Originator: Asmeret Alidane — 4/20/2018 Date

CONCURRENCE:

Research & Development — 4/26/18 Date

Regulatory Affairs — 04/26/2018 Date

Clinical Affairs — 4/24/2018 Date

Medical Affairs — 4/25/2018 Date

Marketing — 6/18/2018 Date

1. PURPOSE

COOL-AMI EU Pivotal Trial is: A MULTICENTER, PROSPECTIVE, RANDOMIZED CONTROLLED TRIAL TO ASSESS THE SAFETY AND EFFECTIVENESS OF COOLING AS AN ADJUNCTIVE THERAPY TO PERCUTANEOUS INTERVENTION IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION is designed to evaluate the safety and efficacy of therapeutic hypothermia, using the ZOLL Proteus IVTM System, as an adjunctive therapy for patients presenting with acute myocardial infarction and undergoing PCI. This trial will be conducted by ZOLL Circulation, Inc., under Good Clinical Practices in accordance with ISO 14155.

2. SCOPE

The scope of the COOL-AMI EU Pivotal Trial is therapeutic hypothermia and will be conducted by ZOLL Circulation, Inc., This document provides the ZOLL Circulation, Inc., Investigational Plan for the COOL-AMI EU Pivotal Trial, and it details all aspects of the study protocol by which the trial will be conducted by ZOLL Circulation, Inc.

3. REFERENCES

3.1. None

4. REQUIREMENTS

4.1. Clinical trial data shall remain confidential per HIPAA and applicable European Regulations.

4.2. Clinical trial data shall be maintained in the Clinical Affairs files.

4.3. Declaration of Helsinki.

5. APPENDICES

1. **Appendix A Rev.6** - For sites that don't require specific Dual Anti-Platelet Therapy details, 125 pages
2. **Appendix B Rev.6** – Germany,122 pages
3. **Appendix C Rev.6** - For sites that require specific Dual Anti-Platelet Therapy details,124 pages
4. **Appendix D Rev.3** – France,127 pages
5. **Appendix E** – Change Log, 2 pages

REVISION HISTORY

Rev.	Description	Originator	Effective Date
01	Initial Release into ZOLL Circulation Quality System Note: The EDC Cover Page has been updated with the statement" ZOLL intends to submit Addendum A to sites that we are not certain adhere to DAPT guidelines as a standard of care" There are no changes to the contents of the main document.	Candace Elek	1/09/2017
02	Revision of the protocol to include Appendix A, B, and C. Appendix A: Main Protocol Appendix B: Germany Protocol Appendix C: Protocol for sites requiring more specific DAPT details.	Candace Elek	3/20/17
03	Revision of the A, B and C appendices. Changes are identical in all appendices Appendix A: Main Protocol Appendix B: Germany Protocol Appendix C: Protocol for sites requiring more specific DAPT details.	Shweta Kalpa	6/15/2017
04	Revision of the A, B and C appendices. Changes are identical in all appendices Appendix A: Main Protocol Appendix B: Germany Protocol Appendix C: Protocol for sites requiring more specific DAPT details.	Shweta Kalpa	07/25/2017
05	Added New Appendix D Appendix A –unchanged Appendix B -unchanged Appendix C -unchanged Appendix D –Rev 1	Shweta Kalpa	10/10/2017
06	Appendix A – Rev.4 to Rev.5 Appendix B – Rev.4 to Rev.5 Appendix C – Rev.4 to Rev.5 Appendix D – Rev.1 to Rev.2 Appendix E - Change Log	Asmeret Kidane	2/23/2018
07	Appendix A – Rev.5 to Rev.6 Appendix B – Rev.5 to Rev.6 Appendix C – Rev.5 to Rev.6 Appendix D – Rev.2 to Rev.3 Appendix E - Change Log	Asmeret Kidane	6/19/2018

APPENDIX A

COOL-AMI EU Pivotal Trial Clinical Investigational Plan

For sites that don’t require specific Dual Anti-Platelet Therapy details (Rev. 6)

(125 pages)

Clinical Investigation Plan

COOL-AMI EU PIVOTAL TRIAL: A MULTICENTER, PROSPECTIVE, RANDOMIZED-CONTROLLED TRIAL TO ASSESS THE SAFETY AND EFFECTIVENESS OF COOLING AS AN ADJUNCTIVE THERAPY TO PERCUTANEOUS INTERVENTION IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

PROTOCOL NO.: EDC-3135

Revision: 6

EFFECTIVE DATE: JUNE 19, 2018

CONFIDENTIAL & PROPRIETARY

CLINICAL INVESTIGATION PLAN APPROVAL PAGE

CLINICAL INVESTIGATION PLAN:	COOL-AMI EU Pivotal Trial: A multicenter, prospective, randomized controlled Trial to assess the safety and effectiveness of cooling as an adjunctive therapy to percutaneous intervention in patients with acute myocardial infarction
PROTOCOL NO.:	EDC-3135
SPONSOR:	ZOLL Circulation, Inc. 2000 Ringwood Avenue San Jose, CA 95131
SPONSOR REPRESENTATIVE:	ZOLL Medical Deutschland GmbH Emil-Hoffmann - Straße 13 50996 Köln, Germany
CLINICAL TRIAL SPONSOR'S CONTACT:	Philippa Hill
REVISION NUMBER:	6

Approval of Clinical Investigation Plan by Sponsor:

Philippa Hill
Senior Director, Clinical Affairs

June 19th 2018
Date

Signature Page

Clinical Investigation Plan

COOL-AMI EU PIVOTAL TRIAL: A MULTICENTER, PROSPECTIVE, RANDOMIZED-CONTROLLED TRIAL TO ASSESS THE SAFETY AND EFFECTIVENESS OF COOLING AS AN ADJUNCTIVE THERAPY TO PERCUTANEOUS INTERVENTION IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

PROTOCOL NO.: EDC 3135

Revision: 6

Effective Date: JUNE 19, 2018

Signatures of Investigator below constitute their approval of this clinical investigation plan (CIP) and provide necessary assurances that they have read the CIP, understand it, and will work according to all stipulations of it, and to the ethical principles stated in the latest version of the Declaration of Helsinki and the ISO 14155:2011 (Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice).

Investigator Name (Please Print)	
Investigator Signature	**Date**
Institution Name	
Institution Address	
ZOLL Circulation, Inc. **Sponsor Name**	
2000 Ringwood Avenue, San Jose CA 95131 **Sponsor Address**	
ZOLL Medical Deutschland GmbH **Sponsor Representative**	

Table of Contents

1 SYNOPSIS

Clinical Trial Title	**COOL-AMI EU PIVOTAL TRIAL: A MULTICENTER, PROSPECTIVE, RANDOMIZED-CONTROLLED TRIAL TO ASSESS THE SAFETY AND EFFECTIVENESS OF COOLING AS AN ADJUNCTIVE THERAPY TO PERCUTANEOUS INTERVENTION IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION**
Clinical Trial Sponsor	ZOLL® Circulation, Inc.
Clinical Trial Sponsor's Contact	Philippa Hill Senior Director, Clinical Affairs ZOLL Circulation, Inc. 2000 Ringwood Ave. San Jose, CA 95131 Main: +1 (408) 541-2140 Fax: +1 (408) 541-1030 PHill@zoll.com@zoll.com
Trial Number	EDC-3135
Investigational Device	**Proteus™ Intravascular Temperature Management (IVTM) System**
Trial Objective	The objective of this trial is to evaluate the safety and effectiveness of therapeutic hypothermia, using the ZOLL Proteus IVTM System, as an adjunctive therapy for patients presenting with acute anterior myocardial infarction (AMI) and undergoing percutaneous coronary intervention (PCI) in comparison with patients with acute anterior myocardial infarction and undergoing PCI only.
Trial Design	A multicenter, prospective, interventional, randomized-controlled trial. Randomization will be in a 1:1 ratio, Test Arm (PCI + Cooling) or Control Arm (PCI alone) in up to 500 randomized subjects (250 subjects in each arm).

	Roll-In Subjects: To enhance each site's ability to successfully integrate steps of the protocol and for training purposes prior to randomizing subjects in the trial, each site may enroll up to 4 Roll-In subjects in a non-randomized fashion. Roll-In subjects will be treated and followed in the same manner as subjects in the Test Arm of the protocol (PCI + Cooling). Up to a total of 280 Roll-In subjects (up to 4 per site) may be enrolled. Due to limited cMR data available in patients with inferior MI who received an adequate dose of cooling prior to revascularization, Inferior MI subjects will be allowed to be included as Roll-Ins to further evaluate inferior MI infarct size by cMR imaging. Evaluation of infarct size will be performed by cMR imaging at 4-6 days.
Primary Effectiveness Endpoint	Relative reduction of 20% in mean anterior myocardial infarct size as determined by Cardiac Magnetic Resonance (cMR) imaging at 4-6 days post infarct in the Test Arm (cooling + PCI) relative to the Control Arm (PCI only).
Primary Safety Endpoint	Per-patient rate of composite Major Adverse Cardiac Events (MACE) in randomized subjects, defined as Cardiac Death (CD), All Myocardial Infarction (All MI) and Clinically-Indicated Target Lesion Revascularization (CI-TLR) at 30 day follow-up; non-inferiority to the control.
Investigational Sites	Up to 70 clinical sites in Europe
Inclusion & Exclusion Criteria	Patients shall be screened to the following inclusion and exclusion criteria. Subjects are qualified for participation only if all Inclusion Criteria have been met and all Exclusion Criteria have been confirmed not present. **Inclusion Criteria** All Inclusion Criteria must be answered YES for subject to satisfy Inclusion Criteria: 1. The patient is ≥ 18 years of age. 2. The patient must have symptoms consistent with AMI (i.e. chest pain, arm pain, etc.) and unresponsive to nitroglycerin, with symptoms beginning greater than 30 minutes <u>but less than</u> 4.5hours prior to presentation at hospital.

	3. Qualifying Infarct location: a. **Roll-In subjects**: Evidence of Acute Anterior or Inferior MI with ST-segment elevation of ≥ 0.2 mV in two or more anterior or inferior contiguous precordial leads (V1 –V4). b. **Randomized subjects**: Evidence of Acute Anterior MI only with ST-segment elevation of ≥ 0.2 mV in two or more anterior contiguous precordial leads (V1 –V4). 4. The patient is eligible for PCI. 5. The patient is willing to provide written informed consent to participate in this clinical trial. **Exclusion Criteria** All Exclusion Criteria must be answered NO for subject to satisfy Exclusion Criteria: The patient has had a previous myocardial infarction. 1. The patient has had a previous Myocardial Infarction. 2. The patient is experiencing cardiogenic shock, systolic blood pressure [SBP] <100 mmHg, HR>100 bpm and arterial oxygen saturation (pulse oximetry) ≤92% without additional oxygen. 3. The patient is presenting with resuscitated cardiac arrest, atrial fibrillation, or Killip risk stratification class II through IV. 4. The patient has an aortic dissection or requires an immediate surgical or procedural intervention other than PCI. 5. The patient has known history of Congestive Heart Failure (CHF), hepatic failure, end-stage kidney disease or severe renal failure (clearance < 30ml/min/1.73m²). 6. The patient is febrile (temperature > 37.5 °C) or has experienced an infection with fever in the last 5 days. 7. The patient has a known previous CABG. 8. The patient has a known recent stroke within 90 days of admission. 9. Cardio-pulmonary decompensation that has occurred en route to the hospital or, in the opinion of the physician, that is imminent or likely to occur following presentation to the clinical site. 10. Contraindications to hypothermia, such as patients with known hematologic dyscrasias which affect thrombosis (e.g., cryoglobulinemia, sickle cell disease, serum cold agglutinins) or vasospastic disorders (such as Raynaud's or thromboangitis obliterans). 11. Any contraindication to cardiac MRI, or any implant in the upper body which may cause artifacts on cardiac MRI imaging.

