutely ensure that there are no risks of any electrical injury
- Smart high voltage DC-DC converter from Emco with an internal shutdown feature for short circuit protection
- Neurostimulator has a maximum current value of 50mA on the output electrodes limited by a 2kiloohm resistance in series.
- LED indicators on the instrument turn on whenever stimulus is being applied
- The equipment has been tested thoroughly and abides by the same safety standards applied to the predicate devices. These limits provide reasonable protection against electromagnetic interference when operated in the intended uses' environments (e.g. hospitals, research laboratories).

#### Labeling, Storage, and Maintenance

Per 21CFR812, an investigational device or its immediate package shall bear a label with the following information: the name and place of business of the manufacturer, packer, or distributor (in accordance with 801.1), the quantity of contents, if appropriate, and the following statement: "CAUTION--Investigational device. Limited by Federal (or United States) law to investigational use." The label or other labeling shall describe all relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings, and precautions."

The AlgometRx device was manufactured by General Digital Corporation (South Windsor, CT). The caution label as described above is displayed on the back of the NSM and the side of the CPCM, as visualized in the User Manual.

The gold electrodes are disposable. The eyecup of the device is cleaned with an alcohol wipe between uses.

### **C. Preliminary Studies**

The investigators have extensive experience with pupillometry and neurostimulation and the ability of it to be used to assess various pharmacokinetic and pharmacodynamics relationships in both children and adults. The basis for this technique is derived from ongoing clinical research examining the ability of pupillometry to assess the effects of ketamine on morphine tolerance and hyperalgesia. Previous studies have utilized the Neurometer, a predicate to the AlgometRx device, for selective neurostimulation and have established a great deal of acceptability for this procedure among a population of children and adolescents. To date more

than 50 patients across multiple trials including some ongoing trials have utilized this neurosimulation technique with no reportable difficulties or patient complaints.

- Modulation of  $\mu$ -Opioid Receptor Mediated Analgesia, Tolerance and Hyperalgesia in Children and Adolescents. J.C. Finkel, S.R. Pestieau.
- Quantitative sensory testing and pupillometry in sickle cell disease patients. Z. Quezado, J.C. Finkel. Currently enrolling patients. Pro00003614.
- Pupillometry as a screening tool for POTS. J.C. Finkel. Ongoing. Pro00004950.
- Pupillometry as a screening tool for autonomic neuropathy in diabetic patients. J.C. Finkel. F. Cogen. Ongoing. Pro00006483

## **D. Research Design and Methods**

This is a single center infrared pupillometry device study that monitors the analgesia response provided by an opioid to a controlled and selective neurostimulation.

### **Eligibility Criteria and Recruitment**

This study will recruit patients from two populations: patients in perioperative care and patients admitted for chronic pain. For both populations, patients will be identified from the pain management service as patients requiring the use of one of three types of opioids: morphine, hydromorphone or fentanyl. Once identified, patients will be approached and consented in their private rooms and given ample time to review all necessary information and ask any questions prior to agreeing to participate.

### **Study Oversight and Monitoring**

Testing will be conducted in a controlled environment and the direct observation and implementation of testing procedures will be conducted by trained study staff. The Principal Investigator will oversee the testing conducted at each visit and ensure that the device is handled properly and data collection is conducted according to protocol.

### **Prior and Concomitant Therapy**

Medications taken within the last 30 days prior to consent will be recorded as well as those taken from the time of informed consent until the completion of all study related procedures.

### **Study Procedures**

Patients and parents will be informed on all aspects of the study and given ample time to review all documentation and ask questions prior to signing the consent forms. Once consented, the participant will provide a threshold for the electrical stimulus level that induces a neuro-

specific neurostimulus evoked PRD (nPRD) will be determined for each test subject. This will occur by measuring the pupillary response to a neurostimulus, starting at 50 $\mu$ A and increasing by 50 $\mu$ A until an nPRD appears that demonstrates a 20% increase in pupil size above the initial pupil size. Each sensory nerve fiber will be assessed for the stimulus intensity to be used at the frequency of stimulation that corresponds to their activation (5 Hz, 250 Hz, and 2000 Hz for C, A $\delta$ , and A $\beta$ , respectively). This determination of intensity serves as the baseline nPRD measurement. A baseline PLR measurement will occur as well. To establish the baseline PLR measurement, researchers will use the pupillometer function of the AlgometRx Device to assess the pupillary light reflex in each eye. This assessment consists of a simple flash of light followed by 10 seconds of measurement by the infrared camera in the device. During this time the patient will simply be asked to hold their eye open for the duration of the assessment, there will be a wait of at least 30 seconds between the two measurements.

