Application of Mild Hypothermia for COVID-19 Acute Respiratory Distress Syndrome (ARDS)

Protocol Number: Version 1.0

Principal Investigator: Pey-Jen Yu, MD

Funded by: Department of Cardiothoracic Surgery

Version Number: v1.0

18 May 2020

Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale

Table of Contents

STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR), and the Northwell Health Terms and Conditions of Award. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Investigational New Drug (IND) or Investigational Device Exemption (IDE) sponsor, funding agency and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

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

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Application of Mild Hypothermia for COVID-19 Acute Respiratory Distress Syndrome (ARDS)
Study Description:	Some patients with COVID have abnormally high carbon dioxide and low oxygen levels despite being on the ventilator. The hypothesis of the study is that the application of mild hypothermia to patients with COVID will decrease their metabolic rate and improve their oxygenation and carbon dioxide levels.
Objectives:	Primary Objective: To determine if the application of mild hypothermia will decrease the patient's metabolic rate and improved carbon dioxide and oxygenation levels Secondary Objectives: To determine if the application of mild hypothermia reduces the pro-inflammatory response to COVID-19
Endpoints:	Primary Endpoint: (1) Changes in metabolic requirement during and after hypothermia, (2) Changes in oxygen requirements and levels during and after hypothermia, (3) Changes in carbon dioxide levels during and after hypothermia

	Secondary Endpoints: (1) Changes in inflammatory markers, CRP, ESR, D-Dimer, Ferritin, during and after hypothermia
Study Population:	This study aims to enroll 20 patients, 18 years or older who are admitted to North Shore University Hospital with critical COVID-19 illness requiring intubation.
Phase:	N/A
Description of Sites/Facilities Enrolling Participants:	North Shore University Hospital will be the only enrolling site. It is a 766 bed tertiary care hospital located in Long Island, New York.
Description of Study Intervention:	Study patients will undergo mild hypothermia to 34.5^{0}C utilizing the Arctic Sun Temperature Management System (Bard Inc., Louisville, Colorado). The Arctic Sun is a non-invasive targeted temperature management system used to modulate patient temperature with precision by circulating chilled water in pads directly adhered to the patient's skin.
Study Duration:	2 months
Participant Duration:	4 days

1.2 SCHEMA

Day 1 Screening

- Total n= 20
- Obtain informed consent
- Screen potential participants by inclusion and exclusion criteria
- Obtain history, document

Day 1 Begin hypothermia

- Perform indirect calorimetry, arterial blood gas, CRP, ESR, D-Dimer, Ferritin prior to hypothermia
- CBC, basic metabolic profile, magnesium, phosphorus, coagulation profile to be drawn every 12 hours during hypothermia.

Day 2 Continue hypothermia

- Perform indirect calorimetry, arterial blood gas, CRP, ESR, D-Dimer, Ferritin
- CBC, basic metabolic profile, magnesium, phosphorus, coagulation profile to be drawn q12 hours during hypothermia.

Day 3 Rewarm

- Perform indirect calorimetry, arterial blood gas, CRP, ESR, D-Dimer, Ferritin prior to rewarming

Day 4 End of study assessments

- Perform indirect calorimetry, arterial blood gas, CRP, ESR, D-Dimer, Ferritin

1.3 SCHEDULE OF ACTIVITIES (SOA)

The schedule below is provided as an example and should be modified as appropriate.

Procedures	Screening/Baseline Day -1 to Day 1	Day 2	Day 3	Day 4
Informed consent	X			
Demographics	X			
Inclusion/Exclusion	X			
Medical history	X			
Targeted Physical Exam Height/weight/ Pulmonary Status	X	X	X	X
Hypothermia protocol study intervention	X	X		
Metabolic Rate (Calorimetry)	X	X	X	X
Temperature	X	X	X	X
Vital signs (BP, HR, RR)	X	X	X	X
ABG	X	X	X	X
Hematology (CBC)	X	X	X	X
BMP	X	X	X	X
Magnesium	X	X	X	X
Phosphorus	X	X	X	X
Coags	X	X	X	X
Inflammatory markers (Ferritin, CRP, ESR, D-Dimer)	X	X	X	X
Concomitant Medication	X	X	X	X
Ventilator Settings	X	X	X	X
Adverse Event Review	X	X	X	X
Complete Case Report Forms (CRFs)	X	X	X	X

2 INTRODUCTION

2.1 STUDY RATIONALE

COVID-19 pandemic is an ongoing pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). A significant percentage of patients with COVID-19 require invasive mechanical ventilation. However, certain percentage of patients with COVID-19 continues to have inadequate oxygenation and carbon dioxide removal despite being on maximal ventilatory support. As there has not been any treatment to show mortality benefit in patients with COVID-19, current standard of care centers around supportive management. We seek to conduct this study to investigate a possible therapeutic treatment for patients with COVID-19 with critical illness.

2.2 BACKGROUND

A significant contributor to the morbidity and mortality from COVID-19 is from the abnormal carbon dioxide and oxygen levels in COVID-19 patients. Metabolic studies done on COVID-19 patients have shown that these patients have abnormally high metabolic rates. High metabolic rates results in increased carbon dioxide production and increased oxygen usage, both of which can result in high

carbon dioxide and low oxygen levels. As some patients with severe COVID-19 continue to have high carbon dioxide levels and/or low oxygen levels despite being on the ventilator, we hypothesize that decreasing the metabolic rate in these COVID-19 patients will help their oxygen and carbon dioxide levels. Mild hypothermia is currently used in comatose survivors of cardiac arrest to improve mortality and neurological outcomes. Mild hypothermia is also an effective way to reduce metabolic demand. We therefore propose to apply mild hypothermia to COVID-19 patients to decrease metabolic rate in order to improve their oxygen and carbon dioxide levels. Although the application for mild hypothermia has been widely adopted in some patient populations, it has never been applied in COVID-19 patients. If we can develop a strategy to help improve the oxygen and carbon dioxide levels in COVID-19 patients, it may lead to improvements in their overall outcomes.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

- Coagulopathy, infections, arrhythmias, electrolyte abnormalities, skin burns, bruising or skin tears from the placement and/or removal of the cooling pads
- There are no known or anticipated long- range risks for this study
- The above stated risks are from the application of hypothermia. There are no known non-invasive treatment options for COVID-19 patients who remain hypoxic and/or hypercarbic on maximal ventilatory support. Extracorporeal Membrane Oxygenator Support (ECMO) is a possible invasive treatment that may be considered; however, ECMO is a highly invasive procedure and most patients do not qualify for ECMO.

