Transnasal Induction of Normothermia in NCCU Fever Patients

Contents

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NOTES to STUDY PROTOCOL REVIEWERS

NOTE 1: Throughout this protocol and case report forms, the term **"investigator"** may be used. In such circumstances only an approved sub-investigator or the PI may execute the action. These actions specifically include decisions to enroll, start COOLSTAT therapy, stop COOLSTAT therapy and withdrawal the subject for any reason. If any requirement is the sole jurisdiction of the Principal Investigator, it is specifically identified. The Site Principal Investigator will supervise the study and oversee that all clinical personnel assigned to this study have been trained to protocol requirements and device operation as necessary for their responsibilities.

Additional study investigators (sub-investigators) may be designated and supervised by the Site Principal Investigator and shall conform to the requirements described below, including providing their curriculum vitae.

PROTOCOL REVISION TABLES

Rev	Date	Prepared By	Reviewed By	Approved By
P2	10/13/17	---	---	
P3	8/8/18	E. Bigelow	B. Lipford	B. Lipford
P4	1/30/19	C. Hannan	W. DeMore	B. Lipford
P5	6/10/19	C. Hannan	B. Lipford	B. Lipford
P6	7/24/19	C. Hannan	B. Lipford	B. Lipford
A	12/5/19	C. Hannan	W. DeMore	B. Lipford
B	7/23/20	C. Hannan	W. DeMore	B. Lipford
C	2/15/21	C. Hannan	W. DeMore	B. Lipford
D	7/7/21	C. Hannan	W. DeMore	B. Lipford

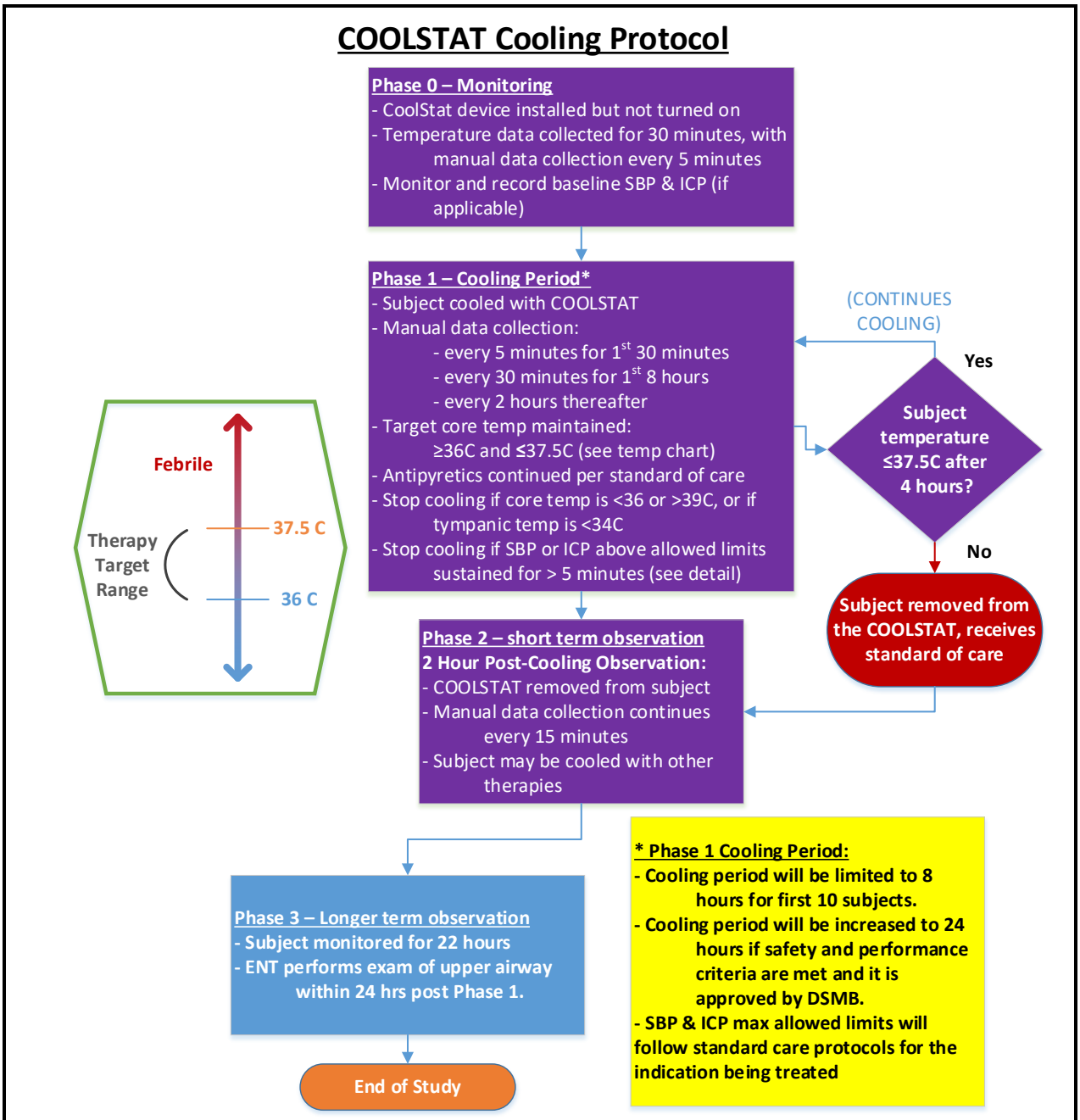
Rev	Details of Revision
P2	Original version approved by FDA for IDE and by UM IRB

P3	Added revision table, corrected all references to the definition of fever to ≥38.3°C on pgs. 7, 25, 36, and 37; Added BMI range exclusion criteria on p.35; Fixed typo on p. 34
P4	Expanded indications to include seizure and metabolic encephalopathy on pgs. 6, 7, 8, 10, 16, 19, 23, 27, 32, 34, 38; Added SpotOn as core temperature probe on pgs. 10, 18, 19, 26, 32, 36, 37, 38, 39, 45; Allow otolaryngology residents to perform pre- and post-intervention nasal exams on pgs. 9, 11, 40, 52; Changed "systolic blood pressure" to "blood pressure" on pgs. 9, 10, 23, 26, 34, 37, 40, 50; Changed Product Designer to Will DeMore on pg. 1.
P5	Removed site specific information to make protocol applicable to multiple investigational sites on pgs. 1, 5, 7, 8, 10, 11, 12, 18, 19, 20, 23, 25, 26, 27, 28, 31, 32, 36, 37, 38, 41, 42, 55, 56; Clarified hypothesis and statistical plan to account for cooling interruptions due to clinically required patient transport on pgs. 11, 12, 30, 31, 38, 39, 52; Allow tracheostomy patients on mechanical ventilator to be enrolled on pgs. 9, 20, 34, 35, 37, 41; Added section 6.11, which describes a staged approach to transition "history of cardiac arrhythmia" out of the exclusion criteria on p. 32; Fixed typos on p. 11, 12, 23, 24, 26, 30, 31, 34, 38, 39, 51, 52.
P6	Allow intensivist to perform pre-intervention nasal exams if an otolaryngologist is unavailable on pgs. 8, 10, 51. Fixed error in revision table on p. 5
A	Allow for enrollment of up to 70 subjects to account for a 55% screen failure rate (note that the total number of subjects who receive CoolStat therapy will remain unchanged at N = 30) on pgs. 9, 10, 29. Removed "tympanic" as specified core temperature probe on p. 39. Fixed typos on p. 7, 9, 36, 50. Note 2/5/2020: Revision changed from P7 to A upon PDM Pro transition.
B	Allow intensivist to perform post-intervention nasal exams if an otolaryngologist is unavailable on pgs. 10, 39, 52.
C	Update sponsor contact info on pg. 1. Revised descriptions of air flow paths to describe both double nostril and single nostril flow paths on pgs. 14, 17, 20, 52. Added description of serial data logger on p. 50. Provided criteria for assignment to double nostril vs single nostril flow on p. 52.
D	Added description for dose escalation procedures for subjects 21 through 30 on p. 52. Added new section for list of serious adverse events on p. 45.

1.0 Summary of Study Plan

Study Objective	The objective of this study is to evaluate safety and performance of the COOLSTAT® Transnasal Thermal Regulating Device in reducing temperature in a population of febrile subjects who meet the inclusion/exclusion criteria.
Indication for use	The CoolStat Transnasal Thermal Regulating Device is intended for temperature reduction to achieve normothermia, as an adjunct to anti-pyretic therapy, in adult patients with ischemic or hemorrhagic stroke, seizure, or metabolic encephalopathy who are intubated and sedated.

Intended use	The COOLSTAT Transnasal Thermal Regulating Device is designed to be used inside a hospital or other healthcare setting for temperature reduction, operated by trained healthcare professionals.
Device	**The COOLSTAT® Transnasal Thermal Regulating Device** [hereafter COOLSTAT or CoolStat] cools febrile patients using dry filtered air at ambient temperature to induce an evaporative cooling energy exchange in the turbinates and upper airway.
Prior testing to support safety	A prototype system based upon CPAP equipment was evaluated in a porcine model which demonstrated no adverse events due to the airflow and showed cooling efficacy. A similar prototype was evaluated in a non-significant risk, proof of concept study in humans which similarly demonstrated the safety of transnasal dry airflow. The clinical COOLSTAT device has been tested in a porcine model over 8 and 24 hour periods, which demonstrated safety and cooling efficacy.
Study Design	This will be a prospective, observational study of COOLSTAT in a neuro-ICU setting. Below is a flow chart which summarizes the study protocol:



Adverse Events	**Adverse Events:** Treating physicians may discontinue treatment at any time if adverse events are encountered or, in their opinion, alternate cooling methods are required on an urgent basis. If at any point the physician switches to an alternate cooling method, the subject is not withdrawn from the study and data will continue to be collected manually for the remainder of the study period (if possible). Follow-up continues per protocol. Anticipated adverse events are detailed in the protocol Section 10.

Data Collection	• Pre-therapy evaluation and decision to apply COOLSTAT Therapy when subject has met additional screening requirements, within 7 days of enrollment. This will include a visual exam by a board-certified otolaryngologist or an otolaryngology resident (under supervision of board certified otolaryngologist) of the upper airway. The intensivist will perform the pre-therapy nasal exam if an otolaryngologist is not available. • Core and tympanic temperatures and blood pressure (SBP) will be recorded in the hospital's data collection system as part of normal care, with alarms set at specified points (as noted herein). Data will also be recorded manually in CRF (see timing details below). • Tracheal tube placement will be recorded prior to initiation of COOLSTAT therapy (Phase 0), and checked and recorded in the CRF three times a day (every ~8 hours) for the remainder of the study. • Suctioned tracheal water volume will be recorded prior to the initiation of COOLSTAT therapy (during Phase 0), and recorded twice daily in the CRF for the remainder of the study. • COOLSTAT nasal mask will be removed every 4 hours for visual inspection of nasal area. Observations will be recorded in the CRF. • Level of shivering will be assessed and recorded in the CRF (see timing detail below). • Subjects will be monitored for stomach distention and signs of dehydration as part of standard of care. Observations of both will be recorded every 8 hours in the CRF. • Any intervention that may affect core temperature reading, such as a bolus of cold liquid passing temperature probe in the esophagus, will be manually recorded in the CRF. • Intracranial pressure (ICP), when available, will be collected manually in all study Phases (0-3) with other data (see timing details below). ICP monitoring is required for the first 5 subjects in this study. • Data from first 5 subjects, including ICP monitoring, will be reviewed by the study's Data Safety Management Board prior to enrolling any subjects who do not have ICP monitoring in place. Specific attention will be paid to any increase in ICP that may be due to COOLSTAT use. • Upon occurrence of any adverse events, the subject's medical records will be reviewed. • The COOLSTAT device will be automatically collecting air flow rate, air temperature supplied to the subject, air humidity supplied to the subject, air pressure, and patient core temperature data.