The individual steps of the baseline testing are summarized in figure 2 below.



Figure 2: Flow diagram of baseline testing procedures.

Once the baseline has been established for the PLR and nPRD the study team will visit the subject on a regular basis throughout the remainder of their time at the hospital with no more frequently than visits by the Pain Management team. The study team will operate independently from the Pain Management team and will not interfere with the care of the participant in any way. Visits from the study team will occur separately from those of the Pain Management Team so as to ensure the study is not interfering with normal clinical proceedings. The study aims only to *observe* the intervention put in place by this team. At each visit the study team will assess the pain level of the patient using the standard VAS 1-10 pain scale. For patients on a Patient Controlled Analgesia (PCA), if the patient is reporting a pain score of greater than or equal to a 6 and wishes to administer analgesic, the researchers will begin the testing procedure. For patients receiving a bolus dose of an opioid at regularly scheduled intervals, the researchers will evaluate the patient prior to the regularly scheduled dose to determine their pain score, if the patient is reporting a score greater than or equal to a 6 the researcher will begin the testing procedure. The subject will receive a dose of an opioid from the PCA pump or via bolus when indicated. After, 10 minutes the subject will undergo testing via the testing procedure outlined below. This sequence will be repeated if the patient continues to have pain (a pain score  $\geq 6$ ) until they have self-administered adequate analgesia. This will occur no more than four times in one day but will be done at least once daily while the patient is receiving an opioid. For patients in the PICU, twice daily testing will be done at specified times. To limit the potential burden on the participant, prior to each subsequent testing cycle the study team will give the participant the option to decline a running of the testing procedure at that time.

#### Testing Procedure:



The subject will participate in two rounds of testing each consisting of two steps, the assessment of the PLR and the assessment of the PRD.

First, using the pupillometer function of the AlgometRx device, the researchers will assess the pupillary light reflex in each eye. This assessment is identical to the PLR procedure above and consists of a simple flash of light followed by 10 seconds of measurement by the infrared camera in the device. During this time the patient will simply be asked to hold their eye open for the duration of the assessment, there will be a wait of at least 30 seconds between the two measurements.

Using the threshold of neurostimulation established at baseline the researchers will stimulate the subject 2 times at the threshold intensity for each of the three frequencies for a total of 6 stimulations. Each stimulus will occur for exactly 1 second with a break of at least 60 seconds between. During each stimulus, the researchers will monitor the subject's pupillary reflex dilation using an infrared pupillometer in the AlgometRx device. The device will be placed over the patient's eye and passively monitor the pupillary reaction before, during and for 10 seconds following the stimulus. Unlike the PLR assessment, this examination does not involve a flash of light and instead measures the reaction of the pupil to the stimulation created by the neurostimulatory component of the device.



Figure 3: Flow diagram of subsequent study procedures.

### **Information Management and Statistical Considerations**

#### Collection and Management of Study Data:

As part of PLR and PRD assessments we will record the parameters presented in Table 1 and Table 2 below. The curves produced during the PRD assessments will be compared taking into account the varying doses of opioids received to determine if there is a dose dependent impact on the PRD.

Static Measures	Dynamic Measures
Maximum Pupil Diameter	Latency of Constriction
Minimum Pupil Diameter	Constriction Velocity
Amplitude of Pupil Constriction	Redilation Velocity
	Recovery Time (75%)

Table 1. Measured parameters of the Pupillary Light Reflex (PLR).

Measures
Amplitude of Dilation
Area Under the Curve

Table 2. Measured parameters of the Pupillary Reflex Dilation (PRD).

### **Data Management Responsibilities**

All study staff will be responsible for ensuring participant confidentiality. All study data will be stored in the appropriate locked containers, and all electronic data should only be handled on hospital issued encrypted computers.

