A Transnasal Evaporative Cooling Device for Acute Treatment of Migraine

Short Title: Transnasal Cooling for Migraine

Protocol Number: P-224011-0040

National Clinical Trial (NCT) Identified Number: NCT04936061

Lead Principal Investigator: Nauman Tariq, MD

IDE Sponsor: CoolTech[1]

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Version Number: 2.0

Version Date: 02 July 2021

[1] Under Contract to Key Technologies Inc.

PROTOCOL AGREEMENT

I have read the protocol specified below. In my formal capacity as Investigator, my duties include ensuring the safety of the study subjects enrolled under my supervision, and providing CoolTech with complete and timely information, as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site. Furthermore, on behalf of the study staff and myself, I agree to maintain the procedures required to carry out the study in accordance with accepted GCP principles and to abide by the terms of this protocol.

I agree to maintain responsibility for all medical devices under investigation.

I agree to await Institutional Review Board (IRB) approval of the CIP and Informed Consent Form (ICF) before initiating the study, to obtain informed consent prior to subject enrollment in the study, to collect and record data as required by this CIP and corresponding Case Report Forms (CRF), to prepare Annual, Final, and Adverse Events (AE) Reports as required, and to maintain study documentation for the period of time required.

Protocol Number:	**P-224011-0040**
Protocol Title:	**A Transnasal Evaporative Cooling Device for Acute Treatment of Migraine**
Protocol Version/Date:	**2.0, July 2, 2021**

Investigator's Printed Name:	
Investigator's Signature:	Date of Signature:

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonization Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

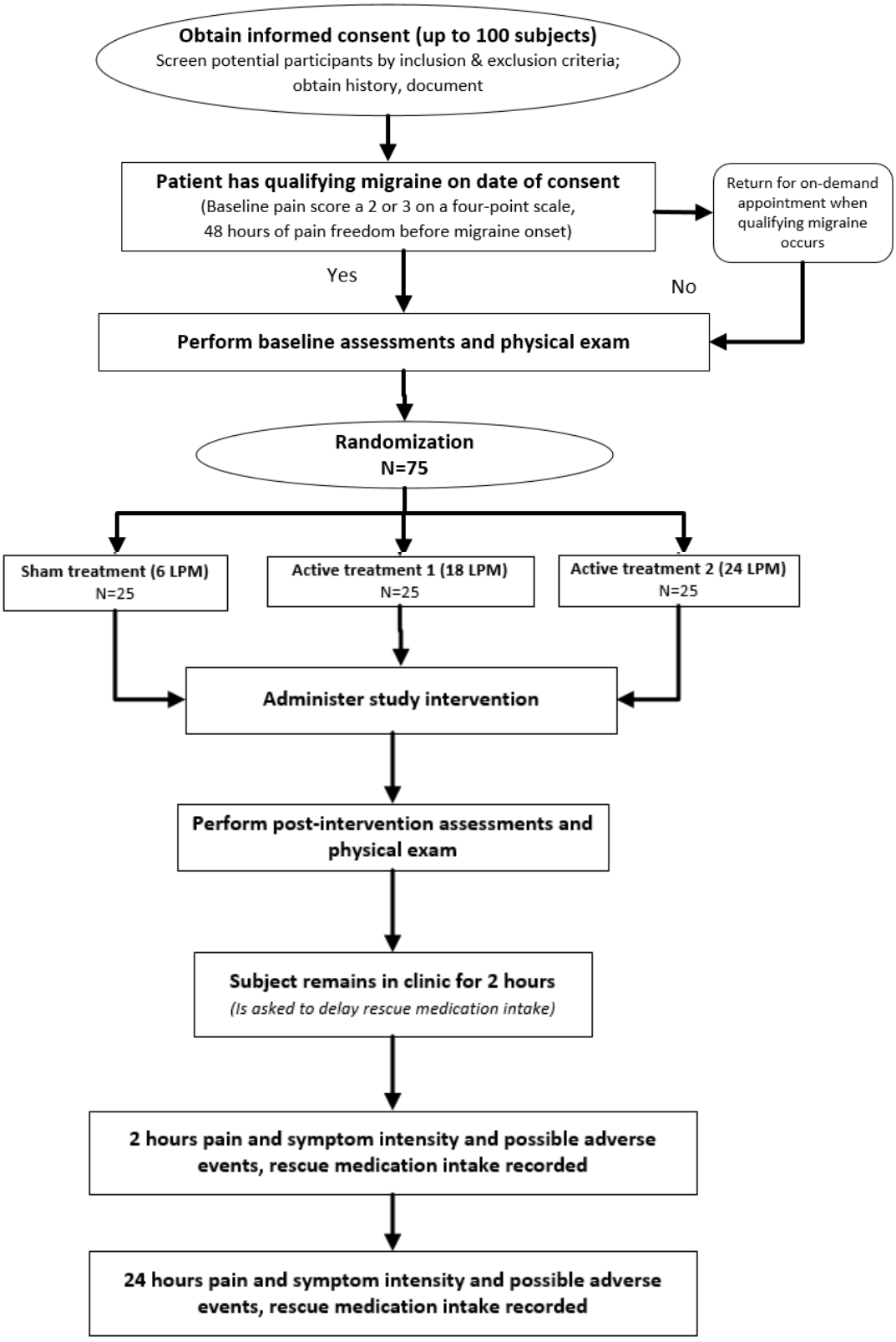
1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	A Transnasal Evaporative Cooling Device for Acute Treatment of Migraine
Study Description:	This is a prospective, double-blind, sham-controlled, randomized study to assess the safety, tolerability, and optimal dose of the COOLSTAT Transnasal Thermal Regulating Device for acute treatment of migraine. The hypothesis is that evaporative cooling induced by the CoolStat using only ambient, dry air will reduce the pain and other symptoms of migraine headaches during an acute migraine episode.
Objectives:	Primary Objective: • To evaluate the safety, tolerability and optimal dose of the CoolStat for acute treatment of migraine Secondary Objectives: • To assess the efficacy of CoolStat, by way of reduction in severity of reported pain and other symptoms post treatment compared to baseline. • To confirm the sham and the blinding procedures • To determine the treatment effect size to use in future sample size calculations for a pivotal randomized trial.

Endpoints:	Primary Endpoints: • Safety of the CoolStat device measured by incidence of adverse events • Tolerability of the CoolStat device by percent of subjects who fail to complete the full treatment session. • Pain relief at 2 hours post treatment. Secondary Endpoints: • Pain relief immediately post treatment and at 24 hours post treatment. • Pain freedom immediately, 2 hours, and 24 hours post treatment. • Relief of migraine associated symptoms (nausea/vomiting, photophobia, phonophobia) immediately, 2 hours, and 24 hours post treatment. • Freedom from migraine associated symptoms (nausea/vomiting, photophobia, phonophobia) immediately, 2 hours, and 24 hours post treatment. • Use of rescue medication between 2 and 24 hours. • % of subjects who believe they received active treatment in each arm.
Study Population:	75 women and men diagnosed with episodic migraine who are at least 18 years of age. Up to 100 patients may be consented, but only 75 will be randomized to treatment.
Phase:	N/A
Description of Sites/Facilities Enrolling Participants:	Participants will be enrolled from up to 3 clinical sites (US only). Study sites will be headache-specific treatment centers.
Description of Study Intervention:	The CoolStat induces evaporative cooling by delivering dry, ambient air into one nostril and over the nasal turbinates in a unidirectional fashion before flowing freely out of the other nostril and the mouth. The nasal turbinates are highly vascularized, mucus-containing membranes with a large, convoluted surface area. As the dry air from COOLSTAT flows over the moist turbinates, it induces the liquid water (mucus) on the turbinates to change phase, from a liquid to a gas. To complete the phase change, the liquid water molecules need energy, which is drawn from the turbinate membrane tissue. This process locally extracts energy from this tissue bed, focused in the region of the turbinates. This extraction of energy causes local cooling in this area, which is believed to reduce symptoms of migraine.
Study Duration:	6 months
Participant Duration:	Up to 60 days (24 hours of study activity)

