INVESTIGATIONAL PLAN

Study Title: Cardiogenic SHock Intravascular CooLing TriaL (CHILL-SHOCK)

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Sponsor: Investigator initiated with support from ZOLL Circulation, Inc.

Intervention: Therapeutic hypothermia using FDA approved ZOLL Intravascular Temperature Management (IVTM™) system to achieve core temperature of 32-34° for 24 hours in patients who present with cardiogenic shock.

Manufacturer of Intervention: ZOLL (Chelmsford, MA)

Background

Cardiogenic shock complicates 2-8% of all myocardial infarctions in hospitalized patients and despite advances in revascularization and mechanical support, the mortality rate in these patients can be as high as 50% during the index hospitalization.[1] Cardiogenic shock from alternative causes such as advanced heart failure, acute myopericarditis, stress-induced cardiomyopathy, and acute valvular regurgitation are also associated with significant morbidity and mortality. Hypothermia, as defined by 32-34° Celsius, has been proposed as a potential adjunctive therapy in patients with cardiogenic shock. The role of mild hypothermia has been well established in out of hospital cardiac arrests due to ventricular tachycardia or ventricular fibrilation for improved neurological outcome.[2] In fact, the American Heart Association (AHA) guidelines recommend therapeutic hypothermia (Class I recommendation) with targeted temperature of 32°C to 34°C for 12 to 24 hours in patients who suffer out-of-hospital cardiac arrest due to ventricular fibrillation (VF).[3] AHA also recommends induced hypothermia for patients after in hospital cardiac arrest due to any initial rhythm or after out-of-hospital cardiac arrest due to pulseless electric activity or asystole. This is a Class IIb recommendation, compared to Class I for out-of-hospital VF arrest.

The proposed mechanism of improved neurological outcomes with therapeutic hypothermia (TH) likely involves changes in cerebral metabolism.[4-6] In addition to neuroprotective effects, hypothermia may improve cardiac performance. Several animal and small human trials have tried to understand the effect of hypothermia on hemodynamics in patients with cardiogenic shock. [7-11] These have showed improved cardiac performance with TH with improved contractility, cardiac output, and reduction in the inflammatory response that accompanies shock. A small trial published in 2012 by Schmidt-Schweda et. al prospectively enrolled 14 patients that were cooled to 33°C and studied their hemodynamics. Interestingly, patients experienced a statistically significant drop in heart rate, but with increased stroke volume, higher mean arterial blood pressure (MAP), and higher cardiac Power index (CPI).[10] All these indices have been associated with improved outcomes in cardiogenic shock.[13] Most importantly, the Schmidt-Schweda trial established that hypothermia is safe in patients with cardiogenic shock with no severe adverse events experienced in their cohort. There were no complications associated with insertion or removal of cooling catheters and anti-shivering measures were effective even in non-ventilated patients (5 out of 14 patients were breathing spontaneously during therapeutic hypothermia (TH)). While there was a decline in platelets with TH, this did not lead to an increase in bleeding. Another study from authors at the Cleveland Clinic retrospectively evaluated the hemodynamic effects of TH on 14 consecutive patients with cardiogenic shock who underwent therapeutic hypothermia.[9] The patients who underwent TH had higher cardiac index, lower SVR, and lower vasopressor requirements.[9] Importantly, TH was deemed safe, and given the positive effects on hemodynamic parameters, the authors proposed that prospective trials are needed to potentially expand the role of TH outside of cardiac arrest.

Patients with cardiogenic shock, regardless of the underlying etiology, present with hypotension, shortness of breath, altered mental status, signs of volume overload (elevated jugular venous pressure, pulmonary rales, lower extremity edema), and evidence of end-organ hypoperfusion. These patients are typically admitted to the Coronary Care Unit (CCU) for aggressive treatment to reverse the course of the disease. Standard of care therapy for these patients involves initiation of ionotropes and/or vasopressors along with diuretics. Often, mechanical circulatory support (i.e Intra-arterial balloon pump or temporary left-ventricular assist devices) and invasive hemodymamic monitoring (i.e. placement of a pulmonary artery catheter) is necessary.

The results of the small trials mentioned above are encouraging, but larger randomized trials are necessary to establish the role of TH in patients with cardiogenic shock. We propose a first-ever randomized clinical trial to prospectively study the effects of TH in patients with cardiogenic shock. In addition to assessing the safety of TH in this patient population, hemodynamic parameters, echocardiographic assessment of cardiac function during hypothermia, as well electrocardiographic changes with hypothermia will be studied. The echocardiographic changes during TH have never been previously reported. Studying TH in patients with cardiogenic shock is important, as therapies for this highly morbid condition have remained largely unchanged for many years. Given the high mortality associated with cardiogenic shock despite advances in medical and mechanical support, the clinical implications of results from this trial may be large.