### **Data Capture Methods**

Data collection is the responsibility of the trial staff. The PI is responsible for ensuring the accuracy, completeness, legibility, timeliness and completeness of the data reported.

Sites will maintain all relevant source data. Source data include all information and original records of clinical findings, observations, or other activities necessary for the reconstruction and evaluation of the trial. Examples of original source documentation include electronic medical records, laboratory reports, memoranda, subject diaries, pharmacy dispensing records, and recorded data from automated instruments.

Paper copies of the electronic CRF (eCRF) will be provided for use as source documents. Study data will be recorded for each participant enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents. Any discrepancies between the eCRF and source documentation should be explained via a CRF comment or a note to file.

### **Study Record Retention Policy**

Study documents will be retained for seven years as per hospital policy, after which they will be disposed in the appropriate HIPAA bins.

## **Statistical Considerations:**

### **Analysis Plan**

To address aims 1 and 2, we will evaluate the pupillary response curve (inverse for PLR) over time based on multiple regression modeling. We will use our models to estimate the following features +/- 95% confidence limits: the area under the curve, peak amplitude and constriction velocity (for PLR) controlling for age and gender as well as pretreatment pain severity and opioid dose?. We will use these features to define specific profiles for each opioid we evaluate. Should we be unable to meet the normality assumption even after applying normalizing transformation we will switch to quantile (median) regression models to develop the aforementioned analyses. We will also explore various methods of data pre-processing (filtering, smoothing, interpolation etc.) to determine the procedure that leads for the most reliable and fastest extraction of these parameters from the raw curve data.

In aim 3, we will use these same parameters to assess the extent to which characteristic change in PRD and PLR parameters can be used to predict either tolerance or hyperalgesia. We will accomplish this by first identifying patients who are diagnosed clinically with each of these outcomes. Tolerance will be defined as experiencing less pain relief at the same or increasing dose of drug and hyperalgesia will be defined as developing neurologic responsiveness that increases the pain sensation, which is considered to place the patient at risk of morbid or mortal outcomes. To evaluate evidence of such associations, we will use multiple logistic regression modeling to assess whether PRD and PLR parameter change in patients experiencing tolerance,

hyperalgesia can be distinguished from those receiving persistent pain relief without tolerance or hyperalgesia. In regard to tolerance, we will evaluate whether patients experiencing or developing tolerance can be differentiated have increasing PRD parameters but static PLR parameters. In regard to hyperalgesia, we will evaluate whether patients experiencing or developing hyperalgesia have increasing PRD parameters with PLR decline. We have consulted with Dr. Robert J. McCarter, Jr, ScD in developing this statistical analysis.

### **Sample size**

PASS 14 was used to estimate the sample size needed in Aims 1 and 2 to provide suitably precise estimates of PLR and PRD parameters detect various effect size differences (expressed in standard deviation units)<sup>12</sup>. If the study enters analysis with at least 30 patients with treated with each opioid species under study, it will be able to derive estimates of the mean or median for each parameter being evaluated at each time point with precision equal to  $\pm 0.37$  standard deviation units. Based on a data from a pilot study of the drug cannabis, we believe this will be adequate to identify distinctive profile characteristics for each opioid medication.

We will use these results to develop reliable estimates of the prevalence of tolerance in clinical practice of pain control and explore the clinical utility of the profiles in aim 3 by comparing PLR and PRD parameters in patients (across all opioid species) to assess the evidence that defined patterns as described in the above analysis plan can differentiate between patients experiencing drug tolerance and hyperalgesia. We may not achieve numbers sufficient to achieve statistical significance but will begin to accumulate evidence of the viability of this approach and provide the statistics necessary to design appropriately powered future studies to resolve the issue.

### **Safety and Effectiveness Assessments**

#### **Safety Assessments**

All subjects will have a complete medical history collected.

#### **Inclusion Criteria:**

All of the following criteria must be met for the potential subject to be eligible for study participation:

- 1) The subject is 7 to 21 years of age
- 2) The subject is receiving an opioid via bolus or a PCA as part of treatment or fentanyl infusion in the PICU (generally postoperative patients).
- 3) The subject is willing and able to provide written informed assent/parental consent to study participation

#### **Exclusion Criteria:**

The potential subject is NOT eligible for participation if any of the following exclusion criteria are met:

- 1) Eye pathology precluding pupillometry
- 2) For patients in the PICU, patients who are hemodynamically unstable

### **E. Study Population – (Gender and Minority Inclusions):**

We anticipate that 100 subjects, from all ethnic backgrounds ages 7-21 will be enrolled. The census on the pain management service will be screened daily for patients receiving an opioid via bolus or a PCA and for patients in the PICU receiving fentanyl infusions.