1.2 SCHEMA


Obtain informed consent (up to 100 subjects)
Screen potential participants by inclusion & exclusion criteria; obtain history, document
Patient has qualifying migraine on date of consent
(Baseline pain score a 2 or 3 on a four-point scale, 48 hours of pain freedom before migraine onset)
Return for on-demand appointment when qualifying migraine occurs
Yes
No
Perform baseline assessments and physical exam
Randomization
N=75
Sham treatment (6 LPM)
N=25
Active treatment 1 (18 LPM)
N=25
Active treatment 2 (24 LPM)
N=25
Administer study intervention
Perform post-intervention assessments and physical exam
Subject remains in clinic for 2 hours
(Is asked to delay rescue medication intake)
2 hours pain and symptom intensity and possible adverse events, rescue medication intake recorded
24 hours pain and symptom intensity and possible adverse events, rescue medication intake recorded

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedure	**Screening (Day -60 to 0)**	**Treatment Visit (Day 0)**	**Post Treatment (2 hours) *± 15 minutes***	**Post Treatment (24 hours) *± 2 hours***
Informed consent	X			
Demographics	X			
Medical history	X			
Eligibility criteria verification	X			
Randomization		X		
Physical exam (height and weight)		X		
Vital signs (blood pressure, pulse oximetry, tympanic temperature)		X*	X	
Administer study intervention		X		
Most Bothersome Symptom		X		
Head pain severity score		X	X	X
Nausea severity score		X	X	X
Photosensitivity severity score		X	X	X
Phonosensitivity severity score		X	X	X
Concomitant medications review	X	X	X	X
Adverse event review and evaluation		X	X	X
Complete Case Report Forms (CRFs)	X	X	X	X

**Vitals will be taken immediately pre and post treatment session.*

2 INTRODUCTION

2.1 STUDY RATIONALE

Migraine is a severely disabling neurologic condition and is the sixth most disabling disorder worldwide, affecting over a billion people. The majority of those with migraines experience them episodically, defined as less than 15 migraine days per month. Migraine can cause a significant reduction in quality of life as well as loss of productivity. The global economic burden of migraine is staggering at approximately $20 billion in the U.S. and $56 billion worldwide per year.

Migraine affects significantly more women than men and is the leading cause of disability in people under fifty (Steiner, 2018). First line treatment options are medications such as triptans and NSAIDs, which are associated with adverse effects, are contraindicated in those with cardiovascular issues, and put patients at risk for medication-overuse headache. In addition, more than 50% of chronic migraineurs discontinue or change their preventive treatment drug at some point due to its lack of efficacy or tolerability (Ford, 2017). Neuromodulation therapies that target the autonomic nervous system are gaining traction due to their safety profile and relative effectiveness.

The pathophysiology of migraine is complex, not fully understood, and not within the scope of this study. There is evidence that the headache phase of migraine is caused by activation of nociceptors in the trigeminal ganglion (Puledda, 2017). The sphenopalatine ganglion (SPG), a large ganglion located behind the superior nasal turbinate, is closely associated with the trigeminal system (Robbins, 2016). Several studies have shown that intranasal SPG nerve block with lidocaine provides relief from acute migraine headaches (Maizels, 1999; Kudrow, 1995; Binfallah, 2018). Another possible mechanism is stimulation through the nasal cerebral pathway via olfactory epithelium. The COOLSTAT Transnasal Thermal Regulating Device has the potential, using a simple non-invasive transnasal evaporative cooling process, to activate these (or other) mechanisms, providing pain and symptom relief reduction in patients with migraine.

The CoolStat device uses transnasal high flow dry air to cause local cooling of the nasopharynx due to evaporation of nasal mucosal water. The device also has a feature that intermittently mists several drops of water (saline) into the nose, which is used to augment the evaporative cooling process, prevent nasal turbinate desiccation, and minimize discomfort to the patient. The overall hypothesis is that optimized transnasal cooling with the CoolStat device will reduce the intensity of migraine headaches during an acute episode. More detail can be found in the ***CoolStat Investigator Brochure*.**

The objectives of this study are to evaluate the safety, tolerability, and optimal dose (air flow rate) of the CoolStat to reduce pain and other symptoms associated with episodic migraine with or without aura.

2.2 BACKGROUND

The prevalence of migraine in the U.S. is increasing, with 15% of the population suffering from either episodic or chronic migraine. Migraine is one of the most common reasons for emergency room visits. Despite treatment recommendations, opioids are still overprescribed for migraine patients. This is especially the case in emergency departments (EDs) where one study found that opioids are prescribed at over 50% of migraine ED visits (Minen, 2014). It is apparent that this phenomenon is contributing

significantly to the growing opioid epidemic. The use of opioids in this population carries a high risk of 'medication-overuse-headache', when used more than 10 times/month, and can quickly lead to opioid dependency (Bigal, 2008). Medication overuse is also the most common reason why episodic migraine transforms into chronic migraine.

Current therapies for migraine are suboptimal, expensive and ineffective in curbing the global opioid epidemic. There is an enormous unmet need for an effective and affordable non-drug abortive therapy for acute migraine to significantly improve quality of life and substantially reduce the cost burden to our healthcare system and society.

Migraine prototype study:

A single-blinded, randomized trial was conducted at the Johns Hopkins Bayview Hospital headache clinic in Baltimore, MD, to study potential therapies for migraine, centered on evaporative cooling (Shah, 2021). This study evaluated the safety and efficacy of four potential therapies consisting of different air mixtures flowing in the nose and out the mouth: 1) a flow of dry oxygen, 2) a flow of dry air, 3) a flow of humidified oxygen, and 4) a flow of humidified air (control). All four gases were warmed to 37°C and delivered through a face mask (not the COOLSTAT device) with the study gases flowing in the nose and freely out of the mouth. The subjects were awake and otherwise healthy, excluding their migraine symptoms. The objective of the study was to assess safety and the ability to reduce symptoms from migraine.

Fifty-one (51) patients were enrolled in the study, of which 13 patients (mean age 49 years, 81% female) received humidified oxygen therapy and 9 patients (mean age 42 years, 82% female) received dry air therapy. Patients were randomized and blinded to their treatment group. There was significant pain relief at 2 hours post treatment compared to baseline reported by patients who received dry air, dry oxygen and humidified oxygen. Patients in the control group did not show significant pain relief from baseline to 2 hours post treatment.

A two-way ANOVA was conducted to examine the effect of gas type and moisture content in reducing headache symptoms in migraine (pain score reduction). There was a statistically significant interaction between the effects of gas type and moisture content on the headache score reduction, $F(1,47) = 10.471$, $p = 0.002$. Simple main effects analysis showed that there were no significant differences between dry oxygen and dry air ($p = 0.906$), but there were statistically significant differences between these gases when they were humidified ($p < 0.001$).

No adverse events were reported in this study. It was concluded that high flow dry air is safe and appears to be effective in treating acute migraine pain and associated symptoms.

Neurogenic fever study:

The CoolStat is also currently being studied in a multi-center, open-label study for targeted temperature management to treat neurogenic fever in adults with ischemic or hemorrhagic stroke, seizure, or metabolic encephalopathy, under IDE G160198. The objective of this study is to evaluate safety and efficacy of the CoolStat in reducing core temperature in the study population. Results from an analysis of the first 10 subjects showed that inducing normothermia with the CoolStat device over an 8-hour period appears to be safe, feasible, and not associated with hemodynamic changes or significant shivering (Badjatia, 2020). No changes were observed in arterial or ICP while delivering transnasal cooling. This study has moved into its next phase, in which the same population is being cooled for 24

hours using the CoolStat device and preliminary results show sustained safety and efficacy during this extended cooling period.