2.3.2 KNOWN POTENTIAL BENEFITS

- Inducing hypothermia may decrease metabolic demand, improve oxygenation, improve level of carbon dioxide production and decrease the need for ventilatory support
- Potential long term benefits include a decreased morbidity and mortality from COVID-19 infection

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

There are no known non-invasive treatment options for COVID-19 patients who remain hypoxic and/or hypercarbic on maximal ventilatory support. Extracorporeal Membrane Oxygenator Support (ECMO) is a possible invasive treatment that may be considered; however, ECMO is a highly invasive procedure and most patients do not qualify for ECMO. This study aims to investigate the use of hypothermia as a possible noninvasive treatment for patients with COVID-19 who are failing maximal mechanical ventilatory support.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To determine if the application of mild hypothermia will decrease the patient's metabolic demand and improve carbon dioxide and oxygenation levels	(1) Changes in resting metabolic rate during and after hypothermia (2) Changes in arterial pO2 during and after hypothermia (3) Changes in arterial pCO2 levels during and after hypothermia	Resting metabolic rate is considered the gold standard way to measure metabolic demand. Arterial pO2 and pCO2 are the accepted measurements for oxygen and carbon dioxide levels.
Secondary		
To determine if the application of mild hypothermia reduces the pro-inflammatory response to COVID-19	Changes in CRP, ESR, D-Dimer, Ferritin, during and after hypothermia.	CRP, ESR, D-Dimer, and Ferritin are inflammatory markers that are have been demonstrated to be elevated in patients with COVID-19 and have been correlated to severity of disease

4 STUDY DESIGN

4.1 OVERALL DESIGN

The hypothesis of this study is that the application of mild hypothermia to patients with COVID-19 will decrease their metabolic rate and improve their oxygen and carbon dioxide levels. This is a single site pilot study of 20 subjects. Subjects will be placed on therapeutic hypothermia for 48 hours. Changes in metabolic rate, and levels of oxygen and carbon dioxide will be compared before, during, and after hypothermia.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Therapeutic hypothermia is routinely used in patients post cardiac arrest and in patients with cerebral edema secondary to a neurological injury. It has, however, not been used in patients with COVID-19. This study is therefore designed as a small scale pilot study in order to evaluate the feasibility and design of the study and the possible efficiency of hypothermia on COVID patients.

4.3 JUSTIFICATION FOR DOSE

The duration of hypothermia for this protocol is 48 hours. This duration is based on existing protocols for the use of hypothermia in non-responsive post-cardiac arrest patients and in patients with cerebral edema after a neurological event.

The degree of hypothermia for this protocol is 34.5^{0}C. This temperature is based on existing protocols for the use of hypothermia in non-responsive post-cardiac arrest patients and in patients with cerebral edema after a neurological event.

4.4 END OF STUDY DEFINITION

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

The end of the study is defined as completion of the last test shown in the SoA in the trial.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

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

1. Provision of signed and dated informed consent form from Legally Authorized Representative.
2. Stated willingness to comply with all study procedures and availability for the duration of the study
3. Male or female, aged 18 years or above
4. COVID positive
5. On mechanical ventilation with ***either***: refractory respiratory acidosis (ph $\leqslant$ 7.20), hypercarbia (pCO2 $\geqslant$ 55 mmHg), refractory hypoxia (pO2/FIO2 <150), ***or*** plateau pressures >30

5.2 EXCLUSION CRITERIA

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

1. Bleeding (active bleeding, platelets less than 50,000)
2. Uncontrolled cardiac arrhythmia
3. History of cryoglobulinemia, major trauma, pregnancy
4. Active non-COVID-19 infection that is not controlled with antibiotic or antifungal regimen

5.3 5. CONDITIONS THAT WOULD PRECLUDE ACCURATE METABOLIC MEASUREMENT BY INDIRECT CALORIMETRY (RENAL REPLACEMENT THERAPY, PRESENCE OF ECMO, PRESENCE OF CHEST TUBE) LIFESTYLE CONSIDERATIONS

During this study, if participants are on tube feeding, it will be decreased to a trickle feed rate of 10-30 cc/hr. This rate will help to maintain gut integrity and function which is important during the course of critical care illness. Trickle feeds will provide the patients with calories that may pose challenges to calculating the metabolic rate, however as described in literature, some tube feeds are necessary for maintenance of gut performance in critical illness.

5.4 SCREEN FAILURES

N/A

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Patients admitted to North Shore University Hospital with a positive serology test for COVID-19 and who remain in critical care units on advanced life support, mechanical ventilation, will be screened for

inclusion. We anticipate screening at least 10-15 patients daily. There remain over 80 patients with COVID-19 infection at North Shore University Hospital in critical care units.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

Determination of metabolic rate by the metabolic cart (noninvasive connection of the device to the ventilator for 20 minutes). Initiate hypothermia (established Northwell hypothermia status post cardiac arrest protocol) using the Arctic Sun. Gel pads will be placed on subject body to cover at least 40% of body surface area. The inner layer of gel pad is made up of a heat conductive hydrogel that changes temperature and sticks to the skin. The middle layer of the pad has channels through which water is circulated and the outer layer is designed to insulate the circulating water, allowing it to maintain a temperature. Using sterile technique, a clinician will insert a temperature probe into subjects' bladder. The machine essentially is a cooling blanket. Many clinicians would use ice bags to cool patients, however using the machine allows for more accurate temperature monitoring and precision with the cooling process. The Arctic Sun 5000® is set to a temperature of 34.5 C to lower the body temperature.