	Phase 0 – Pre-Cooling Monitoring (30 minutes): Manual temperature (core and tympanic), ICP (when available) and blood pressure data collection every 5 minutes (and some additional observations, see above). **Phase 1 – Cooling Treatment:** Manual data collection will occur at a minimum: • 5 minute intervals for first 30 minutes of cooling period. • 30 minute intervals for first 8-hour cooling period. • 2 hour intervals for remaining 16 hour of cooling (if applicable). **Phase 2 – Short-Term Post-Cooling Monitoring:** Manual data collection will occur at 15 minute intervals during this 2-hour period immediately following COOLSTAT cooling. **Phase 3 – Long-Term Post-Cooling Monitoring:** Manual data collection will occur at minimum four hour intervals through this 22-hour post-COOLSTAT cooling period. Any additional data collections and the reasons for them shall be documented in the study case form.
Study Population	70 adult febrile patients in the neurosciences intensive care unit, with ischemic or hemorrhagic stroke, seizure, or metabolic encephalopathy. Hemorrhagic stroke includes both intracerebral hemorrhage and subarachnoid hemorrhage stroke. Only the first 30 subjects who meet post-consent eligibility criteria will receive COOLSTAT therapy.
Regimen	COOLSTAT® Transnasal Thermal Regulating Device will be applied to patients at a pressure not to exceed 30 cm H2O (as automatically regulated by the device). A closed-loop control system in the COOLSTAT will modulate and control air flow and maintain the subject's core temperature between 36 °C and 37.5 °C, as measured by a hospital supplied embedded temperature sensor (esophageal, bladder, or 3M™ SpotOn™ temperature sensor). The device will be set to target of 36.5 °C.
Duration of Study for Subject	The study period for each subject can vary from 7 to 10 days, although the active cooling phase will be 24 hours or less. The primary reason for the extended duration of the study (beyond the active cooling phase) is due to the unpredictable nature in which patients may develop a fever (refractory to antipyretics), and the brief procedural window before additional cooling therapy should be implemented. This necessitates that we overenroll likely candidates (that may develop refractory fever) to be ready to apply the transnasal cooling therapy in short order, if a fever develops. The time frames over which the study may occur are: • 70 candidate subjects will be identified and enrolled (with consent), and will then remain enrolled but not activated for the COOLSTAT cooling protocol for up to 7 days. During this time frame, the subject will be

	inspected by board-certified otolaryngologist, otolaryngology resident, or intensivist and otherwise evaluated to see if the subject meets all eligibility criteria. • If the subject is determined to be eligible for COOLSTAT cooling, and the subject develops a refractory fever, he/she will enter the cooling phase of the protocol, which will start with a monitoring period (for 30 minutes) to ensure the temperature and vitals of the subject continue to be acceptable and stable (Phase 0). Only 30 subjects will enter this phase of the protocol, as slightly more than half of the enrolled subjects are expected to be post-consent screen failures. • Next, the subject will be cooled by the COOLSTAT for up to 24 hours maximum during Phase 1 (first 10 subjects will only be cooled for 8 hours) with a 2 hour short-term Post-Cooling Observational Phase (Phase 2). • An additional 22 hours of observation will occur (Phase 3), with a post-cooling visual nasal exam by a board-certified otolaryngologist, otolaryngology resident, or intensivist.
Estimated time to complete feasibility study	This trial will last until 30 subjects complete COOLSTAT Therapy; it is estimated that this will take less than 1 year. The study may be terminated at any time if there is insufficient data supporting the feasibility of COOLSTAT cooling or upon decision by the Sponsor that the study cannot achieve its stated objectives.
Hypothesis	The primary hypothesis regarding cooling performance is that at least 75% of the subjects will reach normothermia (core temperature ≤37.5 °C) within 4 hours of starting COOLSTAT cooling. The primary hypothesis regarding temperature maintenance is that at least 75% of the subjects' core temperatures remain between 36 °C and 37.5 °C for 80% of the steady state[2] time following the initial achievement of 37.5 ˚C.
Outcomes	*Performance Outcomes* 1) This feasibility study is intended to confirm that the COOLSTAT system can cool within expected performance parameters and can reach and maintain normothermic cooling therapy over the study period. Subjects are expected to reach normothermia (core temperature <37.5°C) within 4 hours of starting COOLSTAT cooling. Subject temperatures are expected to be maintained within a 1.5 °C temperature band, between 36 °C – 37.5 °C, for 80% of the steady state time following the initial achievement of 37.5 ˚C.[1]

[1] This recognizes that some subjects will have short periods of break-through fever over the course of the study.

[2] If a subject must be disconnected from the CoolStat device for transport from the NCCU to another unit (e.g., to radiology or angiography suite), they will be reconnected to the device at steady state if their core temperature

	2) Data collected will help to confirm cooling models and the control system algorithm by examining subject cooling response as a function of air flow rate and properties of the air supplied to the subjects. 3) The study will demonstrate that the COOLSTAT System can perform in the clinical setting and identify possible human and equipment interface refinements. *Safety Outcomes* Safety will be assessed by the following: 4) The incidence and severity of all adverse events (including, but not limited to serious adverse events and non-related adverse events). 5) Assessment as to any potential contribution to the adverse event that may be device related or related to transnasal cooling therapy. *Secondary Outcomes* This study may provide insight into the incidence of shivering, although the study design is not sufficiently powered to expect definitive conclusions.
Statistical Methodology	The primary efficacy analysis for temperature maintenance will be based on the evaluable population of subjects who achieve normothermia by 4 hours and continue cooling treatment with the COOLSTAT System. The proportion of subjects fulfilling success criteria and 90% confidence intervals will be reported and compared to the a priori minimum acceptable criteria: • at least 75% of the subjects will reach normothermia (core temperature ≤37.5 °C) within 4 hours of starting COOLSTAT cooling, and • at least 75% of the subjects' core temperatures remain between 36 °C and 37.5 °C for 80% of the steady state time following the initial achievement of 37.5 °C. All adverse events (AEs) reported during the study will be presented in tabular format to include: time of onset, whether or not the patient continued in the study, the nature of intervention and resolution. The potential contribution to the AE by the device will be assessed by the attending physician who reports the AE and the investigator.
Data Safety Monitoring Board	A DSMB will be formed to monitor this study. The DSMB will meet: 1) before any subjects are enrolled (to review the study), 2) after the first 5 subjects (all with ICP monitoring), 3) after the first 10 subjects (before proceeding to 24-hour

upon being reconnected to the CoolStat is ≤ 37.5 °C. If the subject's temperature is > 37.5 °C upon being reconnected to the device, the device will be given up to an additional 4 hour-period to bring the patient to normothermia (≤ 37.5 °C). Once the subject's core temperature is ≤ 37.5 °C, the device will be considered in steady state.

	cooling treatment), 4) after each 6-month period of study, 5) at the end of the study, and 6) after any serious adverse event. A clinical monitor will also be used to periodically visit the study sites and monitor the activities of the study to ensure that the study protocol, consent activities and data collection are being completed in accordance with specified procedures. The Clinical Monitor and DSMB will be comprised of: • Paul Manberg, PhD - Clinical Monitor • Jose Suarez, MD (Johns Hopkins) – Chair of DSMB – Voting Member • Romergryko Geocadin, MD (Johns Hopkins) – DSMB Voting Member • Samuel Tisherman, MD (UMMC) – DSMB Voting Member • Daniel Herr, MD (UMMC) – DSMB Voting Member • Neeraj Badjatia, MD (UMMC) – PI (Non-Voting Member) • Harikrishna Tandri, MD (CSO, CoolTech) – Sponsor (Non-Voting Member) Additional details on the charter of the Clinical Monitor and the DSMB are provide as Appendices with the IDE application, including biographical information on each member.

2.0 Literature review: Background and Rationale

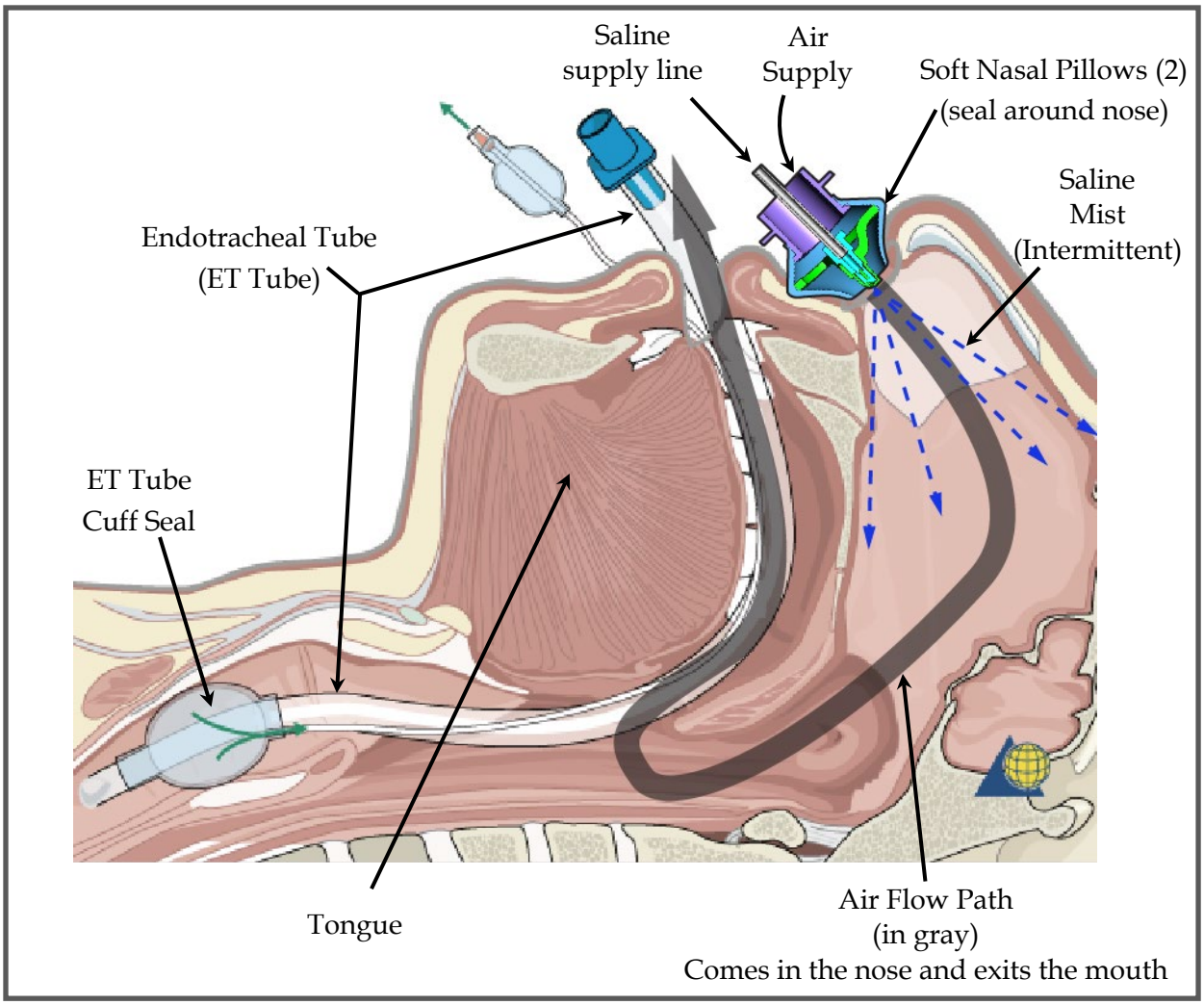
2.1 Neurogenic Fever

Fever is a common occurrence among patients with a brain injury or ischemic event, and studies have shown that fever can exacerbate the effects of that injury and result in poor patient outcomes [1, 2, 3, 4]. It is recommended to immediately cool these patients to at least a normothermic temperature, however there is no universally accepted gold standard of cooling [1, 2, 3, 4]. Generally, subjects are started on an antipyretic drug treatment [5]. If this is unsuccessful at lowering their temperature, then active cooling methods may be initiated. Surface cooling methods such as ice bath and cooling blankets are sometimes used, but are not always effective and can induce a shivering response (which has significant neurological consequences) [4, 6]. Intravenous cooling methods have demonstrated some of the fastest patient temperature cooling rates, but require an invasive procedure to install a large catheter, which must be completed by a trained specialist and creates an infection site risk [6]. The COOLSTAT Transnasal Therapy Device [hereafter COOLSTAT or CoolStat] has the potential to be an easy and safe means to cool a febrile patient, and potentially with a lower risk of inducing a shivering response compared with surface cooling methods.

2.2 Principles of the COOLSTAT Technology

The body naturally controls core temperature by regulating the balance between energy generated internally (basal metabolic rate and shivering) and energy lost to the environment through conduction, convection and evaporation (perspiration). External cooling devices that are trying to reduce core temperature do so by shifting the energy balance to remove more energy than the body is capable of generating. Existing surface target temperature management (TTM) systems use cold pads on the skin to induce energy loss through conduction, while others use catheters with circulating cold fluids to remove energy, such as the Esophageal Cooling System (DEN140018). The COOLSTAT employs evaporative cooling at the nasal turbinates and upper airway to remove energy from the body. In all of these methodologies, basic thermodynamics govern the degree to which the core temperature is reduced.

The COOLSTAT creates evaporative cooling by blowing dry, ambient air into the nose and over the nasal turbinates in a unidirectional fashion before flowing freely out of the mouth (as shown in the figure below for double nostril air flow) or the other nostril and the mouth (for single nostril air flow). The nasal turbinates are highly vascularized, mucus-containing membranes with a large, convoluted surface area. The primary purpose of the turbinates is to humidify inspired air before it reaches the sensitive tissue of the lungs. 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. Hence, the process locally extracts energy from the body, focused in the region of the turbinates, directly adjacent to the brain.

Looking at this cooling effect on the rest of the body, the normal circulating blood through the turbinates replenishes the lost energy caused by the phase change. This in turn cools the blood flowing through this region, which ultimately cycles back to the heart. Basic thermodynamics requires that the core temperature of the body will slowly fall if the energy extraction from this process exceeds the heat generation of the body.