Objective

The purpose of the study is to prospectively randomize patients with cardiogenic shock to standard therapy plus therapeutic hypothermia or standard medical therapy alone in order to assess the safety of TH in patients with cardiogenic shock. This study will also help understand the physiologic effects of TH in cardiogenic shock. This will be a pilot study to establish the safety of TH and to assess tolerability of TH in this patient population.

Methods

A. Patient Population:

All patients meeting criteria for cardiogenic shock (defined as systolic blood pressure <90mmHg for at least 30 minutes, Cardiac Index < 2.2 L/min/m2, pulmonary capillary wedge pressure (PCWP) ≥ 15mmHg, need for vasopressors, or need for mechanical support to keep systolic blood pressure ≥ 90mmHg) admitted to the University of Chicago Coronary Care Unit (CCU) will be randomized to standard medical therapy or to therapeutic hypothermia (32-34°) for 24 hours plus medical therapy in a non-blinded manner with 1:1 randomization using computer-generated random numbers (simple randomization). The cardiogenic shock may be a result of acute coronary syndromes (STEMI, NSTEMI, or UA), ischemic or non-ischemic cardiomyopathy, myocarditis, hypertrophic cardiomyopathy, stress-induced cardiomyopathy, peripartum cardiomyopathy, or cardiogenic shock in a patient with HF with preserved EF. Patients less than 18 years of age or greater than 89 years of age will be excluded. Patients with

baseline heart rate less than 60 beats per minute, baseline temperatures less than 35°C, recent cardiotomy, history of cardiac transplantation, or those who are pregnant will be excluded.

All patients between the ages of 18 and 89 who meet the criteria for cardiogenic shock in the CCU will be screened. Inclusion and exclusion criteria are listed below.

Inclusion Criteria:

1) Cardiogenic shock
    a) Systolic blood pressure <90mmHg for at least 30 minutes
    b) Cardiac Index < 2.2 L/min/m2
    c) Pulmonary capillary wedge pressure (PCWP) ≥ 15mmHg
    d) Need for central venous access, vasopressors, inotropes and/or mechanical circulatory support (i.e. intra-aortic balloon pump, Impella, ECMO) to maintain systolic blood pressure ≥ 90mmHg
2) Etiology of shock
    a) Acute coronary syndromes (STEMI, NSTEMI, or UA)
    b) Ischemic or non-ischemic cardiomyopathy
    c) Myocarditis
    d) Hypertrophic cardiomyopathy
    e) Stress-induced cardiomyopathy
    f) Peripartum cardiomyopathy
    g) Cardiogenic shock in a patient with HF with preserved EF
3) Age ≥ 18 years AND ≤ 89 years
4) Admission to the University of Chicago CCU

Exclusion Criteria:

1) Baseline heart rate < 60 beats per minute
2) Baseline temperatures < 35°C
3) Recent cardiotomy
4) History of cardiac transplantation
5) Current pregnancy
6) Contraindication to 9.3 French femoral venous access for placement of intravascular cooling catheter
7) Hospice designation (either currently in hospice or previously enrolled within the past 30 days)

B. Data Collected:

The data elements of interest include, but are not limited to the following:

1. *Patient information*
    a. Name

b. Date of birth
c. Medical record number
d. Phone number
e. Primary diagnosis
f. Relevant social and family history
g. Previous medical history such as clinic notes, current medications, results of all tests, procedures and laboratory assessments.
h. Medications
i. Weight and height

2. *Transthoracic echocardiogram (TTE)*
3. *Hemodynamics via pulmonary artery catheter*
   a. RA pressures
   b. RV pressures
   c. PA pressures
   d. Pulmonary capillary wedge pressure (PCWP)
   e. Fick cardiac output and cardiac index
   f. Systemic vascular resistance (SVR)
   g. Pulmonary vascular resistance (PVR)
   h. Cardiac power and cardiac power index
   i. Mixed venous saturation (MVO_2)
4. *Metabolic parameters*
   a. Serum lactate level
   b. Basic metabolic panel - Renal function and serum electrolytes
   c. Hepatic function
   d. Coagulation parameters
   e. Complete blood count (CBC)
   f. Arterial blood gas (ABG)
5. *Physiologic parameters and vital signs*
   a. Urine output
   b. Blood pressure
   c. Heart rate
   d. Bladder or esophageal temperature
   e. Respiratory rate
6. *Electrocardiogram*
7. *Vasoactive medication requirements*
   a. Cumulative inotrope (i.e. milrinone, dobutamine) and vasopressor (i.e. norepinephrine, phenylephrine, dopamine, vasopressin) doses
8. *Blood samples for future research*
   a. Stored without identifying information for future research, which may include genetic testing

b. May be shared with outside collaborators for research purposes, with identifiers removed