Duration of hypothermia will be 48 hours after which the subject will be rewarmed. Metabolic rate, or indirect Calorimetry, will be assessed at baseline, day 1 of hypothermia, day 2 of hypothermia before rewarming, and after full rewarming. CBC, basic metabolic profile, magnesium, phosphorus, coagulation profile, ABG, inflammatory markers would be drawn every 12 hours during hypothermia until subject has achieved full rewarming and once after full rewarming.

The entire hypothermia procedure will last 48 hours. The length of time it takes to cool the patient is a maximum of 3 hours. Once the desired temperature is reached that temperature will be maintained as tolerated by subject. The new temperature of 36.5C will be manually entered into the machine initiating re-warming. Acceptable rewarming range is a temperature of 36.5C to 37.5C. The subject body temperature rewarming is typically set over 6-8 hours. Therefore, the final 6-8 hours of the 48 hour time period is set to rewarm the subject.

6.1.2 DOSING AND ADMINISTRATION

N/A

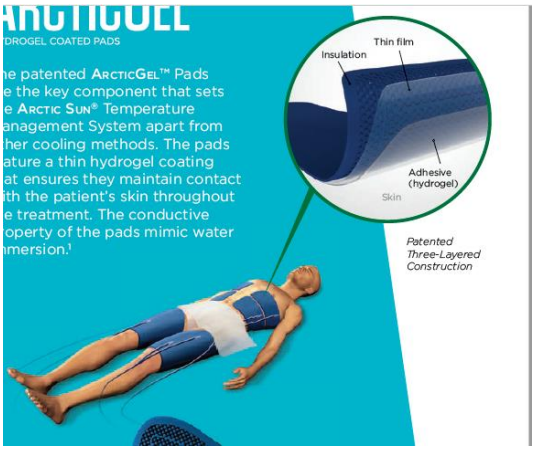
6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

North Shore University hospital has six (6) Arctic Sun 5000® Machines. They will be obtained through materials management when a study patient is identified and consented. The machines are maintained on a regular basis as outlined in the Northwell Health System Medical Equipment Management Plan (MEMP) issued by the Biomedical/ Clinical Engineering Departments.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Hypothermia Case



6.2.3 PRODUCT STORAGE AND STABILITY

The purpose of the Medical Equipment Management Plan (MEMP) is to assess and control the clinical and physical risks of fixed and portable equipment used for the diagnosis, treatment, measuring/monitoring, and the care of patients. The MEMP is designed to identify which items in the inventory of clinical equipment will be included in the management plan, and to establish minimum inspection standards for the identified equipment. The Director/Manager of Biomedical Engineering uses manufacturer recommendations, applicable codes and standards, accreditation requirements, and local or hospital experience to determine the appropriate maintenance strategy for assuring safety and maximizing equipment availability and service life. The strategies may include predictive maintenance, reliability-centered maintenance, interval-based inspections, corrective maintenance, or metered maintenance to ensure reliable performance.

6.2.4 PREPARATION

N/A

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

N/A

6.4 STUDY INTERVENTION COMPLIANCE

Hypothermia protocol will be initiated in the intensive care unit setting. A daily log will be kept documenting patient status throughout the course of cooling. In addition, an accurate account of time of hypothermia induction will be documented, vitals every 15 minutes during induction for the first hour and every hour thereafter. Subject's hemodynamic stability will be monitored regularly, at least hourly, including blood pressure and heart rate. The ventilator settings required will be documented as well. In addition, medications given to subject during the course of cooling will be documented.

6.5 CONCOMITANT THERAPY

N/A

6.5.1 RESCUE MEDICINE

Routine FDA approved medications for pain and sedation, such as Fentanyl, Dilaudid, Versed, Ketamine or Precedex may be administered to make the subject more comfortable during the course of cooling and to treat any shivering. These medications will be administered through an intravenous line. Expected body reactions to cooling include shivering and administration of such medications would not be considered treatment for an adverse event.

A paralytic infusion such as cisatracurium or rocuronium may rarely be necessary for shivering. A lot of patients, however, are already paralyzed due to their critical illness.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

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

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

- Vitals including blood pressure, heart rate and temperature, indirect Calorimetry
- Labs as outlined in the SoA- CBC, magnesium, BMP, phosphorus, ABG, coagulation panel (coags) and inflammatory markers
- Ventilatory Settings- oxygen percentage, respiratory rate setting, tidal volume and positive end expiratory pressure (PEEP)

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue or withdraw a participant from the study for the following reasons:

- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Disease progression which requires discontinuation of the study intervention
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Participant unable to receive hypothermia protocol for 48 hours

The reason for participant discontinuation or withdrawal from the study will be recorded on the Study Withdrawal Case Report Form (CRF).

The hypothermia protocol will be discontinued and full rewarming will be initiated prior to 48 hours if the following conditions occur: (1) hemodynamically unstable arrhythmia, (2) severe bradycardia (< 40bpm), (3) MAP less than 60mm Hg while on more than one vasopressor after resuscitation, (4) severe bleeding.

7.3 LOST TO FOLLOW-UP

N/A

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

Patients admitted to the critical care unit who remain on ventilator support will be screened by the research team for eligibility. Qualifying patients' will be considered and their LAR contacted by an IRB approved investigator authorized to obtain informed consent. Once informed consent obtained as outlined, study data will be collected as documented in Section 1.3 Schedule of Activities (SoA). Data for research protocol will be collected as outlined below by a study member who is authorized by IRB and trained to the protocol.