It is worthwhile to note that the evaporative cooling process employed by the COOLSTAT removes energy without the use of anything that is cold. The process uses only ambient temperature room air that has been dried through a desiccant. It is noninvasive and there

are no evaporative chemicals or drugs. The nasal interface is a standard nasal pillow design that creates a seal around the outer diameter of each nostril. The nasal pillows are noninvasive, with no tubing or parts inserted into the nose. The device also includes air supply pressure limits, air filters and other features to prevent damage to the turbinates and upper air way, which will be discussed later.

2.3 Study Rationale

Existing surface TTM systems impede patient care with large surface cooling pads that can limit patient access and cause surface skin care concerns. Intravascular cooling devices require an invasive procedure to install a large catheter, which must be completed by a trained specialist, creating an infection site risk. These systems are also generally intolerable in awake patients. See Section 5.5.1 for the COOLSTAT's primary anticipated benefits.

This study will evaluate the performance and safety in a limited number of subjects with fever who require cooling therapy to achieve normothermia and who will be closely monitored in an intensive care setting. We have previously explored the feasibility and safety of using dry nasal air as a means of cooling subjects, albeit in small feasibility study, in febrile subjects. This study shall demonstrate the performance of the COOLSTAT Transnasal Thermal Regulating System under controlled conditions in febrile subjects.

3.0 Description of the COOLSTAT Device

3.1 Device Description

The COOLSTAT® Transnasal Thermal Regulating Device is generally designed for temperature reduction in patients where clinically indicated. For this study, the device will be limited to subjects with ischemic or hemorrhagic stroke, seizure, or metabolic encephalopathy. Hemorrhagic stroke includes both intracerebral hemorrhage and subarachnoid hemorrhage stroke.

The COOLSTAT® Transnasal Thermal Regulating Device [hereafter COOLSTAT or CoolStat] cools without an invasive catheter or the use of 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. <u>COOLSTAT is not used in any way to support or assist with life support, patient breathing or respiratory functions.</u>

The COOLSTAT is a relatively small device, weighing less than 15 lbs, and can be mounted on an IV pole or placed next to a patient's bed on a table or cart. The primary functional component inside the device is a blower which is used to generate a flow of air.

Inlet air is supplied to the device from either a medical grade wall air port or it can be 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 an in-line air filter, and is delivered to the patient with a custom nasal mask. The flow of air enters the patient's nose and exits the mouth (during double nostril air flow) or the mouth and other nostril (during single nostril air flow), 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. If the air supply is taken from the wall air port, the pressure from this air source is dissipated across an orifice (in the device) to reduce it to slightly above atmospheric pressure (before entering the blower of the device). The medical grade air from a wall port is only provided as an option to extend the life of the desiccant cartridge, since the air supply from the wall port is typically drier than ambient air.

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

The subjects in this trial are already intubated. As such, the air flow from COOLSTAT does not enter the patient's lungs and is not used in any way to assist with life support, patient breathing or respiratory function. 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. The pressure is limited to 30 cmH2O 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 COOLSTAT is designed to operate primarily inside a hospital or other healthcare setting in a controlled environment. This helps 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.

In addition, the device delivers isotonic saline solution directly to the nasal mucosa to reduce drying and to facilitate improved evaporative cooling. The device uses a peristaltic pump as the motive force to intermittently spritz a small amount of isotonic saline solution into the patient, where the amount of saline delivered is proportional to the airflow. A standard saline bag used in the hospital provides the source of the isotonic saline solution, which is hung on a standard IV pole next to the device. The saline bag is not provided as part of the device and is supplied by the hospital. The saline is pumped to the patient and delivered via small misting nozzles in the nasal mask, in parallel with the delivery of the dry air. To ensure a clean supply of saline to the patient, the saline never touches the device; it is contained within the delivery tubing from the saline bag to the patient.

3.2 Control System

The COOLSTAT device can be operated in either an open loop cooling mode or a closed-loop cooling mode. In the open loop mode, the air flow of the device is set by the operator over a range of 5 flow settings (from low to high), limited by the max pressure supply of the device to ensure safety (discuss herein). The energy removed by the device is expected to be proportional to the air flow setting and the duration of time used. In the closed-loop control mode, the device's control system is designed to lower the subject's temperature as quickly as practical using a high flow rate of air provided by the blower. As the patient's temperature approaches a pre-set target temperature (as selected by the operating clinician), the air flow of the device is automatically reduced, at which point the blower driver controls to a target patient temperature by adjusting the flow rate. The blower will use PID control (proportional-integral-derivative) to cool the patient to the target temperature by adjusting the flow rate between approximately 0 and 60 LPM.

This study will use the closed-loop control setting only. The COOLSTAT receives temperature feedback from an esophageal, bladder, or 3M SpotOn™ temperature sensor, all of which are standard sensors used at the study sites with other hospital devices. The selection of which sensor will be at the discretion of clinical staff, following existing

protocols. The SpotOn is currently used as a first line sensor since it has been validated by the University of Maryland Medical Center as providing a quality core temperature reading and is non-invasive. While patient interventions, such as a bolus of cold liquid briefly flowing over an esophageal temperature probe, may temporarily alter the probe's reading from the true core temperature, such events are brief and will not affect COOLSTAT function. The COOLSTAT control system prevents the machine from a rapid or exaggerated response to a brief change in core temperature input. Bladder temperature sensors are used less frequently, but are considered an acceptable core temperature sensor in the event that a subject is unable to have a SpotOn or esophageal temperature probe. The COOLSTAT has a display that shows both the patient's current temperature (from the core temperature sensor) and the target temperature. The integrity of the control system to control and maintain the subject's temperature will be closely monitored in this study.

4.0 Indication for Use and Contraindications

4.1 Indication for Use

The CoolStat Transnasal Thermal Regulating Device is intended for temperature reduction to achieve normothermia, as an adjunct to anti-pyretic therapy, in adult patients with ischemic or hemorrhagic stroke, seizure or metabolic encephalopathy who are intubated and sedated. Hemorrhagic stroke includes both intracerebral hemorrhage and subarachnoid hemorrhage stroke.

4.2 Contraindications

All contraindications are listed below in the exclusion criteria.

5.0 Risk/Benefit Analysis

5.1 Analysis of Risks to Subjects and Potential Benefits

The risks to the subjects in this study are broken into risks of the COOLSTAT device and risks to the subject since they will not be receiving standard of care. Although summaries are provided below, detailed risk evaluations (e.g., hazards analyses and failure modes and effects) have been completed and are available as part of the IDE application.

The most significant risk mitigation is that throughout this study, the subject will be under regular clinical and study supervision and can be easily and quickly switched to the standard of care for cooling therapy if necessary.

5.1.1 Risks Associated with Use of the Device

Risks from the COOLSTAT device are summarized here based on its different systems, including the 1) air delivery system, 2) device and disposable setup, and 3) software.

1. **The Air Delivery System:** The COOLSTAT System has similar operating parameters to a CPAP (Continuous Positive Airway Pressure) device used to treat sleep apnea. As a design intent to ensure safety, the COOLSTAT was designed following applicable requirements of *ISO 80601-2-70, Medical electrical equipment -- Part 2-70: Particular requirements for basic safety and essential performance of sleep apnea breathing therapy equipment*. For example, the maximum air pressure allowed to be delivered to a patient when using a CPAP device is 30 cmH2O, to avoid potential overpressure and damage to the lungs. The COOLSTAT has been conservatively designed to adopt this pressure limit. This is conservative for this study since the patient's lungs are isolated from overpressure via the intubation seal and at no point does the delivered air come in contact with the patient's lungs. This is considered an added level of protection to ensure an over pressure event cannot occur. Any leakage past the intubation cuff would be detected and alarmed by the ventilation monitor. Endotracheal tube (ET) migration due to COOLSTAT use is not expected, but would be detected by the ventilation monitor alarm. ET tube position will be recorded at COOLSTAT therapy initiation (Phase 0) and will be verified three (3) times a day, per standard of care, by visual inspection by clinical personnel. The COOLSTAT has also been designed to limit the maximum temperature of air flowing to the patient to 38 °C (conservative per the CPAP standard, which allows up to 43 °C). The device continuously monitors both pressure and temperature that is supplied to the subject in real time and will reduce or turn air flow off to ensure that neither limit is exceeded. It is also worth noting that the subjects to be in this proposed study will be intubated. Patients with a tracheostomy tube who are receiving mechanical ventilation will also be included, provided that they meet all of the eligibility criteria. The air supply by the COOLSTAT will run in the subject's nose and out of their mouth. The <u>COOLSTAT will not be used in any way to support or assist with life support, patient breathing or respiratory functions.</u>

   The COOLSTAT system differs from CPAP systems in that the mouth is required to be open during double nostril COOLSTAT therapy. The mouth is normally closed during CPAP use, although there are reported cases of mouth leakage when using a CPAP, particularly when the CPAP devices were initially being developed and used; this was also at a time when the CPAP airflow was not pre-humidified. This type of mouth leakage when using the CPAP creates a very similar end condition to that produced by the COOLSTAT. A flow of air is created that goes in the nose and exits

the mouth. The mouth leakage with CPAP reportedly caused headache and sore throats from overnight use, but no reported cases could be found where this mouth leakage caused serious damage of the tissue or membranes in the turbinates or upper airway [9, 10, 11].

Potential Nasopharyngeal Membrane Desiccation: The COOLSTAT also has the potential to desiccate the turbinates if used for extended periods. To reduce this potential risk, the device has a design feature to replenish some of the water it has removed, i.e., the device delivers to the body a small amount of sterile, isotonic saline solution. Clinical staff will be trained as part of the study procedure to monitor for signs of dehydration of the subject based on the World Health Organization (WHO) scale for dehydration, such as general appearance, sunken eyes, and skin turgor. Evaluation for dehydration will be recorded as noted in the CRF data collection forms. In addition, the study will monitor the amount of fluid suctioned off of the subject via tracheal suction, before COOLSTAT cooling is started, during COOLSTAT cooling and after COOLSTAT cooling. This method will indicate whether excess fluid is being delivered, or there is a reduction in baseline fluid produced in the mouth and upper airway. The study team will examine this data after the first five (5) subjects, combined with the ENT assessments of the tissue quality of the upper away post-cooling, to assess the need to change the water supply setting on the COOLSTAT device. Tracheal suction volumes will be recorded by having a separate canister for tracheal fluids (apart from other suctioned fluids), and will be recorded at initiation of COOLSTAT therapy, and twice daily for the remainder of the study.

No nasopharyngeal membrane desiccation was observed as part of long-term preclinical swine studies (8 and 24 hour cooling studies) using the final CoolStat device, which indicates the delivered saline effectively mitigates this risk. Details of the preclinical study are provided as part of the IDE and IRB applications. The COOLSTAT nasal mask will be removed every 4 hours during the study for visual inspection of nasal tissue and observations will be recorded in the CRF. Vaseline will be applied every 4 hours to ensure a good seal between the mask and the nostrils and to limit the amount of sealing pressure needed.

Potential Preferential Brain Cooling: The COOLSTAT has the potential to preferentially cool the brain region, due to the location in which the cooling therapy is applied, close to the brain region. This was seen in pig testing, where the pig brain was measured to drop about 2 to 3 °C degrees lower than the core [7]. This is considered an extreme comparison to humans since the pig nasopharynx has a unique countercurrent cooling mechanism called the "Rete Mirabile" which is an intricate

plexus of arterial and venous blood vessels that directly exchanges heat from the internal carotid artery thereby cooling the brain [19, 20]. Further the pig brain is about 1/10th the volume of the human brain, and the turbinates of the pig are significantly larger compared to humans. This creates a condition where the pig has a higher energy transfer rate and a smaller brain volume being cooled. As such, the brain cooling in a human is expected to be significantly less than the pig.

Previous human studies using a comparable transnasal cooling device (RhinoChill), showed preferential brain cooling of about 1 °C [16, 24], i.e., the brain temperature was about 1C cooler than the core temperature. The RhinoChill cooling process is similar to the COOLSTAT but includes the use of a liquid perfluorocarbon, evaporative coolant that is sprayed in the nose, along with a high flow of oxygen at 60 LPM. This is considered a more aggressive cooling process than the COOLSTAT, which does not use an evaporative coolant (other than a saline mist). These studies, as well as other studies [21, 22], have also shown a reasonable correlation between brain temperature and tympanic temperature. As such, it is proposed for this study that a separate tympanic temperature be monitored and recorded for each subject as a surrogate for brain temperature. Given that the lower target core temperature limit for this study is 36°C, the estimated brain temp should be limited to about 35°C, with a worst-case limit of about 33°C (if we conservatively assume cooling that is comparable to the pig model). This is expected to provide a safe margin to the subjects, given that humans are regularly cooled down to 32°C as part of standard of care for ischemic events and cerebral vascular injuries [23]. The tympanic temperature measurement will have a lower limit of 34°C and an upper limit of 39°C, at which points the hospital's temperature monitor will be set to alarm. If the tympanic temperature is observed below 34 C for a sustained period of at least 5 minutes, use of COOLSTAT device will be discontinued on that subject.