	12. The patient has a known hypersensitivity or contraindication to aspirin, heparin, or sensitivity to contrast media, which cannot be adequately pre-medicated. 13. The patient has a known history of bleeding diathesis, coagulopathy, cryoglobulinemia, sickle cell anemia, or will refuse blood transfusions. 14. The patient has a height of <1.5 meters (4 feet 11 inches). 15. The patient has a known hypersensitivity or contraindication to buspirone hydrochloride or Pethidine (Meperidine) and/or has been treated with a monoamine oxidase inhibitor in the past 14 days. 16. Patient has a known history of severe hepatic or renal impairment, untreated hypothyroidism, Addison's disease, benign prostatic hypertrophy, or urethral stricture that in the opinion of the physician would be incompatible with Pethidine administration. 17. The patient has an Inferior Vena Cava filter in place (IVC). 18. The patient has a pre-MI life expectancy of <1 year due to underlying medical conditions or pre-existing co-morbidities. 19. The patient has a known, unresolved history of drug use or alcohol dependency, or lacks the ability to comprehend or follow instructions. 20. The patient is currently enrolled in another investigational drug or device trial. 21. The patient is apprehensive about or unwilling to undergo the required MRI imaging at follow-up, has a documented or suspected diagnosis of claustrophobia, or has Gadolinium allergy, or is in permanent Atrial Fibrillation. 22. The patient has received thrombolytic therapy en route to the hospital. 23. The patient shows clinical evidence of spontaneous reperfusion as observed symptomatically and/ or from baseline ECG findings (partial or complete ST resolution in baseline ECG prior to informed consent and randomization). 24. The patient is a vulnerable subject, for instance, a person in detention (i.e., prisoner or ward of the state). 25. The patient is a female who is known to be pregnant.
Clinical Trial Population	Adult male and female patients presenting with an acute myocardial infarction. To qualify, patients must have symptoms consistent with AMI (i.e. chest pain, arm pain, etc.) unresponsive to nitroglycerin,

	with symptom onset greater than 30 minutes but less than 4.5 hours prior to presentation at hospital and be eligible for PCI. **Randomized subjects** must have evidence of Acute Anterior MI only with ST-segment elevation of ≥ 0.2 mV in two or more anterior contiguous precordial leads (V1 –V4)will be included. **Roll-In subjects** with evidence of Acute Anterior or Inferior MI with ST-segment elevation of ≥ 0.2 mV in two or more anterior or inferior contiguous precordial leads (V1 –V4) will be included.
Intervention	Intravascular permissive hypothermia as an adjunct to PCI. Cooling will be initiated prior to PCI with infusion of up to 1 L of cold saline (4°C) (according to the guideline) and with the Proteus Console set at 32.0 degrees Celsius. Total cooling time will be 3 hours (± 15 minutes) and will be followed with active rewarming with the Proteus IVTM System to attain normothermia [36 °C (96.8°F)].
Length of Follow Up	12 months
Enrollment	Initiation of enrollment: January 2017 Completion of Enrollment: June 2019 Follow up completed: June 2020
Summary of Statistical Analysis	Primary efficacy endpoint of infarct size measured as percentage of total LV mass by cMR, the null hypothesis of equal infarct size between two arms will be tested with t-test for the study population. For the safety endpoint, comparison of per patient MACE rate for non-inferiority will be made with Fisher's exact Test.
Planned Interim Analyses	Two interim analyses are planned to be performed at approximately 50% and 75% of randomization, once subjects have completed 4-6 day cMR follow-up. At the interim stage, the trial will be stopped to reject the null hypothesis of no difference or continue enrollment.
Analysis Sets	The **Intention-to-Treat (ITT)** population will be used for primary statistical analyses and summaries for all analyses except for Safety endpoints. The ITT population includes subjects who have signed an informed consent and have been randomized to the Test Arm or the Control Arm of the trial. ITT subjects will be evaluated according to the group to which they were randomized.

	The **Per-Protocol (PP) population** includes those subjects who met inclusion and exclusion criteria, were randomized to either the Test Arm or Control Arm, received the treatment to which they were randomized, and complied substantially with the treatment timeline and steps of this protocol without major protocol violations. The **Safety Analysis Set** will be used to evaluate safety endpoints. These will be all subjects included in the study as defined by the ITT analysis set and Roll-In subjects. For the safety analysis subjects will be followed for all Adverse Events 30 days post procedure. Additionally, all subjects will be followed through 12 months post procedure for the incidence of Serious Adverse Events (SAEs), Death and Heart Failure (as assessed by NYHA and Kansas City Cardiomyopathy Questionnaire (KCCQ),).
Trial Oversight	Each participating site will dedicate one Principal Investigator to oversee the execution of the clinical trial in accordance with the protocol.

2 INTRODUCTION

Clinical investigations have shown that induction of hypothermia before reperfusion of acute coronary occlusion reduces infarct size. A pilot study from Lund University demonstrated that the induction of mild hypothermia (<35°C) in ST Elevation Myocardial Infarction (STEMI) patients prior to performing Percutaneous Coronary Intervention (PCI) can save (preserve) 38% more cardiac tissue compared with the PCI alone.[1]

Hypothermia has proven to be one of the most potent and consistent adjunctive therapies for infarct size reduction in numerous preclinical studies, when administered prior to reperfusion. This is unlike the well accepted approach for therapeutic hypothermia for cardiac arrest, where cooling is applied after reperfusion. The mechanisms leading to protection are multifactorial. However, unlike the consistent findings in preclinical studies, clinical trials (COOL -MI, ICE-IT, CHILL-MI) have failed to show a decrease in infarct size. The major reason is likely due to the difficulty in achieving adequate cooling prior to reperfusion. As shown in **Table 1** below, none of the clinical trials to date has reached target temperature prior to reperfusion, as has been done in all of the animal studies.

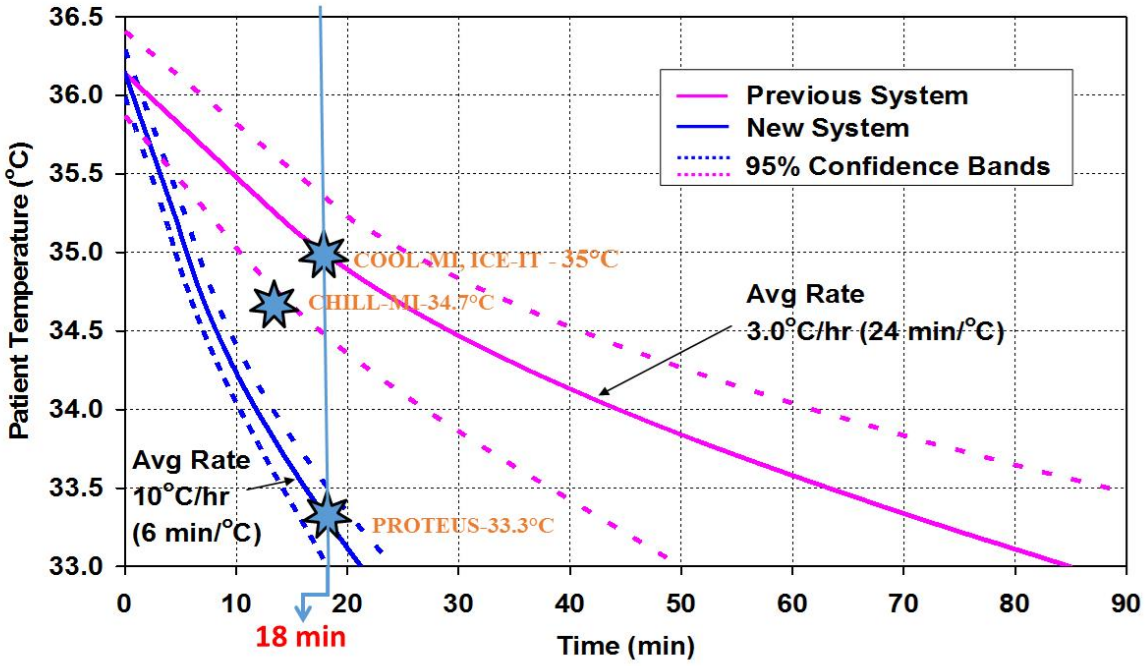
Table 1: Major Cooling Trials in STEMI.

Major Cooling Trials in STEMI					
Trial	**Sample Size**	**Target Temp (°C)**	**Actual Temp at Reperfusion (°C)**	**Temp Miss (°C)**	**Cooling Time before Reperfusion (min)**
COOL -MI	168 – Hyp 157 – Control	33.0	35.0	2.0	18
ICE-IT	105 – Hyp 99 – Control	33.0	35	2.0	16
CHILL-MI	61 – Hyp 59 – Control	33.0	34.7	1.7	13

The target temperature for each trial was 33.0 °C. The actual temperature at the time of reperfusion was 1.7-2.0 °C higher than target. This is a miss in temperature "dose" of around 50% [normal temperature is 37.0 °C, target temperature was 33.0 °C, (37.0 – 35.0) / (37.0 – 33.0) = 50%].

Post hoc analysis of these trials showed that patients with anterior MI that were cooled to less than 35°C at the time of PCI showed a significant reduction in infarct size, supporting the idea of a dose response (**See Figure 1**). Recent preclinical results (Stanford-ZOLL data) have shown that temperature at reperfusion of 32 °C is superior to 35 °C for reducing infarct size, confirming a dose response. Future clinical trials will require more powerful cooling devices, and more consistency in implementing 18 minutes of cooling before reperfusion across all study sites in order to evaluate the actual effectiveness of therapeutic hypothermia as a protection strategy.

Figure 1: Temperature at reperfusion for the Major Therapeutic Hypothermia in AMI Clinical trials.



The Proteus device has a confirmed faster cooling rate. With a duration of cooling of 18 minutes prior to reperfusion, as occurred in the COOL -MI trial, the expected temperature at reperfusion is 33.3°C with the Proteus device. This is significantly better than the 35°C achieved in COOL -MI and ICE-IT, and 34.7°C achieved in CHILL-MI. The relative effectiveness of the Proteus device for cooling, compared to the performance of the prior studies is shown in Figure 1 above. The addition of a bolus infusion of 4°C cold saline is expected to further enhance the temperature achieved at reperfusion with the Proteus System.

This Investigational Plan was developed in accordance with the requirements set forth in the Good Clinical Practices (E6)[2], ISO 14155:2011 Clinical investigation of medical devices for human subjects[3] - Good clinical practice, the Declaration of Helsinki, and the local regulatory requirements an adjunctive therapy to PCI.

3 BACKGROUND

Coronary heart disease complicated by acute myocardial infarction (AMI) remains a leading cause of death and disability worldwide. AMI most commonly occurs when a coronary artery becomes occluded by thrombus following the rupture of an atherosclerotic plaque. Factors that may affect the size of the subsequent infarction include duration of ischemia, size of ischemic territory, collateral blood flow, and myocardial metabolic rate. Long-term sequelae of AMI include ventricular remodeling, loss of ventricular function, congestive heart failure, dysrhythmias, and sudden death.

Although major gains have been made in improving the outcome of patients suffering AMI, and early myocardial reperfusion with the use of thrombolytic therapy or primary percutaneous coronary intervention (PCI) are effective, morbidity and mortality remain substantial. This may be because restoration of blood flow to the ischemic myocardium can itself induce injury through myocardial "ischemia reperfusion injury" (IRI), which can be defined as that portion of the ischemia-reperfusion continuum which is preventable by treatment initiated after restoration of blood flow.[4] It has been proposed that 50% of the final infarct size may be a function of IRI. [4]

Ischemia reperfusion injury is protean in its components, likely including free radical and reactive oxygen species, disordered vasculature, inflammatory injury, programmed cell death, and pathologic remodeling among others.[5] Unfortunately, the cascading nature of these events challenge and, in the end, may defeat the single molecular target pharmacologic model. The long list of failed IRI pharmacologic agents includes antioxidants, calcium channel blockers, anti-inflammatory drugs, sodium hydrogen exchange inhibitors, among others, has led some to question the importance of reperfusion injury in the myocardium.[6] Large infarctions still occur despite timely reperfusion, due to reperfusion injury. Numerous treatments have been studied to reduce reperfusion injury, with little success to date. [7-9]

Therapeutic hypothermia (TH) has been studied for many years as a potential therapy for ischemia and reperfusion.[10 -16] The past few years have seen development of a broad literature reporting both laboratory and clinical trials of mild post-reperfusion TH in the treatment of disease entities as diverse as acute cardiac arrest, stroke, and myocardial infarction, among others. Unlike single pharmacologic agents, TH has the potential to modify and ameliorate multiple pathways of injury.

4 INTENDED USE, SYSTEM OVERVIEW, & DEVICE DESCRIPTION

4.1 Intended Use / Indication for Use

The ZOLL® Proteus™ Intravascular Temperature Management (IVTM) System is indicated for use in adult subjects with acute myocardial infarction to induce and maintain hypothermia prior to percutaneous coronary intervention as an adjunctive therapy to reduce anterior infarct size. The Proteus IVTM System is to be used only as part of the clinical investigation.