#### **F. Human Subjects (Risks & Benefits)**

If the parent/patient shows interest in the study, the subject will be asked to read through the informed consent form. The informed consent form will also include language concerning HIPAA regulations and the use of personal health information in this research study. The consent process will be conducted when the subject has completed reading the consent and all questions about the study have been answered to the subject's satisfaction. If the subject decides to participate, consent will be obtained. After consent, a thorough medical history will be conducted, including all medications taken in the last 30 days.

#### **G. Risks and Side Effects:**

The study device is non-invasive and integrates two technologies utilized by FDA approved medical devices with which the investigators have extensive experience. Neuro-specific neurostimulation is utilized as a diagnostic tool by Neurotron Inc.'s FDA approved Neurometer® device. The battery on this device can never simultaneously charge and power the device. This ensures that the patient is never directly connected to an electrical circuit that is also connected to the AC main (wall outlet) power supply. Therefore, there is no risk of danger from electrical shock from this device. The current intensity never reaches a level that causes actual pain. The current transmitted is painless. The patient is in control of stopping the stimulation when it reaches a level that they feel is no longer comfortable.

The peak amount of current delivered by the device is 10mA. This translates to a root-square-mean of sinusoidal current that reaches a maximum of 7mA. This is an amount of current that will not cause injury to the patient.

Regarding the opioid aspect of the study, we propose to enroll subjects who are receiving an opioid as part of their already occurring treatment so, there is no increased risk associated with this portion of the study.

No other risks are anticipated

#### **Reporting of Adverse Events, Unanticipated Problems and Serious Adverse Events:**

All adverse events will be captured by a member of the study team in the subject's source document. The principal investigator, Dr. Julia Finkel, will assess all AEs for their severity and relationship to the study device.

The PI will be monitoring the study and available on site to address any SAEs or unanticipated adverse events or problems that involve risks to subjects or others. The Children's National Medical Center IRB will be notified of any Serious Adverse Events within 24 hours and any unanticipated adverse events that may impact patient safety within 5 days. Reporting of SAEs and any unanticipated problems will follow the CNMC IRB guidelines - IRB document 06.02 of 'The IRB Policy and Procedure Manual'. All other AEs will be reported to the IRB in continuing review reports.

### **Reporting of Data Review Outcomes to the IRB:**

Unanticipated problems that pose an immediate threat to patient safety will be immediately reported to the IRB. All SAEs will be reported within 24 hours to the IRB. Semi-annual data monitoring reports will be submitted to the IRB upon completion – generally within 5 days of the data review.

### **ADVERSE EVENT (AE), SERIOUS ADVERSE EVENT (SAE), UNANTICIPATED ADVERSE EVENT (UAE)**

Throughout the study, AEs will be documented on the source document whether or not considered device-related. AEs will be tracked in an AE table and reviewed for incidences of unanticipated AEs. Reported AEs include any new signs, symptoms, injury or illness, including increased severity of previously existing signs, symptoms, injury, or illness. Conditions existing prior to screening will be recorded as part of the subject's medical history. The investigator is responsible for assessing the relationship of AEs to the study device; relationship will be classified as unclassified, unrelated, unlikely, possible, probable, or very likely/certain. All AEs will be collected by the investigator during the study visit.

UAE is any AE with a specificity or severity not consistent with the risk information described in the protocol, or any event occurring more frequently than anticipated. The PI will monitor any UAE and all UAEs will be reported to the IRB.

### **Definition of SAE**

An SAE is defined as an AE that:

- Results in death
- Is life-threatening (there is an immediate risk of death from the AE as it occurred; or if it is suspected that the use or continued use of the study medication would result in the patient's death)
- Results in an inpatient hospitalization (Note: a hospitalization for elective or preplanned surgery, procedure, or drug therapy does not constitute an SAE)
- Results in significant, persistent or permanent disability (permanent or substantial disruption of one's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect
- Results in intervention to prevent permanent impairment or damage;

Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.