C. Timing of Data Collection:

Baseline parameters (prior to initiation of cooling):

1. TTE
2. Hemodynamics
3. Metabolic parameters
4. Physiologic parameters and vital signs (including temperature)
5. Electrocardiogram
6. Blood sample for future research

Parameters collected during cooling protocol (18-24 hours after onset of cooling, prior to rewarming):

1. Hemodynamics
2. Metabolic parameters
3. Physiologic parameters and vital signs (body temperature measurements every 1-2 hours, as per the CCU policy)
4. Electrocardiogram
5. TTE
6. Cumulative inotrope and vasopressor dosing (at the end of 24 hours of intervention)
7. Blood sample for future research

Parameters collected after rewarming (48-96 hours after completion of cooling protocol):

1. Hemodynamics
2. Metabolic parameters
3. Physiologic parameters and vital signs
4. Electrocardiogram
5. TTE
6. Blood sample for future research

Endpoints

Primary safety endpoints:

1. Arrhythmia requiring medical therapy or therapy with temporary pacemaker
2. Bleeding requiring transfusions as a direct result of the cooling catheter insertion or secondary to resulting coagulopathy
3. Clinically important bloodstream infection, as confirmed with 2 positive blood cultures, or suspected sepsis in the absence of positive blood cultures with a sequential organ failure assessment (SOFA) score >2
4. Hypokalemia with potassium levels below 3.0mEq/L, not secondary to other identifiable causes

Secondary endpoints:

1. Hemodynamic changes during intervention period – Cardiac output/Cardiac Index, PCWP, SVR, mixed venous oxygen saturation (MVO_2), cardiac power index
2. Cumulative vasopressor and inotrope dose requirements (i.e. number of vasoactive and/or inotropic drugs used)
3. Echocardiographic % change in ejection fraction at 18-24 hours (from baseline)
4. In-hospital all-cause mortality

Procedures

Patients admitted to the Coronary Care unit (CCU) at the University of Chicago will be screened by the study investigators and the cardiology fellow on the CCU rotation. Patients meeting the inclusion criteria, as defined previously, will be identified and randomized after informed consent within 12 hours of presentation. Patients will be randomized to either TH plus standard medical care or to standard medical care alone. A pulmonary artery (PA) catheter will be placed at the bedside or in the Cardiac Cath lab if difficult anatomy is anticipated. As mentioned earlier, placement of a PA catheter is part of the standard of care for management of cardiogenic shock. Currently, patients who are admitted to the University of Chicago CCU with cardiogenic shock routinely undergo placement of PA catheter by the cardiology fellow in the CCU or in the cardiac cath lab. Data from the PA catheter is vital in initiating vasopressors/inotropes, assessing the response to the therapies, and possible need for escalation of therapy (i.e. mechanical support). In this study, patients in each arm will undergo PA catheter placement.

Cooling will then be initiated and maintained using FDA approved ZOLL (Chelmsford, MA) Intravascular Temperature Management (IVTM™) system with the ZOLL Quattro cooling catheter. The ZOLL IVTM along with the Quattro cooling catheter are currently FDA approved for use in cardiac surgery patients to achieve and maintain normothermia during surgery and in recovery and to induce, maintain, and reverse mild hypothermia in neurosurgery patients during surgery and in recovery [11]. The IVTM is not currently FDA approved to achieve therapeutic hypothermia in cardiogenic shock. The use of the cooling catheter and the temperature management system will be off-label for this study. Notably, although not FDA approved for this purpose, current AHA practice guidelines recommend therapeutic hypothermia with a goal temperature of 32°C to 34°C for 12 to 24 hours in patients successfully resuscitated after cardiac arrest as a Class I recommendation if the arrest is from VT/VF and as Class IIb recommendation for CA from other nonshockable rhythms. The European Resuscitation Council guidelines for resuscitation recommend therapeutic hypothermia for all comatose survivors of CA regardless of initial rhythm

The ZOLL 9.3 French Quattro® catheter is inserted into the central venous system via the femoral approach by personnel certified to insert central venous catheters. Placement of the ZOLL catheter is identical to central venous line insertion, such as triple lumen insertion for

administration of medications or a dialysis catheter for temporary dialysis. After successful insertion of the cooling catheter, it will be connected to the Thermogard XP® thermal regulation system. The Quattro® catheter functions as both a central venous triple lumen catheter as well as a cooling catheter. Cooling is achieved by circulating normal saline in a closed system through the catheter. The flow and temperature (range 4°C to 42°C) of the circulating saline serves as the heat exchange mechanism and is controlled by the external Thermoguard® thermal regulation system. The temperature is measured and adjustments are made by the thermal regulation system to automatically maintain target temperature. The target temperature is achieved within 2-3 hours of initiation of TH. Rewarming is accomplished using the same balloon catheter system and heat exchange occurs without infusion of any saline or fluids into the patient. In clinical trials, intravenous catheter based cooling system has been shown to achieve target temperature faster and maintain target temperature with more precision.[12,14,15]

