# Cryoanesthesia for Intravitreal Injections

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## 1.0 Purpose of the Investigation (Background):

In 2004, Friedman and colleagues (Friedman, O'Colmain et al. 2004) applied age, ethnicity, and gender specific rates of age-related macular degeneration to the 2000 US census and estimated that 1.75 million Americans had exudative macular degeneration. Population based estimates suggest that this number will increase to 2.95 million or more by the year 2020. Using these same principles Western Europe was estimated to have over 3.3 million patients with exudative macular degeneration in 2004. These numbers are likely underestimates of the true prevalence of this disease. The majority of these patients are receiving intravitreal injection therapy (IVT) multiple times per year in one or both eyes. Recent studies have demonstrated that IVT is at least as successful as laser therapy in treating vision threatening retinal disease in patients with diabetic retinopathy and retinal vein occlusions, resulting in IVT becoming the standard of care in these patients as well. In addition, there are several novel therapies in clinical trials that utilize intravitreal delivery.

The rapidly growing demand for IVT has led to severe strain on clinic work flow, as IVT is a time consuming procedure. Ophthalmologists perform these injections in busy clinics, frequently treating 60 to 70 patients a day. These injections are painful, and ophthalmologists typically choose various methods of anesthesia for IVT. The standard of care (SOC) is to provide anesthesia by either applying cotton-tipped applicators soaked in lidocaine, applying lidocaine gel, or giving a subconjunctival lidocaine injection. These methods of anesthesia increase the time for patient preparation by several fold. The other commonly used option is to provide anesthesia via topical eye drops, which is more time efficient, but may result in patient discomfort (Blaha, Tilton et al. 2011, Davis, Pollack et al. 2012, Sanabria, Montero et al. 2013, Xing, Dorrepaal et al. 2014). Developing a device to provide rapid anesthesia of the ocular surface will improve patient comfort and physician efficiency. A recent case report on a patient with an allergy to lidocaine demonstrated that excellent anesthesia is possible with the application of ice to the ocular surface.(Lindsell, Miller et al. 2014) The cryoanesthesia device provides very focal, rapid cooling, resulting in a safer, more reproducible, and more effective way of delivering anesthesia to the ocular surface. With over 8 million injections given annually in the United States alone, the impact of this device would be significant.

**1.1 Name of Investigational Device:**

Cryoanesthesia device

**1.2 Intended Use of the Investigational Device:**

The cryoanesthesia (CA) device is designed to provide anesthesia to a focal area on the surface of the eye immediately prior to intraocular injections. The device is a portable, handheld device that utilizes thermoelectric cooling to rapidly anesthetize a 4x4 mm area on the surface of the eye. It is designed to decrease patient discomfort before, during, and after intraocular injections compared to current anesthetic methods.

**1.3 Risk Analysis:**

*Safety Studies:*

Our confidence in our ability to create a safe device is based on clinical studies that occurred with the advent of cryotherapy to treat ocular tumors and retinal tears. The goal of cryotherapy to treat retinal tears and choroidal and retinal tumors is to create tissue destruction, and the initial pre-clinical and clinical safety studies of these therapies provided a wealth of histopathologic data that has guided our initial safety studies. Chi and Kelman (Chi and Kelman 1967) studied corneal endothelial viability following the application of cryotherapy at various temperatures to the cornea for 20 seconds. They reported **no endothelial cell loss at -10°C with largely reversible cell loss at -20°C**. Irreversible endothelial cell loss occurred at the temperature of -80°C, particularly in eyes treated with a larger probe tip. Maumenee and colleagues (Maumenee and Kornblueth 1949) carried out a safety study looking at the toxicity of -78°C applied to a rabbit cornea for 5 seconds (6 mm treatment spot). They found cellular damage within the first 5 days that completely resolved at days 10 and 12. Curtin and colleagues (Curtin, Fujino et al. 1966) examined the effect of -40°C applied to rabbit sclera via histopathology. The temperature was applied until retinal whitening was seen (generally 10-20 seconds). The authors reported minor cell loss at days 2 and 4 post treatment. These changes were no longer apparent at days 7, 14, and 21 post treatment. In a separate study, scleral bursting strength was found to remain stable following 6 cryotherapy treatments of -60°C applied for 1 minute each.(Beckman, Leff et al. 1975)