Migraine dose escalation study:

A dose escalation and tolerability study was completed using the CoolStat device at the Johns Hopkins Bayview Hospital headache clinic in Baltimore, MD. 15 subjects experiencing migraine on the day of treatment were enrolled. Three air flow rates were tested and tolerability and efficacy were assessed for increasing air flow rates: 24 LPM, 36 LPM and 48 LPM. Five (5) subjects were tested at each flow rate, starting at the lowest flow rate (24 LPM). If the majority (3/5) of the subjects in the lowest flow rate group tolerated the full 10 minute treatment, the next group would receive an incrementally higher flow rate. All of the flow rates were found to be tolerable by study subjects, with 13 of the 15 subjects tolerating the full 10 minute treatment session. Although anecdotal (due to the small size of the study), there was also positive reports of reductions in migraine symptoms, which also appears to be related to flow, i.e., migraine symptoms reduced more with increased flow rates. 73% of the 15 subjects experienced pain relief immediately after treatment compared to baseline and 53% of subjects reported sustained pain relief at 2 hours post treatment. 67% of subjects reported that the benefit of the CoolStat treatment outweighed any discomfort they experienced during the treatment session and 73% said they would use the device again. 60% of subjects said the CoolStat works just as well or better than their current rescue medication. The adverse events that occurred were all graded as mild and anticipated (stuffy nose, burning sensation during treatment session) and resolved on their own. There were no serious adverse events or unanticipated device effects. This study demonstrated that the CoolStat is safe and tolerable for use in patients with acute migraine attacks.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Anticipated risks or adverse events (AEs) that may occur are nasal discomfort, sinus pressure, dry nose or mouth, runny nose, and epistaxis (nose bleed). There is also a minor risk to subject confidentiality.

Subjects will be advised of the potential risks and benefits associated with this study in the IRB approved ICF.

2.3.2 KNOWN POTENTIAL BENEFITS

This is an investigational study in which any direct benefit to participants cannot be guaranteed. There is a chance that the study treatment may provide some relief from the pain and symptoms associated with migraine.

The results from this study will provide information on using a new device, the CoolStat, in a clinical setting, for treating migraine pain and associated symptoms using only a flow of dry, ambient air. Study participants will help the medical community gain new knowledge relating to development of an effective, drug-free process and device to treat acute migraines, which could help to substantially curb the use of opioid medication and subsequent dependence issues in the migraine population.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The risks to subjects in this study are considered minimal. Subjects will be awake and healthy and may stop the treatment session at any time simply by removing the nasal mask. The duration of the treatment is only 15 minutes, and the subjects will be monitored during treatment by a member of the study team.

This is an investigational study which does not guarantee any direct benefit to the subjects, but the proposed treatment may provide some relief of pain and symptoms from acute migraine. In the near term, this study may show the benefit of using a new device, the CoolStat, in a clinical setting, for treating migraine pain and associated symptoms using only a flow of dry, ambient air. In the longer term, this study could also lead to the development of a small, portable device that can be self-administer directly by the migraine sufferer in a non-clinical setting, such as at home or at work. These potential benefits are considered to outweigh the minimal risk associated with participation in this study.

Subjects will be advised of the potential risks and benefits associated with this study in the IRB approved ICF.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To evaluate the safety, tolerability and optimal dose of the CoolStat for acute treatment of migraine	• Safety of the CoolStat device measured by incidence of adverse events • Tolerability of the CoolStat device by percent of subjects who fail to complete the full treatment session • Pain relief at 2 hours post treatment	Validated in several other acute migraine treatment device studies.
Secondary		
To assess the efficacy of CoolStat, by way of reduction in severity of reported pain and other symptoms post treatment compared to baseline. To confirm the sham and the blinding procedures To determine the treatment effect size to use in future sample size calculations for a pivotal randomized trial.	• Pain relief immediately post treatment and at 24 hours post treatment. • Pain freedom immediately, 2 hours, and 24 hours post treatment. • Relief of migraine associated symptoms (nausea/vomiting, photophobia, phonophobia) immediately, 2 hours, and 24 hours post treatment.	Validated in several other acute migraine treatment device studies.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
	• Freedom from migraine associated symptoms (nausea/vomiting, photophobia, phonophobia) immediately, 2 hours, and 24 hours post treatment. • Use of rescue medication between 2 and 24 hours. • % of subjects who believe they received active treatment in each arm.	

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a prospective, multi-center randomized, double-blind, sham controlled trial. It is hypothesized that transnasal evaporative cooling induced by the CoolStat using only ambient temperature, dry air will reduce the pain and other symptoms of migraine headaches during an acute episode.

There will be an active treatment group and a sham group. There will be a 1:1 ratio across groups, stratified by gender.

- Group I (active treatment 1): 18 LPM, dehumidified air, 15 minutes total
- Group II (active treatment 2): 24 LPM, dehumidified air, 15 minutes total
- Sham Group: 6 LPM, ambient air administered via CoolStat, 15 minutes total

Subjects will complete a short screening visit (0-60 days prior to treatment session), followed by a 24 hour study intervention and follow up period (15 minute treatment session, 2 hour monitoring period, 2 hour follow up questionnaire, and 24 hour follow up interview).

To minimize bias, both patient and the outcomes assessor will be blind to the treatment group. In addition, subjects will only be randomized and treated one time to eliminate within-subject bias.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Transnasal evaporative cooling is novel method of drug free migraine treatment that uses nothing but clean, dry air. The CoolStat induces evaporative cooling in the nasal turbinates and upper airway. This area is implicated in migraines for several reasons, including the sphenopalatine ganglion and trigeminal nerve endings. While the mechanism of action for evaporative cooling on migraine relief is not yet well

defined, feasibility testing with a prototype device showed significant pain relief in those with migraines compared to sham, as did a subsequent tolerability study with the CoolStat.

Ambient dry air flowing into one nostril and freely out of the other nostril and the mouth induces an evaporative heat exchange in the nasal turbinates and upper airway. This process locally extracts energy from this area and cools the adjacent tissue in the nasopharynx. The study device will also continuously mist saline into the nose in parallel with the airflow, via the Aura Mini Nebulizer (510(K) Number: K180871). The saline is used to support the evaporative cooling model, to keep the dry airflow from desiccating the adjacent tissue, and to reduce the discomfort from the high air flow.

4.3 JUSTIFICATION FOR DOSE

The air flow rates to be used in this study were determined based on the results of a tolerability study conducted with the CoolStat device using double nostril flow. In this study, 80% of the subjects (4 of 5) in the highest flow arm (48 LPM) tolerated the dose provided (24 LPM per nostril), which is expected to provide the best reduction in migraine symptoms, i.e., the higher the dose (air flow rate), the better local cooling and reduction of symptoms. In the double nostril flow configuration, the total dose is halved per nostril. Thus, 24 LPM was chosen as our high flow dose for this single nostril tolerability study. Based on this, we expect that many subjects will be able to tolerate the higher flow, but not all. As such, we are proposing to test both a high flow as well as a lower flow, to better assess:

- Tolerability at the highest dose setting in the single nostril air flow configuration
- The dose-response on outcomes, i.e., the relation between dose and symptom reduction

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA), Section 1.3.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Meets the International Classification of Headache Disorders (ICHD-3) diagnostic criteria for migraine with or without aura, with the exception of ''complicated migraine'' (i.e., hemiplegic migraine, ophthalmoplegic migraine, migrainous infarction).
2. Patient is between 18 and 80 years of age.
3. Patient experiences 2 to 8 migraine attacks per month.
4. Patient is in good reported general health, with no fever (<38.3C/101F).
5. Patient has had diagnosis of migraine with or without aura over at least 1 year.
6. Migraine onset before 50 years of age.