4.2 System Overview

The Proteus Intravascular Temperature Management (IVTM) System consists of four primary components: a single-use heat exchange catheter; heat exchange cassette; a temperature probe and a reusable microprocessor-driven console. The system is designed to achieve and maintain patient temperatures within the range of 32 - 37°C. Its performance profile includes:

1. Rapid patient cooling and warming

2. Precise achievement and maintenance of a desired patient target temperature

3. Quick and simple deployment: See the catheterization lab, critical care unit, emergency department, and other hospital settings

Reference the Investigator Brochure for additional information on the Proteus IVTM System.

The Proteus IVTM System couples a heat exchange catheter with a dual microprocessor-driven controller to manage patient temperature. The Proteus IVTM System is designed to rapidly cool and warm patients, achieve and precisely maintain a target patient temperature and to be quickly and easily deployed.

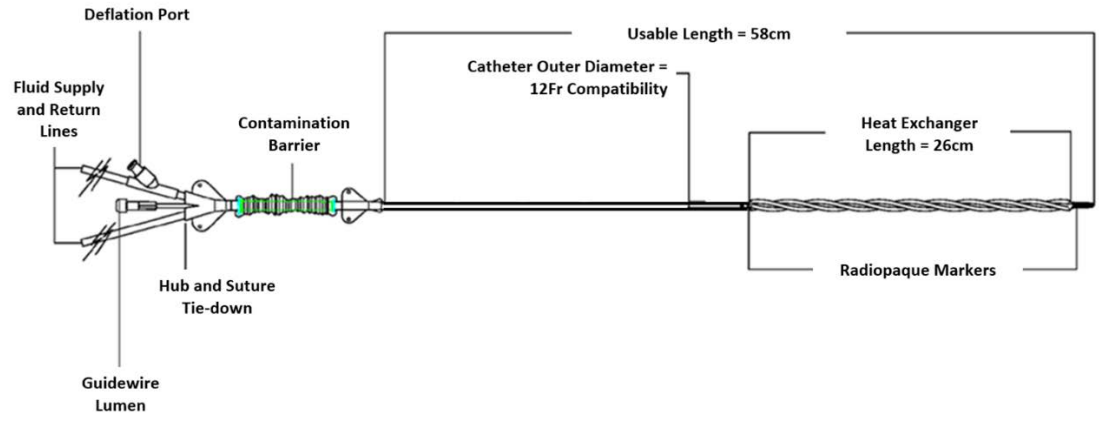
Cool or warm sterile saline is continuously circulated through the catheter, thereby cooling or warming the blood as it flows over the catheter without perfusion of fluids into the body. The saline is transported from the catheter to the cassette (mounted in the console) via extension lines. The cassette has an integral heat exchange element and a pump that couples with the console to cool or warm the saline being pumped through the closed circuit comprised of the cassette and catheter. The Proteus IVTM Console continuously monitors the patient temperature and controls the catheter temperature to cool, warm or maintain the target temperature.

4.3 Device Description

4.3.1 Proteus Catheter

The Proteus Catheter (**Figure 2**) is a single-use, heparin coated, endovascular heat exchange catheter consisting of a triple lobed, helically wound balloon mounted on the distal portion of a multi-lumen shaft. The catheter is designed for placement in the Inferior Vena Cava via the femoral vein using a 12Fr or a 14Fr hemostatic introducer sheath. The catheter has a fluid supply lumen, a fluid return lumen, a guidewire port at the proximal end of the catheter connecting to a guidewire lumen that accommodates guidewires with diameters up to 0.038". The expanded balloon portion of the catheter has an expanded diameter of 17 mm and a length of 26 cm during system operation. The catheter has a radiopaque marker mounted at the distal and proximal end of the balloon portion of the catheter. The distal end of the catheter has a non-traumatic soft tip. The fluid supply and fluid return lumens of the catheter are connected to the cassette via extension lines approximately 2 meters in length, which provide the closed heat transfer fluid circuit. The 0.038", 145-cm. stainless steel guidewire included in the package has a soft atraumatic tip.

Figure 2 Diagram of Proteus Catheter



4.3.2 Proteus Temperature Probe

The Proteus System measures a patient's core body temperature using a heparin-coated endovascular dual output probe (X-Probe) advanced through the guidewire lumen of the Proteus Catheter after the catheter is placed.

4.3.3 Proteus Cassette

The single-use Proteus Cassette consists of a heat exchange element, a pump, a pump coupling to interface with the motor drive in the console and fluid lines to interface with the heat transfer fluid circulated by the console. The cassette is designed to be removed from the portable control console allowing the catheter to remain in the patient to

facilitate moving the patient to another location where temperature management can continue using the same or another control console.

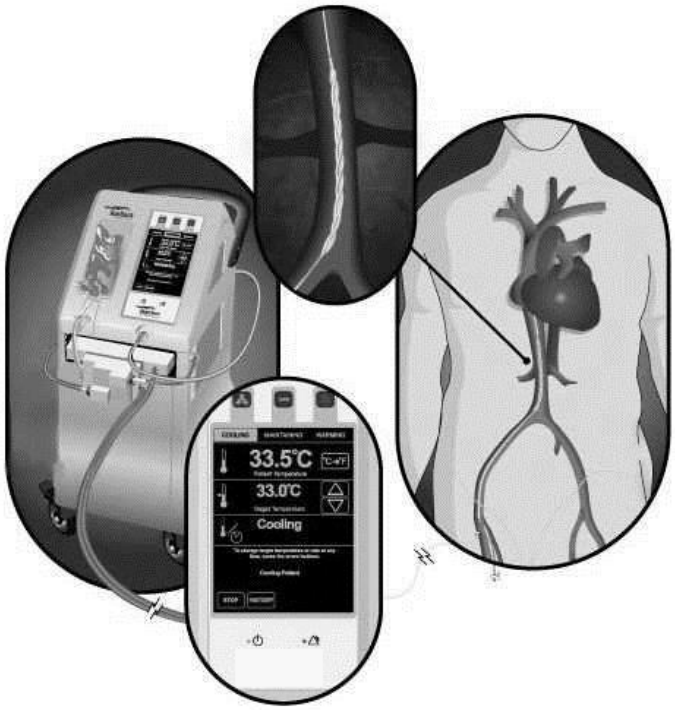
4.3.4 Proteus Console

The Proteus Console **(Figure 3)** consists of solid-state thermoelectric modules, a motor drive, dual fluid level detection systems and dual microprocessors. A dilute polypropylene glycol/water mixture (process fluid) circulates within the console to provide heat exchange with the saline heat transfer fluid loop in the cassette. This technology along with microprocessor proportional control of both the saline and the patient temperature enable the following features:

- Designated patient temperature between 32-37°C is maintained within ± 0.3°C continuous calculation and display, in all ambient lighting conditions, of patient actual temperature, target temperature, and rate of cooling/warming
- Redundant safety system to shut down and warn user of patient overheat or overcool, saline leakage, sensor failure, and electrical or mechanical malfunction
- Control console automatically performs a hardware and software diagnostic check of all functional and safety systems upon startup
- Maximum cooling and heating rates vary from patient to patient depending on the patient's cardiac output, size and weight, room temperature and humidity, and the successful implementation of the anti-shivering medication regimen, type and amount anesthesia, combined use with blankets or active heating/cooling apparatus, body cavity exposure to the environment during surgery and other factors.

Figure 3: Proteus Console

Figure 4: Proteus Catheter and Interconnection between Catheter, Temperature Probe (X-Probe), Cassette and Console.



4.3.5 Device Labeling

Written *Instructions for Use*, *Operation Manual, Quick Reference Guide, and Service Manual* for the Proteus IVTM System will be packaged with product shipped to the investigational sites. The Proteus IVTM System is to be used only as part of the clinical investigation. (See Proteus IVTM System Labeling)

5 PRIOR INVESTIGATIONS

5.1 Pre-Clinical Studies

Hypothermia has been shown to reduce metabolic demand and provide ischemic protection. Recent studies across numerous different animal models have demonstrated a strong direct relationship between myocardial temperature and infarct size.[11,12,14-18] Mild to moderate degrees of hypothermia (32-35°C) have resulted in significant reductions in infarct size when applied either before or after the onset of coronary occlusion in animal studies.

In other studies, in 1996, Duncker et al, and in 1998 Miki et al, both demonstrated a dose response relationship between myocardial temperature and infarct size using a laboratory model of AMI.[11,12]Subsequently, Dae et al in collaboration with Radiant Inc. demonstrated that therapeutic hypothermia can be induced safely and rapidly in animal models using intravascular cooling.[13] They then showed that hypothermic therapy initiated late during ischemia and continuing for several hours after reperfusion significantly improved reflow and reduced macroscopic zones of no-reflow and necrosis in this model.[15] The study showed:

- A striking reduction of myocardial infarct size. The cooled group had an infarct of 9 ± 6% of the area at risk vs. 45 ± 8% of the area at risk for controls
- Preservation of myocardial perfusion and viability in the cooled group as demonstrated by radionuclide imaging
- No evidence of apoptosis in salvaged myocardium in the cooling arm. Well-preserved cardiac output during the cooling process.

Of particular relevance, Gotberg et al reported in 2008 that hypothermia achieved before reperfusion decreased infarct size, while hypothermia initiated at the time of reperfusion prevented microvascular obstruction, but did not decrease myocardial infarct size. [16]

5.2 Human Clinical Studies

5.2.1 COOL MI Trial

The COOL MI Trial[19] was conducted from September 2001 through April 2003. A total of 421 patients were enrolled (199 Control, 193 Intervention, 29 Roll-In) at 27 investigational sites in the US, Germany and Australia. The primary analysis population included 357 patients (180 Control, 177 Intervention) who received the assigned treatment. The COOL MI Trial evaluated the safety and effectiveness of cooling as an adjunctive therapy to percutaneous coronary intervention (PCI) in patients with acute myocardial infarction. **Table 2** below displays enrollment characteristics.

Table 2: COOL MI Trial Enrollment Characteristics

	Control (N=180)	Intervention (N=177)	p-value
Anterior Myocardial Infarction	77 (44%)	74 (42%)	0.77
Inferior Myocardial Infarction	99 (56%)	103 (58%)	0.77
Failed thrombolytic therapy prior to enrollment	23 (12.8%)	18 (10.3%)	0.67
Time in minutes – median (interquartile range)			
From symptom onset to hospital presentation	123 (69 – 201)	114 (60 – 190)	0.08
From hospital presentation to PCI	88 (61 – 114)	104 (80 – 134)	<0.0001

5.2.1.1 Procedural and Angiographic Results COOL MI Trial

The Trial demonstrated that endovascular cooling using the Radiant Medical's (now ZOLL's) Reprieve System ™ in the setting of myocardial infarction was safe, well tolerated, and readily integrated into the existing treatment pathway. While the primary effectiveness endpoint of the study was not achieved, the data provided a strong signal indicating that when patients were sufficiently cooled prior to reperfusion, myocardial damage was reduced.[19]

The Control and Intervention groups were well matched in terms of culprit vessels, percutaneous coronary intervention (PCI) procedures and treatment success. As expected, cooling did not affect the angiographic success of PCI procedures. Of the 357 patients who underwent primary PCI, the majority were treated with stent implantation and a platelet glycoprotein receptor inhibitor. Approximately 20% of study subjects were determined to have Thrombolysis in Myocardial Infarction (TIMI 3) flow prior to PCI. TIMI Grade Flow is a scoring system from 0-3 referring to levels of coronary blood flow assessed during percutaneous coronary angioplasty:

- TIMI 0 flow (no perfusion) refers to the absence of any antegrade flow beyond a coronary occlusion.
- TIMI 1 flow (penetration without perfusion) is faint antegrade coronary flow beyond the occlusion, with incomplete filling of the distal coronary bed.
- TIMI 2 flow (partial reperfusion) is delayed or sluggish antegrade flow with complete filling of the distal territory.
- TIMI 3 flow (complete perfusion) is normal flow which fills the distal coronary bed completely

After PCI, TIMI 3 flow was achieved in approximately 92% of patients. Only about 30% of patients had TIMI myocardial perfusion grade 3; however the percentage was similar in both treatment groups and is consistent with literature reports of myocardial perfusion. Procedural and angiographic data are presented in **Table 3** below.