Important medical events are defined as events that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes. Examples of important medical events include acetaminophen overdose-induced hepatotoxicity that requires treatment with acetylcysteine to prevent permanent damage; burns from radiation equipment that require drug therapy; breakage of screw that requires replacement of hardware to prevent malunion of a fractured long bone.

### **Criteria for Identifying Relationship of AE/SAE to Study Device**

<u>Relationship</u>	<u>Attribution</u>	<u>Description</u>
<u>Unrelated to investigational agent/intervention</u>	<u>Unrelated</u>	<u>The AE is clearly <b>NOT</b> related to the intervention</u>
	<u>Unlikely</u>	<u>The AE is <b>doubtfully</b> related to the intervention</u>
<u>Related to investigational agent/intervention</u>	<u>Possible</u>	<u>The AE <b>may be</b> related to the intervention</u>
	<u>Probable</u>	<u>The AE is <b>likely</b> related to the intervention</u>
	<u>Definite</u>	<u>The AE is <b>clearly</b> related to the intervention</u>

### **Unanticipated Problem (UP) Definition:**

A UP includes unanticipated problems involving risks to participants or others, and includes any incident, experience, or outcome that meets all of the following criteria

- Unexpected in terms of nature, severity, or frequency given the research procedures described in the study documents (e.g., consent, protocol, IB) the participant population; AND
- Related or possibly related to participation in the research-- “Possibly related” means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research; AND
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic or social harm) than was previously known or recognized.

### **Event Severity:**

All AEs will be assessed by qualified investigators (MD, NP or PA) using the CTCAE defined grading system. The following guidelines will be used to determine the severity of the AE:

#### **Grade      Description**

0. No AE (or within normal limits).
1. Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2. Moderate; minimal, local, or noninvasive intervention (e.g., packing, cautery) indicated; limiting age-appropriate instrumental activities of daily living (ADL).
3. Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
4. Life-threatening consequences; urgent intervention indicated.

5. Death related to AE.

In addition to monitoring by the PI, Evonne Greenidge, MD from the Department of Anesthesia will serve as a medical monitor for the study. Dr. Greenidge will review study data quarterly for patient safety.

**H. Benefits:**

This study provides initial data needed to make the first steps toward developing a technique that could meet a serious unmet medical need - objective measurement of pain and assessment of analgesic efficacy in patients.

**I. Outside Consultants/Collaborators**

Neil Goldsman, PhD., Professor of electrical engineering and computer science UMD  
Zeynep Dilli, PhD, computer Science and statistical methods  
Siddharth Potbhare, PhD. Both from CoolCAD LLC, a UMD start-up collaborating on the analysis of the data. CoolCAD is a member of the Technology Advancement Program incubator, an initiative of the Maryland Technology Enterprise Institute (Mtech) in the A. James Clark School of Engineering

**J. Contractual Agreements**

None.

**K. Costs To Subjects:**

There will be no costs to subjects.

**L. Conflicts Of Interest:**

This study's independence from all perceived or actual influence is essential. All actual conflicts of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this study will be disclosed and managed. Furthermore, persons with a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. The study leadership, in conjunction with the Children's Research Institute (CRI) has established policies and procedures for all study group members to disclose all potential conflicts of interest. The CRI has established a mechanism to manage all reported conflicts of interest.

The device being used is a result of technology developed at Children's National Medical Center by Julia Finkel, MD. AlgometRx, Inc. is a spin out company from CNMC that will commercialize the technology. Dr. Julia Finkel is the founder and Chief Scientific Advisor of AlgometRx. The IRB has determined that Dr. Finkel may serve as the PI for this study in previous meetings specifically conducted to discuss a conflict of interest.

**M. Confidentiality:**

All study records will be kept confidential. Provisions to protect the privacy of patients and maintain the confidentiality of data will include the use of an assigned study number instead of the patient's name on all records and documents produced in performing and reporting the results of this study. These records will be kept in a secure location.

## **N. Subject Compensation:**

None. All patients enrolled are receiving standard of care.