Medical therapy in both intervention and non-intervention groups will be based on the current recommendations for management of cardiogenic shock. This includes inotropic therapy (i.e. dobutamine or milrinone) for cardiac support, vasopressor therapy (i.e. norepinephrine, dopamine, phenylephrine, epinephrine) to achieve target blood pressure (mean arterial blood pressure ≥ 60 mmHg), diuretics for volume removal, and mechanical circulatory support as clinically indicated. All patients included in this study will have pulmonary artery (PA) catheters inserted within 12 hours of randomization via either the internal jugular or femoral venous approach to monitor real-time hemodynamics. The clinicians in the CCU will use the data from PA catheters (cardiac output, mixed venous saturation, systemic vascular resistance, etc.) to guide therapy for both the intervention and non-intervention groups. The primary investigator of this study (Dr. Paul) will have no role in the clinical management of the patients.

Laboratory, echocardiographic, and hemodynamic parameters will be obtained for patients prior to randomization, near the end of 24 hour cooling therapy, and after 48-96 hours post-randomization. Core temperature will be measured via either thermal tip at the end of a transurethral urinary catheter or endotracheal temperature probe in intubated patients. Rewarming will be accomplished at 0.3°C per hour until temperature reaches 37°C.

Target Enrollment and Study Duration

In this initial pilot study, we anticipate enrolling 20 patients to the study, 10 randomized to standard medical therapy and 10 patients randomized to standard medical therapy and 24 hours of TH. We anticipate completing enrollment within 6 months.

Statistical Methods

The three-dichotomous primary endpoints will be analyzed using a two-sample independent proportion test or a Fisher's exact test with a Bonferroni method continuity correction for multiple endpoints. Furthermore, numerical secondary endpoints will be presented as either

mean ± standard deviation or median (interquartile range) based upon the distribution of the data. In addition, all numerical secondary endpoints will be assessed using two independent t tests or Mann-Whitney U test for comparisons. Categorical variables will be tested with chi-square tests of association or Fisher's exact tests. Differences will be considered significant using an alpha value of 0.05 for a two-sided test. Analyses will be performed using STATA MP Version 14 (College Station, TX).

Potential risks and benefits to subjects

A. Benefits:

There is mounting evidence that TH has positive effects on cardiac function. Multiple studies have suggested that TH may offer particular benefit in cardiogenic shock. In this prospective trial, the patients will be randomized to TH or standard medical care using simple randomization. With TH, we expect increased cardiac output, increased contractility, lower SVR, and higher cardiac power index which will lead to improved hemodynamics and potentially decreasing pressor requirements.

B. Risks:

Anticipated adverse events that could possibly occur during the study include, but are not limited to:

1. *Risks associated with TH*
    a. Shivering
    b. Arrhythmia
    c. Coagulopathy with or without clinically significant bleeding
    d. Hyperglycemia
    e. Hypothermia
    f. Electrolyte abnormalities
    g. Infections
2. *Risks associated with cooling catheter insertion*
    a. Bleeding
    b. Infection
    c. Vascular injury

Mitigating Risks associated with TH:

Shivering is the most common risk associated with TH. Shivering is a normal physiological response to cooling as it allows the body to expend energy and generate heat. This leads to increasing metabolic demands and subsequent oxygen consumption. Various strategies can be used to combat shivering and have these have been well described in the literature. In patients that are intubated, the most common means of combating shivering is a combination of benzodiazepines, opioid analgesics, and/or neuromuscular blockade.[16] In awake patients, combination of meperedine and warming of skin with air-warming products such a 'Bair Hugger

blanket' (3M, St. Paul, MN) hugger' are utilized.[17] Meperedine is the most beneficial agent to prevent shivering and previous studies have demonstrated significant lowering of the shivering threshold with meperidine.[17,18] Given that intravascular cooling therapy is common in multiple ICU settings, including the cardiac care unit (CCU), protocols are already in place for the management of shivering, with an institutional-approved anti-shivering protocol often used in patients undergoing TH.[18] In the event of persistent shivering despite therapy with intravenous sedatives, anesthetics (i.e. propofol or meperidine) and/or paralytic agents in intubated patients, the TH protocol will be stopped and patients will be rewarmed to normothermia.