Table 3: COOL MI Trial - Procedural and Angiographic Data

	Control (N=180)	Intervention (N=177)	p-value
Infarct related artery, Stent implantation, Glycoprotein & Stenosis Diameter			
Left anterior descending coronary artery	70 (39%)	69 (39%)	0.91
Circumflex artery	13 (7%)	14 (8%)	0.87
Right coronary artery	77 (43%)	74 (42%)	0.93
Stent implanted	153 (92%)	157 (94%)	0.59
Glycoprotein IIb/IIIa receptor inhibitor	140 (78%)	142 (80%)	0.74
Initial diameter stenosis (mean ± std dev)	92 ± 14%	92 ± 12%	0.93
Initial TIMI flow			
Grade 0/1	126 (71%)	122 (69%)	0.77
Grade 2	14 (8%)	21 (12%)	0.28
Grade 3	38 (21%)	34 (19%)	0.74
Final diameter stenosis	7 ± 9%	8 ± 10%	1.00
Final TIMI* flow			
Grade 0/1	2 (1%)	5 (3%)	0.33
Grade 2	7 (4%)	12 (7%)	0.31
Grade 3	170 (95%)	160 (90%)	0.11
Final myocardial perfusion grade			
Grade 0/1	63 (43%)	76 (53%)	0.11
Grade 2	35 (24%)	26 (18%)	0.27
Grade 3	49 (33%)	41 (29%)	0.54

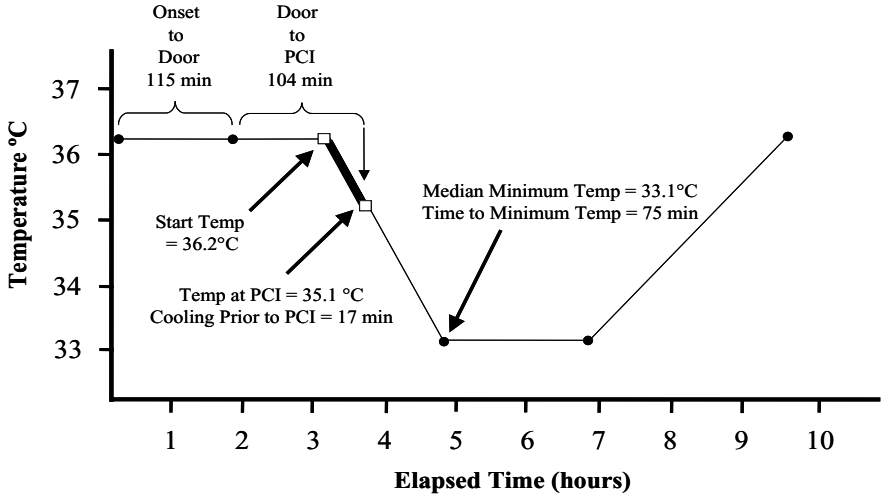
*Thrombolysis in Myocardial Infarction

5.2.1.2 COOL MI Trial Results

Of the 177 Intervention patients, 11 (6.2%) patients had the Reprieve Catheter placed in the emergency room (ER), one (0.6%) patient had the catheter placed in the cath lab holding area, and 165 (93.2%) patients had the catheter placed in the cath lab. Overall, patients in the Intervention group received a median of 17 minutes (interquartile range (IQR): 10-27) of cooling prior to PCI. During that time, patient temperature was decreased from a median of 36.2°C (IQR: 35.8-36.5) at the initiation of cooling to 35.1°C

(IQR: 34.5-35.6) at the time of PCI (**Figure 1**). The median of the minimum temperature reached by each patient was 33.1°C (IQR: 33.0-33.4), which was achieved in 75 minutes (IQR: 50-108). Target patient temperature was set at a 33°C for 3 hours post-PCI. Patients were then re-warmed at 1°C/hr until Investigator-determined normothermia was reached [median=36.5 (IQR: 36.2-36.8]). **Figure 5** below shows patient temperature over time with cooling and time to PCI. The goal to reach target temperature of 33°C at PCI was not achieved in the trial, due to the inadequate cooling power of the Reprieve System. As noted above, target temperature of 33°C was reached after 75 minutes of cooling, long after PCI had occurred.

Figure 5: Median Temperature and Elapsed Times for Intervention Patients



5.2.1.3 COOL MI Trial Tolerability of Cooling

Shivering was managed according to the shivering suppression guidelines recommended for this study by Dr. Daniel Sessler, Chairman of the Department of Anesthesiology at the University of Louisville. The recommended baseline combination of Pethidine, buspirone and skin warming using a forced-air blanket could be supplemented incrementally in the event of shivering or patient discomfort, by additional Pethidine, or by slightly increasing the target temperature. If these steps were unsuccessful, patients could be actively rewarmed to normothermia.

This protocol proved to be quite effective at maintaining patient comfort. Intervention patients received an average of 56 mg of oral buspirone and an average of 267 mg of intravenous Pethidine over the course of the cooling procedure. Of 177 patients in the treatment group, only one patient (0.6%) required premature warming due to intolerability of cooling. Nine patients (5.1%) required a slight increase in target temperature (0.2°C – 0.5°C) to maintain patient comfort. Ninety-eight patients (55.7%) required supplementary

dosing of Pethidine, but 60 of these 98 patients (61.2%) had not received the recommended loading dose of the anti-shivering drugs.

COOL MI Trial Safety Results: The primary safety endpoint of the COOL MI study was the incidence, through 30 days, of Major Adverse Cardiac Events (MACE), defined as the composite of death, recurrent myocardial infarction of the target vessel and the need for urgent revascularization of the target vessel. As shown in **Table 4** below, there was no statistical difference in the incidence of MACE in the Intervention group as compared to the Control group. All MACE were adjudicated by an independent Clinical Events Committee and none were attributed to cooling or use of the Reprieve System. **Table 4** below demonstrates the results of the study with regard to the incidence of Major Adverse Cardiac Events.

Table 4: COOL MI Trial Incidence of MACE

Events through 30 days	**Control (N=180)**	**Intervention (N=177)**	**p-value**
MACE	**7 (3.9%)**	**11 (6.2%)**	**0.45**
Death	4 (2.2%)	6 (3.4%)	0.71
Recurrent MI	3 (1.7%)	1 (0.6%)	0.63
Urgent Revascularization	0 (0%)	4 (2.3%)	0.12

These MACE rates observed in COOL MI compare favorably with those reported for similar patients in recent AMI trials, such as ADMIRAL, CADILLAC, DANAMI and RAPID MI-ICE (**Table 5**).

Table 5 Incidence of MACE for Comparable Patients in Recent AMI Trials

Trial	**Death**	**Reinfarction**	**Revascularization**
COOL MI (Treatment Group) (n=177)	3.4%	0.6%	2.3%
ADMIRAL (n=149)[17]	3.4%	1.3%	4.7%
CADILLAC (n=524)[18]	2.7%	0.8%	1.6%
DANAMI-2 (n=790)[19]	6.6%	1.6%	NA
RAPID MI-ICE (n=20)[1]	0%	0%	0%

5.2.1.4 COOL MI Trial Adverse Events Related to Cooling

Potential adverse events related to cooling (e.g., arrhythmia or hemodynamic complications) and to placement and/or use of the Reprieve Catheter (e.g., vascular or thrombogenic complications) were also evaluated as a secondary endpoint. The incidence

of these types of events is presented. It is important to note that these complications are also risks of myocardial infarction and coronary intervention themselves. **Table 6** below reports the incidence of non-MACE complications.

Table 6: Incidence of Other Complications

Events through 30 days	Control (N=180)	Intervention (N=177)	p-value
Bradyarrhythmia	41 (22.8%)	46 (26.0%)	0.56
Ventricular Tachycardia/Fibrillation	36 (20.0%)	31 (17.5%)	0.64
Cardiogenic Shock	11 (6.1%)	22 (12.4%)	0.06
Pulmonary Edema	3 (1.7%)	6 (3.4%)	0.49
Vascular Complications	15 (8.3%)	15 (8.5%)	0.90
Retroperitoneal bleed	2 (1.1%)	1 (0.6%)	0.95
Hematoma >6cm	12 (6.7%)	13 (7.3%)	0.99
Pseudoaneurysm	1 (0.6%)	3 (1.7%)	0.63
AV fistula	1 (0.6%)	0 (0%)	0.95
Bleeding Requiring Transfusion	14 (7.8%)	20 (11.3%)	0.34
Deep Venous Thrombosis	0	3 (1.7%)	0.24
Pulmonary Embolism	3 (1.7%)	0	0.24
Stroke	1 (0.6%)	0	0.95

Arrhythmias are a known risk of moderate to severe hypothermia. In the COOL MI trial, with its mild hypothermia target temperature, arrhythmias were not more common and appeared to be primarily related to ischemia and/or the coronary intervention. Cardiogenic shock requiring treatment with an intra-aortic balloon pump trended toward a higher incidence in the hypothermic group. However, the majority of shock cases appeared to be more related to complicated MIs and/or complex interventions than to cooling. Other potential contributory factors (e.g., age, weight, Pethidine dose) were compared between shock and stable patients; however, no causal relationships were apparent. The majority of the vascular complications reported in the Intervention group were related to the arterial access site for the PCI procedure rather than the venous access site for the cooling catheter. Three cases of deep venous thrombosis (DVT) were reported in the Intervention group.

5.2.1.5 COOL MI Trial Effectiveness Results

The primary effectiveness endpoint in the COOL MI study was infarct size, measured using SPECT imaging at 30 days. Overall, there was no observed difference in infarct size (%LV) between study groups (**Table 7**). The secondary effectiveness endpoints of LV ejection fraction, CK-MB release, and ST-segment resolution, likewise did not demonstrate a difference between the Intervention and Control groups.

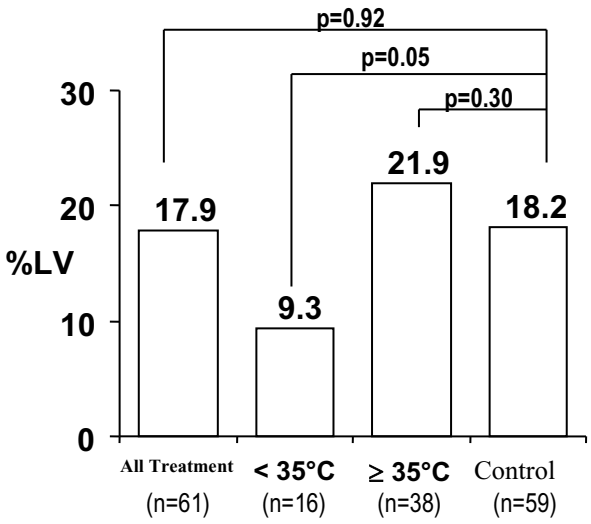
Table 7: COOL MI Results

	Control	Intervention	p-value
% LV Infarct Size (N) mean ± std dev median	157 13.8 ± 15.1 10	168 14.1 ± 14.3 10	 0.83
LV Ejection Fraction (N) mean ± std dev median	104 55.2 ± 11.4 54	115 53.0 ± 12.0 53	 0.17
Peak CK-MB (N) mean ± std dev median	167 42.8 ± 48.1 33.9	168 49.1 ± 50.7 33.6	 0.25
ST-segment resolution - 90 min. post-PCI (N) < 30% 30 - 69% ≥ 70%	90 11.1% 27.8% 53.3%	82 20.7% 35.4% 39.0%	 0.13 0.36 0.09
ST-segment resolution - 180 min. post-PCI (N) < 30% 30 - 69% ≥ 70%	79 10.1% 20.3% 60.8%	80 16.3% 27.5% 51.3%	 0.36 0.38 0.30

In addition, no statistically significant differences were demonstrated when the Intervention and Control patients were compared based on the following stratifications: infarct location, time from onset of symptoms to PCI, prior MI, or TIMI flow prior to PCI. However, subsequent analysis revealed a strong relationship between final infarct size and patient temperature at the time of reperfusion.

The mean temperature at the time of reperfusion, or more specifically, at the time of first balloon inflation, was 35.1°C. As shown in **Figure 6**, in the population of patients with anterior myocardial infarction, those patients who had a temperature <35°C at the time of reperfusion had a statistically significant reduction in final infarct size as compared to both the control group (9.3% vs. 18.2%, p=0.05) and those with a temperature ≥35°C (9.3% vs. 21.9%, p=0.01).

Figure 6: Mean Infarct Sizes (%LV) of Patients with Anterior Infarction



Subject groups:

i) All Intervention patients regardless of temperature at PCI

ii) Intervention patients cooled to < 35°C at PCI

iii) Intervention patients ≥ 35°C at PCI

iv) Control patients

This effect has a strong basis in physiology and was consistent across other clinical measures, i.e., there was a trend toward decreased CK-MB release and increased LV Ejection Fraction in the cooled patients. This effect is not attributable to differences in baseline clinical or angiographic variables. In fact, those patients with a temperature <35°C were more likely to have occlusion of the proximal versus mid left anterior descending coronary artery and a longer time to reperfusion. These factors would be expected to increase infarct size in this group, but the observed reduction in infarct size appears to be the result of cooling.