7. Migraine prophylaxis medication unchanged for 6 weeks prior to study enrollment.
8. Able to attend treatment session within 6 hours of migraine onset, with 48 hours of pain freedom prior to onset of migraine attack.
9. Migraine pain severity of Grade 2 or Grade 3 on day of treatment.
10. Provision of signed and dated informed consent form.
11. Stated willingness to comply with all study procedures and availability for the duration of the study.

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Patient has difficulty distinguishing his or her migraine attacks from tension-type headaches
2. Patient has uncontrolled hypertension.
3. Patient has a fever (≥38.3C / 101F).
4. Patient has used opioid medication or barbiturates in the past month.
5. Patient has Medication Overuse Headache (MOH), New Daily Persistent Headache (NDPH) or Chronic Tension Type Headache (CTTH).
6. Patient has 15 or more headache days per month.
7. Patient has used acute treatment(s) for migraine in the 48 hours preceding treatment i.e. over-the-counter (OTC) medications, prescription medications, or medical device).
8. Patient has received Botox treatment, supraorbital or occipital nerve blocks in the last 4 weeks.
9. Intolerance to intranasal neurostimulation or sensory processing disorder that makes the treatment not applicable.
10. Recurrent epistaxis or chronic rhinosinusitis.
11. Recent facial trauma, sinus or intranasal surgery within the last 4 months.
12. Known or suspected pregnancy.
13. Unable to fully understand the consent process and provide informed consent due to either language barriers or mental capacity.

5.3 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not randomly assigned to a study intervention or entered in the study arms. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) because of a recent treatment with Botox, supraorbital or occipital nerve block, or recent change to their migraine prophylaxis regimen may be rescreened at a later date. Rescreened participants will be assigned the same participant number as the initial screening.

5.4 STRATEGIES FOR RECRUITMENT AND RETENTION

100 women and men of any race or ethnicity will be recruited for participation in this study from the patient population of participating headache clinics. Subjects must have had a diagnosis of migraine for at least one year and meet the specified eligibility criteria. If the patient is deemed eligible based on their medical history, he or she will be approached by the PI or his/her designee to discuss the study and the patient's potential enrollment. Up to 100 subjects may be consented in this study to account for screen failures (patients who consent to participate but do not return to the clinic with a qualifying migraine/are not randomized within the 60 day enrollment period). Up to 75 subjects will be randomized to a treatment group.

It is anticipated that approximately 80% of our sample population will be women, based on the fact that migraine disproportionately affects women. Pregnant women will not be included in this study. We anticipate 25% of our sample population to be in minority groups based on demographic data from our feasibility prototype study. No races or ethnicities will be excluded.

Although we are estimating participation in this study across race, gender and ethnicity as noted above, we will not be specifically controlling or limiting subject participation based on these factors.

Two options are available to recruit patients:

- Eligible patients can be recruited during a standard care visit if they are experiencing a migraine attack and meet the inclusion and exclusion criteria.
- Patients can also be screened beforehand (having been informed about the study at a standard visit or via advertisement), and arrange for an on-demand appointment in the future when they are experiencing an attack.

Subjects will receive study information and consent documents by qualified study personnel, and must sign these documents before study procedures are initiated. Then the investigator will verify that the patient meets all inclusion criteria and none of the exclusion criteria. If this is the case, the subject will be required to provide a value on an 4-point scale (0 = no pain, 3 = maximum pain) of the current pain associated with their migraine. The patient will then be randomized to either the high flow treatment group, low flow treatment group, or the sham group.

Subjects will be compensated $50 for participating in this study, as well as reasonable travel costs. Subjects will be issued their compensation check after completing all parts of the protocol, including the 24 hour follow up study interview.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

The COOLSTAT Transnasal Thermal Regulating Device is intended for acute treatment of migraine with or without aura in adult patients.

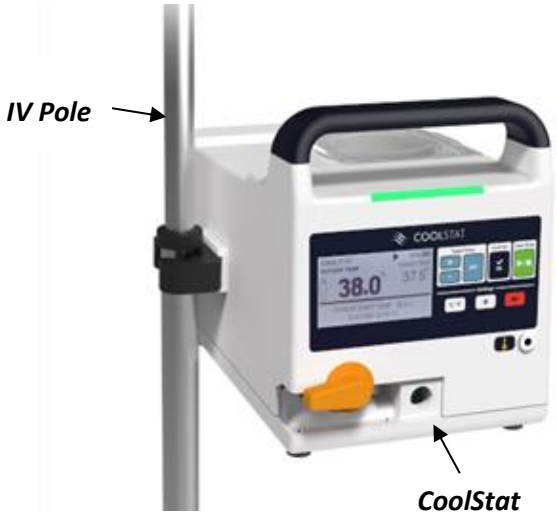
The COOLSTAT Transnasal Thermal Regulating Device produces a flow of dry filtered air at ambient temperature to induce an evaporative cooling energy exchange in the turbinates and upper airway. The air flow is delivered from the CoolStat device to the subject via an air hose and hand-held nebulizer. The air flow will be delivered into one nostril and flow freely out of the other nostril and the mouth. The subject will be able to breathe freely over the operation of the device. The device will also deliver a continuous mists of saline to the subject to keep the turbinates moist and comfortable, and to further promote evaporative cooling. For this study, the device will be limited to subjects with migraine with or without aura.

The COOLSTAT Transnasal Thermal Regulating Device [hereafter COOLSTAT or CoolStat] does not use any invasive catheters or any evaporative chemicals or cooling agents, and the process air and saline do not come in contact with any sterile body tissue, blood or other fluids. COOLSTAT is not used in any way to support or assist with life support, patient breathing or respiratory functions.

The COOLSTAT is a relatively small device, weighing less than 15 lbs, and can be mounted on an IV pole or sit on a bed or table near the patient. The primary functional component inside the device is a blower which is used to generate a flow of air. Inlet air is pulled into the device from the local ambient room air; the internal blower is then used to pump the air across a desiccant material to extract any moisture from the incoming air stream. The dry air then travels to the patient via flexible air tubing with redundant in-line air filters, and is delivered to the patient via a hand-held nebulizer. The flow of air enters the patient's nostril and exits the other nostril and the mouth, inducing an evaporative cooling energy exchange in the turbinates and upper airway. The blower inside the device provides the motive force to move the air supply over the desiccant material and across the patient's turbinates.

An Operator's Manual for use during the study has been developed and will be available for training and to keep at hand during device use.

FIGURE 2: COOLSTAT DEVICE



The subjects in this trial are awake and otherwise healthy and will be allowed to stop the study at any time if they feel discomfort beyond what they feel is tolerable. For safety, the device monitors and limits the pressure and flow rate of the air supply to the patient, as well as the temperature of the air being supplied to the subjects. The pressure is limited to 30 cmH2O max (less than 0.5 psi) and the temperature to 38 °C in accordance with the CPAP ISO standard 80601-2-70. Sensors in the device will alarm and reduce or stop operation if the temperature or pressure exceeds safety limits. A list of the software error codes and their functions are provided in the Operator's Manual.

The current COOLSTAT is designed to operate inside a hospital or other healthcare setting in a controlled environment. This helps to ensure that the temperature of the supply inlet air to the device is relatively controlled at ambient levels. In addition, a passive heat exchanger inside the device is used to keep the air supply temperature within a safe and comfortable range. A future migraine device is envisioned to be much smaller, likely designed for at-home use by the patient.