Potential Blood Pressure Increase and/or Intracranial Pressure Increase: There is a theoretical concern that the COOLSTAT has the potential to induce patient discomfort which results in a vascular response (caused by pain receptors) that can increase the subject's blood pressure. This phenomenon was not seen in our pig testing, but it was reported in a comparable transnasal cooling study (with the RhinoChill), which showed short term increases in systolic blood pressure (SBP) of up to 53 mm Hg [24]. The RhinoChill is known to have significant irritation and discomfort to the patient due to delivery of the evaporative coolant and high flow air. It has been reported that the RhinoChill is not tolerable in awake subjects without the use of anesthesia. We believe the irritation and discomfort from the RhinoChill process produces an arousal and elevation of systemic blood pressure. Conversely, the COOLSTAT is much more

tolerable, even when delivered to an awake subject, with only a slight sensation during use. As such, we do not expect a similar response in blood pressure. However, to account for this potential concern, this study will continuously monitor blood pressure during all stages of using the device. blood pressure will be monitored per standard of care for sustained elevation. If SBP is observed above allowable levels sustained for >5 minutes despite standard of care intervention, use of COOLSTAT device will be discontinued on that subject. Allowable limits for SBP will be followed per institutional standard for the indication being treated. The device can also be discontinued at the discretion of the treating physician for medical reasons.

The COOLSTAT is not expected to cause an increase in intracranial pressure (ICP). A previous human study using a comparable transnasal cooling therapy (RhinoChill), showed no effect on ICP [24]. Although no device-related change in ICP is expected, ICP monitoring will be required to be in place for the first 5 subjects enrolled in this study. The PI and the DSMB will review any subjects with elevated ICP to determine whether the increase was device related. Additionally, ICP data will be recorded for all subsequent study subjects who already have ICP sensors in place (as discussed further below in Section 6.9). If ICP is observed above allowable levels sustained for >5 minutes despite standard of care intervention, use of COOLSTAT device will be discontinued on that subject. The maximum allowable limit for ICP will follow standard of care limits, specific to the indication being treated. The device can also be discontinued at the discretion of the treating physician for medical reasons. Approximately half of the eligible patient population is expected to have ICP monitoring in place. This concern will also be mitigated by continuously monitoring of blood pressure as noted herein.

Potential Pressure Ulcers from Nasal Mask: Although unlikely, it is possible for the nasal mask to be attached too tightly to a subject's face and cause pressure ulcers. Two instances of pressure ulcers were observed in the 24-hour preclinical swine study. These findings were attributed to the use of clinical nasal masks on swine anatomy and to the required tightness to keep the masks in place on the swine while in supine position (see Preclinical Study Report for additional details). The CoolStat mask is quite similar to the CPAP masks that are regularly used without clinical supervision for long periods and are not known to cause pressure ulcers. To further mitigate this risk, patients will have their nasal mask briefly removed every 4 hours to inspect for any potential irritation and/or formation of pressure ulcers. Additionally, Vaseline (petroleum gel) will be used to create a good seal between the nasal mask (nasal pillows) and the subject's nose, as opposed to relying on strap tightness alone.

Vaseline may be reapplied every 4 hours during nasal mask removal for visual inspection.

2. **Device and Disposable Set-Up Risks:** Device and disposable set-up risks will be mitigated by proper training of study staff who may interact with the device. The COOLSTAT has been evaluated for ease of use by preclinical study staff (independent of company and unfamiliar with device prior to the study). Device set-up and disposable use was generally found to be intuitive. The COOLSTAT hardware includes features like a unique connector for the nasal mask attachment that mitigate the risk of improper device use.

   There are two potential risks for disposable misuse during COOLSTAT treatment: 1) desiccant cartridges may be used longer than suggested and allowed to reach room/supplied air humidity level, and 2) failure to replace the saline bag providing the "spritz" delivery. Although there are built-in device warning messages and alarms, desiccant cartridges may not be changed out in a timely manner as air supplied to the subject becomes more humid (and therefore less effective at drying air). The result would be less effective evaporative cooling due to less dry air being delivered. However, the blower would begin to deliver higher air flow (up to the pressure limit) to compensate for any decreased effectiveness (which would be registered by an increase in core temperature). Testing in hospital conditions (using wall air port as air source) has demonstrated an effective operating period for the desiccant cartridge from 2-3 hours on the low end, and up to 5-6 hours on the high end, which is likely a sufficient time to cool the subject to normothermia. If the desiccant cartridge is not changed when indicated, cooling to the subject will likely be reduced and the subject's temperature could begin to rise. This will be detected by temperature alarms, as well as clinical and study personnel monitoring the subject.

   Saline is spritzed into the nose by the COOLSTAT nasal mask to both eliminate the risk of membrane desiccation and to facilitate more efficient evaporative cooling. If the COOLSTAT is allowed to deliver desiccated air without saline delivery, there exists a postulated risk of membrane desiccation. In preclinical studies running the COOLSTAT for 8 hours at maximum flow rate of 60 LPM and also for 24 hours using the closed loop control system, no desiccation or irritation was found in the nasal turbinates or other upper airway tissue (based on post cooling exams by a board certified otolaryngologist). During these studies only ~450 mL of saline was delivered over the course of 8 hours (running at continuous max flow). These pig studies represent a conservative clinical scenario, as lower air flow will occur once the patient has achieved the target temperature and the device only blows air when required to

maintain the target temperature. As such, we don't expect to need to change out the 1L saline drip bag that will be used in the clinical study for the first 10 subjects (receiving 8 hours of cooling treatment). The bag may need to be changed during use on subjects receiving 24 hours of cooling treatment, but likely only once. As a conservative step, the status of the saline bag will be monitored and checked every 4 hours, and recorded in the case report forms to help ensure the saline bag does not run dry.

3. **Software Risks:** Detailed risk evaluations as part of CoolStat device software have been completed and are available as part of the IDE application. Generally speaking, a Software Integrity Level (SIL) was calculated for every software unit in the CoolStat system as a measure of that unit's impact on the performance of the overall system. All software units deemed high risk based on this analysis have undergone formal inspection and statement coverage. All other software units are covered by code review, in addition to system-level verification protocols. As part of this process, the CoolStat firmware has gone through static analysis using PC-Lint, which is a command-line tool for performing static code analysis, indicating suspicious or plain wrong issues in source code.

5.1.2 Risks Associated with Denying Standard of Care

The standard of care for febrile patients in the NCCU starts with antipyretic treatment (acetaminophen 650 – 1000 mg orally) once a fever is detected, as specified by a temperature ≥ 38.3 °C (measured via an embedded core sensor). After 1-2 hours, if the patient's temperature is still above this limit, a temperature modulating device (TMD) is initiated with appropriate anti shivering regimen. Throughout the time period a TMD is utilized, acetaminophen administration is continued (650 – 1000 mg orally every 6 hours).

For this study, the COOLSTAT will be initiated after approximately 1 or 2 hours of antipyretic administration (per institutional guidelines) and will replace the use of any other TMD. This is an investigational study which generally does not provide benefits to the subject above the standard of care. Anticipated advantages to using the COOLSTAT over traditional TMDs are listed in Section 5.5.1, but it is the goal of this study to start to assess the validity of these potential advantages. If at any point the subject is not cooling properly or is otherwise unsafe from the use of the COOLSTAT, the subject can be quickly and easily switched to the standard of care cooling treatment. Subject assessment at 4 hours and 8 hours will be conducted consistent with the current standard of care.

5.2 Manner in Which Risks will be Minimized

This study minimizes risks to participating patients in the following ways:

- Study subjects will be under regular supervision by trained clinical personnel specifically to monitor temperature, as well as to monitor for adverse events and changes in hemodynamic parameters throughout the study period, in addition to normal critical care nursing staff.
- Changes in subject temperature happen over relatively long periods of time, usually over the course of hours (not seconds or minutes). As such, if the CoolStat is not able to cool or hold desired temperature ranges, alternative cooling therapies are available and can be applied in relatively short order.
- High and low monitoring alarms for the subjects will be set as follows:
    - The subject's core temperature (either esophageal, SpotOn, or bladder) will be continuously monitored and recorded in the CRFs, with procedures to stop the CoolStat if the core temperature is <36°C for a sustained period of 5 minutes, to limit the potential to overcool the subject. Subjects must have a core temperature of <39.5°C at the start of the cooling treatment. If subjects have a temperature >39.0°C for over 4 hours, CoolStat treatment will be stopped and an alternative method of cooling will be initiated. Likewise, the CoolStat will be stopped if the subject has a sustained core temp > 39.5 C sustained for 5 minutes.
    - The subject's tympanic temperature will also be continuously monitored by the hospital's normal monitoring system and manually monitored and recorded in the CRFs. The tympanic temperature will alarm in the hospital's monitoring system if the tympanic temperature drops to <34°C, to limit the potential to overcool the subject's brain. Additionally, tympanic temperature will also alarm if the tympanic goes > 39°C, to limit the potential that the subject temperature gets too high. If the temperature is observed <34 C for a sustained period of at least 5 minutes, or > 39 C for over 4 hours, use of COOLSTAT device will be discontinued on that subject. Likewise, the CoolStat will be stopped if the subject has a sustained tympanic temp > 39.5 C sustained for 5 minutes.
    - The subject's blood pressure (BP) will be will be continuously monitored per standard of care by clinical study team members. If systolic BP is observed above a max allowable level sustained for >5 minutes, despite standard of care intervention, use of COOLSTAT device will be discontinued on that subject. Allowable levels (per institutional standard) will be followed, specific to the indication being treated.
    - The subject's intracranial pressure (ICP) will be will be monitored in the first five (5) subjects as a minimum, as well as others that have ICP monitoring in place pre-study. If ICP is observed above a max allowable level sustained for >5 minutes, despite standard of care intervention, use

of COOLSTAT device will be discontinued on that subject. The allowable level (per institutional standard) will be followed for the indication being treated.

- Subjects may receive a bolus dose of meperidine (Demerol) prior to starting the COOLSTAT device to dampen a potential pain response to the COOLSTAT therapy. This can be given 15 minutes prior to initiation of COOLSTAT therapy, and is expected to reduce any potential discomfort and associate blood pressure change that may occur due to initiation of cooling. Each study site will follow their standard guidelines for managing shivering and active cooling tolerability.
- A Clinical Monitor and a DSMB have been appointed to this study to oversee the clinical study progress, patient compliance, investigator management, and data collection in a timely manner (see Section 14.5 for more details).
- Device checkout testing will show the COOLSTAT has passed basic safety requirements. Each device to be used in the study will be individually tested for safety and performance, including a device performance check once delivered to the study site. A device will not be used if it does not pass checkout testing.
- Disposable components in direct contact with the subject will be shown to meet biocompatibility and cleanliness standards.
- Animal and pilot clinical studies have shown that transnasal cooling is effective with no detected clinical or device-related adverse events.
- Identified potential risks have been mitigated through the COOLSTAT's design and study procedures.

5.3 Justification for the Investigation

This study will evaluate the performance and safety in a limited number of subjects who require cooling therapy to normothermia and who will be closely monitored in an intensive care setting. The feasibility and safety of using dry nasal air as a means of cooling subjects was previously evaluated with both non-febrile and febrile subjects using a surrogate device (CPAP) [8, 28]. This study shall demonstrate the performance of the COOLSTAT Transnasal Thermal Regulating Device under controlled conditions in febrile subjects.

5.4 Description of Patient Population

Details concerning the included patient population are provided in Section 8.0.

5.5 Alternative to this Treatment

Currently, the first-line method to cool a febrile patient is administering antipyretics. Patients who continue to be febrile and are clinically indicated for cooling are often prescribed more aggressive target temperature management (TTM) methods using

surface or intravascular systems for restoring normothermia. Multiple means of cooling febrile patients, including usage of ice packs and ice water, surface cooling devices, and catheter cooling devices are commonly available [3]. Examples of surface cooling devices include the CSZ Blanketrol and Arctic Sun Temperature Management System; examples of endovascular cooling devices include the Reprieve Endovascular Temperature Therapy System and Cool Line system [6].

5.5.1 Advantages of COOLSTAT Compared to Predicate Technologies

The primary anticipated benefits of COOLSTAT when compared with alternative TTM methods are:

- it can cool to and maintain normothermia with a simple nasal mask on the patient's nose with minimal disruption to patient care,
- it is portable and has an internal battery that will allow for continued cooling during short transport periods within the hospital (for miscellaneous short procedures),
- it is relatively small and portable with mounting options on an IV pole or sitting next to the patient's bed,
- it does not require cold storage of fluids or ice,
- it does not require the insertion of an invasive catheter,
- it has the potential to be used earlier than predicate treatments since it is quick and easy to setup,
- it is easy to use for long periods of time, needing minimal clinician interaction after setup, and
- it is expected to reduce the incidence of shivering response when compared to surface cooling methods since the cooling method is from the inside out, which may not trigger temperature sensors located in the skin[2] [6, 13].