Therapeutic hypothermia may potentially increase the risk of arrhythmias and will be evaluated in this trial. Bradycardia is expected with TH. In the previously published studies, the reduction in heart rate is not significant enough to cause hemodynamic compromise.[9,17,19] However, if a patient is noted to be persistently bradycardic, with signs or symptoms requiring temporary pacemaker insertion, the TH protocol will be stopped. Bradycardia requiring temporary pacing will be considered an adverse event of cooling if the patient did not have underlying conduction system disease (i.e. first or second degree AV block) prior to cooling, In such cases, patients will be rewarmed to normothermia per the rewarming protocol currently in place for intravascular cooling of critically ill patients.

In addition to bradycardia, ventricular arrhythmias are potential adverse effects of TH. While ventricular arrhythmias have veen reported with TH, data from trials suggests that there is no demonstrable increase in risk of ventricular arrhythmias in patients undergoing therapeutic hypoethermia.[24,25] Importantly, patients in cardiogenic shock have a high risk of developing ventricular arrhythmias either due to ischemia or underlying myocardial scaring. All ventricular arrhythmia epidsodes requiring intervention will be recorded. If arrhythmia is deemed to be as a result of hypothermia and alternative explanations have been exhausted, the patient will be rewarmed to normothermia per the rewarming protocol.

Another risk associated with TH is mild coagulopathy. Temperatures below 33°C have been associated with mild platelet dysfunction in vitro. However, the risk of bleeding with mild TH (32-34°C) is minimal and none of the trials of TH in cardiac arrest or stroke have demonstrated increased risk of bleeding.[20,21] TH has also been used safely in patients with ischemic stroke who are treated with tPA.[22] Based on the currently published data, the risk of bleeding with TH is minimal. Bleeding adverse events will be classified using the GUSTO bleeding criteria.[26] In patients who develop moderate bleeding deemed to be a direct result of TH, initial conservative measures of simple transfusions will be implemented. However, if bleeding does not respond to these conservative measures or progresses to severe bleeding, the TH protocol will be stopped and patients will be safely rewarmed.

Hyperglycemia is common during TH as lower temperatures decrease insulin secretion and increase insulin resistance. Many patients with heart failure and cardiogenic shock have concominant diabetes and glucose control can often be difficult to achieve in these critically ill patients. Clinically significant hyperglycemia will be defined as glucose level exceeding 200mg/d requiring continuous insulin infusion in patients without a diagnosis of diabetes mellitus. Hyperglycemia in patients with diagnosis of diabetes mellitus, or hyperglycemia as a result of other identifiable causes (i.e. administration of steroids, adrenal derangements) will not be considered as a result of TH. In patients who develop hyperglycemia requiring continuous insuling infusion as a direct result of TH, the patient will be treated expectantly and hyperglycemia will be recorded as an adverse event. During TH period, blood glucose will be measured at least hourly during TH, especially in patients receiving intravenous insulin, and during rewarming, when glucose levels can fall.

Hypothermia will lower serum potassium levels, primarily by promoting inward cellular potassium flux, although hypothermia also induces a mild diuresis with concurrent electrolyte wasting. Serum electrolytes will be measured at regular intervals (every 4–6 hours). Potassium will be repleted to maintain levels above 3.5 mEq/L. Rewarming reverses the potassium flux and increases serum levels, so repletion will be held 4 hours before rewarming begins. Clinically significant hyperkalemia is unusual in patients with preserved renal function. In patients with hypokalemia not due to other identifiable causes (diuretic administration, adrenal derangements, etc.), potassium supplements will be administered as per standard of care. Hypokalemia with potassium levels below 3.0mEq/L not secondary to other identifiable causes in patients undergoing TH will be considered an adverse event.

The target temperature of 32-34°C will be achieved using the intravascular cooling catheters. The body temperature will be recorded every 1-2 hours as per the CCU policy in the TH group (as well as the control group). The time spent in the therapeutic window will be recorded and reported. Any deviations outside of the range, specifically <32°C lasting >5 minutes will be reported as an adverse event.

Mitigating Risks associated with cooling catheter insertion:
The risks associated with insertion of a cooling catheter are the same as insertion of any central lumen catheter. These include, but are not limited to, bleeding, infection, and vascular injury. Previously published studies have quoted risk of localized hematomas at 4.7% and risk of vascular injury (most frequently due to inadvertent arterial puncture) at <1%.[23] Incidence of line-associated blood stream infection has been reported as 80-189 episodes per 100,000 patient years.[23]

Insertion of a central venous catheter is standard of care in patients in cardiogenic shock to allow for administration of inotropes/vasopressors. The ZOLL Quattro catheters include three standard

central venous catheter infusion lumens to allow for administration of these vasoactive medications. Therefore, patients randomized to TH arm will not need an additional central venous line. Rather, insertion of a cooling catheter will serve the purpose of initiation and maintenance of TH while also allowing for administration of drugs via the infusion lumens. The risk associated with cooling catheter insertion is not expected to be higher than insertion of a standard central venous line.