## **O. Facilities and Equipment**

Facility: CNMC

## **P. References & Literature Cited**

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9. Finkel JC, Inventor; Children's National Medical Center, assignee. Apparatus and method for determining physiologic perturbations of a patient Submitted 2015 April 30.
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11. Finkel JC, Yang CI, Yarzitz JL, Patel KM. Neuroselective sensory electrodiagnostic evaluation of 4% liposomal topical lidocaine. *Anesth Analg*. May 2002;94(5):1259-1262, table of contents.
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**Q.**    Appendices

Appendix I: Explanation and Visualization of Pupillary Light Reflex and Pupillary Reflex  
Dilation Parameters

## **Appendix I**

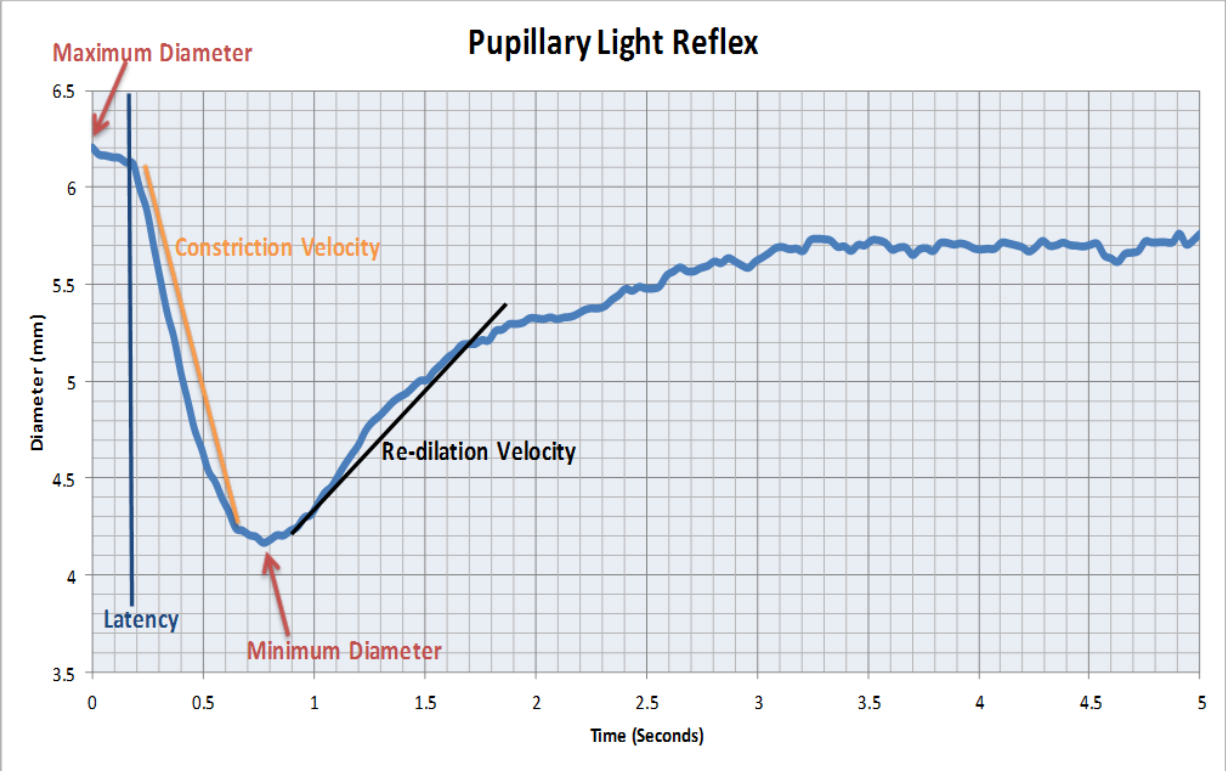


Figure 1. Diagram of PLR curve with parameters labeled.