5.5.2 Risks and Disadvantages of COOLSTAT Compared to Predicate Technologies

Analytical modelling and prior studies have determined that the rate of energy removal, and hence the rate of patient cooling using transnasal cooling provided by COOLSTAT, is somewhere in the mid-range of cooling rates of alternative TTM systems for induced normothermia [2, 3, 4, 12]. Endovascular cooling has the ability to hold a targeted temperature with a high degree of stability [3, 6]. The COOLSTAT is not expected to be as precise, but should still hold temperature within the normothermic range of 36°C – 37.5°C, according to analytical models and as demonstrated in 24-hour pig tests.

[2] Skin temperature receptors contribute to about 20% of the shivering response [13].

6.0 Study Design

6.1 Definitions

AE	Adverse Event
CRF	Case Report Form
GCP	Good Clinical Practice
ISO	The International Organization for Standardization
NCCU	Neurosciences Critical Care Unit
PI	Principal Investigator
SOP	Standard Operating Procedure

6.2 Purpose and Objectives

The objective of this study is to evaluate safety and performance of the COOLSTAT® Transnasal Thermal Regulating Device in reducing temperature in a population of febrile subjects who meet the inclusion/exclusion criteria. Results of this study will provide information about the safety and functionality of the COOLSTAT device in a clinical setting to cool to and maintain subjects at normothermic temperature.

6.3 Primary Efficacy Endpoint and Success Criteria

This feasibility study should confirm that the COOLSTAT system has the ability to safely and adequately achieve and maintain normothermic cooling therapy with its control system over a specified period for subjects who were enrolled in the study.

This cooling aspect of the trial will be considered a success if at least 75% of the subjects achieve the following criteria:

- Cooling Performance: The subjects reach normothermia (core temperature ≤ 37.5 °C) within 4 hours of starting COOLSTAT cooling.
- Temperature Maintenance: The subjects are held within a 1.5 °C temperature band, between 36 °C – 37.5 °C, for 80% of the steady state time following the initial achievement of 37.5 °C.[3]

6.4 Safety Outcomes

An important outcome of this study is to assess the safety of high flow rate transnasal air delivery by the COOLSTAT device. The device safety will be addressed by the following:

[3] This recognizes that some subjects will have short periods of break-through fever over the course of the study.

- The incidence and severity of all adverse events (including non-device-related adverse events) and the potential contribution to the adverse event that may be device related.
- Assessment by the investigator or their designee and attending physician(s) as to any adverse event that may be related directly to transnasal cooling.
- Confirmation based on a visual exam of the turbinates and upper airway that no clinically significant abnormal findings were attributable to transnasal air flow or the COOLSTAT device.

This study should also demonstrate that the COOLSTAT system can perform in the clinical setting.

The study may provide insight into the incidence of shivering, although the study design is not sufficiently powered to expect definitive conclusions.

6.5 Investigational Duration and Follow-up

This study will conclude when 30 subjects receive COOLSTAT Therapy.

6.6 Sample size calculations

The sample size was determined from the calculation below, using the following assumptions:

$$n = \left[\frac{z_\alpha \sqrt{p_0(1-p_0)} + z_\beta \sqrt{p_1(1-p_1)}}{p_1 - p_0} \right]^2$$

n: minimum sample size

$p_0 = 0.9$ Assumed proportion of subjects successfully cooled

$p_1 = 0.75$ Lowest acceptable proportion of subjects successfully cooled

$\delta = |p_1 - p_0| = 0.15$ Difference between ideal and minimum acceptable

Confidence (α): 90%

$z_{95} = 1.28$

Statistical Power (β): 80%

$z_{80} = 0.84$

n = 25 subjects completing treatment, therefore a sample size of 30 subjects was selected to allow for dropouts. The study will enroll up to 70 subjects, accounting for a 55% expected post-consent screen failure rate. Enrollment will stop once the 30th subject receives COOLSTAT therapy.

6.7 Number of Investigational Sites

This feasibility study will be conducted at up to four investigational sites. The University of Maryland Medical Center (UMMC), would continue to be the lead center.

6.8 Methods to Reduce Bias and Conduct of the Investigation

This is an exploratory study that will be conducted in compliance with GCP guidelines, with analysis that is objectively based on temperature measurements with pre-specified success criteria, so bias is not expected to be a significant concern.

6.9 Intracranial Pressure Monitoring

No material response increase in intracranial pressure (ICP) is expected due to the use of COOLSTAT therapy. As noted herein, the first 5 study subjects will be required to have ICP monitoring in place in order to allay any related concerns. Additionally, ICP data will be collected manually for all subsequent subjects that already have intracranial pressure monitoring in place. The PI will report to the DSMB and Sponsor if a material change (increase) in ICP is attributed to the use of the COOLSTAT. The DSMB will be reviewing the initial five (5) cases to assess the impact on ICP of using the COOLSTAT.

6.10 Transition from 8-hour Cooling to 24-hour Cooling

The first 10 subjects will only be cooled for an 8-hour period, the results of which will be reviewed by the DSMB. For these first 10 subjects, if the subject still requires cooling at the end of 8 hours, the clinical site normothermia standard of care protocol will be used. If approved by the DSMB, the remaining subjects will transition to 24-hour cooling only upon satisfying all of the following criteria:

- No significant adverse events (SAEs) attributed to CoolStat
- CoolStat satisfied primary efficacy endpoint and success criteria on first 10 subjects (as specified herein):
    - 8 out of 10 subjects were cooled to ≤ 37.5 °C within 4 hours (based on final study endpoint of 75% subject achievement of this criteria)
    - 8 out of 10 subjects had core temp maintained between 37.5 °C and 36 °C for 80% of the steady state time following the initial achievement of 37.5 ˚C.
- No findings of concern from ENT visual exam of upper airway post cooling
- Tympanic > 34 °C and <39 °C during 8 hours of cooling, with no sustained period of more than 5 minutes < 34 C or more than 4 hours > 39 C.
- No sustained increase of systolic blood pressure for >5 minutes despite standard of care interventions that were above UMMC standard limits (specific to the indication being treated).
- DSMB reviews CRFs and agrees to increasing test period to 24 hours

6.11 Potential Inclusion of Subjects with a Past History of Cardiac Arrhythmia

- Subjects with a history of cardiac arrhythmia will continue to be excluded from the study for subjects #11-20, who will receive up to 24 hours of cooling.
- In the absence of any reports of occurrence of arrhythmia in this set of 10 subjects, then history of cardiac arrhythmia may be removed from the exclusion criteria for the subsequent subjects after review and approval by the DSMB.
- In the event that cardiac arrhythmia does occur during cooling in any of the remaining subjects, history of cardiac arrhythmia will be reinstated to the exclusion criteria.

7.0 Subject Recruitment and Enrollment

7.1 Patient Recruitment

Patients will be recruited for participation in this study from the population of patients in the Neurosciences Critical Care Unit (NCCU) who have an ischemic or hemorrhagic stroke, seizure, or metabolic encephalopathy, are intubated, and their expected stay in the NCCU is > 24 hours. We will only enroll patients with these diagnoses for whom the attending intensivist would otherwise prescribe an active cooling device to treat the patient's fever. The investigator or their designee will review the patient's medical history for eligibility based on the study's inclusion/ exclusion criteria. If the patient is determined to be eligible, either the patient or their legally appointed representative (LAR) will be approached by the PI or their designee to discuss the study and the patient's potential enrollment. Background on the study as well as risks will be provided as part of the informed consent form for review. If the patient or their LAR agree to participate, they will then sign the informed consent form, knowing that the patient can withdraw from the study at any time.

7.2 Point of Enrollment and Therapy Initiation Defined

A subject is considered **enrolled** in the study once the following have occurred:

- informed consent has been given by the subject or their LAR, and
- it is determined that the subject meets all of the inclusion criteria and none of the exclusion criteria.

A subject may be approved for COOLSTAT Therapy once the following additional screening criteria have been met after enrollment:

- the subject has developed a fever (core temperature $\geq$ 38.3 °C) and has remained febrile for at least one hour after the administration of antipyretics (institutional

standards will be followed with respect to duration of antipyretic administration before initiation COOLSTAT Therapy),

- it is confirmed that the subject has a core temperature probe (either esophageal, SpotOn or bladder), and
- an ENT exam is performed (if not done previously to enrollment) to evaluate for craniofacial abnormalities that would exclude the subject.

If the subject does not meet these criteria within 7 days from enrollment, the subject will be withdrawn from the study as a post-consent screening failure and is not eligible for intervention. No further follow-up will be required.

Due to the unpredictable nature of fever development and persistence, the study will be overenrolled in anticipation of many patients not proceeding to fever refractory to antipyretic treatment. The Table of Events below demonstrates the sequence of study activities related to enrolling patients, and then monitoring for eligibility for COOLSTAT therapy.

Table of Study Events

	Admitted to NCCU	Enrolled– Observe for Fever up to 7 day	Many enrolled patients will ultimately not be eligible as fever is unpredictable	Develops Fever Refractory to Antipyretics Treatment	Phase 0	Phase I	Phase II	Phase III
Evaluate for Inclusion/ Exclusion Criteria	X	X			X			
Obtain Informed Consent	X							
ENT Exam		X		X (if not during observation)				X
Antipyretic Treatment Upon Development of Fever	X	X		X	X	X	X	X

Initiate COOLSTAT Treatment						X		
Continuous Monitoring (ICU SOP)[1]		X		X	X	X	X	X
Study Phase Description					30 min. pre-therapy monitoring	8 or 24 hrs. of therapy	2 hrs. post-therapy monitoring	22 hrs. post-therapy monitoring

[1]Subject monitoring includes core and tympanic temperatures, blood pressure, intracranial pressure (when available), suctioned water volume, and level of shivering.

8.0 Study Inclusion and Exclusion Criteria

8.1 Inclusion Criteria

Male or female subjects may be included in the study if he/she meets ALL of the following inclusion criteria:

1. Admitted to the Neurosciences Critical Care Unit (NCCU).
2. Patient has ischemic or hemorrhagic stroke, seizure, or metabolic encephalopathy.
3. Patient is orally intubated or has tracheostomy tube and is mechanically ventilated.
4. Planned stay in NCCU > 24 hours.
5. Must have informed consent from the patient or the legally authorized representative (LAR) making decisions for the patient.

8.2 Exclusion Criteria

A male or female subject will be excluded from the study if he/she meets ANY of the following exclusion criteria:

1. Age < 18 years old or > 95 years.
2. Intubation is contraindicated.
3. With a coagulopathy. INR above 1.5 or PTT above 45 seconds.
4. Hemodynamic instability, including elevated SBP for >5 minutes despite standard of care interventions (SBP ≥ 160 mmHg for intracerebral hemorrhagic stroke; SBP ≥ 220 mmHg for subarachnoid hemorrhagic stroke or ischemic stroke).
5. History of cryoglobulinemia.

6. History of sickle cell disease.
7. History of serum cold agglutinin disease.
8. Active/ongoing nose bleeds.
9. Known or suspected pregnancy.
10. Participation in another ongoing investigational study.
11. Prisoners and/or patients for whom no LAR is available.
12. Patient is in airborne/droplet disease isolation protocol.
13. Patient is or suspected to be immunocompromised;
14. Low platelet count defined as < 100k (thrombocytopenia).
15. Nasal septal deviations (per CT scan; any degree).
16. Chronic rhinosinusitis.
17. Prior skull-based surgery.
18. Penetrating cranial trauma.
19. Recent nasal trauma or anterior base skull fracture.
20. Presence of cardiac arrhythmias including: sustained tachycardia defined as heart rate above 120 beats per minute, or sustained bradycardia defined as heart rate below 60 beats per minute.
21. Refractory hypoxemia defined as partial pressure of oxygen in arterial blood (paO2) below 60 torr or oxyhemoglobin saturation below 90% despite endotracheal intubation, mechanical ventilation, and provision of supplemental oxygen of up to 0.60.
22. Refractory hypercarbia defined as partial pressure of carbon dioxide in arterial blood (paCO2) above 50 torr despite endotracheal intubation and conventional mechanical ventilation.
23. History of cardiac arrhythmia as listed above.
24. BMI of ≤ 15 kg/m^2 or ≥ 40kg/m^2

9.0 Sequence of Investigational Assessments and Procedures

9.1 Study Team Member Activities to Assess Eligibility for Cooling

Potential candidates for the study are evaluated by the Investigator or their designee.