In addition, the CoolStat device delivers a continuous mist of saline directly to the nasal mucosa to reduce drying and to facilitate improved evaporative cooling. The mist is administered to the subject and delivered via a hand-held nebulizer, in parallel with the delivery of the dry air. The nebulizer sits at the entrance of the nose and does not cannulate into the nostrils.

6.1.2 SHAM DESCRIPTION

The sham treatment will also be administered through the CoolStat device via the use of a "used" desiccant cartridge. The CoolStat device consists of a replaceable desiccant cartridge loaded to the device, which normally is used to dehumidify the room air to deliver completely dry air to the patient. For the sham treatment, a 'used' desiccant cartridge will be used, which will result in ambient air delivered to the patient. The normal 'fresh' desiccant cartridges as well as the 'used' desiccant cartridges will appear identical to study personnel, with non-identifying labels, e.g., A, B or C. For the sham treatment arm, study personnel will be instructed to select and use a desiccant cartridge with a label for the 'used' cartridge. The sham group will also receive a low flow air (6LPM) which will result in significantly reduced evaporative cooling effect.

6.1.3 DOSING AND ADMINISTRATION

There will be two active treatment doses and one sham dose evaluated in this study: a high flow (24 LPM) dry air, a low flow (18 LPM) dry air, and the sham flow (6 LPM) of ambient air. All treatment arms will be administered through blinded, pre-set settings on the CoolStat device. Study personnel will be provided an input number, e.g., 1-9 (to put in the CoolStat user screen) that correlates to the two active treatment arms as well as the sham arm. Redundant numbers are used to help protect the blinding process. When the CoolStat is turned on, it displays a series of user-friendly set up instructions on its display screen. The final step in the startup process involves inputting the 'input number', which will be done for each subject.

A randomization process will be used with the proposed study to assign the numerical input value and desiccant cartridge selection (A, B or C) for each subject at each site. We have arranged to use MedNet to support this work, including their cloud-based randomization tool. For example, when a particular study site receives a new subject, study personnel will log on to the MedNet database, which will then provide both a device numerical input value and a cartridge designation based on a preset randomly generated list for this study. For example, the study inputs may be 4C, or 5A or 9B, which would correspond to a high therapy arm, a low therapy arm and a sham arm, respectively. This will ensure that the treatment is assigned randomly to each subject and there will be no risk of the device being pre-programmed to the incorrect flow rate (i.e. from a prior subject).

More detail on the device startup process can be found in the Operator's Manual and CoolStat QuickStart Guide.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

The COOLSTAT device will be delivered by hand to the study site by CoolTech personnel. The Principal Investigator is responsible for ensuring that accurate records are maintained for the receipt and dispensing of all investigational devices, including dates and number of investigational devices received, to whom dispensed (subject-by-subject accounting), and accounts of any investigational devices accidentally or deliberately destroyed. Upon receipt, inventory will be performed and an accountability log completed and signed by the person accepting the investigational product. In the event of a device, desiccant cartridge or nasal mask malfunction or failure, the faulty item will be bagged and retained until picked up by the Sponsor. In this event, the Sponsor will evaluate and document the reason for the malfunction or failure.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

The investigational medical device is labeled “CAUTION - Investigational Device. Limited by Federal (or United States) Law to Investigational Use”. This will help to ensure that the investigational products are not accidently used for other non-trial related procedures. (Any original equipment manufacturers labeling will not be removed but shall be over-labelled for the purpose of the IDE labeling.)

The device (hardware/software) will not have a separate package. Labelling will be directly on its enclosure.

The disposables are split into two different packages:

- each set of air tubing manifold and nebulizer is sealed in a plastic bag, and
- each desiccant cartridge is sealed in a heat seal foil pouch to protect from moisture.

Each air tubing and nebulizer set will be used on only one subject and then disposed of by study personnel. Likewise, the desiccant cartridges are single-use and will be disposed of by study personnel after each subject. A photograph of disposables is included in the Operator’s Manual.

- Device Package Labels

  The device labels will include the following information:

  - “CAUTION – Investigational Device. Limited by Federal (or United States) Law to Investigational Use.”
  - “COOLTECH LLC, 40 East Cross St, Baltimore, MD 21230”
  - Study name
  - Device name
  - Device serial number
  - “Be familiar with device operation before use”

- Disposable Package Labels

  The disposable labels will include the following information:

- "CAUTION – Investigational Device. Limited by Federal (or United States) Law to Investigational Use."
- "COOLTECH LLC, 40 East Cross St, Baltimore, MD 21230"
- Lot number
- Expiration date (Use by date)
- "NON-STERILE"

6.2.3 PRODUCT STORAGE AND STABILITY

The COOLSTAT device, the desiccant cartridges, and the air tubing disposable sets will be stored at room temperature and maintained by designated study personnel in a locked room. The equipment may only be handled by designated study personnel.

6.2.4 PREPARATION

Please refer to the QuickStart Guide when setting up the CoolStat for use.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Subjects will be randomly assigned to one of the three study groups. Investigational devices will be programmed in a 1:1:1 ratio in order to achieve the desired ratio between the active and control groups.

Subjects will be blinded to treatment assignment until the completion of the study. All efforts will be made to keep the subject blinded during the study treatment and during the follow up assessments, including the 24 hour follow up interview.

To minimize bias, both the subject the outcomes assessor(s) will be blind to the treatment group. In addition, subjects will only be randomized and treated one time to eliminate within-subject bias. The device will operate in Blind mode for this study, in which the different flow settings are coded to a set of nine numbers. The randomization tool within the MedNet electronic data capture (EDC) will allocate each subject a coded flow number. In addition, the 'used' desiccant cartridges will look and be packaged in exactly the same way as the 'fresh' cartridges. The foil packaging will be marked with a set of three letters, and the randomization tool will also allocate each subject to a desiccant cartridge lot via these letters.

Data are to remain blinded per protocol throughout the study. However, unblinding of subjects by the study monitor, data manager and/or statisticians may occur in the event of a SAE that is deemed related to the study intervention. If time permits, the Investigator should make every attempt to contact the Sponsor and/or Medical Monitor before unblinding any subjects' treatment. The Investigator may conduct emergency unblinding if necessary using the MedNet data capture system. The Investigator will have a one-time view of the treatment arm for one patient in such a situation, and will not be unblinded to the treatment arms for other any subjects.

6.4 STUDY INTERVENTION COMPLIANCE

Not applicable. The study intervention will occur under supervision of study personnel.

6.5 CONCOMITANT THERAPY

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the Case Report Form (CRF) are concomitant prescription medications, over-the-counter medications and supplements.

6.5.1 RESCUE MEDICINE

Although the use of rescue medications is allowable at any time during the study, the use of rescue medications should be delayed, if possible, for at least 2 hours following the administration of study intervention. The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Discontinuation from the 15 minute CoolStat treatment session does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol, when possible. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the Investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The data to be collected at the time of study intervention discontinuation will include the following:

- Reason for discontinuation
- Time of discontinuation

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.

An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy
- Significant study intervention non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that the Investigator feels continued participation in the study would not be in the best interest of the participant
- Disease progression which requires discontinuation of the study intervention

- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Participant unable to receive CoolStat treatment session for >60 days

The reason for participant discontinuation or withdrawal from the study will be recorded on the Subject Withdrawal Case Report Form (CRF). Subjects who sign the informed consent form but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to answer the scheduled follow up phone calls from study staff or if the subject is unable to be contacted by the study staff.