- **Demographics:** At screening/baseline demographic data collected will include name, MRN, age and sex
- **Medical History:** documentation of prior medical history
- **Physical examination:** daily targeted exam highlighting the location and placement of pads
- **Indirect Calorimetry**- gas exchange information collected from the mechanical ventilator to calculate the metabolic rate
- **Hypothermia Protocol**- subject is connected to the Arctic Sun 5000®, an FDA approved temperature management system. Gel pads will be placed on subjects' body to cover at least 40% of the body surface. The gel pads are soft, pliable and stick to the skin; the inner layer is made up of a heat conductive hydrogel that changes temperature and sticks to the skin. The middle layer of the pad has channels through which water is circulated and the outer layer is designed to insulate the circulating water, allowing it to maintain a temperature. Using sterile technique, a licensed and trained clinician will insert a temperature probe into subjects' bladder. The Arctic Sun 5000® is set to lower the body temperature to 34.5C. The machine will be set to reduce the body temperature by 0.5 degrees C per hour to complete the cooling period within a 3 hour time period. Vitals will be monitored continuously and charted every 15 minutes for the

first hour then every hour thereafter. Once the desired temperature is reached that temperature will be maintained as tolerated by subject. Once the cooling period is completed, the new temperature of 36.5C will be manually entered into the machine initiating re-warming. Acceptable rewarming range is a temperature of 36.5C to 37.5C. The subject body temperature rewarming is typically set over 6-8 hours. The body will be rewarmed at a rate of 0.25 degrees C an hour. Therefore, the final 6-8 hours of the 48 hour time period is set to rewarm the subject. The subject will be connected to the machine by a certified and trained clinician (nurses trained to use the Arctic Sun 5000® which is essentially a cooling blanket).

- **Medications:** routine FDA medications for pain and sedation, such as fentanyl, dilaudid, versed, ketamine and/or precedex may be administered as needed to make the subject comfortable during the cooling and to treat any shivering. Routine medications are administered via an IV line by trained and licensed medical practitioners who are trained to assess medical events. Potential medications to be administered for symptoms related to hypothermia include paralytic infusions such as cisatracurium or rocuronium. These drugs are FDA approved medications; side effects of rocuronium include rash, nausea, vomiting and changes in blood pressure both high and low. Side effects of cisatracurium include slow heart rate, dizziness and redness or flushing of the skin. Patients remain on continuous monitoring when these infusions are used; also, all patients in the critical care unit and those included in this study are monitored continuously.
- **Laboratory Assessments*:*** blood work will be collected at screening and baseline and every 12 hours while hypothermia protocol in course including complete blood count (CBC), basic metabolic panel (BMP), coagulation panel (coags), arterial blood gases (ABGs), inflammatory markers including D-dimer, ferritin, c reactive protein (CRP) and erythrocyte sedimentation rate (ESR). These blood specimens are collected as part of the analysis to evaluate the oxygenation and carbon dioxide production while on the hypothermia cooling protocol and during rewarming. Additionally, blood will be tested for levels of inflammatory marker assessment, white blood cell count and electrolytes assessment. Blood samples will be collected from the central lines already inserted in the critically ill patient and there will be no requirement for additional sticks for blood draws required for research analysis.
- **Ventilator Settings:-** ventilator modes and settings to be documented including percent oxygen delivered, set respiratory rate, tidal volume set (if on volume control ventilation) and tidal volume delivered by patient, set pressure support (if on pressure support ventilation),the set positive end expiratory pressure (PEEP), plateau pressures. The hypothesis is that hypothermic protocol may offer overall improvement in oxygenation and ventilation status and perhaps clinicians will be able to decrease the amount of ventilator support.
- **Primary Endpoint-** lab specific to primary endpoint includes serial ABGS as outlined in SoA; ABG will be collected every 12 hours. Arterial Blood Gas (ABG) will document the oxygenation and the amount of carbon dioxide in patient serum. Indirect calorimeter measurements will also be compared.
- **Secondary Endpoint-** laboratory assessments specific to secondary endpoint include the collection of inflammatory markers as outline above (ESR, Ferritin, D-Dimer and ESR) every 12 hours.

8.2 SAFETY AND OTHER ASSESSMENTS

Patients enrolled in the protocol are monitored continuously while on the hypothermic protocol to verify and assure that the patient is tolerating the protocol. The patients are managed in critical care

units by a critical care team and the investigators on this study will evaluate the patient daily for AEs and SAEs as well as any unanticipated problems (UPs).

- **Physical examination** – daily assessments are captured per standard of care. Any other changes in physical exam related to cooling protocol will be documented including symptoms of shivering.
- ***Vital signs*** – temperature will be documented continuously during the initial stages of cooling, every 15 minutes for the first hour and then hourly thereafter. Other vitals to assure hemodynamic stability include heart rate and blood pressure.
- **Electrocardiograms (EKGs)**: will be collected only in the event of an AE or SAE; specifically if it is noted that the patient has any bradycardia or any other type of new onset arrhythmia, then the clinician will obtain a 12 lead EKG
- **Assessment of adverse events.** The patients enrolled in this study are cared for in critical care units and therefore have continuous nursing monitoring per routine care. The investigator who is IRB approved will round regularly while patients' are on this cooling protocol. AE and SAEs will be documented accordingly and subject treated per standard of care based on the adverse event.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