More recently, cryotherapy histopathologic damage on human cadaveric eyes was studied using atomic force microscopy. 3 eyes were sectioned into 30 scleral sections. A cryoprobe at -80°C was used for treatments. Three groups were treated for 5, 10, or 20 seconds respectively (N=6 in each group). One group received a sham treatment (room temperature probe applied to sclera, N=6) and one group did not come into contact with the probe (control, N=6). All scleral sections were examined via atomic force microscopy. Lee and colleagues found that eyes treated at -80°C for 5 seconds showed mild changes in scleral thickness and collagen fibril density (mild increase due to inflammation). These changes were more marked in the eyes treated for 10 or 20 seconds. Eyes treated for 5 seconds had no significant nanostructural differences in the diameter of collagen fibrils compared to controls. There were significant changes in eyes treated for 10 or 20 seconds. (Lee, Choi et al. 2013) This study showed that temperatures that are designed to cause tissue damage, and are many times colder than our device is capable of achieving, do not cause significant damage if applied for short periods of time. Studies of cryosurgery have demonstrated reversible nervous system blockade at temperatures ranging from 0°C to -10°C, with no pathologic tissue damage.(Garamy 1967)

*Testing Completed – Animal Safety Study:*

Our team completed preliminary safety testing using a specialized and more powerful non-portable prototype with the capability of achieving temperatures as cold as -40°C. We treated 20 New Zealand rabbits, utilizing 2 treatment times (10 and 30 seconds) and the following 10 temperatures: 20°C, 0°C, -5°C, -10°C, -15°C, -20°C, -25°C, -30°C, -35°C and -40°C. Each rabbit received

treatments just posterior to the limbus at the 1:30, 4:30, 7:30, and 10:30 meridians in both eyes. A total of 10 animals were included in phase 1, and each rabbit received 4 treatments per eye for 30 seconds. A total of 10 animals were included in phase 2, and each rabbit received 4 treatments per eye for 10 seconds. All animals were sacrificed 1 week following application of the cryo-anesthesia probe. The eyes were removed and sent to Comparative Biosciences Inc. for processing and histopathologic evaluation.

Comparative Biosciences, Inc. offers GLP and non-GLP preclinical toxicology, efficacy, pharmacology, pharmacokinetics-pharmacodynamics, histopathology, and safety studies on all laboratory species. They are a fully-staffed, state-of-the-art, AAALAC-accredited purpose-built facility with both an in house histopathology laboratory and a full time quality assurance unit. They are registered with the FDA, USDA, and OLAW. Histopathology was read by certified veterinary pathologist.

None of the eyes manifested signs of clinical toxicity immediately following treatment. Histopathologic toxicity at the limbal zone was minimal and consisted of small microhemorrhage, with scattered lymphocytes and monocytes and some local edema seen in a few eyes. The majority of these findings were located in myocytes. However, no ocular muscles were treated in any animal during this study. The pathologic findings of focal hemorrhage, inflammation, and myocyte damage relate to artifact/crush injuries to the muscles/ocular surface that occurred using 0.5 forceps to position the eyes of the anesthetized rabbits in a way that permitted exposure of the treatment sites (**Fig 1**). **In all eyes, the anterior segment (cornea, iris, ciliary process, lens and sclera were within normal limits, as was the retina and optic nerve. Of note, none of the eyes treated with -40°C for 10 seconds had any histopathologic findings. The coldest temperature planned for the proposed study is -10°C (23°F) for 20 seconds.**

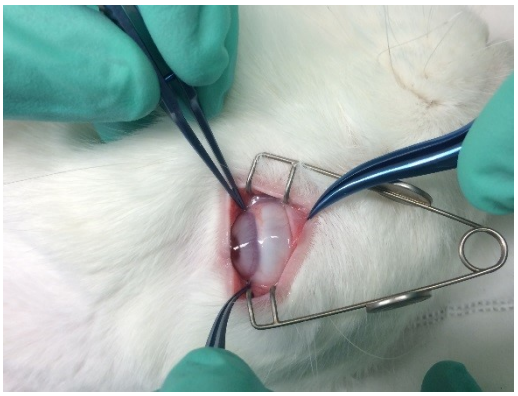


**Figure 1 | Site of cryotherapy treatment, preclinical safety study**

*Risks of the Proposed Study:*

The primary risks patients will be exposed to relate to those that occur with IVT (SCH, conjunctival hyperemia and injection, and corneal keratopathy). The risks of the CA device include mild ocular discomfort secondary to the cold temperature.

All patients will receive topical anesthetic drops (proparacaine) prior to focal anesthesia (either CA or SOC). These drops will help reduce the occurrence of pre-injection discomfort. The topical anesthetic drop will provide baseline anesthesia if there is minimal anesthetic effect achieved by cryoanesthesia. Topical proparacaine use as stand-alone anesthesia prior to intravitreal injections is one of the common methods of providing anesthesia and is considered within the standard of care for intravitreal injections (Blaha et al., 2011, Davis 2012).