The following actions must be taken if a participant fails to return the study team's phone calls for their follow up phone interviews:

- The site will attempt to contact the participant once per day for 3 consecutive days to conduct the follow up phone interview(s).
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

8.1.1 SCREENING VISIT

Potential candidates for the study are evaluated by the Investigator or their designee as described below:

- The investigator or their designee must approve the candidate to be enrolled by verifying that the subject meets all of the inclusion criteria and none of the exclusion criteria, and that informed consent has been obtained from the patient. As part of the consenting process, the subject will be instructed on the scope of the study, potential risks and activities required to participate in the study, following a signed Informed Consent Form (ICF).
- If the subject meets the specified criteria and signs the ICF, they will be eligible to participate in the study for a period of 60 days. Over this period, the subject may return to the clinic upon onset of a migraine for an "on-demand appointment." The subject will receive the treatment, which will last up to 15 minutes, and will be followed for a period of 24 hours after the treatment, as specified herein.

- A subject may re-consent after the initial 60-day period if they did not receive a study intervention during that time period, if they continue to meet all inclusion/exclusion criteria. See ***Section 5.3 Screen Failures*** for more information.

8.1.2 BASELINE/TREATMENT VISIT

Upon arrival to the headache clinic during the acute onset period of a migraine, the subject will complete a short questionnaire (migraine symptom questionnaire) rating headache pain on a 4-point scale (0 = no pain, 1 = mild pain, 2 = moderate pain, 3 = severe pain) and associated symptoms (nausea, photophobia and phonophobia) on a binary scale, as well report if their headache is unilateral, throbbing, and aggravated by physical activity. Only subjects with Grade 2 or Grade 3 pain at baseline may be randomized to receive study intervention.

A member of the study team will obtain the subject's height, weight, tympanic membrane temperature, blood pressure, and oxygen saturation and record findings in the Case Report Form.

The study team member will ask the patient to confirm that they are of general good health, other than their migraine diagnosis, and if there are any updates to the subject's medical history and record any concomitant medications.

If the subject meets the criteria for a qualifying migraine (Grade 2 or 3 severity, onset of head pain was less than 6 hours ago), the study team member will randomize the subject.

Upon setting up the device for a subject, the study team member who will administer the therapy will run a quick test to confirm the nebulizer is propelling mist into the CoolStat airstream. Once completing the device apparatus setup, they will turn the CoolStat on and hold a piece of paper up to the airstream for 5 seconds. If the paper becomes wet, then they can move forward with treatment. If it does not become wet, they should check the attachment interface of the nebulizer and nasal mask.

8.1.3 POST TREATMENT EVALUATION 1 (0 MINUTES)

Immediately after the CoolStat treatment is completed or discontinued, the subject will repeat the migraine symptom questionnaire and answer questions about their experience using the CoolStat.

The investigator or his designee will obtain the subject's tympanic membrane temperature, blood pressure, and oxygen saturation and record the data in the Case Report Form.

The investigator or his designee will monitor the subject for any adverse events.

8.1.4 POST TREATMENT EVALUATION 2 (2 HOURS)

The subject will remain in the clinic for 2 hours after they complete treatment session and will be monitored for adverse events during that time period. During this 2 hour period, subjects will remain in the exam room or another quiet space in the clinic, and will be allowed to rest. Subjects will be asked to delay taking rescue medications until this 2 hour period is over, if possible.

At the end of the 2 hour monitoring period, subjects will repeat the migraine symptom questionnaire, and the investigator or his designee will obtain the subject's tympanic membrane temperature, blood pressure, and oxygen saturation and record the data in the Case Report Form.

The investigator or his designee will record any adverse events.

Upon completion of these items, the subject may resume other care activities.

The study team member will record use of any rescue medications during this 2-hour period.

8.1.5 POST TREATMENT EVALUATION 3 (24 HOURS)

The investigator or his designee will call the subject approximately twenty-four hours after CoolStat treatment was completed and ask the subject to complete the migraine questionnaire over the phone. If the subject cannot be reached, study personnel will continue to try to reach the subject on regular intervals over the course of this day and the next consecutive 2 days. It will be noted in the case report forms if the subject could not be reached for the final follow up.

The investigator or his designee will record any additional treatments used by the subject within the 24 hours since CoolStat (e.g. NSAIDs, ice), and will also ask if they have experienced any adverse events.

8.2 SAFETY AND OTHER ASSESSMENTS

- **Physical examination** including height, weight and temperature will be obtained at baseline
- **Vital signs** will be taken at baseline, immediately post treatment session, and at 2 hours post treatment
- **Administration of questionnaires** immediately post treatment, at 2 hours and 24 hours post treatment.
- **Assessment of adverse events.** Patients with ongoing AEs/SAEs will be followed up with on a daily basis until the AE/SAEs are deemed to be resolved.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

For adverse events (AEs), the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Related** – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

8.3.3.3 EXPECTEDNESS

The Principal Investigator will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The study coordinator(s) will record all reportable events with start dates occurring any time after informed consent is obtained until 1 (for non-serious AEs) or 7 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3.5 ADVERSE EVENT REPORTING

The study period during which AEs must be reported is defined as from the initiation of any study treatment or randomization through the end of the study intervention follow-up.

Any AE (clinical sign, symptom, or disease) temporally associated with the use of this study device, whether or not considered related to the study device, shall be documented on the AE CRF, except those physical assessment findings that are considered to be clinically insignificant.

All AEs meeting the above noted criteria reported by the subject or observed by the Investigator will be individually listed. The description of the event (confirmed diagnosis, if available), date of onset, date of resolution, severity and relationship to study device, action taken, outcome, and seriousness will be reported.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

For any **SAE** the Principal Investigator must notify the Sponsor's Medical Monitor, within 24 hours of becoming aware of the event and send the completed Serious Adverse Event/Unanticipated Adverse Device Effect (SAE/UADE) Report to the Sponsor's Medical Monitor within 48 hours. In addition, all IRB reporting requirements will be followed.

Any SAE or UADE must be reported to the Sponsor's Medical Monitor via telephone, fax, or email within 24 hours of becoming aware of the event:

SPONSOR'S MEDICAL MONITOR CONTACT INFORMATION:
Zubair Ahmed, MD

Cleveland Clinic
9500 Euclid Avenue
Cleveland, OH 44195
216-339-5605
Ahmedz2@ccf.org

Within 48 hours after the initial report, the Investigator must provide further information to the Sponsor's Medical Monitor on the SAE or UADE in the form of a written narrative. This should include a copy of the completed SAE/UADE Report Form and any other related diagnostic information that will assist in the understanding of the event. Significant new information on ongoing SAEs should be provided promptly to the Sponsor's Medical Monitor. All identifiable reference to the subject except for the subject screening number will be redacted from any report sent to the Sponsor's Medical Monitor.

The study investigator shall complete an Unanticipated Adverse Device Effect Form and submit to the study sponsor and to the reviewing Institutional Review Board (IRB) as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect. The study sponsor is responsible for conducting an evaluation of an unanticipated adverse device effect and shall report the results of such evaluation to the Food and Drug Administration (FDA) and to all reviewing IRBs and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter, the sponsor shall submit such additional reports concerning the effect as FDA requests.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

Not applicable.

8.3.8 EVENTS OF SPECIAL INTEREST

Not applicable.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- 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.

This definition could include an unanticipated adverse device effect, any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3(s)).

8.4.2 UNANTICIPATED ADVERSE DEVICE EFFECT (UADE) REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and to the Data Coordinating Center (DCC)/lead principal investigator (PI). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

An Unanticipated Adverse Device Effect is described as any serious adverse effect on health or safety or any life-threatening problem or death caused by or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3(s)).

An investigator shall submit to the sponsor and to the reviewing Institutional Review Board (IRB) a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect (21 CFR 812.150(a)(1)).