5.2.2 COOL MI II Trial

Because of the encouraging results in patients with anterior AMI's in whom hypothermia had been achieved at the time of PCI, COOL MI II was initiated. Additionally, COOL MI II Trial was intended to verify the feasibility of initiating cooling earlier in the treatment pathway (e.g., in the emergency department). Only a fraction of the anticipated sample size were enrolled before the trial was ended early because the sponsor became financially insolvent after only41 patients were enrolled. The study data were submitted by the sites to a Data Management CRO. As a result, the final report is not currently available because the data was not released to ZOLL by the Data Management CRO upon ZOLL acquisition of Radiant Medical.

In COOL MI II, all cooling was initiated in the Cath Lab even though the focus was on earlier cooling. Since earlier initiation of cooling was not accomplished, reaching the goal of a core temperature of 35° C before PCI was dependent on the more powerful GTO System. This was accomplished in 26 of the 27 patients without the intentional delay of PCI. Pivotal data for 23 patients were available and the mean time to reach 35°C was 6.1

minutes (± 3.0), 34°C was 14.5 minutes (± 7.9) and 33°C was 31.3 minutes (± 29.9). Data showed 15 of the patients were cooled to 32°C; the mean time was 36.1 minutes (± 14.0).

Efforts to initiate cooling as early as possible resulted in a median of 39 minutes of cooling time prior to PCI, a significant improvement over the median of 18 minutes of cooling time achieved in the previous study. In addition, the median door-to-balloon time was 106 minutes for these COOL MI II patients, compared to a median of 104 minutes for Test patients in the previous study, indicating that PCI was not delayed by the introduction of cooling. By focusing on cooling earlier in the treatment pathway, additional cooling time can be achieved without significant adverse impact on time to reperfusion.

5.2.2.1 COOL MI II Trial Adverse Events

As with COOL MI, the primary safety endpoint of the COOL MI II study was the incidence, through 30 days, of MACE. Shown below are the adverse events in the COOL MI II trial in the intent to treat (ITT) population. **Table 8** combines the Feasibility and Pilot hypothermia groups for a total of 41 patients (12 Feasibility and 29 Pivotal).

Table 8*:* Incidence of MACE and Other Complications

Events through 30 Days	**Normothermia**	**Hypothermia**
Enrollment	*10*	*41*
UADE	0	0
Cardiac		
Death	0	1 (2.4%)
Repeat MI	0	1 (2.4%)
Repeat PCI	1 (10%)	3 (7.3%)
CABG	0	2 (4.9%)
Hypotension / Shock	1 (10%)	6 (14.6%)
CHF	0	2 (4.9%)
Pericardial Effusion	0	1 (2.4%)
Pericarditis	0	1 (2.4%)
HTN	0	1 (2.4%)
Arrhythmias		
Ventricular Fibrillation	0	4 (9.8%)
Vent. Tachycardia	1 (10%)	7 (17.1%)
Frequent PACs	1 (10%)	0
SVT	0	1 (2.4%)
Atrial Fibrillation	0	11 (26.8%)
Vascular Events		
Bleeding requiring transfusion	0	3 (7.3%)
Thrombocytopenia	0	2 (4.9%)
Anemia	0	2 (4.9%)
Hematoma > 6cm	0	2 (4.9%)
DVT	0	1 (2.4%)
Local Tissue Trauma	0	1 (2.4%)
Epistaxis	1 (10%)	0
Hemoptysis	0	1 (2.4%)
Stroke	0	0
Respiratory Events		
Pulmonary Edema	0	8 (19.5%)
Pulmonary Embolism	0	0
Hypoxia	0	1 (2.4%)
Respiratory Failure	0	1 (2.4%)
Plural Effusion	0	3 (7.3%)
Increased Pulmonary HTN	1 (10%)	0
Pneumonia	1 (10%)	0

Renal		
Renal requiring Treatment	1 (10%)	2 (4.9%)
Hemodialysis	0	0
UTI	0	2 (4.9%)
Hematuria	1 (10%)	0
Other		
Nausea / Vomiting	1 (10%)	15 (36.6%)
Systemic Infection	0	3 (7.3%)
Fever	0	3 (7.3%)
Muscular Pain	1 (10%)	3 (7.3%)
Rhabdomyolysis	1 (10%)	0
Mental Status Changes	0	2 (4.9%)
Hypokalemia	0	1 (2.4%)
Vaginal Infection	0	1 (2.4%)

5.2.3 COOL RCN Trial

The COOL RCN (Radio-Contrast nephropathy) trial was undertaken to evaluate whether endovascular cooling provides more effective protection for patients at high risk of experiencing RCN. The trial was designed as an international, multicenter, 1:1 randomized controlled trial of up to 400 subjects at up to 35 investigational sites. Subjects with a calculated Creatinine clearance of 20 – 50 mL/min and scheduled for a diagnostic or interventional catheterization procedure were enrolled. The trial utilized Radiant Medical's Reprieve System. The study was commenced in March 2006 and was terminated after enrolling only 136 subjects due to the financial insolvency of Radiant Medical.

Table 9: COOL RCN Trial*:* Adverse Events Incidence of Complications In-Hospital

	Normothermia	**Hypothermia**	**P Value**
Enrollment	*70*	*58*	
Nausea/Vomiting	6 / 70 (8.6%)	26 / 58 (44.8%)	<0.01
Bradycardia	2 / 70 (2.9%)	7 / 58 (12.1%)	0.04
Bleeding Requiring Transfusion	7 / 70 (10.0%)	1 / 58 (1.7%)	0.05
Atrial Fibrillation	2 / 70 (2.9%)	3 / 58 (5.2%)	0.5
CABG	4 / 70 (5.7%)	1 / 58 (1.7%)	0.25
Pulmonary Edema	4 / 70 (5.7%)	1 / 58 (1.7%)	0.25

	Normothermia	Hypothermia	P Value
Renal Complication	2 / 70 (2.9%)	3 / 58 (5.2%)	0.5
Acute Renal Failure	2 / 70 (2.9%)	2 / 58 (3.4%)	0.85
Elevated Serum Creatinine	0 / 70 (0%)	1 / 58 (1.7%)	--
Hemodialysis	2 / 70 (2.9%)	0 / 58 (0%)	--
Urinary Tract Infection	3 / 70 (0.4%)	1 / 58 (1.7%)	0.41
Hypotension/Shock	1 / 70 (1.4%)	3 / 58 (5.2%)	0.22
Hematoma >6cm	0 / 70 (0%)	3 / 58 (5.2%)	--
SVT	0 / 70 (0%)	2 / 58 (3.4%)	--
MI	0 / 70 (0%)	1 / 58 (1.7%)	--
Ventricular Tachycardia	1 / 70 (1.4%)	1 / 58 (1.7%)	0.89
Death	0 / 70 (0%)	1 / 58 (1.7%)	--
Repeat PCI	1 / 70 (1.4%)	1 / 58 (1.7%)	0.89
Stroke	0 / 70 (0%)	1 / 58 (1.7%)	--

Table 10: COOL RCN Trial: Incidence of Complications to 30 Days

	Normothermia	Hypothermia	P Value
Enrollment	*70*	*58*	
Renal	7	2	0.15
Acute Renal Failure	5	1	0.15
Renal Stent	2	0	--
Kidney Infection	0	1	--
Cardiac	8	14	0.1
MI	1	1	0.89
CABG	2	3	0.5
PCI	1	3	0.22

	Normothermia	Hypothermia	P Value
PCI or CABG	3	6	0.18
Death - Cardiac	1	2	0.45
Shock	0	3	--
CHF	2	1	0.67
Angina	1	0	--
Hypertension	0	1	--
Arrhythmia	3	3	0.81
Atrial Fibrillation	2	1	0.67
Bradycardia	0	2	--
SVT	1	0	--
Ventricular Fibrillation	0	0	--
Non-Cardiac	3	3	0.81
Stroke	1	0	--
Bleed/Transfusion	2	3	0.5
Dialysis	0	0	--
Vascular Complications Requiring Surgery	0	0	--
Rehospitalization	13	13	0.59
Other	9	12	0.23
Anasarca	1		--
Fatigue	1		--
Ischemic Bowel	1	1	0.89
Hypoglycemia	1		--
Lesion Excision	1		--
Anemia	1		--
Hiatal Hernia	1	1	0.89
Pulmonary Edema	1		--
Knee Injury	1		--
Rash		1	--
Debridement of Sternal Wound		1	--
Leg Weakness		1	--
Nausea/Vomiting		2	--
Dehydration		1	--
Acute Respiratory Failure		1	--
Metabolic Acidosis		1	--
Back Pain		1	--
Systemic Infection		1	--

5.2.3.1 Unanticipated Adverse Events

(i) COOL MI Trial – Unanticipated Adverse Events

There was one Unanticipated Adverse Device Effect (UADE) in the COOL MI Trial; A patient experienced nasopharyngeal trauma and bleeding potentially caused by the nasoesophageal temperature probe used as part of the Reprieve System. This resulted in a modification to the Informed Consent Form to explain the risk of nasal trauma and/or bleeding due to the nasoesophageal probe.

(ii) COOL MI II Trial – Unanticipated Adverse Events

There were no UADE's in the COOL MI II Trial.

(iii) COOL RCN Trial – Unanticipated Adverse Events

There was one UADE in the COOL-RCN Trial. A 73 year old male with chronic renal insufficiency and a history of aortobifemoral bypass scheduled for cardiac catheterization. The patient was randomized to the Hypothermia arm. The Reprieve catheter was placed via the left femoral vein. The angiogram and stenting procedures were performed via right radial arterial access. After approximately 1 hour of cooling, the patient complained that his feet were itching and it was noted that the patient's left foot and leg were cyanotic up to mid-thigh, with no left DP pulse, and the right foot was slightly discolored. He was subsequently rewarmed at the maximum rate for approximately 40 minutes. It was observed that the cyanosis lightened as the patient rewarmed and was apparently resolved with no further sequelae after discontinuation of treatment with the Reprieve catheter, indicating that cooling with the device contributed to the reduced peripheral circulation. The already compromised peripheral vascular circulation is suspected to have been exacerbated by hypothermia induced vasoconstriction. It is known that hypothermia induces superficial vasoconstriction, but this degree of cyanosis had not been observed with previous use of the device. Additionally, after the patient had received Pethidine and versed as part of the anti-shivering protocol, his respiration became depressed, requiring assisted ventilation, Romazicon and Narcan. It is possible that this transient hypoxic event may have also contributed to the cyanosis.

Lower extremity cyanosis in the presence of peripheral vascular insufficiency had not been identified in the protocol or informed consent document as a potential risk of mild hypothermia or use of the Reprieve catheter. The resolution of the cyanosis upon rewarming and removal of the catheter indicated that these may have contributed to the event. The risk section of the protocol and informed consent were subsequently revised.

5.2.4 ICE- IT Trial

The Intravascular Cooling Adjunctive to Percutaneous Coronary Intervention for Acute Myocardial Infarction Trial (ICE-IT) [23]randomized 228 patients presenting with an acute

MI within 6 hours of symptom onset to endovascular cooling concomitant with PCI versus routine PCI. The primary endpoint of infarct size at 30 days as measured by SPECT imaging was similar between the 2 groups (10% for the hypothermia group versus 13% for the control group, p = 0.14). Like the COOL MI trial, ICE-IT was also an overall negative trial. But while TH did not demonstrate any significant decrease in infarct size overall, a trend towards benefit was again observed on post-hoc analysis of the subgroup with anterior infarction who were sufficiently cooled to a temperature of < 35°C at the time of revascularization (infarct size of 12.9% of the left ventricle in the TH population compared to 22.7% in the control group, p = 0.09).[23]

5.2.5 RAPID-MI ICE Trial

Recently, Lund University presented a preliminary report of their RAPID-MI ICE Trial.[1] This trial enrolled 20 patients presenting with acute myocardial infarction, and 10 patients each were randomized to TH by intravascular cooling or a control group. Cooling was accomplished with a combination of 2L of cold saline infusion and the Phillips InnerCool catheter-based cooling system. The endpoint was infarct size normalized to myocardium at risk assessed by cardiac magnetic resonance using T2 weighted imaging and late gadolinium enhancement. Although the sample size is relatively small, the trial produced a number of potentially important results:

- Core body temperature less than for 35°C was achievable before reperfusion without significant delay in the door to balloon time.
- Infarct size normalized to myocardium at risk was reduced by a remarkable 38% in patients receiving hypothermia.
- There were also significant decreases in peak and cumulative Troponin I or T in the hypothermia group.