Patients receiving SOC undergo the risk of increased corneal keratopathy. In addition, patients receiving the SOC have an increased risk of post injection pain. The risk of mild ocular discomfort

with CA is mitigated by the use of proparacaine and also poses less risk to patients than topical lidocaine.

#### 1.3.1 Primary Objective:

We plan to carry out a pilot study to collect preliminary data on the effectiveness of the cryoanesthesia (CA) device in minimizing the pain caused by intravitreal injections (IVT) and determine the most effective temperature and time of treatment. Specifically, we intend to record patients' subjective injection pain. The study will be carried out in patients receiving bilateral injections, and one eye will be anesthetized using the CA device, with the fellow eye receiving anesthesia via a topical lidocaine gel (SOC), a common method of providing anesthesia in current clinical practice.

#### 1.3.2 Exploratory Objective(s):

We will measure injection preparation pain, 4-hr, and 24-hr post injection pain. Patients will rate ocular irritation immediately after injection as well as 4 and 24 hours after injection (1 – no irritation; 2 – mild irritation 3 – moderate irritation 4- marked irritation). Patients will rate visual function in the treated eye immediately after injection as well as 4 and 24 hours after injection (1 – no changes from baseline; 2 – mild blurring of vision 3 – moderate blurring of vision 4- marked blurring of vision). Physicians will record patients' objective response to intraocular needle penetration (1 – no pain/movement; 2 – mild pain/movement 3 – marked pain/movement with the injection). In addition, physicians will record the following common ocular side effects following IVT: subconjunctival hemorrhage (SCH), conjunctival hyperemia, and conjunctival injection. These will be assessed via a slit lamp examination performed within 30 minutes and 24 hours of the administration of the intravitreal injection. In addition, each eye will be assessed for other signs of anterior segment toxicity, including AC reaction or hypotony. Patients will be examined or receive a call 1 week after the injection to assess any adverse effects.

### 1.4 Anticipated duration of the clinical investigation:

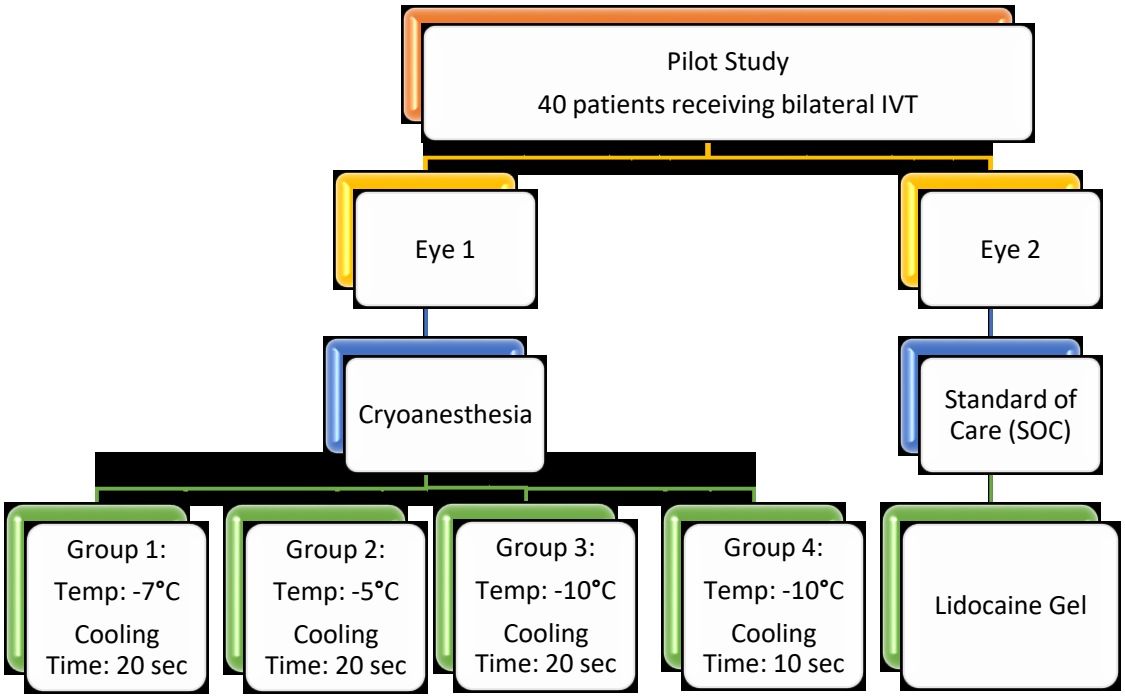
We plan to recruit 40 patients for this study, and each patient will receive a single injection in each eye. Most patients receiving bilateral injections receive both injections in a 1-2 week period (1 eye at day 0, and the second eye by day 14). This is the current standard period between intravitreal injections, and is used regardless of the form of local anesthesia delivered. Some patients receive bilateral injections during the same clinic visit. First eye treatment will be randomly assigned to one of the CA treatment groups and the other eye will be randomly assigned to SOC.