A sponsor who conducts an evaluation of an unanticipated adverse device effect under 812.46(b) shall report the results of such evaluation to the Food and Drug Administration (FDA) and to all reviewing IRB's and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter the sponsor shall submit such additional reports concerning the effect as FDA requests (21 CFR 812.150(b)(1)).

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

- Primary Efficacy Endpoint(s):
  1. Dose response comparison for pain relief at 2 hours

a. Null hypothesis:

H_0: πA - πS = 0; where πA is the proportion of subjects who show pain relief at 2 hours after active treatment (flow rate of x or Y) and πS is the equivalent value for the sham-control treatment group.

b. Alternative hypothesis:

H_a: πA - πS > 0; where πA is the proportion of subjects who show pain relief at 2 hours after active treatment (flow rate of x or Y) and πS is the equivalent value for the sham-control treatment group.

- Secondary Efficacy Endpoint(s):
  1. Dose response comparison for pain relief immediately and 24 hours post treatment.
     a. Null hypotheses:
        i. H_0: πA - πS = 0; where πA is the proportion of subjects who show pain relief immediately after active treatment (flow rate of x or Y) and πS is the equivalent value for the sham-control treatment group.
        ii. H_0: πA - πS = 0; where πA is the proportion of subjects who show pain relief at 24 hours after active treatment (flow rate of x or Y) and πS is the equivalent value for the sham-control treatment group.
     b. Alternative hypothesis:
        iii. H_a: πA - πS > 0; where πA is the proportion of subjects who show pain relief immediately after active treatment (flow rate of x or Y) and πS is the equivalent value for the sham-control treatment group.
        iv. Ha: πA - πS > 0; where πA is the proportion of subjects who show pain relief at 24 hours after active treatment (flow rate of x or Y) and πS is the equivalent value for the sham-control treatment group.
  2. Dose response comparison for pain freedom immediately, 2 hours, and 24 hours post treatment.
     a. Null hypotheses:
        i. H_0: πA - πS = 0; where πA is the proportion of subjects who show pain freedom immediately after active treatment (flow rate of x or Y) and πS is the equivalent value for the sham-control treatment group
        ii. H_0: πA - πS = 0; where πA is the proportion of subjects who show pain freedom 2 hours after active treatment (flow rate of x or Y) and πS is the equivalent value for the sham-control treatment group.
        iii. H_0: πA - πS = 0; where πA is the proportion of subjects who show pain freedom 24 hours after active treatment (flow rate of x or Y) and πS is the equivalent value for the sham-control treatment group.
     b. Alternative hypothesis:
        i. H_a: πA - πS > 0; where πA is the proportion of subjects who show pain freedom immediately after active treatment (flow rate of x or Y) and πS is the equivalent value for the sham-control treatment group.
        ii. H_a: πA - πS > 0; where πA is the proportion of subjects who show pain freedom 2 hours after active treatment (flow rate of x or Y) and πS is the equivalent value for the sham-control treatment group.
        iii. H_a: πA - πS > 0; where πA is the proportion of subjects who show pain freedom 24 hours after active treatment (flow rate of x or Y) and πS is the equivalent value for the sham-control treatment group.

3. Dose response comparison for relief of migraine associated symptoms (nausea/vomiting, photophobia, phonophobia) immediately, 2 hours, and 24 hours post treatment.
    a. Null hypotheses:
        i. H_0: πA - πS = 0; where πA is the proportion of subjects who show relief from migraine associated symptoms immediately after active treatment (flow rate of x or Y) and πS is the equivalent value for the sham-control treatment group.
        ii. H_0: πA - πS = 0; where πA is the proportion of subjects who show relief from migraine associated symptoms 2 hours after active treatment (flow rate of x or Y) and πS is the equivalent value for the sham-control treatment group.
        iii. H_0: πA - πS = 0; where πA is the proportion of subjects who show relief from migraine associated symptoms 24 hours after active treatment (flow rate of x or Y) and πS is the equivalent value for the sham-control treatment group.
    b. Alternative hypothesis:
        i. H_a: πA - πS > 0; where πA is the proportion of subjects who show relief from migraine associated symptoms immediately after active treatment (flow rate of x or Y) and πS is the equivalent value for the sham-control treatment group.
        ii. H_a: πA - πS > 0; where πA is the proportion of subjects who show relief from migraine associated symptoms 2 hours after active treatment (flow rate of x or Y) and πS is the equivalent value for the sham-control treatment group.
        iii. H_a: πA - πS > 0; where πA is the proportion of subjects who show relief from migraine associated symptoms 24 hours after active treatment (flow rate of x or Y) and πS is the equivalent value for the sham-control treatment group.
4. Dose response comparison for freedom from migraine associated symptoms (nausea/vomiting, photophobia, phonophobia) immediately, 2 hours, and 24 hours post treatment.
    a. Null hypotheses:
        i. H_0: πA - πS = 0; where πA is the proportion of subjects who show freedom from migraine associated symptoms immediately after active treatment (flow rate of x or Y) and πS is the equivalent value for the sham-control treatment group.
        ii. H_0: πA - πS = 0; where πA is the proportion of subjects who show freedom from migraine associated symptoms 2 hours after active treatment (flow rate of x or Y) and πS is the equivalent value for the sham-control treatment group.
        iii. H_0: πA - πS = 0; where πA is the proportion of subjects who show freedom from migraine associated symptoms 24 hours after active treatment (flow rate of x or Y) and πS is the equivalent value for the sham-control treatment group.
    b. Alternative hypothesis:
        i. H_a: πA - πS > 0; where πA is the proportion of subjects who show freedom from migraine associated symptoms immediately after active treatment (flow rate of x or Y) and πS is the equivalent value for the sham-control treatment group.
        ii. H_a: πA - πS > 0; where πA is the proportion of subjects who show freedom from migraine associated symptoms 2 hours after active treatment (flow

rate of x or Y) and πS is the equivalent value for the sham-control treatment group.

iii. H_a: πA - πS > 0; where πA is the proportion of subjects who show freedom from migraine associated symptoms 24 hours after active treatment (flow rate of x or Y) and πS is the equivalent value for the sham-control treatment group.

5. Superiority comparison for use of rescue medication between 2 and 24 hours.
   a. Null hypothesis: H_0: πS - πA = 0; where πA is the proportion of subjects take rescue medication between 2 and 24 hours after active treatment (flow rate of x or Y) and πS is the equivalent value for the sham-control treatment group.
   b. Alternative hypothesis: H_a: πS - πA > 0; where πA is the proportion of subjects who take rescue medication between 2 and 24 hours after active treatment (flow rate of x or Y) and πS is the equivalent value for the sham-control treatment group.

9.2 SAMPLE SIZE DETERMINATION

We conducted a preliminary study using an alpha prototype of our cooling device in which subjects were blinded to the treatment. In that study, 56% of subjects in the dry air treatment group reported freedom from headache pain at two hours post treatment compared to 8% of subjects in the sham group. A power analysis using this effect size as a basis for calculation indicated a minimum sample size of 17 patients in each group would be required to achieve at least 80% power to detect a significant difference at two-tailed alpha level = 0.05. We realize that the effect size from this initial study seems quite large, and we propose a conservative n=25 per group to account for error in estimates based on the preliminary results, for a total sample size of 75 subjects.

100 subjects will be consented to account for screen failures. Only the first 75 subjects who return with a qualifying migraine will be randomized to a treatment group.

9.3 POPULATIONS FOR ANALYSES

- **Intention-to-Treat (ITT) Population**: The Intention-to-Treat (ITT) population is defined as all randomized subjects. The ITT analysis population will be used as the primary analysis population for the primary endpoint.