C. Monitoring of Safety:

During the intervention period, participants will be monitored by physicians, nurses, and technicians in accordance with standard medical care. This includes 24-hour monitored telemetry, with measurement of heart rate, blood pressure, oxygen saturation, and respiratory rate. Real-time hemodynamic monitoring will be measured using pulmonary artery catheters. Blood glucose and electrolyte measurements will be performed as per protocol for patients undergoing therapeutic hypothermia, and correction of abnormalities will be performed by the treating team. Shivering will be monitored by the treating nurse, per ICU protocol, and will be reported to the treating team. TH will not influence the clinician's medical decisions – any medical or mechanical intervention necessary based on clinical status will be allowed.

D. Data Safety Monitoring Board:

Adverse events will be reviewed by the Data Safety Monitoring Board as described below. The study will be halted upon the discovery of unanticipated adverse device events that present a significant or unreasonable risk to subjects enrolled in the study.

The DSMB will meet (in person or via telephone conference) a minimum of 3 times:

- after treatment of the first 4 subjects (2 in the TH arm and 2 in the control arm)
- after treatment of the first 10 subjects (5 in the TH arm and 5 in the control arm)
- at the conclusion of the study

In addition, the DSMB may convene additional meetings if necessary to ensure the ongoing monitoring and safety of the subjects treated with therapeutic hypothermia (TH). A copy of the DSMB charter is located in Appendix 2.

We will collect all treatment emergent and serious unsolicited adverse events during the index hospitalization. A treatment emergent adverse event is any untoward medical occurrence associated with the use of therapeutic hypothermia, whether or not considered related. The DSMB will be informed of expected adverse events, such as shivering, bleeding, and bradycardia, that result in termination of the protocol. Additionally, any unexpected adverse events while undergoing TH will be reported to the DSMB, whether deemed related to TH or not. All adverse event details will be provided to the DSMB prior to the meeting with ample time allowed for analysis. This will include details of the individual adverse events as well as the PI's analysis related to causality, severity and frequency. The DSMB will be responsible for

confirmation of the PI's assessment of all adverse events and final adjudication of all adverse events.

The DSMB will include the following individuals who have agreed to serve on it:

Dr. Gabe Sayer (University of Chicago Medicine – Section of Cardiology)
Dr. Mardi Gomberg-Maitland (Inova Health System – Section of Cardiology)
Dr. Gene Kim (University of Chicago Medicine – Section of Cardiology)

Payment to Subjects

Participants will not receive monetary compensation for their participation in this study. The cost of the TH catheters, thermal regulation system and associated monitoring will be part of the study costs and patients will not be charged for these services.

Informed Consent

Informed consent for the study will be obtained from the patient if possible, or the medical decision maker in the event that the patient is incapable of making informed decisions. Due to the nature of the study, we expect that the patient's clinical status will preclude consent directly from the patient. We anticipate that a majority of the consents will be obtained from family and medical decision makers. Once the referring physician has given approval and solicited a patient's or decision maker's interest, a co-investigator will approach and discuss the possibility of participating in this research protocol. The co-investigator will discuss the background and significance of the study, the inclusion and exclusion requirements, and why they are suitable for participation. The study will be summarized for the subject. They will also be informed that they may withdraw at any time during the study without influencing their medical care. The potential participant, including decision maker, will be given the opportunity to ask questions.

Confidentiality

A study file containing all study related information will be kept by the primary investigator in a file cabinet within a locked office or on an encrypted electronic file. Each subject enrolled will have their own file including: study ID number, physician's consent, clinical data as described in Methods, the original signed consent form, proof of eligibility, and any other forms or information.

Protection of Special Populations

Patients younger than 18 years or older than 89 years will be excluded. Additional exclusions will be made as described in Methods. No group of patients will bear disproportionate risk or burden. This includes all eligible Medicare and Medicaid beneficiaries and will not discriminate any patient on the basis of gender, age, disability, and racial or ethnic background. As such, we believe that the results obtained from this study will be generalizable to the Medicare and Medicaid beneficiary population within our specifically stated inclusion/exclusion criteria.