## 2.0 Study Design:

### 2.1 General Study Design:

Prospective, interventional pilot study.

#### 2.1.1 Study Design Schematic:




## 2.2 Subject Selection:

### 2.2.1 General characteristics of the proposed subject population(s):

Patients age >18 years old with bilateral macular disease due to either exudative macular degeneration or diabetic retinopathy requiring bilateral IVT and who had at least one prior IVT. To be included in this study, patients must be able to give informed consent.

Patients with bilateral macular disease requiring bilateral IVT will enable us to compare the effectiveness of CA compared to SOC in terms of pain reduction, with each patient serving as their own control.

### 2.2.2 Anticipated Number of Research Subjects:

We anticipate recruiting and enrolling 40 patients to complete this study (10 for each CA group). We expect that all 40 patients will complete the study.

### 2.2.3 Inclusion Criteria:

Inclusion criteria: Patients age >18 years old with bilateral macular disease due to either exudative macular degeneration or diabetic retinopathy requiring bilateral IVT. Only patients with at least one previous IVT will be recruited. To be included in this study, patients must be able to give informed consent.

### 2.2.4 Exclusion Criteria:

Exclusion Criteria: Patients < 18 years of age. Patients with unilateral disease, or patients with bilateral disease who are not able to give informed consent. Patients with preexisting conjunctival, episcleral or scleral defects or disease will be excluded.

## 2.3 Study Procedures:

**2.3.1 Screening Procedures:**

Physician will verify the need for IVT prior to beginning the study.

**2.3.2 Study Treatment or Diagnostic Product Procedures:**

*Device Overview*:

The cryoanesthesia device is a handheld instrument measuring approximately 10 inches in length and 1.5 inches in diameter. A 4×4 mm area at the tip of the device is placed against the eye and cooled to the temperature setpoint (e.g., -5°C, -7°C, or -10°C) via activation of a switch on the device. Cooling slows conduction of pain fibers in the conjunctiva (outermost layer of the eye) and the sclera (white of the eye) to a depth less than a millimeter. The key features of the device include a temperature regulating feedback loop to maintain highly accurate temperature control and a lockout mechanism to prevent excessive cooling. Two small protrusions on the tip leave temporary indentations on the surface of the eye to guide subsequent placement of the intravitreal needle. The cooling region of the device is located on a replaceable metal tip. An "ON" switch is first activated to cool the contact region of the device, after which this region is placed against the eye, initiating rapid cooling to anesthetize the injection site while simultaneously marking the cooled location. After the specified cooling time is reached, the device is removed, immediately after which the physician performs intravitreal injection.

*Instructions for administering CA:*
All physicians taking part in this study will receive a practical training session on use of the prototype prior to study initiation to ensure that they are comfortable operating the device.

*Injection procedure:*
After obtaining written consent, the brow above the eye to receive intravitreal treatment will be marked. Next, one drop of proparacaine will be applied into the eye to at least 5 minutes before any additional steps. Once the patient is ready, another drop of proparacaine will be applied and the physician or his assistant will then swab the lids with betadine. The physician will place a lid speculum in the patient's eye. A drop of betadine will be applied at the site of treatment. The physician or his assistant will then activate the CA device by pressing the main button. He or she will review the LED display to verify that the device is set to achieve the correct temperature and time setpoints depending on the arm of the study to which the patient is randomized. The physician will adjust the temperature and time set points using the main device button if they are not correctly entered. The physician will then verbally review the selected treatment temperature and time, after which he or she will activate the device to enable the device tip to reach the required temperature. Immediately prior to placing the device tip against the eye, the physician will press the activation switch, after which he or she will apply the device to the surface of the eye. When the timer sounds, he or she will remove the device from the surface of the eye. The device tip has markers on it that will leave a temporary indentation 3 and 4 mm from the limbus. Immediately before giving the injection, the physician will place a drop of betadine on the surface of the eye at the site marked for the injection and wait 20 seconds. The physician will then give the intravitreal injection.

The procedure for the patients receiving SOC will be similar to that described above. After obtaining written consent, the brow above the eye to receive intravitreal

treatment will be marked. Next, one drop of proparacaine will be applied into the eye to receive at least 5 minutes before any additional steps. Once the patient is ready, another drop of proparacaine will be applied and the physician or his assistant will then swab the lids with betadine. The patient will then have lidocaine gel placed on the eye and left in place for a minimum of 3 minutes prior to IVT. The 3-minute waiting period is needed to allow the lidocaine gel to diffuse through the sclera. Following completion of numbing, the eyelids will be swabbed with betadine and the physician will place the lid speculum. The physician will use a caliper to measure 3 or 4 mm from the limbus of the eye, place a drop of betadine over this spot, wait 20 seconds and then administer the injection.