5.2.6 CHILL-MI Trial

Lund University recently reported the results of the CHILL-MI trial[37], which was a multi-center study of 120 patients with STEMI (< 6 hours) planned to undergo PCI who were randomized to hypothermia induced by rapid infusion of 600 – 2000 ml of cold saline and endovascular cooling, or standard of care. Hypothermia was initiated before PCI and continued for 1 hour after reperfusion. The primary endpoint was infarct size as a percentage of the myocardium at risk (IS/MaR), assessed by cardiac MRI at 4±2 days. The goal to reach target temperature of 33°C at reperfusion was also not achieved in the CHILL-MI trial, due to the inadequate cooling power of the cooling device. Patients randomized to cooling achieved a core body temperature at reperfusion of 34.7°C with a 9 minute longer door-to-balloon time. Hypothermia induced by cold saline infusion and endovascular cooling was feasible and safe, however, there was no significant difference in IS/MaR between the groups. Exploratory analysis of early anterior infarctions (0-4 hrs) showed a significant reduction in IS/AAR of 33% ($p<0.05$). Further, the incidence of

heart failure was lower with hypothermia at 45 days (3% vs 14%, p<0.05). This trial, as the others cited above, shows potential efficacy of cooling in patients with anterior STEMI, supporting further research for confirmation.

5.2.7 Induction of Mild Systemic Hypothermia With Endovascular Cooling During Primary Percutaneous Coronary Intervention for Acute Myocardial Infarction

This multi-center study included 42 patients with acute myocardial infarction (AMI) (onset less than 6hrs) and evaluated the safety and feasibility of endovascular cooling during primary PCI for AMI. [39] Subjects were randomized to PCI with or without endovascular cooling (target core temperature 33°C). Cooling was maintained for 3 h after reperfusion. Skin warming, oral buspirone, and intravenous meperidine were used to reduce the shivering threshold. The primary end point was major adverse cardiac events at 30 days. Infarct size at 30 days was measured using SPECT imaging. All patients successfully cooled did achieved a core temperature below 34°C (mean target temp 33.2 ± 0.9°C). MACE events occurred in 0% vs. 10% (p = NS) of treated versus control patients. The median infarct size was not significantly smaller in patients who received cooling compared with the control group (2% vs. 8% of the left ventricle, p = 0.80).

5.2.8 VELOCITY Trial

The VELOCITY trial[38] randomized 54 STEMI patients at 7 centers in the United States and Canada to emergent PCI with (n = 28) or without (n = 26) hypothermia induced by the Velomedix Automated Peritoneal Lavage System (Velomedix; Menlo Park, CA) between January 2013 and January 2014. Baseline characteristics were similar between the 2 groups, and 46.3% of all infarcts were anterior.

Hypothermia (core temperature at or below 34.9°C) was achieved in 96.3% of patients and PCI was performed in all but 1 patient in each treatment group. Median door-to-balloon time was shorter in the control vs hypothermia group (47 vs 62 minutes; *P* = .007). Among the 46 PCI patients who underwent MRI 3 to 5 days post procedure, the median myocardial infarct size was similar in the control vs hypothermia group (16.1% vs 17.2% of LV mass; *P* = .54).

VELOCITY Investigators observed that prolonged door-to-balloon time in the hypothermia group may have attenuated the effect of hypothermia on infarct size though it is unlikely to have been totally responsible for absence of effect as DTB times were short in both groups and within the range wherein further reductions in mortality may not be realized.

At 30-day follow-up, no patients in the control group had a primary composite safety endpoint event, compared with 6 (21.4%) of the patients who underwent hypothermia (P = .01). Further details in Section 5.2.8.1.

In conclusion, the VELOCITY study found that controlled systemic hypothermia through automated peritoneal lavage may be safely and rapidly established in patients with evolving STEMI undergoing primary PCI at the expense of a modest increase in door-to-balloon time. In the VELOCITY randomized trial, peritoneal hypothermia was associated with an increased rate of adverse events (including stent thrombosis) without reducing infarct size. Adequately powered randomized trials (likely limited to patients with anterior MI) are needed to assess the effect of rapidly induced hypothermia on myocardial salvage and clinical outcomes after primary PCI.

5.2.8.1 VELOCITY Trial Adverse Events at 30 Days

At 30-day follow-up, no patients in the control group had a primary composite safety endpoint event (death, reinfarction, ischemia-driven TLR, major bleeding, sepsis, pneumonia, peritonitis, severe arrhythmias, or renal failure), compared with 6 (21.4%) of the patients who underwent hypothermia (P = .01). Four patients (14.3%) experienced MACE (cardiac death, reinfarction, or ischemia-driven TVR), and 3 (11.0%)—all in the hypothermia arm—developed definite stent thrombosis.

Table 11: VELOCITY Trial Clinical Event Rates Within 30 Days

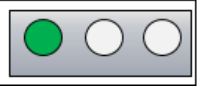
	Control (N=26)	Hypothermia (N=28)	*P* Value
Primary composite safety end point	0% (0)	21.4% (6)	0.01
Cardiac death	0% (0)	3.6% (1)	0.34
Noncardiac death	0% (0)	0% (0)	…
Reinfarction	0% (0)	3.6% (1)	0.34
Ischemia-driven target vessel revascularization	0% (0)	11.0% (3)	0.09
Major bleeding	0% (0)	3.6% (1)	0.34
Ventricular tachycardia or fibrillation	0% (0)	3.6% (1)	0.34
Sepsis	0% (0)	3.6% (1)	0.34
Pneumonia	0% (0)	0% (0)	…
Renal failure	0% (0)	0% (0)	…
Peritonitis	0% (0)	0% (0)	…
Major adverse cardiac events	0% (0)	14.3% (4)	0.047
Stent thrombosis	0% (0)	11.0% (3)	0.09
Acute (≤24 h)	0% (0)	7.1% (2)	0.17
Subacute (1–30 days)	0% (0)	3.6% (1)	0.34
Definite	0% (0)	11.0% (3)	0.09
Probable	0% (0)	0% (0)	…

Data are expressed as Kaplan–Meier estimates, % (n). *P* values are from the log-rank test.

5.2.9 EU AMI Case Series

ZOLL is currently enrolling patients in the COOL-AMI EU Case Series Trials to assess the ability to integrate hypothermia into the current pathway for patients receiving PCI for ST elevation MI. To date, 308 patients have been enrolled at 36 sites in the EU. Both anterior and non-anterior STEMI patients have been enrolled, and cooling is performed using the ZOLL Thermogard XP (TGXP) System or Proteus IVTM system. A series of six standards has been developed and monitored to enable consistency in the execution of the protocol. The standards include delivery of the antishivering regimen correctly, delivery of 1 L of iced saline before PCI, and at least 18 minutes of cooling delivered prior to wire crossing the lesion. Feedback in the form of a report card (**Figure 7**) is provided to the site after each case as indicated in the following diagram:

Figure 7: Report Card Standards

Standards	Measured	Expected	
1. Anti-shivering Regimen Delivered prior to Iced Saline Delivery	C-B-P-S	Per-protocol C-B-P-S	
2. 1 Liter Iced Saline delivered with pressure bag prior to PCI	1 Liter	1 Liter	
3. At least 18 minutes of cooling delivered prior to PCI	18 min	18 min	
4. Door-to-Balloon Time	59 min	< 90min	
5. Ischemic Time	3 hrs. 9 min	< 6 hrs.	
6. DAPT Agent Administered	Yes	Pre-PCI	

These six standards are consistently achieved at all sites. The 18 minute duration of cooling matches the average duration of cooling in the previous EU COOL AMI trial. The ability to deliver 18 minutes of cooling prior to PCI is consistently achieved in the recent EU Case Series, where the door to balloon (DTB) times, at all sites, were less than 60 minutes (ranging from 38 minutes to 58 minutes). This is far less than the maximum door to balloon time of 90 minutes recommended by the current guidelines for PCI, 2011 ACCF/AHA/SCAI PCI Guideline[24,50]). The experience of one of the sites has been published[26], and notes that the average DTB time for the first 11 patients enrolled in the trial was 38 minutes, compared to a mean DTB time of 37 minutes for all patients presenting with STEMI without cooling. In view of the validation that implementation of hypothermia in the treatment pathway for PCI of STEMI patients is feasible, ZOLL has also conducted the COOL-AMI EU PILOT Trial, following the same standards of implementation, with cooling done by the more powerful Proteus device. The goal is to maximize the dose of cooling prior to PCI.

5.2.10 COOL-AMI EU PILOT Trial

ZOLL has completed enrollment in the COOL-AMI EU PILOT Trial that evaluated the retention of subjects after integrating therapeutic hypothermia using the ZOLL Proteus IVTM System into existing STEMI treatment protocols for subjects who presented with acute anterior myocardial infarction. 50 subjects were randomized at 16 sites in the EU. 22 patients (88%; 95% confidence interval [CI]: 69-97%) in the hypothermia group and 23 patients (92%; 95% CI: 74-99) in the control group completed cardiac magnetic resonance imaging at four to six days and 30-day follow-up. A series of three standards were monitored to enable consistency in the execution of the protocol. The standards included delivery of the antishivering regimen correctly, delivery of up to 1 L of iced saline, and 18 minutes of cooling delivered prior to wire crossing the lesion. Patients with

anterior STEMI were rapidly and safely cooled. Intravascular temperature at coronary guidewire crossing after 20.5 minutes of endovascular cooling decreased to 33.6° C (range 31.9-35.5° C), which is ≥1.1° C lower than in previous cooling studies. There was a 17-minute (95% CI: 4.6-29.8 min) cooling-related delay to reperfusion. In the "per protocol" analysis, median infarct size/left ventricular mass was 16.7% in the hypothermia group versus 23.8% in the control group (absolute reduction 7.1%, relative reduction 30%; p=0.31) and median left ventricular ejection fraction (LVEF) was 42% in the hypothermia group and 40% in the control group (absolute reduction 2.4%, relative reduction 6%; p=0.36). There were no statistically significant differences between the groups, in adverse events or serious adverse events.[49]

5.3 Summary and Clinical Trial Rationale

Previous clinical trials in patients experiencing acute myocardial infarction (AMI) have demonstrated that therapeutic hypothermia is safe, well tolerated and showed reductions in infarct size.[19] Additionally, recent preclinical results (Stanford-ZOLL data) have shown that temperature at reperfusion of 32 °C is superior to 35 °C for reducing infarct size, confirming a dose response. Future clinical trials will require more powerful cooling devices, and more consistency in implementing 18 minutes of cooling before reperfusion across all study sites in order anterior infarctions. It is therefore the objective of the COOL-AMI EU PIVOTAL Trial to evaluate the actual effectiveness of therapeutic hypothermia as a protection strategy.

Further clinical trials are needed to evaluate more powerful cooling devices, along with a refined therapeutic hypothermia protocol (target temperature of 32°C + 18 minutes of cooling prior to PCI). It will also be important to understand whether adequate cooling to 32°C + 18 minutes of cooling prior to PCI can be implemented into existing STEMI treatment protocols with no significant delay in door-to-balloon times. This trial aims to address the need for a powered clinical evaluation assessing the safety and effectiveness of the Proteus IVTM for this refined therapeutic hypothermia protocol as an adjunct therapy for AMI patients undergoing PCI. Among these refinements are: 1) A larger dose of cooling was achieved with the Proteus System (temp at PCI was 33.6°C as opposed to 35°C for COOL MI), 2) Delivery of at least 18 minutes of cooling prior to PCI was possible (mean 20 minutes in the EU Pilot Study), 3) the anti-shivering protocol was refined and worked successfully, and 4) the use of report cards for every case to track : a) anti-shivering protocol impementation, b) infusion of 1 liter of cold saline prior to PCI, c) 18 minutes of cooling prior to PCI, d) door to balloon time less than 90 minutes, e) total ischemic time less than 6 hours, and f) proper administration of dual antiplatelet therapy (DAPT) are all refinements ready to be implemented.

6 CLINICAL TRIAL PLAN

6.1 Trial Objective

The objective of this randomized clinical trial is to evaluate the safety and effectiveness of therapeutic hypothermia, using the ZOLL Proteus IVTM System, as an adjunctive therapy for patients presenting with acute anterior myocardial infarction and undergoing PCI, in comparison with patients with acute anterior myocardial infarction and undergoing PCI only.