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Appendix 1 – Schedule of Study Activities

	Baseline	18-24 hours (after randomization)	48-96 hours (after randomization)	30-day Follow-Up	90-day Follow-Up
Informed Consent	X				
Review Medial History	X				
Review Medication History	X				
Height and Weight	X				
Vital Signs [a]	X	X	X		
Echocardiogram (TTE)	X	X	X		
Electrocardiogram (ECG)	X	X	X		
Hemodynamics [b]	X	X	X		
Blood Tests [c]	X	X	X		
Vasoactive Medication Dosing		X			
Potassium (pts randomized to cooling)		Q 4 hours			
Glucose Checks (pts randomized to cooling)		Q 1 hour			
Urine Output	X	X	X		
Randomization	X				
Adverse Events		X	X	X [d]	X [d]

[a] blood pressure, heart rate, temperature (bladder or esophageal), respiratory rate

[b] RA pressures, RV pressures, PA pressures, pulmonary capillary wedge pressure (PCWP), Fick cardiac output and cardiac index, systemic vascular resistance (SVR), pulmonary vascular resistance (PVR), cardiac power and cardiac power index, mixed venous saturation (MVO2)

[c] serum lactate level, basic metabolic panel, hepatic function, coagulation parameters, complete blood count (CBC), arterial blood gas (ABG), and optional blood samples for future research

[d] to be completed in clinic, when possible, or by phone

[e]items to be charged to research during cooling include: meperidine

Appendix 2 – DSMB Charter

1. Introduction

This Charter is for the Data and Safety Monitoring Board (DSMB) for Cardiogenic Shock Intravascular Cooling Trial (CHILL-SHOCK). The DSMB will consist of a team of clinical researchers who are unaffiliated with this project. The members of the DSMB will not be investigators in this study and will be experienced in conducting and interpreting clinical trials. Their responsibilities will include reviewing the efficacy and safety endpoints at the set times points, as stated below. The Charter is intended to be a living document. The DSMB may wish to review it at regular intervals to determine whether any changes in the procedure are necessary.

2. Responsibilities of the DSMB

The DSMB is 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 is an independent group advisory to the study PI and is required to provide recommendations about starting, continuing, and stopping the study. In addition, the DSMB is asked to make recommendations, as appropriate, to/about:

- Selection, recruitment, and retention of participants
- Adherence to protocol requirements
- Completeness, quality, and analysis of measurements
- Amendments to the study protocol and consent forms
- Confirmation of the PI's assessment of adverse events
- Final adjudication of all adverse events, as defined by *Table A* below
- Participant safety
- Notification of and referral for abnormal findings

3. DSMB Members

***DSMB Chair**:* *Gabe Sayer, MD* University of Chicago Medicine Department of Medicine Section of Cardiology Assistant Professor of Medicine	*Mardi Gomberg-Maitland, MD, MSc* Inova Health System Department of Medicine Section of Cardiology Professor of Medicine	*Gene Kim, MD* University of Chicago Medicine Department of Medicine Section of Cardiology Assistant Professor of Medicine

4. Scheduling, Timing, and Organization of Meetings: Data and Safety Monitoring Meetings

The DSMB will meet (in person or via telephone conference) a minimum of 3 times:

- after treatment of the first 4 subjects (2 in the TH arm and 2 in the control arm)
- after treatment of the first 10 subjects (5 in the TH arm and 5 in the control arm)
- at the conclusion of the study

The DSMB may convene additional meetings if necessary to ensure the ongoing monitoring and safety of the subjects treated with TH.

A quorum of at least two (2) DSMB members needs to be present for a meeting to commence. Members may either be present in person or have the option to phone-in if unable to arrive at the meeting location.

All DSMB members will receive an agenda prior to the meeting. In the event that a DSMB member is unable to attend a meeting, that member will receive minutes, as well as any additional notes, with the opportunity to share any additional thoughts on the distributed information.

5. Grading and Attribution Methods for Adverse Events

Grading Scale

The DSMB and the study team will utilize the Adverse Event Grading Scale provided in Table A. All adverse events will be graded according to this scale, the PI will prepare data regarding adverse events for review by the DSMB prior to meeting, and any additional details will be provided to the DSMB by the PI, as necessary.

Table A – Safety Reporting Definitions

Term	Definition
Adverse Event (AE) ***Ref: ISO 14155-2011*** ***Ref: MEDDEV 2.7/3 12/2010***	Any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, whether or not related to the investigational medical device. This definition includes events related to the procedures involved (any procedure in the clinical investigation plan).
Adverse Device Effect (ADE) ***Ref: ISO 14155-2011*** ***Ref: MEDDEV 2.7/3 12/2010***	Adverse event related to the use of an investigational medical device NOTE 1: This definition includes any adverse event resulting from insufficient or inadequate instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device. NOTE 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.
Serious Adverse Event (SAE) ***Ref: ISO 14155-2011*** ***Ref: MEDDEV 2.7/3 12/2010***	Adverse event that: • Led to death, • Led to serious deterioration in the health of the subject, that either resulted in: o a life-threatening illness or injury, or o a permanent impairment of a body structure or a body function, or