2.3.2.1 Allocation to Treatment:

Patients will be randomly assigned to 1 of the 4 CA treatment groups and the SOC arm. Patients will be randomized to have their first eye receive either CA or SOC.

2.3.2.2 Treatment Adherence/Study Compliance:

If a patient is does not require, or refuses, an injection in either eye, they will be removed from the study. Because IVT prevents blindness, the refusal of IVT is extremely rare. In addition, it is extremely rare for patient who have been determined to need IVT to have improvement in vision prior to IVT.

If patients withdraw from the study, we will plan to recruit additional patients to replace them.

**2.3.3 Follow-up Procedures:**

2.3.3.1 Procedures to Assess Efficacy**:**
Patients will record their subjective pain (pre-injection preparation pain, injection pain, and 24 hr post injection pain) using a visual analog scale (1 to 10, with 10 being severe pain and 1 being no pain). The study coordinator will call the patients within 4 hours after their injection to review their 4-hr post procedure pain scores with them. Patients will be asked to return in 24 hours for anterior segment examination and 24-hr post injection pain assessment. Patients treated on Friday will be asked to return on Saturday for their 24-hr post injection assessment.

2.3.3.2 Procedures to Assess Safety:
Physicians will record the following common ocular side effects following IVT: SCH, conjunctival hyperemia, and conjunctival injection. These will be assessed via a slit lamp examination performed within 30 minutes and 24 hours of the administration of the intravitreal injection. Patients will undergo an anterior segment ocular examination 1 day following their intravitreal injection, and the physician will again record the presence of SCH, conjunctival hyperemia, conjunctival injection, and corneal keratopathy. In addition, each eye will be assessed for other signs of anterior segment toxicity, including AC reaction or hypotony. Patients will be assessed by a phone call 1 week after injection in each eye for any adverse events.

Physicians will score ocular side effects of CA and SOC. We will conduct interim analysis every 12 weeks or following every $10^{th}$ patient treated, whichever happens first, and will suspend the study if there appears to be significantly more ocular side effects following CA. For the reasons laid out

above (in the device description), we believe this device is minimal risk and has a very low probability of causing ocular side effects.

## 2.4 Study Outcome Evaluations:

### 2.4.1 Study Endpoints.

Primary Endpoint:

1. Injection pain - Pain rating on a visual analogue scale (1 to 10)

Exploratory Endpoints:

1. Injection preparation pain - Pain rating on a visual analogue scale, 1 to 10.
2. 4-hr post injection pain - Pain rating on a visual analogue scale, 1 to 10.
3. 24-hr post injection pain - Pain rating on a visual analogue scale, 1 to 10.
4. Physician recorded time from initiation of treatment to completion of the intravitreal injection.
5. Physician scored patient response to pain (1: no pain/movement; 2: mild pain/movement 3: marked pain/movement with the injection)
6. Physician scored ocular side effects within 30 minutes of administration of the intravitreal injection and 1 day following the injection (SCH, conjunctival hyperemia, conjunctival injection, and corneal keratopathy): 1: No ocular side effects; 2: mild ocular side effects (trace to 1+ SCH, conjunctival hyperemia, conjunctival injection, or corneal keratopathy; 3: Marked ocular side effects (SCH involving at least 25% of the ocular surface, 2-4+ conjunctival hyperemia or conjunctival injection, or 2-4+ corneal keratopathy). In addition, each eye will be assessed for other signs of anterior segment toxicity, including AC reaction or hypotony.
7. Time required to deliver IVT. The assistant will start timing the procedure from immediately after proparacaine instillation into the eye until after the eye receives IVT.
8. Patients rating of ocular irritation immediately after injection as well as 4 and 24 hours after injection: 1 – no irritation; 2 – mild irritation 3 – moderate irritation 4- marked irritation.
9. Patients rating of visual function in the treated eye immediately after injection as well as 4 and 24 hours after injection: 1 – no changes from baseline; 2 – mild blurring of vision 3 – moderate blurring of vision 4- marked blurring of vision.

### 2.4.2 Outcome Data and Data Analysis:

Primary Endpoint: Pain rating on a visual analogue scale (1 to 10): 1, no pain, to 10, severe pain.