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

Complications associated with standard administration of hypothermic protocol could lead to prolonged hospitalization, permanent disability, permanent end organ damage or death.
There may be other risks that are unknown at this time. All safety events will be collected and reviewed throughout the entire trial periodically. The Investigator will notify the local IRB of any additional risks identified that could affect the health, safety or welfare of the trial patients.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of the investigator, it results in any of the following outcomes: death, a life-threatening adverse event, prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or irreversible organ impairment. Important medical events that may not result in death or be life-threatening may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include arrhythmia requiring intensive treatment and bleeding requiring transfusions or proven infection requiring initiation of antibiotics. The investigator must report any suspected adverse event that is serious as outlined to the local IRB.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

Potential Adverse events include impaired clotting and bleeding. Severity of bleeding will be graded based on the Bleeding Academic Research Consortium (BARC), standardized set of definitions for all bleeds.
Type 0 equals no bleeding
Type 1- Bleeding that is not actionable and does not cause the patient to seek or require treatment,
Type 2- any overt, actionable sign of hemorrhage, more bleeding that would be expected for the clinical circumstance, including bleeding found by imaging alone that does not fit the criteria for type 3, 4 or 5 but does not meet at least one of the following criteria:

Requiring non-surgical, medical intervention
Leading to hospitalization or an increase level of care if currently hospitalized
Prompting evaluation

Type 3a- overt bleeding plus hemoglobin drop of 3 to <5 g/dl

Any transfusion with overt bleeding

Type 3b- Overt bleeding plus hemoglobin ≥ 5 g/dl

Cardiac tamponade
Bleeding requiring surgical intervention for control
Bleeding requiring intravenous vasoactive agents

Type 3c- Intracranial hemorrhage

Subcategories confirmed by imaging or lumbar puncture
Intraocular bleeding compromising vision

Type 4 Coronary Artery Bypass Graft (CABG) related bleeding

Perioperative intracranial bleeding in 48 hours
Reoperation after closure of sternotomy for the purpose of controlling bleeding
Transfusion of ≥ 5 units of whole blood or packed red blood cells within a 48 hour period
Chest tube output more than or equal to 2 liters within a 48 hour period

Type 5 fatal bleeding
Type 5a probably fatal bleeding (no autopsy or imaging confirmation) but clinically suspicious
Type 5b definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

Additional adverse events include increased chance of infection. Patients with an active bacterial or fungal infection superimposed on current COVID-19 infection are excluded from this study. New infections that develop post hypothermic protocol induction will be rated based on the following grading scale. Patients who develop new infection as documented by focal findings on physical exam, culture, blood work who respond to course of one treatment (anti-bacteria or antifungal agents) will be graded as mild; new infection that requires more than one antibacterial or antifungal, persistent or worsening findings beyond the typical course of the infection will be graded as moderate; severe infection will be defined as infection causing sepsis and organ failure requiring the use of supportive medications such as vasopressors, or additional means of support (additional changes in medication regimen targeted to infection, changes in ventilator management, or additional surgical procedures to treat infection for example thoracentesis for extensive infectious pleural fluid).

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.

- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

Adverse Events of bradycardia, a known arrhythmia and adverse event of hypothermia, will also be rated based on above mild/moderate and severe scale. Other arrhythmias will be rated based on above criteria of mild/moderate and severe scale. Adverse events of reduced blood pressure or hemodynamic instability will be defined as a mean arterial pressure of less than 60 mmHg that is not stable and requires vasoactive pressors support. It will be graded as mild if no treatment required and mean arterial pressure returns to normal, moderate if it persists and a vasoactive medication initiated and severe if more than one vasoactive pressor is initiated and is worsening in nature requiring a halt of the hypothermic protocol.

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

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

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

8.3.3.3 EXPECTEDNESS

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

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

The principal investigator and investigators on the study will review labs and vitals continuously and as outlined in the protocol. The patients are monitored in a critical care unit; as per standard of care, vitals are documented and monitored continuously. The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during the course of treatment.

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

occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

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

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

The study coordinator will record all reportable events with start dates occurring any time after informed consent, during hypothermic protocol and through full rewarming. The principal investigator will review all AE and SAE in a timely manner to determine severity and relation to study intervention.

8.3.5 ADVERSE EVENT REPORTING

AE will be reported to local IRB per Northwell Health Policy and procedure within 5 business days of event. The Principal Investigator is responsible for accurate and timely reporting of adverse events in the source document and case report forms. All investigators and study coordinators are responsible for recording all new clinical experiences, exacerbations and/or deterioration of an existing clinical condition occurring after the subject has been enrolled in the study on the appropriate case report form. They will also provide follow up on the adverse events until a resolution or an appropriate end point is reached.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

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

According to 21 CFR 312.64(b), a principal investigator must report to the sponsor, here the Department of Cardiothoracic Surgery, any serious adverse event, whether or not considered related to the hypothermic protocol, the study intervention, including those listed in the protocol and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event. AE as defined in ***Section 8.3.2*** will be reported in accordance to the local rules and regulations of local IRB reporting structure and will be reported to the Department leadership. These AEs will be reported at set time points to the DSMB (at enrollment of 3 subjects, 10, 15 and 20 subjects; four set time points.) We will pause after subject enrollment 3 and present to the DSMB. We will wait for the DSMB to assess safety and determine if enrollment should continue.

Furthermore, according to 21 CFR 312.32(c)(2), the sponsor and investigator must notify FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

AEs and SAEs will be reported to the DSMB established for this study per the data safety monitoring plan and the subjects' LAR will be contacted and informed of the event on an individual basis. Under current circumstances of the COVID-19 pandemic, families and LARs of patients are unable to enter the hospital facility to visit with patients and see clinicians in person. Therefore, daily communication and updates are provided to LAR over the telephone. AEs and SAEs will be reported to the participants' LAR on a daily basis as these patients remain critically ill and daily updates are important.