Table A – Safety Reporting Definitions

Term	Definition
	○ in-patient or prolonged hospitalization of existing hospitalization, or ○ medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function • Led to fetal distress, fetal death, or a congenital abnormality or birth defect. NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigational plan, without serious deterioration in health, is not considered a serious adverse event.
Serious Adverse Device Effect (SADE) ***Ref: ISO 14155-2011*** ***Ref: MEDDEV 2.7/3 12/2010***	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Unanticipated Adverse Device Effect (UADE) ***Ref: 21 CFR Part 812***	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.
Device Deficiency ***Ref: ISO 14155-2011*** ***Ref: MEDDEV 2.7/3 12/2010***	A device deficiency is any inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. NOTE: Device deficiencies include malfunctions, misuse or use errors, and inadequate labeling.

Abbreviations: EC=Ethics Committee; IRB=Institutional Review Board

Underlying diseases are not reported as AEs unless there is an increase in severity or frequency during the course of the investigation.

Relationship to Study Device(s) and Reporting Requirements
The Investigator will assess the relationship of the AE to the study device as related or unrelated.

Table B – Criteria for Assessing Relationship of Study Device to Adverse Event

Classification	Description
Unrelated	The adverse event is determined to be due to a concurrent illness or effect of another device/drug and is not related to the investigational product.
Related	• The adverse event is determined to be potentially related to the investigational product, and an alternative etiology is equally or less likely compared to the potential relationship to investigational product, or • There is a strong relationship to investigational product, or recurs on re-challenge, and another etiology is unlikely, or • There is no other reasonable medical explanation for the event.

Table C – Adverse Event Reporting

Event Classification	Event Recording	Communication to FDA	Communication to IRB
Adverse Event	• Event reviewed and classified by PI • Event recorded in Oncore Adverse event database	Detail of all AE's will be given at time of annual report.	Details provided at time of annual review, per IRB policy.
Serious Adverse Event including Serious Adverse Device Effects	• Event reviewed and classified by PI • Event recorded in Oncore Adverse event database	Reported via From 3500 within 48 hours of PI knowledge.	Details provided at time of annual review, per IRB policy (as these are not unanticipated events).
Unanticipated Adverse Device Effect / Unanticipated Serious Adverse Device Effect	• Event reviewed and classified by PIStudy will be halted if event presents a significant or unreasonable risk to subjects enrolled in the study • Event recorded	Reported as soon as possible, but within 48 hours of PI knowledge, via From 3500.	UADE reported within 10 days of PI knowledge USADE reported directly to IRB Chairman upon PI knowledge, followed by formal reporting to the IRB within 48 hours. Study will be halted if event presents a

Table C – Adverse Event Reporting

Event Classification	Event Recording	Communication to FDA	Communication to IRB
	in Oncore Adverse event database		significant or unreasonable risk to subjects enrolled in the study
Device Deficiencies (including but not limited to failures, malfunctions, and product nonconformities) Note: Any Investigational Device Deficiency that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate is considered a reportable event.	• Event reviewed and classified by PI • Event recorded in Oncore Adverse event database	Investigational Device Deficiency that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate is considered a reportable event and will be reported to the FDA within 48 hours of PI knowledge, via Form 3500. All other device deficiencies will be reported within 10 days.	Investigational Device Deficiency that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate is considered a reportable event will be reported to the IRB within 10 days of PI knowledge.

6. Example of Format for Minutes

Data and Safety Monitoring Meeting Minutes

Date:

Title of Protocol/IRB Number:

Principal Investigator/Designee:

Recommendations:

□ **Continue the trial without modification**

□ **Accrual:**
□ Recommend study be closed because of slow accrual
□ Continue to monitor study, but consider closure because of slow accrual

□ **Recommend study is amended/changed:**
□ For patient safety reasons

□ Rate of adverse events
□ To extend accrual because of an event rate slower than expected

□ **Other: _____**

Signature of Principal Investigator: _____

Signature of DSMB Chair:_____

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.

6. Reports of DSMB Deliberations and Reporting

Initial summary: The DSMB Chair is responsible for assuring the accuracy and transmission of a brief summary of the DSMB's discussion and recommendations to study PI and team within 7 days of the meeting or call. The study team will review this summary and either approve recommendation(s), or request additional information until agreement is reached.

Formal minutes: The DSMB Chair is responsible for the accuracy and transmission of the formal DSMB minutes for the Study PI within 30 days of the meeting or call. These minutes are prepared accordingly to summarize the key points of the discussion and debate (with the first priority being safety evaluation), requests for additional information, response of the investigators to previous recommendations, and the recommendations from the current meeting.