Exploratory Endpoints:

1. Pain rating on a visual analogue scale (1 to 10): 1, no pain, to 10, severe pain.
2. Physician recorded time from initiation of treatment to completion of the intravitreal injection.
3. Physician scored patient response to pain (1 – no pain/movement; 2 – mild pain/movement 3 – marked pain/movement with the injection)
4. Physician scored ocular side effects within 30 minutes of administration of the intravitreal injection and 1 day following the injection (SCH, conjunctival hyperemia, conjunctival injection, and corneal keratopathy): 1 No ocular side effects; 2 mild ocular side effects (trace to 1+ SCH, conjunctival hyperemia, conjunctival injection, or corneal keratopathy; 3. Marked ocular side effects (SCH

involving at least 25% of the ocular surface, 2-4+ conjunctival hyperemia or conjunctival injection, or 2-4+ corneal keratopathy). In addition, each eye will be assessed for other signs of anterior segment toxicity, including AC reaction or hypotony.

5. Time from anesthesia initiation (proparacaine drops) to IVT delivery.
6. Patients rating of ocular irritation immediately after injection as well as 4 and 24 hours after injection: 1 – no irritation; 2 – mild irritation 3 – moderate irritation 4- marked irritation.
7. Patients rating of visual function in the treated eye immediately after injection as well as 4 and 24 hours after injection: 1 – no changes from baseline; 2 – mild blurring of vision 3 – moderate blurring of vision 4- marked blurring of vision.

## 3.0 Reporting of Adverse Effects to the IRB:

In accordance with applicable policies of the University of Michigan Institutional Review Board (IRBMED), the investigator-sponsor will report, to the IRB, any observed or volunteered adverse effect that is determined to meet all of the following criteria: 1) *associated with the investigational device or, if applicable, other study treatment or diagnostic product(s)*; 2) *a serious adverse effect*; and 3) an *unexpected adverse effect*. Adverse event reports will be submitted to the IRB in accordance with the respective IRB procedures.

Applicable adverse effects will be reported to the IRB as soon as possible and, in no event, later than 10 calendar days following the investigator-sponsor's receipt of the respective information. Adverse effects which are 1) *associated with the investigational drug or, if applicable, other study treatment or diagnostic product(s)*; 2) *fatal or life-threatening*; and 3) *unexpected* will be reported to the IRB within 24 hours of the investigator-sponsor's receipt of the respective information.

Follow-up information to reported adverse effects will be submitted to the IRB as soon as the relevant information is available. If the results of the sponsor-investigator's follow-up investigation show that an adverse effect that was initially determined to not require reporting to the IRB does, in fact, meet the requirements for reporting; the investigator-sponsor will report the adverse effect to the IRB as soon as possible, but in no event later than 10 calendar days, after the determination was made.

### 3.1 Withdrawal of Subjects Due to Adverse Effects:

Patients will only have a single exposure to the device (10 to 20 seconds in length). Should a patient not tolerate the discomfort of the cold tip for the entire duration and be unable to receive full CA, that patient would be removed from the study.

If a patient withdraws from the study, the patient data will be destroyed. Another patient will be recruited to take their place, provided that the additional patient can be recruited and treated within the allotted study time frame.

### 3.2 Monitoring Plan:

This monitoring plan will be followed in monitoring the University of Michigan as a single site approved for performance of a Nonsignificant Risk Device protocol under FDA guidance for Significant and Nonsignificant Riske devices, entitled, Cryoanesthesia. As the scope of this study is utilizing a Nonsignificant risk device involving 40 adults, this monitoring plan will be performed by the Sponsor-Investigator (S-I). The monitoring frequency shall be as follows: after 20 participants have been enrolled and again after all 40 patients have been enrolled.

Purpose:

The purpose of the monitoring plan is to facilitate compliance with good clinical practices, FDA guidelines and regulations which require monitors to verify the following:

- The rights and well-being of participants are protected
- Reported data are accurate, complete, and verifiable from source documents
- Trial conducted in compliance with currently approved protocol and other applicable regulatory requirements

This document identifies key monitoring activities and specifies the date to be reviewed over the course of a clinical trial.

Site initiation and Qualification:
Prior to study initiation, the S-I will review the following information:

- IRB approved version of the approved protocol for the study
- IRB approved Informed Consent Forms and processes
- AE and SAE definitions and reporting procedure, including plans for S-I review of all adverse events. It is recommended that the S-I contact the Michigan Institute for Clinical and Health Research IND/IDE Assistance Program (MIAP) for assistance with any reporting requirements to the FDA.
- CRF completion and maintenance process
- Creation and organization of the Investigator Study Binder

Device accountability (e.g. access to storage, storage location, and dispensing of the device) will be maintained in study records. If not, the study records, state where the investigational product accountability records will be maintained.