1. The investigator or their designee must approve the candidate to be enrolled by confirmation of inclusion / exclusion criteria, including the informed consent received from the patient or the patient's Legally Appointed Representative (LAR).
2. Every 12 hours, from time of enrollment up to 7 days, the volume of fluid collected from tracheal suction will be recorded. (The volume of oral fluid suctioned from the subject should not be collected with other suctioned fluids.) These volumes will be averaged to be used as a baseline for comparison to fluid volumes collected during the use of the CoolStat device.
3. The investigator may approve the enrollee for COOLSTAT therapy if all of the following are satisfied within 7 days of enrollment:
   - the subject has or develops a fever (core temperature $\geq$ 38.3 ˚C, but <39.5 ˚C) and remains febrile for at least 1 or 2 hours (based on institutional standard) after the administration of antipyretics,
   - the subject is confirmed to have core temperature probe (esophageal, SpotOn or bladder), and
   - an ENT exam is performed (if not done previously to enrollment) to evaluate for craniofacial abnormalities that would exclude the subject.

4. The investigator shall withdraw the subject if the above criteria are not met within 7 days after "enrollment". No further monitoring or follow-up is required for such subjects.

9.2 Phase 0 – Monitoring Before Cooling

1. Prior to starting the COOLSTAT device, clinical personnel will confirm that the subject is intubated and mechanically ventilated.
2. The COOLSTAT device shall be brought into the subject's room and the core temperature sensor (either esophageal - Smiths Medical Esophageal Stethoscope Temperature Sensor; Series 400. Model ES 400-12 – or bladder - Foley Catheters, BARDEX® I.C., Temperature-Sensing, Dual Connector 5 mL balloon, 16 French – or 3M Spot On™ Temperature Monitoring System) will be plugged into the COOLSTAT device. The subject's core temperature should be confirmed at this time to be ≥ 38.3 ˚C, but <39.5 ˚C, as displayed on the CoolStat device.
3. Delivery of any medications or other fluids orally will be recorded on the CRF due to potential temporary effect on esophageal temperature probe. Even room temperature fluids may affect the temperature reading, and time of administration should be recorded.
4. A tympanic temperature sensor will be placed in the subject's ear and connected to the hospital's temperature monitoring system to record temperature. The acceptable tympanic temperature range is 34 to 39˚C, and the hospital system temperature alarms will be set to indicate any readings outside that range. NOTE – in this study, tympanic

temperature is only considered as a surrogate for brain temperature for safety monitoring. Either esophageal or bladder temperature will be used as core temperature. It can take about 5 to 10 minutes for the tympanic temperature sensor to reach a steady state monitoring condition when initially placed in the subject's ear.

5. The COOLSTAT device will be prepared and the set up initiated, but not turned on. COOLSTAT set up and operation procedures are provided in the Operator's Manual, as well as a Quick Start Guide.
6. The subject target temperature will be set to 36.5 ˚C on the CoolStat device.
7. The subject's core temperature will be monitored and recorded in the CRFs, from the esophageal, SpotOn, or bladder temperature sensor. The acceptable core temperature range is 36˚C to 39˚C. The patient may remain >39.0 ˚C but <39.5 ˚C for up to 4 hours, at which point the CoolStat treatment will be discontinued and an alternative cooling method initiated. Likewise, the CoolStat will be stopped if the subject has a sustained core temp > 39.5 C sustained for 5 minutes.
8. Position of the endotracheal tube will be verified and recorded in CRF (distance measured at subject's teeth), per normal procedure.
9. For the first 5 subjects, ICP monitoring and measurement of < 20 mmHg will be confirmed.
10. The subject will be monitored, without turning on the COOLSTAT, for 30 minutes to ensure the subject's temperature is stable and febrile. Over this time period, an assessment will also be made to assess blood pressure and ICP (if available) of the subject, which will be recorded in the CRFs.
11. A bolus dose of meperidine (Demerol) may be given to the subject prior to starting the COOLSTAT device to dampen a potential pain response to the COOLSTAT therapy. This can be given 15 minutes into Phase 0 recording (and therefore 15 minutes prior to initiation of COOLSTAT therapy; see explanation below).
12. Upon starting the cooling therapy, the provided stopwatch is started and the start time is recorded on the therapy monitoring form. The time will also be recorded from a room clock (with source noted) to facilitate alignment of data records.

Each investigational site will follow their standard procedures for managing shivering and active cooling tolerability in their patients.

9.3 Phase 1 – Active Cooling Phase

Subjects will receive COOLSTAT cooling treatment, with a maximum of 30 cmH2O of air pressure (as automatically controlled by the device). The COOLSTAT will be operated in closed-loop control mode and will automatically modulate and control air flow and maintain the subject's core temperature between 36 ˚C and 37.5 ˚C, as measured by the esophageal, SpotOn, or bladder temperature sensor. The device will be set to target 36.5 ˚C.

The COOLSTAT will attempt to cool to and maintain this temperature range over the phase period. The core temperature will be recorded automatically by the COOLSTAT device, and is displayed on the COOLSTAT screen.

While the COOLSTAT is in use, no other cooling therapies will be used other than antipyretics.

Throughout Phase 1, the subject's temperature and vital signs will be monitored per NCCU protocol, as well as data collected in the CRFs. If any alarms occur, the appropriate action will be taken as described herein. COOLSTAT device errors will be addressed via an available trained technician and study team training (See Operator's Manual for a description of the possible device errors). Treatment may be discontinued at any time if adverse events are encountered or alternate cooling methods are required on an urgent basis. The Investigator or their designee must review any such emergency changes to therapy and complete an Adverse Event form detailing the reason for the change.

Per standard of care in the NCCU, maximum allowed limits will be imposed for a sustained increase in SBP >5 minutes above existing SBP threshold limits (specific to the indication being treated) despite standard of care intervention. In this event, COOLSTAT use will be discontinued for that subject. Once the COOLSTAT is discontinued due to SBP elevation, it will not be restarted for that subject. However, the study team will continue to monitor SBP to see if it recovers back to baseline value after the COOLSTAT is turned off. The Investigator or their designee must complete an Adverse Event form detailing the event and the value of the SBP prior to, during and after the COOLSTAT was used.

Similarly, per standard of care in the NCCU, a maximum allowed limit will be imposed for a sustained increase in ICP >5 minutes above max threshold despite standard of care intervention (using existing max institutional limits for the indication being treated). In this event, COOLSTAT use will be discontinued for that subject. Once the COOLSTAT is discontinued due to ICP elevation, it will not be restarted for that subject. However, the study team will continue to monitor ICP to see if it recovers back to baseline value after the COOLSTAT is turned off. The Investigator or their designee must complete an Adverse Event form detailing the event and the value of the ICP prior to, during and after the COOLSTAT was used. See Section 10.0 on procedures following the occurrence of an Adverse Event.

The Investigator or their designee will perform an initial cooling assessment 4 hours after COOLSTAT cooling has begun to determine if the subject has reached normothermia (≤ 37.5 C) sometime within the 4-hour cooling period. Starting from the initiation of normothermia, a subject's core temperature may fluctuate (within about 36.0-37.5 C), but

if the core temperature >39.0C for 4 hours, CoolStat treatment will be stopped and the subject will be switched to an alternative cooling method. If normothermia (≤ 37.5 C) is not achieved within the 4-hour period, the Investigator or their designee will remove the subject from the COOLSTAT device. The subject will be classified as a treatment failure and placed on standard of care treatment at the discretion of the Investigator or their designee and manual data collection will continue per the instructions for Phase 2 in Section 9.4. NOTE – if the Investigator feels that the subject's temperature is approaching the target and the subject is being adequately cooled, CoolStat device operation can be allowed to continue beyond the 4-hour period. The Investigator should note if this is the case in the CRF.

If a subject must be disconnected from the CoolStat device for transport from the NCCU to another unit (e.g., to radiology or angiography suite), they will be reconnected to the device at steady state if their core temperature upon being reconnected to the CoolStat is ≤ 37.5 °C. If the subject's temperature is > 37.5 °C upon being reconnected to the device, the device will be given up to an additional 4 hour-period to bring the patient to normothermia (≤ 37.5 °C). Once the subject's core temperature is ≤ 37.5 °C, the device will be considered in steady state. Only the total steady state time will be used for analysis. Subjects who are disconnected from the CoolStat for transport may be given a bolus of cold saline before transport. This will be determined by the clinical provider a case-by-case basis.

The COOLSTAT does not have a re-warming function. If the subject's core temperature drops below 36 ˚C, warming therapies can be initiated at the discretion of the Investigator or the attending clinician(s). The subject can stay on the COOLSTAT and continue with the study as long as core temperature can be adequately controlled at the discretion of the Investigator or the attending clinician(s). Any change to therapy must be recorded in the case report form. COOLSTAT therapy will be discontinued if tympanic temperature drops below 34C for a sustained period of at least 5 minutes.

The CoolStat nasal mask will be removed at least every 4 hours to inspect nasal tissue for the development of any pressure sores. Petroleum gel may be applied to facilitate a strong seal below the nasal mask pillows and the nostrils without requiring much pressure from the mask straps.

The COOLSTAT therapy will be discontinued at the end of Phase 1, at which point the subject can be placed on alternate cooling therapies at the discretion of the attending clinician.

9.4 Phase 2 – Post-Therapy Monitoring Phase

After Phase 1, the COOLSTAT will be stopped by pressing the 'Start/Stop' button on the control panel of the device. Once the device is in the pause mode, the nasal mask will be removed from the subject and the temperature probe disconnected from the COOLSTAT, however, the hospital core temperature sensor will remain connected to the subject, or it can be replaced with the esophageal, SpotOn, or bladder sensor at the discretion of the PI. This will conclude any cooling with the COOLSTAT. Manual data collection will continue for two hours after COOLSTAT cooling has concluded to capture the subject's response post-cooling.

Any new cooling therapies can be applied to the subject as directed by clinicians, but will need to be noted in the case report forms. Phase 2 ends at the conclusion of this two-hour observational period. The COOLSTAT must be prepared for the next subject according to the procedures in Section 9.8.

9.5 Phase 3 - Post-Cooling Follow-up

For the next 22 hours, the subject's vital data will continue to be manually collected every 4 hours, and a qualified board-certified otolaryngologist or otolaryngology resident (under the supervision of a board-certified otolaryngologist) will perform a follow-up examination of the upper airways within 24 hours of the end of Phase 1 COOLSTAT Therapy. The intensivist will perform the post-therapy nasal exam if an otolaryngologist is not available.

9.6 Tasks during Cooling

Once the COOLSTAT cooling has commenced, data will be manually collected and recorded on the supplied Therapy and Observation Record (requirements are also listed in Section 12.7). Data collection activities will be performed throughout the therapy phase (Phase 1.) These activities will include:

- Note the time when collecting data during this time interval.
- Note and record blood pressure and ICP values, prior to starting COOLSTAT, as well as during its use and after it is turned off.
- Record any antipyretic or other medications given and its dose during this time interval.
- Record the subject's core and tympanic temperatures displayed on the CoolStat and hospital monitor.
- Assess and record the subjects' level of shivering according to the Bedside Shivering Assessment Scale (scale written on the Data Record).
- Record any anti-shivering actions taken during this time interval.
- Check that the nasal mask has not inadvertently shifted during the study, and readjust if necessary during Phase 1. Apply a small amount of Vaseline to nasal

pillows to facilitate a good seal to nostrils without needing to apply much pressure.

- Briefly remove the nasal mask every 4 hours to inspect for any sign of pressure ulcer. Reapply Vaseline to facilitate good seal between nasal pillows and nostrils.
- Check that the saline bag is periodically dripping to ensure it is supplying saline to the disposable set during Phase 1 and record.
    - If the saline bag is observed to have <500 mL of saline remaining, replace saline bag with 1L bag to ensure continuous availability of saline.
    - Note when a bag is replaced on the Data and Observation Record.
- Record the tracheal volumes of fluid collected in the canisters from the tracheal tube at COOLSTAT therapy initiation (Phase 0) and twice daily for the remainder of the study. Oral fluids should be suctioned into a third canister and should not be included in the fluid volume measurements.
- Record if there was any AE during this time interval (a separate AE form must be completed.)
- Per standard of care, verify correct positioning of the endotracheal tube and record (three times daily). Exam subject for abdominal distension and record every 8 hours.
- There is an increased risk of insensible losses during the cooling period. Clinical providers will be made aware of this and advised to take this into account as they monitor for possible dehydration and provide maintenance IV fluids for study participants. Clinical and study personnel will evaluate the patient for any signs of dehydration and record every 8 hours.
- Device alarms will be responded to as described during training and in the error table in the COOLSTAT Operator's Manual. An alarm for high relative humidity of air delivered to the patient is to be expected; it indicates that the desiccant cartridge needs to be changed according to instructions in the manual.

9.7 Anti-Shivering Regimen

Shivering during cooling increases oxygen consumption and generates heat that interferes with the cooling process. If the subject starts shivering, anti-shivering regiment will be performed following existing hospital routines. A shivering response due to the application of an active, external cooling system is not unexpected. Any anti-shivering protocol that is used will be documented in the subject's case forms. The subjects will be actively monitored for signs of shivering. The proactive use of prophylactic anti-shivering agents should not be used.