8.3.8 EVENTS OF SPECIAL INTEREST

N/A

8.3.9 REPORTING OF PREGNANCY

N/A

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

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

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

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

8.4.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and to the Data Safety Monitoring Board. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;

- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB and to the study sponsor (Department of Cardiothoracic Surgery) within 24 hours or one (1) business day of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the study sponsor within three (3) business days of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within three (3) business days of the IRB's receipt of the report of the problem from the investigator.

An investigator shall submit to the sponsor (Department of Cardiovascular and Thoracic Surgery) and to the reviewing Institutional Review Board (IRB) a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect (21 CFR 812.150(a)(1)), A sponsor who conducts an evaluation of an unanticipated adverse device effect under 812.46(b) shall report the results of such evaluation to the Food and Drug Administration (FDA) and to all reviewing IRB's and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter the sponsor shall submit such additional reports concerning the effect as FDA requests (21 CFR 812.150(b) (1)).

Any unanticipated problems related or possibly related to use of the Arctic Sun 5000® machine will also be reported to the Biomedical Engineering Department for review and reporting back to the manufacturer. Per the Biomedical Equipment Management Plan, internal quality checks will be initiated.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Unanticipated problems will be reported to the DSMB established for this study. The Principal Investigator will determine the need to withdraw the subject from the study for subjects' safety. The subjects' LAR will be contacted and informed of the event on an individual basis. These events will be shared with the DSMB and reported to the IRB of record. At the termination of the study, unanticipated problems will be reported on an aggregate level in the context of a descriptive statistical analysis and manuscript write up.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Primary Efficacy Endpoint(s): (1) Decrease in metabolic rate to 10% during and after hypothermic period as compared to baseline metabolic requirement, (2) Increase in oxygen levels during and after hypothermia as compared to baseline oxygen levels, (3) Decrease in carbon dioxide levels during and after hypothermia as compared to baseline carbon dioxide levels

- Secondary Efficacy Endpoint(s): Decreased inflammatory markers (CRP, ESR, D-Dimer, Ferritin) during and after hypothermia as compared to baseline

9.2 SAMPLE SIZE DETERMINATION

N/A – this is a pilot study and the study team will enroll 20 subjects. The study will make 20 attempts, meaning 20 patients will be enrolled and the intervention attempted; if any patients withdraw prior to the completion of the intervention, they will not be replaced.

9.3 POPULATIONS FOR ANALYSES

All patients enrolled in the study will be used in all analyses

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

The following variables will be examined: Changes in metabolic rate, changes in pO2, changes in pCO2, and changes in inflammatory markers.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

The metabolic rate, p02, and pCO2 during each time point after induction of hypothermia will be compared to baseline using the Wilcoxon rank sum test.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

The levels of inflammatory markers measured at each time point after induction of hypothermia will be compared to baseline using the Wilcoxon rank sum test.

9.4.4 SAFETY ANALYSES

Safety endpoints will be reported as summary statistics.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

N/A

9.4.6 PLANNED INTERIM ANALYSES

N/A

9.4.7 SUB-GROUP ANALYSES

N/A

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

As this is a pilot study, individual participant data will be listed by measure and time point.

9.4.9 EXPLORATORY ANALYSES

N/A

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

All study related activities conducted at participating site, North Shore University Hospital, will be regulated by one local Institutional Review Board titled Northwell Health, IRB. The Federalwide Assurance (FWA) number is 00002505; this documentation demonstrates the commitment to the Federal Department of Health and Human Services (DHHS) and the Office of Human Research Protections (OHRP) indicating that our Health System and the IRB functions in compliance with the federal regulations governing research with human subjects. All investigators involved in this clinical trial will conduct research within the ethical standards recited in the Belmont Report.

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

Informed Consent Form
Enrollment /Process Note

In accordance with Northwell Health Consent policy and in adherence to ICH GCP, the Investigator will have IRB written approval for the protocol and the written informed consent form to be provided to the participant. Informed consent will be obtained orally by the IRB approved primary or co-investigator via telephone conversation with the patient's health care proxy or designated next-of-kin who serves as the research participant's legally authorized representative (LAR). Consent will be verified via telephone by the primary clinician with a witness. Given the circumstances surrounding the COVID-19 pandemic, family members are prohibited from physically entering the hospital. Therefore, Informed consent is to be obtained from LAR via telephone process.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant (or LAR) and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's (LAR) comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants (or LAR) will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participant (or LAR) will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

Given the circumstances surrounding the COVID-19 pandemic, family members are prohibited from physically entering the hospital. Informed consent will be obtained from the participants' LAR via telephone by an IRB approved and authorized investigator. The telephone consent process will be witnessed by another personnel member, either from the clinical team or the research team.

A copy of the consent form will be sent via email to the LAR. The LAR will be instructed to respond via email authorizing subject enrollment into the study. When the LAR has an opportunity to print and sign the informed consent, they will be instructed to do so and email it back to Investigator and regulatory lead coordinator.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

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

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

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

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the IRB.

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor and/or Principal Investigator, as the sponsor of this study is the Department of Cardiothoracic Surgery of Northwell Health.

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

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

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

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the Department of Cardiovascular and Thoracic Surgery at North Shore University Hospital, 300 Community Drive, Manhasset New York 11030. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by North Shore University Hospital research staff, assigned to the Department of Cardiovascular and Thoracic Surgery, will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the Department of Cardiovascular and Thoracic Surgery of North Shore University Hospital, 300 Community Drive, Manhasset New York 11030.