Interim Monitoring:
At the two study team meetings (after enrollment of 20 subjects and again after enrollment has been completed), the S-I will review the following:

- Informed consent obtained for each participant
- Adherence to protocol eligibility criteria
- CRF completion
- Documentation of device use on the subject
- Monitor data and quality through routine review of submitted data to identify and follow-up on missing data, inconsistent data, or data outliers
- Check and review of the regulatory binder and all essential documents
- Review of all SAEs and subject withdrawals
- Enrollment issues and targets
- Protocol amendments and their approval by the IRB
- Protocol deviations
- Personnel changes and required training
- Verifying continuous institutional review board (IRB) approval
- Any other issue as deemed important to the conduct of the study

Reporting and Follow-up:
If there are any significant findings, the S-I will follow-up any noncompliance, potential noncompliance, data irregularities, or other deficiencies identified along with a description of any actions taken, to be taken, or recommended, including the person responsible for completing actions and the anticipated date of completion.

## 4.0 Description of the Investigational Device:

*Prototype Description:*

The cryo-anesthesia device is a handheld instrument measuring approximately 10 inches in length and 1.5 inches in diameter, and weighing 0.8 pounds. A 4×4 $mm^2$ area at the tip of the device is placed against the eye and cooled to a user-specified temperature setpoint between -5 and -10°C via activation of a switch on the device (**Figure 2**). The temperature setpoint is selected prior to device activation. Ocular surface cooling slows conduction of pain fibers in the conjunctiva (outermost layer of the eye) and the sclera (white of the eye) to a depth less than a millimeter. The key features of the device include a temperature regulating feedback loop that maintains highly accurate and precise temperature control and an integrated timer that controls the duration of cooling, both of which facilitate sufficient cooling and prohibit excessive cooling. Two small protrusions on the tip leave temporary indentations on the surface of the eye to guide placement of the intravitreal needle. The cooling region of the device is located on a replaceable metal tip. An "ON" switch is first activated to cool the contact region of the device, after which this region is placed against the eye, initiating rapid cooling to anesthetize the injection site while simultaneously marking the cooled location. After the specified cooling time is reached, the device is removed, immediately after which the physician performs intravitreal injection.


**Figure 2 | Cryoanesthesia device.**

*Safety Features:*

- At maximum power, the device achieves a temperature of -12°C. Any device malfunction would result in an increase in this temperature rather than a decrease.
- Prior studies as well as our own histological studies with rabbits indicate that this minimum cooling temperature (-12°C) is not low enough to cause ocular tissue damage, even with extended exposure. For the purpose of the study, the device will not be set to a temperature colder than -10°C.
- A temperature regulating feedback loop maintains highly accurate and precise temperature control, and an integrated timer controls cooling time.
- The device tip is replaced with a new sanitized or sterile tip before each use to help ensure safe contact with the eye surface.
- Device tip indents the eye surface, guiding subsequent needle placement.
- Ergonomic and lightweight design, facilitating safe use on or near the eye.
- Low operating voltage (11 V).

*Prototype Description:*

The device uses thermoelectric (Peltier) cooling to create the low temperature required for cryoanesthesia; thermoelectric cooling has the advantages of being lightweight, small, solid-state (thus no fluids or moving parts), and electrically driven (thus allowing straightforward control of temperature). The device uses a unique design for efficient heat spreading in which an inner arm made from a thermally conductive metal (**1** in Fig. 3: cold arm) is simultaneously cooled by a group of Peltier modules (**2** in Fig. 3) and is thus able to achieve a large cooling power and maintain a low temperature at the cooling surface on the replaceable tip (**3** in Fig. 3). This configuration also allows the Peltier modules to reject heat to an area of a heat sink (**4** in Fig. 3) that is not only large and hence efficient but also extended away from the cooling surface, thus allowing a narrow shape with better visual clearance during use.