- **Per Protocol (PP) Population:** The per-protocol analysis set (PP) includes all subjects in the ITT analysis set who received at least 10 minutes of treatment without any major protocol deviation. The PP analysis population will be used as the secondary analysis population for sensitivity analyses.

- **Safety Analysis Dataset:** The Safety population is defined as all randomized subjects who underwent the study intervention. This population will be used for the analysis of safety parameters.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

- **Categorical data summaries will include:**
  - Absolute (n) and relative (%) frequency tables

- **Continuous data summaries will include:**
  - Number of patients (n), the arithmetic mean and the standard deviation, the coefficient of variation as a percentage (CV%), the median, the interquartile range, the minimum and the maximum value.

- **Subject Disposition**
  - The disposition of all subjects who sign an ICF will be provided. The numbers of subjects screened, randomized, completed, and discontinued during the study, as well as the reasons for all post-treatment discontinuations will be summarized by treatment group. Disposition and reason for study discontinuation will also be provided as a by-subject listing.

- **Demographic and Baseline Characteristics**
  - Demographic and baseline characteristic data will be summarized descriptively and/or presented as a by-subject listing for the Safety Analysis population.

- **Protocol Deviations**
  - The deviations occurring during the clinical study will be summarized and/or presented as a by-subject listing.

- **Prior and Concomitant Medications**
  - Concomitant medications will be summarized separately for the Safety population. Descriptive summaries, by treatment group, will be prepared using the coded term. All concomitant medications recorded in the case report form will be listed.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

Both primary efficacy endpoints are scored categorically (Grade 0: no pain, Grade 1: mild pain, Grade 2: moderate pain, Grade 3 severe pain).

These categorical data will be summarized by absolute (n) and relative (%) frequency tables.

For categorical variables/proportions, we will perform Kruskal-Wallis test (the nonparametric equivalent of the ANOVA) to determine if there is a difference across the three study groups.

If there is a difference, then the Mann-Whitney test will be performed to compare the groups to each other to determine where the difference lies. We will correct for multiple comparisons using Bonferroni correction. The multiple imputation method will be used as the primary method for handling missing data in this study.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Our secondary outcomes (pain relief and relief from symptoms at 2 hours, 24 hours and immediately after treatment) are graded on the same scale, and the same statistical methods used as for the primary outcomes will be used.

All relevant general, safety and efficacy data will be descriptively summarized at each time point.

Continuous data will be summarized by the number of patients (n), the arithmetic mean and the standard deviation, the coefficient of variation as a percentage (CV%), the median, the interquartile range, the minimum and the maximum value.

9.4.4 SAFETY ANALYSES

All safety assessments will be tabulated and no hypothesis testing will be conducted in this analysis. For continuous variables data, will be summarized by treatment group using n, mean, standard deviation, median, minimum and maximum values. For categorical variables, data will be summarized by treatment group using frequency and percentage.

For each adverse event, the start date, stop date, severity, relationship, expectedness, outcome, and duration will be reported.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Descriptive statistics (n, mean, standard deviation, median, minimum and maximum) will be calculated by treatment group for continuous variables. Frequencies and percentages will be presented by treatment group for categorical variables.)

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention. The following consent materials are submitted with this protocol:

- Informed Consent (English)
- Informed Consent (Spanish)

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study.

Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (aka the electronic medical record) and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, the Investigational Device Exemption (IDE) sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or Food and Drug Administration (FDA).

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in

strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored by the study Sponsor. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by the study Sponsor research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the study Sponsor.

10.1.4 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator	**Medical Monitor**
Nauman Tariq, MD	Zubair Ahmed, MD
Atrium Health Neurosciences Institute	Cleveland Clinic
1010 Edgehill Road N, Charlotte, NC 28207	9500 Euclid Avenue, Cleveland, OH 44195
848-203-1709	216-339-5605
Nauman.Tariq@atriumhealth.org	Ahmedz2@ccf.org

10.1.5 SAFETY OVERSIGHT

The SMC will consist of three members; two physicians and one statistician. The physicians will be appointed by the Principal Investigators and will have the appropriate expertise in the fields of neurology and headache medicine. The SMC will be independent from study conduct and free of conflict of interest, or measures will be in place to minimize perceived conflict of interest. The SMC will provide their input to CoolTech (the study Sponsor).

10.1.6 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonization Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

- Monitoring for this study will be performed by an employee of the Sponsor or its designee.
- Clinical monitoring for this study will be conducted using a risk-based approach. Over the course of the study, the monitors will perform at least three on-site visits: a startup visit, an interim visit, and a closeout visit. Depending on findings at the first interim visit, the site-level monitoring plan may be adjusted based on any findings that would trigger more frequent interim visits.
- Source document verification will be conducted for 30% of the study data on a random basis. Study monitors will perform 100% remote monitoring of the electronic database.
- Principal Investigators will be provided copies of monitoring reports within 10 days of visit.
- Details of clinical site monitoring are documented in a **Clinical Monitoring Plan (CMP)**. The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

10.1.7 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonization Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

10.1.8 DATA HANDLING AND RECORD KEEPING

10.1.8.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

Source data is all information, original records of clinical findings, observations, or other activities in a study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents. Examples of source documents include but are not limited to: clinical and office charts, hospital records, laboratory notes, memoranda, pharmacy dispensing records, recorded data from

automated instruments, copies or transcriptions certified after verification as being accurate and complete, and subject files. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

The CRF is an integral part of the study and subsequent reports. Hardcopies of the CRF for study visits will be provided by the Sponsor for use as source document worksheets for recording data for each participant enrolled in the study. The CRF provided by the Sponsor must be used to capture all study data recorded in the subject's medical record. The CRF must be kept current to reflect subject status during the course of the study. Only a subject screening number will be used to identify the subject. The Investigator must keep a separate log of subject names and medical record numbers (or other personal identifiers). After obtaining written source document information from each subject at each visit, the study site will enter the data into the CRF (paper or electronic).

Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

The study monitor is responsible for performing on-site and/or remote monitoring at regular intervals throughout the study to verify adherence to the protocol and applicable regulations on the conduct of clinical research as well as to ensure completeness, accuracy, and consistency of the data entered in the CRF. At the study site, the monitor must have access to subject medical records, study-related records, and written source documentation needed to verify the entries on the CRFs.

Final monitored and/or audited CRFs will be available at all times, unless specified in writing to the Sponsor. These CRFs must be reviewed and verified for accuracy by the Principal Investigator and signed off (via electronic and/or paper signature). A copy of the final CRFs will remain at the Investigator's study site at the completion of the study.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into iMedNet, a 21 CFR Part 11-compliant data capture system provided by the study Sponsor. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.1.8.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 3 years after the last approval of a marketing application in an International Conference on Harmonization (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 3 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

If the Principal Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept responsibility. The Sponsor must be notified in writing of the name and address of the new custodian.

10.1.9 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol or International Conference on Harmonization Good Clinical Practice (ICH GCP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation, or within 10 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents, reported to the NINDS Program Official and to CoolTech. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements.

10.1.10 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers 5 years after the completion of the primary endpoint by contacting the study Sponsor.

10.1.11 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the biomedical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the NINDS has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem

Protocol Amendment History

Version	Date	Prepared By	Reviewed By	Approved By
1.0	27 April 2021	Casey Hannan	Brian Lipford	Will DeMore
2.0	02 July 2021	Casey Hannan	Brian Lipford	Will DeMore

Version	Date	Description of Change	Brief Rationale
1.0	27 April 2021	Original Version	
2.0	02 July 2021	Added NCT number on p. i and name of FDA cleared nebulizer on p. 10.	NCT number has been assigned since V1.0 was released. CoolTech selected and completed testing on an FDA-cleared nebulizer.

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