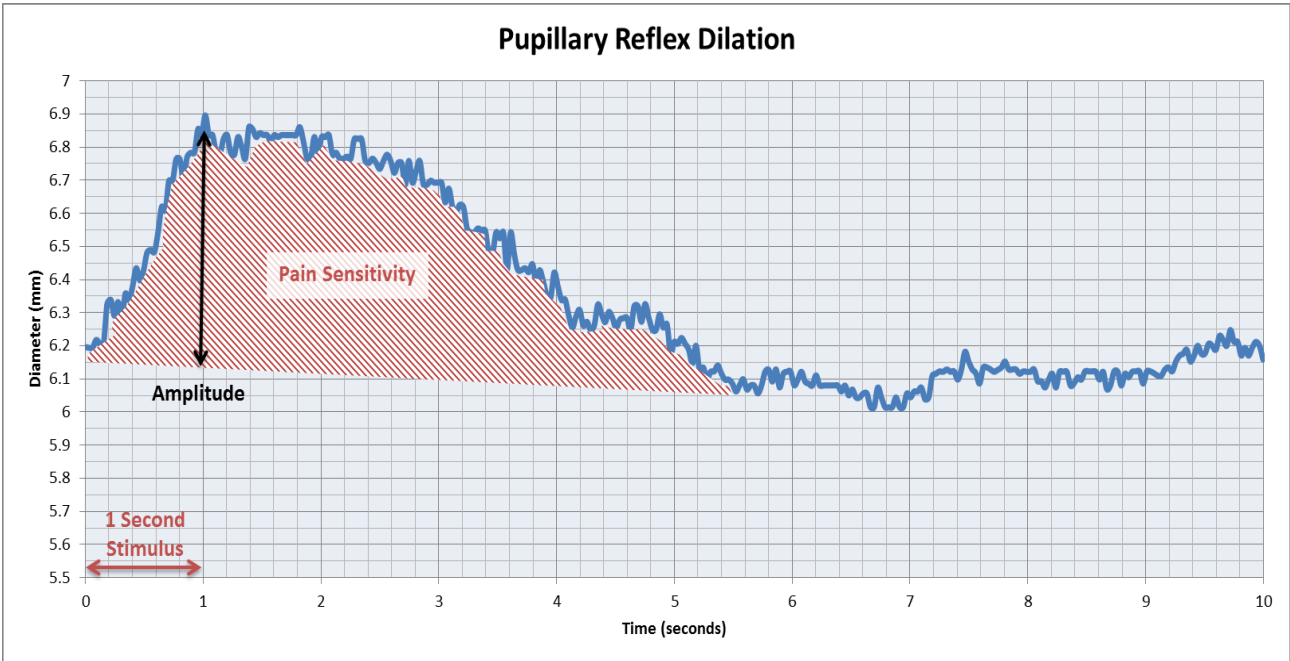


Figure 2: Diagram of PRD curve with parameters labeled.