6.2 Trial Endpoints

6.2.1 Primary Effectiveness Endpoint

Relative reduction of 20% in mean anterior myocardial infarct size (IS), as determined by Cardiac Magnetic Resonance (cMR) imaging at 4-6 days post-infarct in the Test Arm (cooling + PCI) compared to the Control Arm (PCI only). Infarction Size (IS) is defined as % Left Ventricular Mass as measured by Cardiac Magnetic Resonance (cMR) imaging. Infarct Size (IS) will be assessed by Cardiac Magnetic Resonance (cMR) at 4 – 6 days following the index procedure. The trial is considered to have met the primary efficacy endpoint if the Test Arm demonstrates a 20% relative reduction in infarct size compared to the Control Arm.

The ITT analysis set will be used for primary statistical analyses and summaries. The ITT population includes those subjects who have signed an informed consent and have been randomized to the Test Arm or the Control Arm of the trial. ITT subjects will be evaluated according to the group to which they were randomized.

The PP analysis set will also be evaluated. The PP population includes those subjects who met inclusion and exclusion criteria, were randomized to either the Test or Control arm, received the treatment to which they were randomized, and complied substantially with the treatment timeline and steps of this protocol without major protocol violations.

6.2.2 Primary Safety Endpoint

Per-patient rate of composite Major Adverse Cardiac Events (MACE) subjects, defined as Cardiac Death (CD), All Myocardial Infarction (All MI) and Clinically-Indicated Target Lesion Revascularization (CI-TLR) at 30 day follow-up; non-inferiority to the control.

6.2.3 Additional Assessments: Demographics and Other Parameters

Subject demographics and various baseline characteristics will also be collected. Additional clinical data collected and evaluated will include the number of patients who can successfully be enrolled and randomized, the timing of subject presentation to hospital, the timing of therapeutic and adjunctive interventions, the timing of reaching the target temperature zone, temperature at PCI, subsequent maintenance of hypothermia and

temperature data from the IVTM System. Observations will be evaluated relating to the use of the ZOLL Proteus IVTM System and how it performs in relation to the induction of therapeutic cooling and follow-up cMR imaging. New York Health Association[24] (NYHA) Functional Class and Kansas City Cardiomyopathy Questionnaire[25] (KCCQ) will be evaluated at 12 month follow-up.

6.3 Trial Design

This clinical trial is a multicenter, prospective, interventional, randomized-controlled trial. Randomization will be in a 1:1 ratio, Test Arm (PCI + Cooling) or Control Arm (PCI alone) in up to a total of 500 patients (250 subjects in each arm), at up to 70 clinical sites.

To enhance each site's ability to successfully integrate steps of the protocol and for training purposes prior to randomization, each site may enroll up to 4 Roll-In subjects in a non-randomized fashion. Roll-In subjects will be treated and followed as subjects in the Test Arm of the protocol (PCI + Cooling). Up to a total of 280 Roll-In subjects (up to 4 per site) may be enrolled. Due to limited cMR data in patients with inferior MI who received an adequate dose of cooling prior to revascularization, Inferior MI subjects will be allowed to be included as Roll-Ins to further evaluate inferior MI infarct size by cMR imaging. Evaluation will be done of cMR imaging at 4-6 days following the index procedure.

6.4 Patient Population

Subjects will include those who present to the Emergency Department (ED) and / or Cath lab, who meet the trial eligibility requirements and who can provide informed consent for cooling treatment. Subjects considered for enrollment inthis trial will include adult patients presenting with an acute anterior myocardial infarction. To qualify, patients must have symptoms consistent with AMI (i.e., chest pain, arm pain, etc.) unresponsive to nitroglycerin, qualifying ST-segment elevation of ≥ 0.2 mV in two or more anterior contiguous precordial leads (V1-V4), with symptom onset greater than 30 minutes, but less than 4.5 hours prior to presentation at hospital, and be eligible for PCI. This ensures that the overall ischemic time from symptom onset to time of wire crossing is less than 6 hours.

Subjects randomized to the Test Arm, as well as all Roll-In subjects, will receive intravascular cooling with the Proteus IVTM device. While undergoing temperature management, the Anti-shivering Protocol must be followed (see **Attachment II**).

6.5 Selection Criteria

Patients shall be screened to the following inclusion and exclusion criteria. Patients are qualified for participation only if all Inclusion Criteria have been met and all Exclusion Criteria have been confirmed not present.

6.6 Inclusion Criteria

All Inclusion Criteria must be answered YES for subject to satisfy Inclusion Criteria:

1. The patient is ≥ 18 years of age.
2. The patient has symptoms consistent with AMI (i.e. chest pain, arm pain, etc.) and unresponsive to nitroglycerin, with symptoms beginning greater than 30 minutes but less than 4.5 hours prior to presentation at hospital.
3. Qualifying Infarct Location:
    a. **Roll-In subjects**: Evidence of Acute Anterior or Inferior MI with ST-segment elevation of ≥ 0.2 mV in two or more anterior or inferior contiguous precordial leads (V1 –V4).
    b. **Randomized subjects**: Evidence of Acute Anterior MI only with ST-segment elevation of ≥ 0.2 mV in two or more anterior contiguous precordial leads (V1 –V4).
4. The patient is eligible for PCI.
5. The patient is willing to provide written informed consent to participate in this clinical trial.

6.7 Exclusion Criteria

All Exclusion Criteria must be answered NO for subject to satisfy Exclusion Criteria:

1. The patient has had a previous Myocardial Infarction.
2. The patient is experiencing cardiogenic shock, systolic blood pressure [SBP] <100 mmHg, HR>100 bpm and arterial oxygen saturation (pulse oximetry) ≤92% without additional oxygen.
3. The patient is presenting with resuscitated Cardiac Arrest, Atrial Fibrillation, or Killip risk stratification class II through IV.
4. The patient has an aortic dissection or requires an immediate surgical or procedural intervention other than PCI.
5. The patient has known history of Congestive Heart Failure (CHF), Hepatic Failure, end-stage kidney disease or severe Renal Failure (clearance < 30ml/min/1.73m²).
6. The patient is febrile (temperature > 37.5 °C) or has experienced an Infection with Fever in the last 5 days.
7. The patient has a known previous CABG.
8. The patient has a known recent Stroke within 90 days of admission.
9. Cardio-Pulmonary Decompensation that has occurred en route to the hospital or, in the opinion of the physician, that is imminent or likely to occur following presentation to the clinical site.

10. Contraindications to hypothermia, such as patients with known Hematologic Dyscrasias which affect thrombosis (e.g., cryoglobulinemia, sickle cell disease, serum cold agglutinins) or Vasospastic Disorders (such as Raynaud's or thromboangitis obliterans).
11. Any contraindication to cardiac MRI, or any implants in the upper body which may cause artifacts on cardiac MRI imaging.
12. The patient has a known hypersensitivity or contraindication to aspirin, heparin, or sensitivity to contrast media, which cannot be adequately pre-medicated.
13. The patient has a known history of Bleeding Diathesis, Coagulopathy, Cryoglobulinemia, Sickle Cell Anemia, or will refuse blood transfusions.
14. The patient has a height of <1.5 meters (4 feet 11 inches).
15. The patient has a known hypersensitivity or contraindication to buspirone hydrochloride or Pethidine (Meperidine) and/or has been treated with a monoamine oxidase inhibitor in the past 14 days.
16. Patient has a known history of severe hepatic or renal impairment, untreated hypothyroidism, Addison's disease, benign prostatic hypertrophy, or urethral stricture that in the opinion of the physician would be incompatible with Pethidine administration.
17. The patient has an Inferior Vena Cava filter in place (IVC).
18. The patient has a pre-MI life expectancy of <1 year due to underlying medical conditions or pre-existing co-morbidities.
19. The patient has a known, unresolved history of drug use or alcohol dependency, or lacks the ability to comprehend or follow instructions.
20. The patient is currently enrolled in another investigational drug or device trial.
21. The patient is apprehensive about or unwilling to undergo the required MRI imaging at follow-up, has a documented or suspected diagnosis of claustrophobia, or has Gadolinium allergy, or is in permanent Atrial Fibrillation.
22. The patient has received thrombolytic therapy en route to the hospital
23. The patient shows clinical evidence of spontaneous reperfusion as observed symptomatically and/or from baseline ECG findings (partial or complete ST resolution in ECG prior to informed consent and randomization).
24. The patient is a vulnerable subject, for instance, a person in detention (i.e., prisoner or ward of the state).
25. The patient is a female who is known to be pregnant.

6.8 Clinical Trial Procedures

6.8.1 Patient Screening

Patients presenting at participating centers with clinical signs and symptoms of AMI will be expeditiously triaged and offered the opportunity to participate in this clinical trial

without regard to age, gender or ethnicity. To ensure that patients are approached for potential trial participation without bias, patient screening information will be maintained on a patient screening log at each site. This log will track patients that were enrolled in the trial as well as patients who were excluded from participation and the reason(s) for their exclusion. The use of a patient screening log assures that all eligible subjects are given an opportunity to participate or decline participation in the trial.

The subject's eligibility for treatment with the Proteus IVTM System will be evaluated based on the medical and anatomical criteria outlined above in the inclusion/exclusion criteria section. The Investigator will explain the elements of this clinical trial, including the risks, potential benefits and required interventional and follow-up procedures, to each subject prior to obtaining informed consent.

If a subject is found to be ineligible during baseline screening and routine diagnostic tests, the subject shall be considered a screen failure and will be documented on the patient screening log. Roll-In subjects are considered enrolled in the trial when all inclusion and exclusion criteria have been satisfied, and informed consent has been signed. Randomized subjects are considered enrolled in the trial when all inclusion and exclusion criteria have been satisfied, informed consent has been signed, and the patient is randomized to either Test or Control Arm of the trial.

6.8.2 Informed Consent

The reviewing Medical Ethics Committee (MEC) must review and approve an Informed Consent Form (ICF) specific to this study. The Sponsor will provide each study center with an example ICF. The study center, to meet specific requirements, may modify this example ICF; however, the ICF to be used for subject consent under this protocol must contain all of the elements required by the study Sponsor and the governing regulatory requirements for informed consent (21 CFR Part 50). Therefore, each investigational site will provide the Sponsor with a copy of the MEC approved ICF - as well as any amendments - for the duration of the study.

Informed consent will be required from each subject. The MEC approved Informed Consent document must be signed by the patient or by the legal authorized representative (LAR) prior to any related procedures (or according to the MEC's approved guidelines), including the collection of data on case report forms (CRFs). Only subjects that have the appropriate informed consent form will be included in the trial.

The informed consent process (including time and date of discussion), should be documented in the subject's medical record and signed/dated by the individual (investigator or designee) who recorded it. The original signed consent form must be filed in the subject's medical record and a copy of the signed informed consent documentation given to the subject.

All subjects must sign, date and note the time on the Institutional Medical Ethics Committee (MEC) approved informed consent prior to any clinical trial/investigation-specific procedures. Obtaining the consent with the documented date and time, and the provision of a copy to the subject will be documented in the subject's medical record.

Due to the emergent nature of treating acute myocardial infarction, patients who have been enrolled in the study may receive a subsequent consent which provides more detailed information about their participation in the trial (based on MEC requirements), which may be reviewed and signed after the acute phase of their treatment has been completed. If the patient decides they no longer want to be included in the study, they will be withdrawn and their data will be included in the analysis up until the time of withdrawal.

If in the course of the pre-study evaluations prior to consent, the patient is found not to be eligible for inclusion in the study, the patient should be notified and the reason for ineligibility documented on the appropriate Screening Log.

All information pertinent to this clinical investigation (including at a minimum the description and purpose of the study, potential benefits, potential risks and inconveniences, active procedures, confidentiality, compensation, circumstances for termination and site contact persons) will be provided to the subjects in writing and in their native, non-technical, language by Investigator or designee, who has been trained on the protocol.

If new information becomes available that can significantly affect a subject's future health and medical care, this information shall be provided to the affected subject(s) in written form. If relevant, all affected subjects shall be asked to confirm their continuing informed consent in writing.