9.8 Turning Off and Clean-up

At the end of Phase 1, the COOLSTAT device will be turned off by pressing the 'Start/Stop' button. At this point, the nasal mask will be removed from the subject by loosening the head straps. The temperature connection to the COOLSTAT will be

removed from the device. The nasal mask component and the desiccant cartridge will be disposed of per standard hospital protocols. Specific steps are detailed below:

1. Power off COOLSTAT device using the power switch per Operator's Manual.
2. Disconnect the nasal mask component from the COOLSTAT and dispose of mask assembly.
3. Open device lid and remove and dispose of desiccant cartridge.
4. Remove saline bag from IV hanger, record the remaining amount of fluid in the bag, and dispose of the bag and any remaining saline per standard hospital protocols.
5. Wipe down external device surfaces with standard, hospital supplied wipes.
6. Return the device to the designated storage area (per study team personnel).

9.9 Subject Study Completion

The study Subject Completion Form section of the therapy case form is to be completed after 22 hours of additional follow-up (end of Phase 3).

10.0 Adverse Events, Warning, and Precautions

For this Feasibility IDE Clinical Trial, the definitions outlined in the FDA Guidance for Clinical Investigators, Sponsors, and IRBs, Adverse Event Reporting to IRBs – Improving Human Subject Protection (January 2009) will be applied to adverse events.

The investigational device exemption (IDE) regulations define an unanticipated adverse device effect (UADE) 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)). UADEs must be reported by the clinical investigator to the sponsor and the reviewing IRB, as described below:

- For device studies, investigators are required to submit a report of a UADE to the sponsor and the reviewing IRB as soon as possible, but in no event later than 10 working days after the investigator first learns of the event (§ 812.150(a)(1)).

- Sponsors must immediately conduct an evaluation of a UADE and must report the results of the evaluation to FDA, all reviewing IRBs, and participating investigators within 10 working days after the sponsor first receives notice of the effect (§§ 812.46(b), 812.150(b)(1)).

- The IDE regulations, therefore, require sponsors to submit reports to IRBs in a manner consistent with the recommendations made above for the reporting of unanticipated problems. Possible exceptions would include situations in which the specificity or severity of the event is not consistent with the description in the investigator's brochure, or it can be determined that the observed rate of occurrence for a serious, expected AE in the clinical trial represents a clinically important increase in the expected rate of occurrence.

  To report an adverse event or unanticipated adverse device effect, the proximate investigator will complete an Adverse Event Form. All adverse events must be reported to the sponsor immediately (within 24 hours of becoming aware of the event). It is also the responsibility of the Principal Investigator to inform the representative of the center's IRB according to the IRB policies and procedures.

10.1 Adverse Event Definitions

On the Adverse Event Form, each adverse event will be classified as anticipated or unanticipated; device related or not device related; and classified as mild, moderate or severe. The severity classification will be determined by the investigator proximate to the event, who will use his or her clinical judgment and assign a severity classification based in the following definitions.

- **MILD** (resolved without intervention within study period)
- **MODERATE** (medical intervention required, not life threatening, did not alter study course)
- **SEVERE (**potentially life-threatening and required immediate intervention, could or has altered study)

10.2 Unanticipated Adverse Device Effect (Event)

An Unanticipated Adverse Device Effect (UADE) will be defined as per FDA Regulation 21 CFR 812.3(s) 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".

As per FDA regulations 21 CFR §812.150(a)(1), §812.46(b), and §812.150(b)(1), all UADEs must be reported by the clinical investigator to the sponsor and the reviewing IRB, as described below:

- An investigator is required to submit a report of a UADE to the sponsor and the reviewing IRB as soon as possible, but in no event later than 10 working days after the investigator first learns of the event (§ 812.150(a)(1)).
- The sponsors must immediately conduct an evaluation of a UADE and must report the results of the evaluation to FDA, all reviewing IRBs, and participating investigators within 10 working days after the sponsor first receives notice of the effect (§§ 812.46(b), 812.150(b)(1)).

10.3 Actions in Response to Adverse Events

During training, the study team member will learn the appropriate actions to take in response to an adverse event. These actions may include, but are not limited to:

- **Suspending COOLSTAT Cooling**: COOLSTAT cooling may need to be removed from the subject at the discretion of the investigator or their designee. This would involve stopping the air flow and removing the nasal mask, but otherwise keeping the device on and continuing to collect temperature data for the study period.
- **Switching to Alternative Cooling Method**: The investigator or their designee may switch the subject onto an alternative cooling method if it is deemed necessary for the subject's safety; the subject will be completely removed from the COOLSTAT device. Manual data will continue to be collected for the following 22 hours.
- **Removing the Device Without Alternate Cooling**: The COOLSTAT can be completely removed from the subject without starting alternate cooling if, at the discretion of the investigator or their designee, the safety of the subject is at risk and/or cooling is no longer needed.

10.4 Anticipated Adverse Events

- Nose bleeds (epistaxis)
- Shivering
- Pressure or skin breakdown because of mask
- Aspiration
- Nasal congestion
- Over-cooling
- Insufficient cooling
- Increase in insensible losses (subject dehydration)
- Induced brain hypothermia
- Adverse effects on systemic blood pressure

10.5 Serious Adverse Events

- Severe nasal mucosal ulceration
- Severe oral mucosal ulceration
- Uncontrolled epistaxis requiring stopping of therapy or intervention
- CSF rhinorrhea
- Any other potentially life threatening event requiring immediate intervention
- Any other unanticipated device related adverse event.

10.6 Technical Device Failures

Technical device failures will be recorded on a device performance CRF, and evaluated for possible adverse effects for the patient. For the purposes of this study, a technical device failure is defined as a failure of the COOLSTAT system to perform its intended function when used in accordance with the Instructions for Use, or to perform any aspect of the study protocol.

If a device failure results in an adverse experience for the patient, this adverse experience should be recorded on the Adverse Event Form. Device failures that do not result in an adverse effect for the patient will be noted on the device performance report form, but will not be considered an adverse event in and of themselves.

10.7 Warnings

Note: These warnings are specific for the investigational device.

- Use of the COOLSTAT device should only be undertaken by a study team member who is thoroughly familiar with the proper use of the device as provided in all provided instructional and guidance documents, and only under the supervision of the clinical investigator.
- Do not attempt to service the COOLSTAT device. COOLSTAT includes potentially hazardous moving parts and the risk of electrical shock if the device cover is removed. Contact CoolTech for all servicing needs.
- The COOLSTAT device should only be used with appropriately grounded electrical outlets.
- When setting a target temperature, the user should exercise care and proper device procedures to avoid incorrect therapy – the COOLSTAT device may have the ability to overcool the patient below normothermia temperatures.

10.8 Precautions

Note: These precautions are specific for the investigational device.

- Proper placement of the core temperature sensor is important for COOLSTAT to appropriately cool subjects – clinicians are responsible for properly placing the

sensor in accordance with standard practice. Esophageal, SpotOn, and bladder temperature probes are acceptable core temperature sensors for use with COOLSTAT.

- COOLSTAT disposables are for single subject use only. Do not reuse and do not use with multiple subjects.

10.9 Follow-up of Unresolved Events

Any unresolved adverse events, adverse device effects and/or unexpected adverse device effects still unresolved when the subject ends the study will be followed until they are resolved but no longer than 24 hours.

11.0 Investigational Medical Devices

11.1 Description of Investigational Medical Devices

The investigational medical device will be 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.)

11.2 Product Packaging and Labelling

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 tubing manifold and nasal mask is sealed in a plastic bag, and each desiccant cartridge is sealed in a heat seal foil pouch to protect from moisture. A photograph of disposable labels is included in the Operator's Manual.

11.2.1 Device Operating Instructions

All safety and operational information are included in the Operator's Manual.

11.2.2 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"

11.2.3 **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"

11.3 Required Experience and Training

The investigators and any site personnel directly involved in the study or protocol execution must be trained in accordance with their responsibilities about the COOLSTAT device and protocol requirements at the study initiation visit; and whenever new investigator or study personnel are added. The training will be documented in the training case form. Only qualified personnel may handle the device.

11.4 Storage and Handling

The COOLSTAT device, the desiccant cartridges, and the mask 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.

11.5 Accountability of Investigational Medical Devices

Receipt, use and return of the medical devices will be documented on a device transport log. Additionally, each subject's therapy record case form must identity devices (hardware and disposables) specifying the device by serial number, and all reference numbers for disposables used. All "service" conducted per unit will also be maintained in a service record log maintained for each unit, including records of removal of any unit from the study premises for any reason. Each used disposable set must be accounted for on the transport log and by patient ID. Use and disposal of disposables will be recorded on CRFs (e.g. number of desiccant cartridges used). In the event of a desiccant cartridge or nasal mask malfunction or failure, the faulty item will be bagged and retained until communication with Sponsor to determine follow up procedures to failure mode analysis.

12.0 Data Collection and Management

12.1 Case Report Forms

The data for this study will be collected using Case Report Forms (CRFs), not including the data collected by the COOLSTAT device. Blank template forms are provided.

Prior to the start of the clinical trial, the study center will be provided with a sufficient number of Case Report Forms and these may be replenished as needed. All entries are to be made in blue or black ink and are to be legible. All information in the CRFs should be in English. All corrections made on paper based forms are to be completed by placing a single line through the incorrect data, leaving the incorrect data clearly visible (e.g. ~~352~~ 325), and the individual making the correction must initial and date the correction. Erasure by any method is not allowed. The personal data recorded on all documents will be regarded as confidential.

The investigator will be responsible for the timely and accurate completion of specific CRFs (or certain areas on the CRF) for an individual subject for whom he/she may be responsible, wherein an investigator's signature is required. Where so designated trained study personnel may record information on case report forms.

Except for adverse event forms which have a limited time to be completed and forwarded, each set of CRFs for a specific subject must be completed as soon as practical as each subject completes (or is withdrawn from the study).

Completed CRFs shall be transmitted to the Sponsor in a timely manner. Original case forms shall be stored in a designated area convenient for the Monitor and Principal Investigator. The Principal Investigator shall review data from the study at any time throughout the course of the study. The monitor and PI may request data queries in the event of incomplete records or recording discrepancies.

12.2 Review and Query of Completed CRFs

Any corrections of data (by PI or Sponsor) after CRF pages have been collected will be done by way of a written query. The query should state the question or data to be clarified. The query and correction will be included with the Sponsor's copy of the CRF and retained together with the original CRF in the Principal Investigator's files.

The receipt of the scanned form must be verified by an alternative method, such as an email to indicate forms have been sent to the Sponsor. The exact method for transmission will be detailed in the Investigator's Manual and may change from time to time based

upon Sponsor and Investigator's needs. Any such changes shall be documented and approved by the Sponsor and PI in advance. In any case, the Principal Investigator shall retain the original and make the original Case Report Forms (with any associated data queries) available to the Sponsor's designated Monitor at each monitoring visit.

12.3 Retention of Records and Documentation

The clinical investigator will be required under FDA Regulation 21 CFR §812.140(d) to retain all copies of the records for a period of 2 years after the latter of two dates: (1) the date on which the investigation in terminated or completed, or (2) the date that records are no longer required for purposes of supporting a premarket application. In all cases, the investigator must contact the sponsor prior to disposing of any records related to the clinical investigation. Included in the records to be maintained are signed Clinical Protocols, source records for any data, copies of any paper Case Report Forms, signed consent forms, ethics committee approval letters, product use records, and any correspondence concerning the clinical trial.

12.4 Data Management

The processing of all data on the Case Report Forms will be the responsibility of the sponsor. All data recorded from the Case Report Forms to data analysis software will be subject to independent verification for accuracy. Comparison of the data entries will then be performed and any resulting discrepancies adjudicated by an independent third person with reference to the Case Report Form. All data queries will be resolved with the assistance of monitoring staff and documented in writing as described above.

The Monitor will use controlled Standard Operating Procedures in all aspects of data management, data verification, archiving and retention.

12.5 Collection of Medical History Data for Patient

The following medical history data will be collected from each subject:

- Normal or abnormal eyes, ears, nose, throat
- Normal or abnormal neurological
    - CVA (cerebrovascular accident)
    - TIA (transient ischemic attack)
    - Shunt for hydrocephalus
    - CEA (carotid endarterectomy)
    - Myasthenia gravis
    - Seizures
    - Multiple sclerosis
    - Encephalitis

  - Meningitis
  - Subdural hematoma
  - Epidural hematoma
- Normal or abnormal gastrointestinal
- Normal or abnormal respiratory
  - Current/past tobacco use
- Normal or abnormal cardiovascular
- Normal or abnormal genitor-urinary
- Normal or abnormal musculoskeletal
- Normal or abnormal dermatological
- Normal or abnormal endocrine
  - Diabetes
  - Hypothyroidism
  - Hyperthyroidism
- Drug/alcohol use
- Normal or abnormal hematological
- Normal or abnormal hepatic
- Allergies and drug intolerance

12.6 Collection of Data by Device

Each second, the COOLSTAT device will be automatically collecting air flow rate, air temperature supplied to subject, air humidity supplied to subject, air pressure, and the subject's core temperature data. This data is automatically stored to a micro SD card, with a new file started with each device power-on. The SD card is embedded in the device and is not accessible unless the device external housing is removed, which would require the use of tools. A serial data logger will be used to transfer device data from the CoolStat to a secure data storage cloud. This will allow the study Sponsor and monitor to review and verify the source data in a timely manner, without requiring the retrieval of devices. The data collected by the COOLSTAT has a time and date stamp, but no other subject identifying information. Therefore, in order to tie the data to a specific subject, the time and date stamp will be matched to the time that was manually recorded when the subject began COOLSTAT therapy. All data collected by the COOLSTAT will be subject to audit by the study monitor and may not be used in analysis of the effectiveness of cooling if not verifiable.