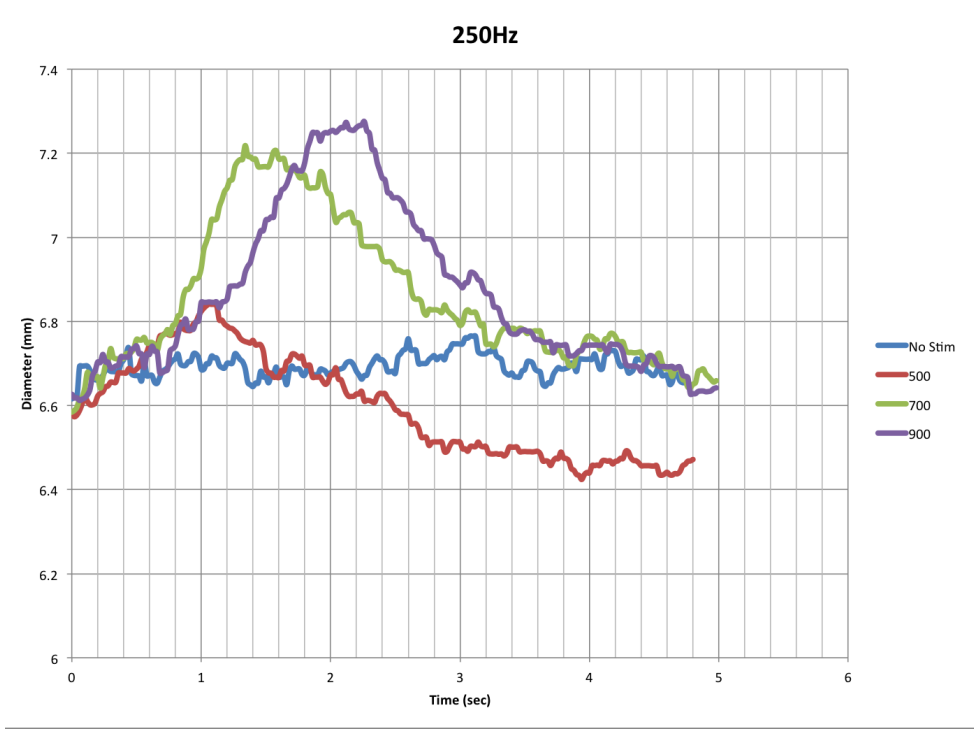


Figure 5 PRD intensity –response relationship using the 250Hz (A-delta nerve fiber type). Image represents 1 sec of stimulation followed by the PRD. Blue is no stimulus, red is 5milliampere (mA) and green resulted from 7mAof stimulus and the purple curve resulted from 9mA.

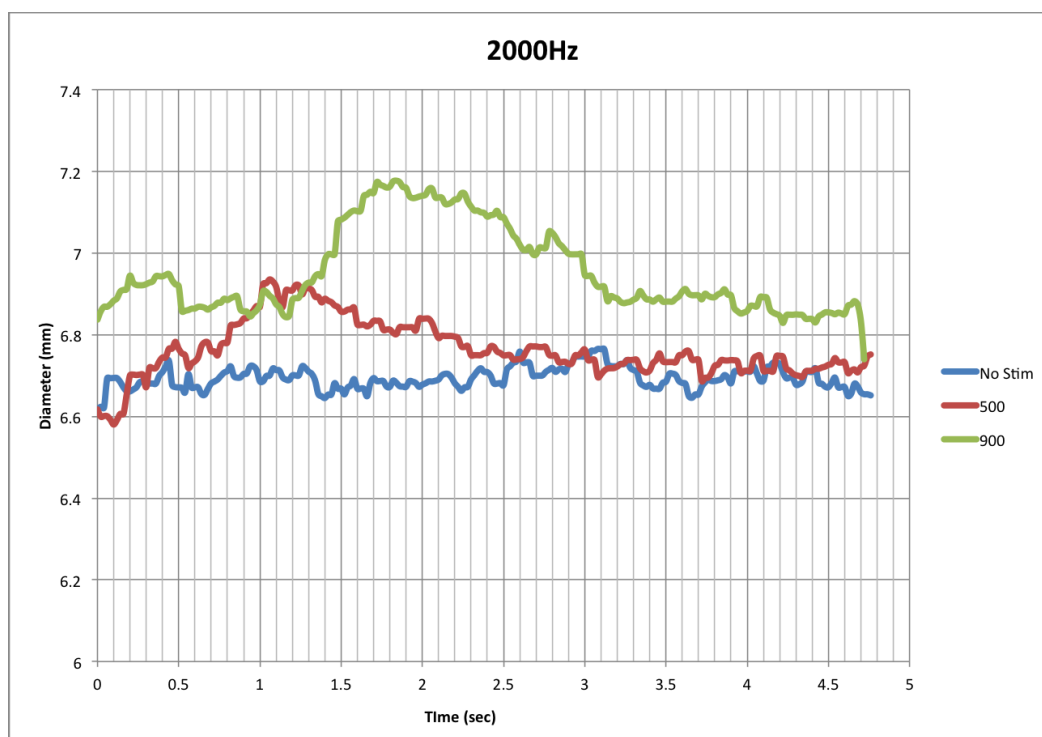


Figure 6 PRD Intensity –response relationship using the 2000Hz (A-beta nerve fiber type). Image represents 1 sec of stimulation followed by the PRD. Blue is no stimulus, red is 5milli amps and green resulted from 9mA of stimulation. Note that the A beta nerve is normally not a pain fiber but transmits neuropathic pain. The PRDs are therefore flatter in normal subjects. (At high intensities, A delta nerves are recruited accounting for the peak amplitude in the 9 m A curve) A patient with neuropathic pain would have high amplitudes in response to low intensity stimulation.



Figure 7 PRD Intensity –response relationship using the 5Hz (C nerve fiber type). Image represents 1 sec of stimulation followed by the PRD. Blue is no stimulus, red is 5 mA and green resulted from 9 mA of stimulation. Note that the c fiber transmits slow burning pain and are populated by the opioid receptors.