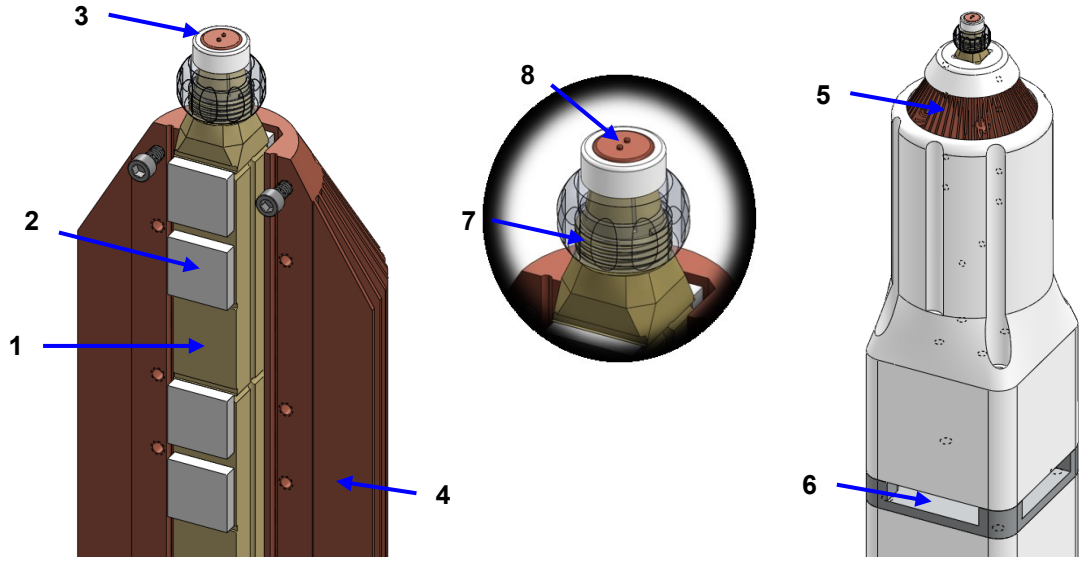



**Figure 3 | Device structure.** 1–cold arm, 2–Peltier module, 3–replaceable cold tip, 4–heat sink, 5–air inlet, 6–air vent, 7–vice-like mechanism, 8–protrusions

Air is received from the inlet openings (**5** in Fig. 3) by an electric fan, cools the fins, and exits through vents at a location far from the replaceable tip (**6** in Fig. 3). The location of the vents far from the replaceable tip not only reduces parasitic convection heating at the tip surface but also prevents the airflow from drying the eye surface. A rechargeable lithium ion battery pack (28 Wh), which provides sufficient energy on a single charge to operate the device at -10˚C for approximately one hour (~100 treatments), can be easily removed from the rest of the device to facilitate simple charging. Temperature control is achieved by an electrical feedback loop that samples the tip temperature using a thermal sensor and provides appropriate power to the thermoelectric coolers via pulse width modulation (PWM) of the DC battery source. While the cooling surface is unable to reach a temperature lower than -12˚C when the device is operated at typical room temperature (20˚C), a failsafe automatically powers the device off if the cooling surface falls below -12˚C. Other automatic power offs occur if the battery temperature exceeds 60˚C or the heat sink temperature exceeds 50 ˚C. A single button on the device is used to set the cold tip temperature and timer duration, as well as power the Peltier modules. Operation of the button comprises: 1) Clockwise rotation to increase the cold tip temperature setpoint, 2) Counter-clockwise rotation to decrease the cold tip temperature setpoint, 3) Clockwise rotation while the button is pushed, to increase the timer duration, 4) Counter-clockwise rotation while the button is pushed, to decrease the timer duration, and 5) Double-pressing to activate the Peltier modules. A second tactile button located near the grip position is used to activate (or deactivate) the timer. When the timer is activated, the device produces two consecutive beeping sounds at low and high frequencies, followed by beeping sounds every 10 seconds during the timer duration, and finally two long consecutive beeping sounds at high and low frequencies when the timer

duration has expired. If the "Timer" button is pushed again before the set time is reached, two short consecutive beeps at high and low frequencies occur and the timer is immediately terminated.

A user readies the device by first inserting the replaceable tip into the cold arm. A vice-like mechanism (**7** in Fig. 3) is used to provide both convenient tip replacement and sufficient pressure between the replaceable tip and cold arm for good thermal contact. The replaceable tip is coated by a thin hydrophobic polymer layer that mitigates ice adhesion between the device and tissue. Two small protrusions (**8** in Fig. 3) on the replaceable tip leave temporary indentations on the eye surface to guide subsequent treatment (e.g., placement of the intravitreal injection needle 3 or 4mm from the corneal limbus).

After setting the desired cold tip temperature setpoint and timer duration and inserting the replaceable tip, the user operates the device by first double-pressing the main ("rotation & push") button, which turns on the Peltier modules and brings the tip temperature to the setpoint (this takes approximately 20 seconds for a setpoint of -10˚C). He or she then brings the tip into contact with the patient's eye and presses the "timer" button (which responds with a beep). If the timer duration is set to 10 (or 30) seconds, the device maintains -10 ˚C for 10 (or 30) seconds and then beeps. After the timer duration, the device returns to ambient temperature.

*There are no anticipated changes to the device during the course of this study.*

## 5.0 Future Studies:

We plan to conduct a second phase of the study where we will compare the SOC to only one cryoanesthesia temperature setpoint and one time setpoint, selected after the analysis of the first 40 patients.

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