To validate the data saved by the COOLSTAT, testing will be performed on each COOLSTAT unit to ensure the expected outputs result from a range of inputs. The data for each sensor (flow rate, air temperature, humidity, and pressure, and subject's core temperature) is compared with readings from an external calibrated sensor. Multiple

conditions will be tested for each sensor to ensure the saved data are accurate over expected operating ranges.

The COOLSTAT's screen displays the subject's current temperature measurement for reference during the trial (this data is automatically collected by the COOLSTAT) – this measurement is the same as the core temperature displayed on the hospital monitor.

12.7 Collection of Manual Data

Subject core and tympanic temperatures, blood pressure, intracranial pressure (when available), suctioned water volume, and level of shivering will be monitored and recorded in the Therapy and Observation Record throughout the therapy period. Data to be collected during the course of the study is detailed in Section 9.0.

Data collection will occur at a minimum 5 minute intervals for the first 30 minutes of cooling, 30 minute intervals during the first 8 hours, and then every 2 hours for the remaining 16 hours (if applicable). During Phase 2, data collection will occur at a minimum of 15 minute intervals. After Phase 2, manual data will continue to be collected at a minimum of every 4 hours for the next 22 hours.

13.0 Statistical Analysis Plan

The primary efficacy analysis for cooling performance will be based on the evaluable populations of subjects who undergo cooling treatment with the COOLSTAT System. Analysis will be performed on treatment initiated and treatment completed populations. Subjects who achieve normothermia (core temperature ≤ 37.5 ˚C) within 4 hours of starting COOLSTAT treatment and maintain normothermia for the duration of the treatment will be determined to have been treated successfully.

The primary efficacy analysis for temperature maintenance will be based on the evaluable population of subjects who maintain normothermia (core temperature between 36 ˚C and 37.5 ˚C) for at least 80% of the time following the initial achievement of 37 C will be determined to have been treated successfully.

The proportion of subjects fulfilling success criteria and 90% confidence intervals will be reported and compared to the a priori minimum acceptable criteria:

- at least 75% of the subjects will reach normothermia (core temperature ≤37.5 ˚C) within 4 hours of starting COOLSTAT cooling, and
- at least 75% of the subjects' core temperatures remain between 36 ˚C and 37.5 ˚C for 80% of the steady state time following the initial achievement of 37.5 C.

Continuous measurements will be summarized using the mean and standard deviation. Categorical variables will be reported using percentages and confidence intervals. Data collected will be plotted to demonstrate the change in core temperature from baseline.

An exploratory analysis of participant subgroups will be performed, stratified by stroke presentation (ischemic versus hemorrhagic). Cooling performance and AEs will be evaluated by subgroup.

Double nostril air flow and single nostril air flow subjects will not be merged or directly compared. The results from subjects treated with single nostril flow will be analyzed separately from subjects treated with double nostril air flow.
Subjects 1 through 20 will be assigned to the double nostril air flow treatment group:

- Subjects 1 through 10 will be treated for 8 hours (N=10)
- Subjects 11 through 20 will be treated for 24 hours (N=10)

Subjects 21 through 30 will be assigned to the single nostril air flow treatment group

- Subjects 21 through 30 will be treated for 24 hours (N=10).
- Subjects 21 through 30 will be treated using a dose escalation model:
    - Dosing for this cohort (flow rate) will begin at 30 LPM.
    - The dose will be increased by 10 LPM if 3 consecutive subjects complete the study protocol with no serious adverse events (as listed in section 10.5) or unanticipated adverse device events.
    - Up to three doses will be evaluated in this cohort (30 LPM, 40 LPM, 50 LPM).
- The purpose of this cohort is to assess the safety of and optimal dose for the single nostril air flow configuration of the CoolStat.
- Each subject will be examined for adverse events, serious adverse events, and unanticipated adverse device events by an intensivist or otolaryngologist within 24 hours of completing CoolStat therapy.
- Each flow rate cohort must be evaluated by an intensivist or otolaryngologist prior to advancing the protocol to the next increased flow rate cohort.

13.1 Primary Performance Outcome Analysis

The primary hypothesis regarding cooling performance is that at least 75% of the subjects will reach normothermia (core temperature ≤ 37.5 ˚C) within 4 hours of starting COOLSTAT cooling.

The primary hypothesis regarding temperature maintenance is that at least 75% of the subjects' core temperatures remain between 36 ˚C and 37.5 ˚C for 80% of the steady state time following the initial achievement of 37.5 C.

13.2 Secondary Performance Outcome Analysis

To analyze the COOLSTAT's impact on the shivering response, the incidence of anti-shivering actions will be assessed.

13.3 Safety Assessment

13.3.1 Nasal Examination

To ensure the COOLSTAT has not resulted in damage to the subject's nasal passages, a nasal examination is performed before and after testing by a board-certified otolaryngologist or otolaryngology resident (under the supervision of a board-certified otolaryngologist). These exams may be performed by a board-certified otolaryngologist or otolaryngology resident (under the supervision of a board-certified otolaryngologist), or by an intensivist if an otolaryngologist is unavailable. The post-test exam must occur within 24 hours after cooling has completed..

In the pre-test exam, the clinician will examine the subject for the following:

1. Deviation of nasal septum
2. Nasal polyps
3. Ulceration of the mucosa
4. Nasal bleeding / bloody discharge
5. Nasal septal perforation

In the post-test exam, the clinician will examine the subject for the following:

1. Ulceration of the mucosa
2. Nasal bleeding / bloody discharge
3. Nasal septal perforation

13.3.2 Adverse Events

All adverse events will be analyzed to determine if the cause is from the COOLSTAT device or other related activities from the study protocol.

14.0 Study Management and Responsibilities

14.1 Informed Consent

A subject (or LAR) may withdraw their consent to participate in this study at any time. If the subject withdraws, standard of care will be provided.

14.2 Withdrawal of Subjects

A subject may be withdrawn from the study for the following reasons:

- if it is the subject or their LAR desire to withdraw,
- if it is medically necessary, as judged by the investigator, or
- if the subject does not receive COOLSTAT therapy within 7 days of enrollment, or if after enrollment it is determined that the patient may not receive COOLSTAT Therapy due to disqualifications at the pre-therapy evaluation.

If a subject is withdrawn from the study, the date and reason for the withdrawal will be recorded in the case report form provided.

14.3 Urgent Change in Therapy

If it is determined by the investigator that alternate cooling methods are required, the subject is removed from COOLSTAT therapy but data will continue to be manually collected according to the schedule outline starting in Phase 2 and continuing through the remainder of the protocol to subject completion.

14.4 Investigator Responsibilities

It is the responsibility of the Principal Investigator to supervise and ensure adequate training for any personnel involved in the conduct of the study, including the Study Coordinator and nursing staff who may be involved in the performance of the study. If any other physicians in the institution agree to participate in the trial, the Principal Investigator agrees to:

- obtain agreement with the Sponsor to add the additional investigator(s),
- obtain all required information from the additional investigator(s) which document qualifications (and release of this information to the FDA and IRB),
- add the investigator to the Investigator Agreement list, and advise the additional investigator(s) as to their obligations under regulation and institutional policy, and
- supervise the investigator's participation in the study in so far as necessary to ensure consistency of practice and data collection.

The Principal Investigator (or the investigator proximate to the oversight of the specific subject in the study) is responsible for the accuracy and timeliness of the data collection under his/her direction. (Data collected by the COOLSTAT device is not the responsibility

of the Investigator. Such data are retrieved from the data storage card in the device by a technician as directed and trained by the Sponsor.)

The investigator is responsible for ensuring that the study is performed according to the protocol. The investigator shall co-sign the informed consent form to indicate the patient is accepted as an enrolled subject in the study.

All unused product must be returned to the Sponsor at the end of the study. The Principal Investigator shall permit the Sponsor to conduct pre-announced site monitoring visits and a site close-out visit, including a review of product and accessory use and retrieval.

14.5 Study Monitoring and Data Safety Review Boards

A Clinical Monitor will be hired by the Sponsor and will be independent of UMMC and the study site. The Clinical Monitor will be generally responsible to periodically visit the study site and monitor the activities of the study to ensure that the study protocol, consent activities and data collection are being completed in accordance with specified procedures.

The DSMB will be generally responsible for safeguarding the interests of study participants, assessing the safety and efficacy of study procedures, and for monitoring the overall conduct of the study. The DSMB will review adverse event data, other safety data, quality and completeness of study data, and enrollment data at each meeting to ensure proper trial conduct. The DSMB is required to provide recommendations about starting, continuing, and stopping the study.

Additional details on DSMB's meeting schedule, composition and activities are described in the Appendices provided as part of the IDE application. Briefly, the DSMB is composed of voting members from both within UMMC as well as other institutions outside of UMMC. The DSMB will be meet: 1) before any subjects are enrolled, 2) after the first 5 subjects (all with ICP monitoring), 3) after the first 10 subjects (before proceeding to 24-hour cooling treatment), 4) after each 6-month period of study, 5) at the end of the study, and 6) after any serious adverse event.

IDE Study close-out report will summarize all data collected and detail any statistical analysis conducted on the raw data.

14.6 Institutional Review Board

Prior to the initiation of this clinical investigation, the investigator must submit the protocol, patient information sheet, patient consent form and any other documents as may be required to the appropriate Investigational Review Board (IRB) for review and approval. The investigator shall obtain from the IRB, documentation showing that the IRB is duly constituted and registered with the US FDA. The investigator, and any other member of the clinical study team, if a member of the IRB, must not participate in the decision-making.

A signed and dated letter granting approval must be provided to the Sponsor prior to the initiation of the clinical investigation. A copy of the IRB approval and all investigator qualifications will be submitted promptly to FDA under IDE amendment prior to initiation of the study at the proposed site. Identification of the IRB Chairperson, and its contact information will be provided to the sponsor.

14.7 Cost to the Subjects

Enrolled subjects in the study will not be charged or financially responsible for the cost of the investigational device, the disposables used, or any procedures that occur as a part of the study protocol. The study sponsor will pay the usual and standard costs of treatment or hospital care received as a direct result of a study-related injury that are not covered by a health insurer (provided the costs are not the result of care required to treat the underlying disease or condition). Back-up standard of care is provided by the clinical center according to their own protocol. Costs associated with standard of care or any other treatments will be billed as it normally would without participating in the study.

14.8 Financial Compensation to Patients

Patients will not receive compensation for participating in this study.

14.9 Cost to the Clinic

The Investigational device and associated supplies will be made available to the participating clinical site at no charge throughout the clinical study.

14.10 Financial Considerations and Study Support

The investigational sites are receiving financial compensation for all personnel time and any direct costs associated with this study.

14.11 Conflicts of Interest

Investigators will not participate if they have a known conflict of interest. Proper reporting and divulgation of potential conflict of interest shall be the policy of the Sponsor

and investigators throughout the course of the study. If any new conflict of interest develops during the course of the study, clear reporting to stake holders will be expected and will follow the best practices and regulatory requirements currently in place. Financial interests shall be reported when and as required.

14.12 Confidentiality

All efforts will be taken throughout the study to maintain compliance to all rules and regulations surrounding patient confidentiality, including all forms of protected health information defined under HIPPA.

14.13 Principal Investigator Qualifications and Training

The Principal Investigator shall have clinical expertise in neurocritical care and neurogenic fever. . The Principal Investigator, under the terms described in Section 14.4 may identify and designate co- or sub-investigators and designate their level of responsibility, if different than described in this protocol for such additional investigators.

14.14 Early Termination of the Study

Both the Sponsor and the Principal Investigator reserve the right to terminate the study at any time. In terminating the study, the Sponsor and the Principal Investigator shall assure that adequate consideration is given to the protection of the subject's interests and that all required reports are filed to the FDA and IRB in a timely manner.

14.15 Protocol Deviations and Amendments

Any amendments to the approved protocol will be approved by FDA prior to implementation. Deviations from the protocol are not allowed. All deviations from the protocol shall be promptly reported to the Sponsor and Principal Investigator for determination of the impact on the study, any risks to study subject(s) that may have occurred as a result of the deviation, and any reporting obligations to the IRB and FDA.

14.16 Final Report

The final report will be compiled by the Sponsor and reviewed by each participating investigator and the Principal Investigator. The report will be submitted to FDA as part of the IDE process. Use of the data may be submitted in support of future premarket notifications, publications or additional investigational studies.