Data collected for this study will be captured and stored on case report forms created for this study and entered into the electronic data capture system of REDCap. There will be no identifiers stored on paper. All patient identifiers will be removed. Once enrolled, patients will be assigned a research ID number, beginning with subject number 01, 02, 03 etc. Data will be stored in Northwell REDCap, a compliant database that is a secure web based application used for building and managing trials; it is 21 CFR Part 11, FISMA and HIPAA compliant and will be used to store both identifiable and de-identifiable information. When clinicians use a hypothermia protocol, data including vitals, temperature, laboratory values and medications issued are routinely collected. These variables are what we will collect for this study; therefore, the variables will exist in the EMR system. IRB approved researchers assigned to this study will be assigned this REDCap project by the Research Director. Variable collection and completion of electronic case reports forms will be conducted without the need to write on paper and they can be transferred directly from EMR to REDCap project electronic case report forms. One enrollment log will be created on paper and stored in the Principal Investigator's office. This office is protected by a door with a lock requiring key access only available to the PI. In addition, this office is located in a wing that is secure and accessible only to Northwell Health employees with authorized key card access; these patients' names will be entered into the demographic electronic case report form with two identifier: MRN number and name. There will be no other identifiers stored in the database. Once the analysis is complete, the two identifiers will be removed and the de-identified data will remain in REDCap for the length outlined for this study.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored at the North Shore University Hospital of Northwell Health. After the study is completed, the de-identified, archived data will be transmitted to and stored at the North Shore University Hospital, Department of Cardiothoracic Surgery, for use by other researchers including those outside of the study. Permission to transmit data to the <specify name of Data Repository> will be included in the informed consent.

When the study is completed, access to study data and/or samples will be provided through the Department of Cardiothoracic Surgery, Northwell Health.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator
Pey-Jen Yu, MD
North Shore University Hospital
300 Community Drive
(516) 562-4970
Pyu2@northwell.edu

A Data Safety Monitoring Board (DSMB) has been established for this clinical trial. A DSMB will be assembled to review the data analysis at set time points; at a minimum they will convene when 25% of the subjects enrolled, 50% of subjects enrolled, 75% of subjects enrolled and at completion of study enrollment. They will also convene immediately upon any AE or SAE and/or subject withdrawal. A DSMB report will be filed with the IRB of record. The DSMB will be comprised of Christina Brennan, MD, MBA, VP of Clinical Research, Dr. Jamie Ullman, Neurosurgeon and Director of Traumatic Brain Injury, Dr. David Meyers, Pediatric Cardiothoracic Surgeon and Dr. Eric Gottesman, Critical Care Specialist.

10.1.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) composed of individuals with the appropriate expertise, including clinical research regulatory experience and clinical experience using hypothermic protocols on patients in a critical care setting and/or in the operating room. Members of the DSMB should be independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. The DSMB will meet at least at four time points during this pilot study to assess safety and efficacy data. The DMSB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will provide its input to the Principal Investigator and lead regulatory coordinator who will then report it to the IRB of record.

Enrollment Pause After Three Patients
The study team will take a pause of the protocol after the 3rd patient has received the study intervention, so the DSMB can evaluate any adverse event, concerns, or new adverse events due to COVID-19 patients. Any further pausing of the remaining 17 subjects will be determined by the DSMB.

The PI, Dr. Pey-Jen Yu will prepare a safety report for these regular reviews comprised of anticipated safety events and actions taken. The PI will contact the DSMB for ad hoc reviews of any unanticipated safety events. In the event of a serious adverse event during the study protocol, it will be reported immediately to the PI, the co-investigators, and the DSMB. It will also be reported to the Northwell IRB and to all members of the research team. With the approval of the participants and families, the information will be provided to other care providers as directed.

This study involves a major increase above minimal risk to the subjects. The primary concern is the development of coagulopathy, infections, arrhythmias, electrolyte abnormalities.

Subjects will be monitored throughout the study for these potential adverse events by: blood tests every 12 hours (PT/PTT/INR, Fibrinogen, CBC, Basic metabolic profile, magnesium, phosphorus, ABG), continuous telemetry as part of ICU standard of care, continuous arterial blood pressure monitoring as part of ICU standard of care. The PI (or another designated Investigator in her absence) will be notified of any abnormal results so that the safety measures outlined below are implemented. The primary physician will also be notified of any abnormal results and any changes to the subject's care, and will also be provided with the test results. The potential risks and protections are as follows:

1. Coagulopathy**:**

Monitoring: CBC, PT/PTT/INR/Fibrinogen every 12 hours. Evaluate for clinical evidence of active bleeding by ICU staff.

Actions:

- If evidence of active bleeding at screening, subject will not be enrolled.
- If there are evidence of active bleeding at any time during the study, subject will be taken off hypothermia and re-warming will be initiated to achieve systemic temperature of 37^0C.

2. Infection**:**

Monitoring: CBC every 12 hours.

Actions:

- If there is culture evidence of systemic bacterial infection at screening, subject will not be enrolled.
- If patient develops a systemic bacterial infection at any time during hypothermia, subject will be taken off hypothermia and re-warming will be initiated to achieve systemic temperature of 37^0C. Antibiotics will be administered as per ICU standard of care.

3. Arrhythmias**:**

Monitoring: Continuous cardiac telemetry and arterial blood pressure monitoring as per ICU standard of care

Actions:

- If subject has uncontrolled cardiac arrhythmia at screening, subject will not be enrolled.
- If the subject develops hemodynamically unstable arrhythmia or severe bradycardia (< 40 beats per minute) during the study, subject will be taken off hypothermia and re-warming will be initiated to achieve systemic temperature of 37^0C. Arrhythmias will be treated as per ICU standard of care.

4. Electrolyte abnormalities:

Monitoring: Basic metabolic profile, magnesium, phosphorus every 12 hours

Actions:

- If subject has uncorrected electrolyte abnormalities at screening, subject will not be enrolled.
- Any electrolyte abnormalities will be corrected as per ICU standard of care protocol during the hypothermia protocol. In the event the electrolyte abnormalities are

refractory to therapy, the subject will be taken off hypothermia and re-warming will be initiated to achieve systemic temperature of 37^0C.

10.1.7 CLINICAL MONITORING

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

- A designated representative from the Northwell Health Department of Cardiothoracic Surgery will conduct a review of the variables collected in the REDCap EDC created. Monitoring can be conducted on-site and at four time points during the course of the study, after enrolling 5, 10, 15, and 20 subjects. Clinical site monitor will review data for accuracy, and evaluate SAE or AE for date and time of occurrence and PI review. Data will be reviewed at random but be inclusive of data related to primary and secondary endpoints.
- Independent audits will be conducted to ensure monitoring practices are performed consistently across all participating sites. Principal Investigator will maintain accurate and organized regulatory records and electronic database for independent review by a designated representative from the Office of Research Compliance.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

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

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

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).
The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

SOPs are available for review upon request. SOPs are in place pertaining to assessment of protocol feasibility, review and approval, Investigator and Study coordinator qualifications, the informed consent process, how to approach and consent subjects of limited English proficiency, data management and documentation processes, study confidentiality, reporting of Adverse events, protocol deviations and noncompliance and study close out processes. In addition, SOPs are in place on how to engage with study monitors and how to prepare for internal or external audits and inspections.

There are clear procedural manuals as described in ***Section 6.2.3*** pertaining to all medical devices used in Northwell Health Facilities. The manual describes the regular upkeep and maintenance strategies for all medical devices and machines owned by Northwell Health institutions and practices. There are clear SOPs created by Biomedical Engineering that describe the servicing and maintenance of the Arctic Sun 5000®. This device is used per standard of care in the operating room on select patient cases as well as outside of the operating room. Quality metrics are in place to assure it is operating effectively. The study team will use the device only in the manner described in the manual and a licensed and certified clinician trained on the device, and IRB approved on this study, will utilize the machine to induce the hypothermia protocol.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

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

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. All case report forms shall be completed by the study coordinator assigned to the project within seven (7) days of completed study assessment.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

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

Original documents, data and records, such as hospital records, clinical records and office records, laboratory results, diagnostic test results, are considered source documents. These source documents will be made available to monitor when required for trial review to verify accuracy. The following information is obtained and maintained on study subjects continuing in the study: enrollment log, device accountability log. While this study does not involve a device implant, it will track the use of the Arctic Sun 5000® for each subject enrolled. Documentation of study subjects' participation in the study will be documented in the medical record of the patient as well. Due to the COVID-19 pandemic, many paper medical charts or records may not be readily available to the research team as they may be maintained in contaminated areas. Under normal circumstances, a copy of the informed consent would be printed and placed in the medical record. To protect the study team from unnecessary exposure, the Investigator enrolling the subject will document a note in the electronic medical record so other providers will realize the patient is enrolled in a clinical trial.

This study will use electronic case report forms. Electronic Data records requires administrative, physical and technical safeguards to ensure its confidentiality, integrity and security. The research IT security department will approve the EDC platform prior to the study onset. The Principal Investigator will ensure that the following parameters are met: each member of the research team is responsible for collecting data and will be fully trained on the electronic system operations prior to study start; each member will have proper security privileges assigned prior to entering data into the system; no member with security privileges will grant another person access under their identity or password.
A data dictionary will be created within the EDC to indicate to the study coordinator the definitions of each variable. This will ensure accurate and consistent data collection processes. Variables are collected routinely when hypothermia protocols are initiated. This study focuses on evaluating the safety and efficacy of using hypothermia protocol in a new indication, COVID-19 patients. Therefore, variables such as initial start temperature, vitals and medications will be captured at set defined time points. Blood tests values collected per routine will be entered into EDC from set time points.

10.1.9.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 2 years. These documents should be retained for a longer period, however, if required by local regulations. As outlined below, the study team will retain the de-identified data for up to five years.

10.1.10 PROTOCOL DEVIATIONS

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

These practices are consistent with ICH GCP:

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

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 3 working days of identification of the protocol deviation, or within 3 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents, reported to Northwell IRB. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements.

10.1.11 PUBLICATION AND DATA SHARING POLICY

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

Every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers 5 years after the completion of the primary endpoint by contacting Dr. Pey-Jen Yu. Data that is to be shared will be de-identifiable and never can be traced back to any individual subject. All data published in any peer-reviewed journals shall be de-identifiable and never be linked back to any individual subject.

10.1.12 CONFLICT OF INTEREST POLICY

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

10.2 ADDITIONAL CONSIDERATIONS

N/A

10.3 ABBREVIATIONS

The list below includes abbreviations utilized in this template. However, this list should be customized for each protocol (i.e., abbreviations not used should be removed and new abbreviations used should be added to this list).

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

SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

10.4 PROTOCOL AMENDMENT HISTORY

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A Summary of Changes table for the current amendment is located in the Protocol Title Page.

Version	Date	Description of Change	Brief Rationale

11 REFERENCES

Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med 2002; 346:549.

Nielsen N, Wetterslev J, Cronberg T, et al. Targeted temperature management at 33°C versus 36°C after cardiac arrest. N Engl J Med 2013; 369:2197.

Arrich J, Holzer M, Havel C, et al. Hypothermia for neuroprotection in adults after cardiopulmonary resuscitation. Cochrane Database Syst Rev 2016; 2:CD004128.

Mehran R, et al. (2011). Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the bleeding academic research consortium. Circulation. 123 (23): 2736-47.

Arctic Sun 5000® Temperature Management System Indications for Use. . Bard, Inc.

Wang HE, Wells JJ, Rizk DV. The Hypothermia Temp Manag. 2013 Sep; 3 (3): 1470150. Doi: 10.1089/ther.2013.0013

Northwell Health Policy Title: Therapeutic Hypothermia After Cardiac Arrest- Effective Date October 2010 and Last revised January 2017.Prepared by A. Kaplan, MD, Leah Aversa, RN, NM, D. Friedl, RN, MS. Found on Northwell Intranet