6.8.3 Roll-In Enrollment

Prior to randomizing patients, each participating center (except German centers) may enroll up to 4 patients Roll-In subjects in a non-randomized fashion. Roll-In subjects are treated and followed as patients in the Test Arm (PCI + Cooling) for training purposes. The justification for the number Roll-In patients in this study is based on ZOLL's previous clinical trial experience in relationship to a site's ability to successfully incorporate the cooling protocol including consent, anti-shivering regimen and an adequate dose of cooling without significantly delaying door-to-balloon time. Successful implementation takes teamwork and often several cases to assure the cooling protocol is adhered to with consistent accuracy.

In light of the fact that previous clinical trials (e.g., COOL –MI[19], ICE-IT[23] and CHILL-MI[37]) have failed to provide an adequate dose of cooling prior to reperfusion, ZOLL has implemented a tool called a "Report Card". This Report Card notes the site's success in achieving critical aspects of the protocol, called "Standards", and is provided to the site

after every patient is enrolled into the trial. The objective of the Report Card is to report back to the site their success in implementing a set of standards according to the protocol, and to encourage continuous improvement following each enrollment. The Standards, as noted on the Report Card, include but are not limited to accuracy of antishivering regimen administration and 18 minutes of cooling delivered prior to the wire crossing the lesion. The Standard of 18 minutes of cooling has been demonstrated in previous ZOLL trials to be the amount of time required to deliver an optimal dose of cooling so the patient's core body temperature is as close to target temperature as possible prior to reperfusion without significantly delaying door-to-balloon time.

Consistent achievement of each standard allows sites to move from Roll-In to randomization and enables consistency in execution of the protocol. Feedback will be provided to the site after each enrollment to assure the standards have been met and an adequate dose of cooling has been achieved. Use of the Report Card and Standards is intended to assist sites in ascending their learning curve as rapidly as possible. All centers will transition from Roll-In to Randomization as soon as possible once they have demonstrated their ability to enroll patients while consistently meeting the standards, thereby minimizing the number of Roll-In patients but ensuring accurate, precise adherence to the investigational protocol. Based on the site's performance with the Roll-In patients, as determined by the Sponsor, the site will be notified of authorization to randomize patients in the trial.

Additionally, Roll-In patients will undergo cMR as part of the cMR training process at each site. This will allow the site to train and qualify acquisition of cMR images per cMR protocol and ensure high quality and consistent imaging throughout the study across sites. Roll-In patients will not be included in the primary endpoint analysis; however, they will be included in the safety endpoint analysis. All performed activities on Roll-In subjects will be recorded as if performed in the Test Arm of the trial and hence documented in the Case Report Forms (CRF) for training and evaluation.

Roll-In subjects will be considered to be enrolled when all inclusion and exclusion criteria have been met and the informed consent form has been signed.

6.8.4 Approval to Randomize in the Trial

It will be at the discretion of the sponsor to advance a site to Randomization. Based on the site's performance with the Roll-In patients, as determined by the Sponsor, the site will be notified of authorization to randomize patients in the trial.

6.8.5 Randomization

In the randomization phase, patients who meet eligibility criteria for participation will be randomly assigned to either the Test Arm (PCI + Cooling) or Control Arm (PCI alone) in a 1:1 ratio.

Randomization will be applied using an internet based Interactive Web Response Systems (IWRS). In the trial, randomization will be done using random permuted blocks (based on procedure outlined in Pocock SJ. Clinical Trials: A Practical Approach. Wiley, Chichester, 1983), stratified by site, with 1:1 allocation ratio using a randomization list. At randomization, inclusion and exclusion criteria will be verified, and confirmation of informed consent signature will be done.

Subjects will be considered to be enrolled in the Test Arm and Control Arms of the trial when all inclusion and exclusion criteria have been met, the informed consent form has been signed, and randomization assignment has been completed.

6.8.6 Acute Care and Emergency Room Triage

Prior to the initiation of this trial at each participating institution, training will be conducted by the Sponsor targeted toward the integrated care of each trial subject and emphasizing the shared responsibility between the Departments of Emergency Medicine and Interventional Cardiology, where applicable at each center, with the goal of rapid screening, enrollment and treatment of appropriate patients.

Each center will clearly delineate departmental responsibilities for the following:

- Assessment of patient clinical features, signs and symptoms
- Administration of Informed Consent
- Review of Inclusion/Exclusion Criteria
- Assurance that diagnostic procedures mandated by the protocol are completed prior to randomization into this trial and are appropriately documented
- Patient Randomization
- Administration of pre-treatment medication(s)
- Administration of Anti-shivering medications to subjects randomized to the Test Arm of the trial
- Consensus on location in hospital where cooling using the Proteus IVTM System will be initiated
- Set-up of Proteus IVTM System, including insertion of the Proteus Catheter into the femoral vein induction of cooling, initiation of re-warming, Proteus IVTM System shutdown and catheter extraction for Test Subjects.

6.8.7 Standardized Care Prior to the Cooling Procedure

It is anticipated that subjects may receive one or more of the following therapies as part of current clinical practice in the treatment of acute myocardial infarction:

- Intravenous fluids and electrolytes
- Oxygen
- Antiplatelets and/or antithrombotics
- Vasoactive agents and diuretics

Clinicians will be encouraged to manage the subject in a standardized manner with respect to oxygenation, anti-coagulation and/or anti-platelet medications.

6.8.8 Documentation Procedures

Trial procedures and treatment data will be documented on standardized Case Report Forms (CRFs) which may be on paper or via an electronic data capture system (EDC). The completion of the CRFs may be delegated to a member of the study team (e.g., the study coordinator) as long as that person is listed on the Delegation of Authority Log. However, the Principal Investigator retains responsibility for the accuracy and integrity of the data entered on the CRF. The CRF will be monitored for accuracy and completeness per the source documents (medical records, charts, interventional systems, worksheets as applicable, etc.) at each clinical center. Temperature data from the Proteus IVTM System will be downloaded and sent to Sponsor. A flow diagram for the Test Arm is represented in **Figure 10**.

It is anticipated that technology and/or techniques such as edit checks and double entry of data may be utilized to minimize the rate of error. Additionally, ZOLL or its assignees may ask for data clarification or re-check of data for accuracy. Monitoring visits and CRF completion logs will be used to track data entry in accordance with trial logistics and expectations.

Any source documentation (procedure reports, imaging studies, lab reports, death certificates, etc.) that is sent to the Sponsor should have all patient identifiers removed and replaced with the subject's trial ID, and processes ensuring patient privacy and clinical data confidentiality will be followed in accordance with local regulations and applicable laws.

6.8.9 Study Flow and Procedures

Figure 8 Screening and Enrollment Flow

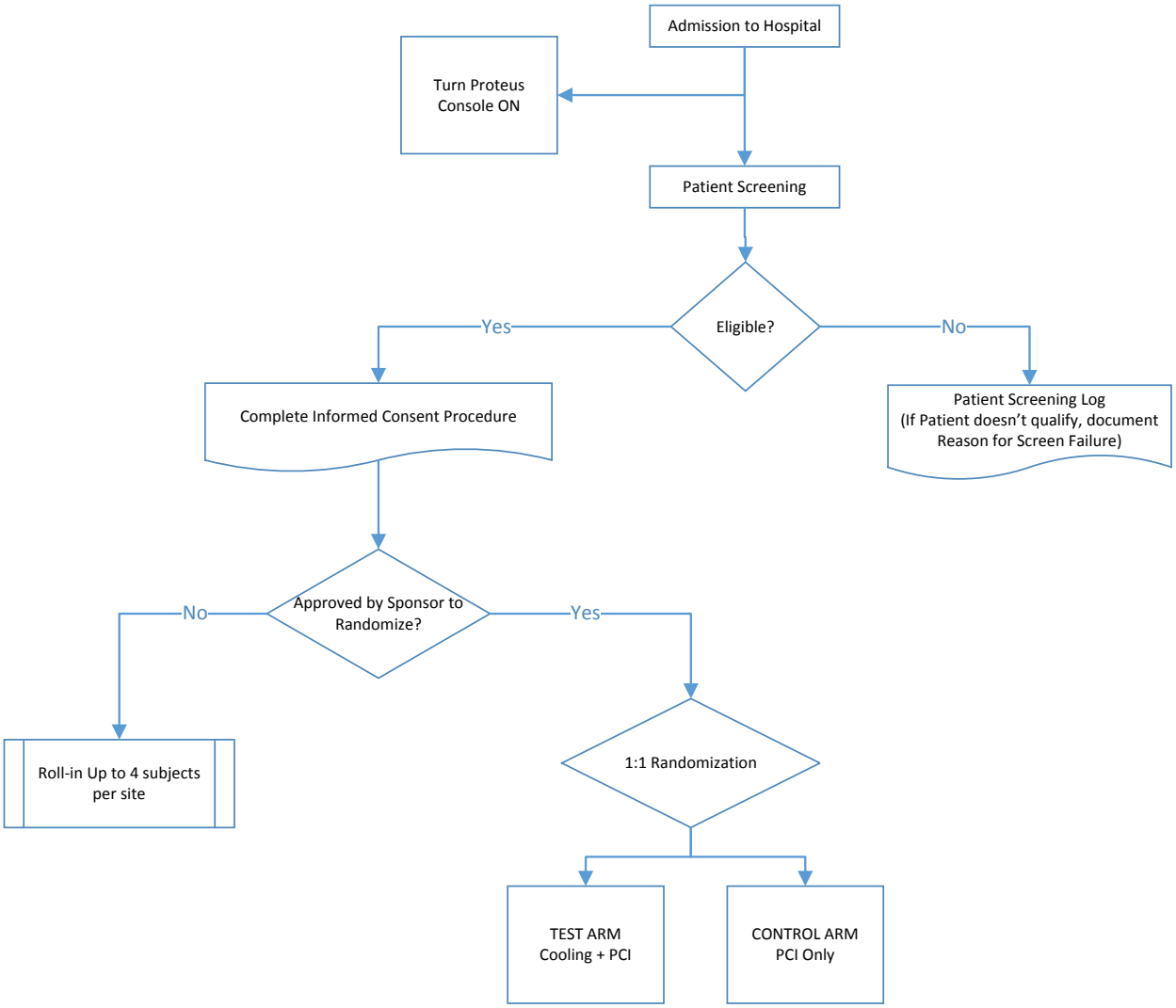


Figure 9 Control Arm Flow

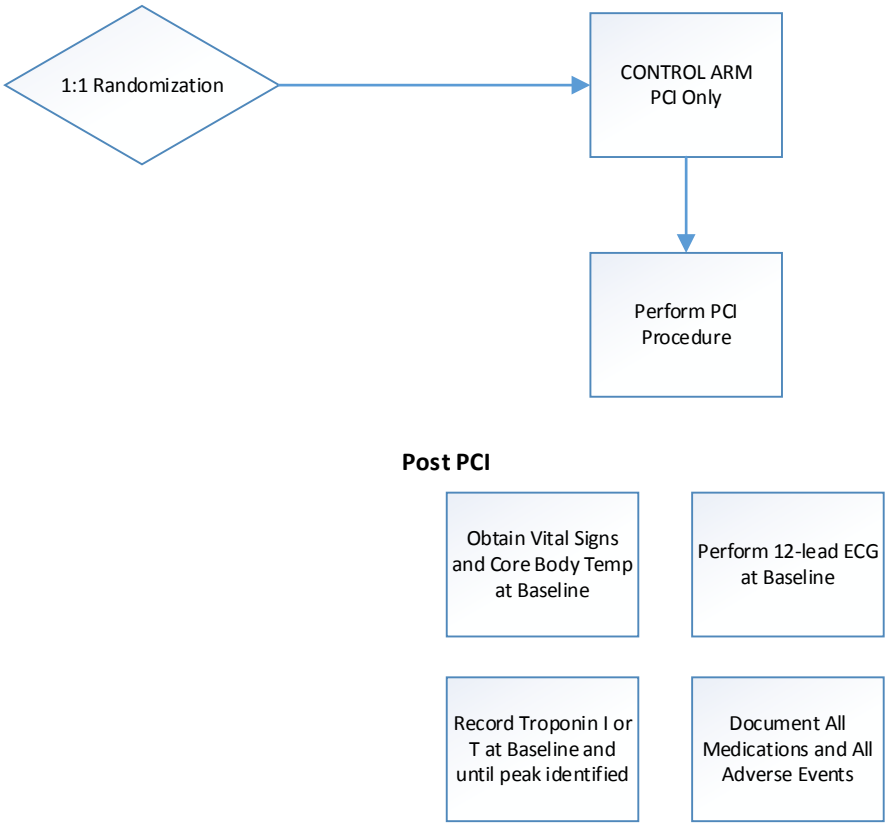


Figure 10 Test Arm Flow

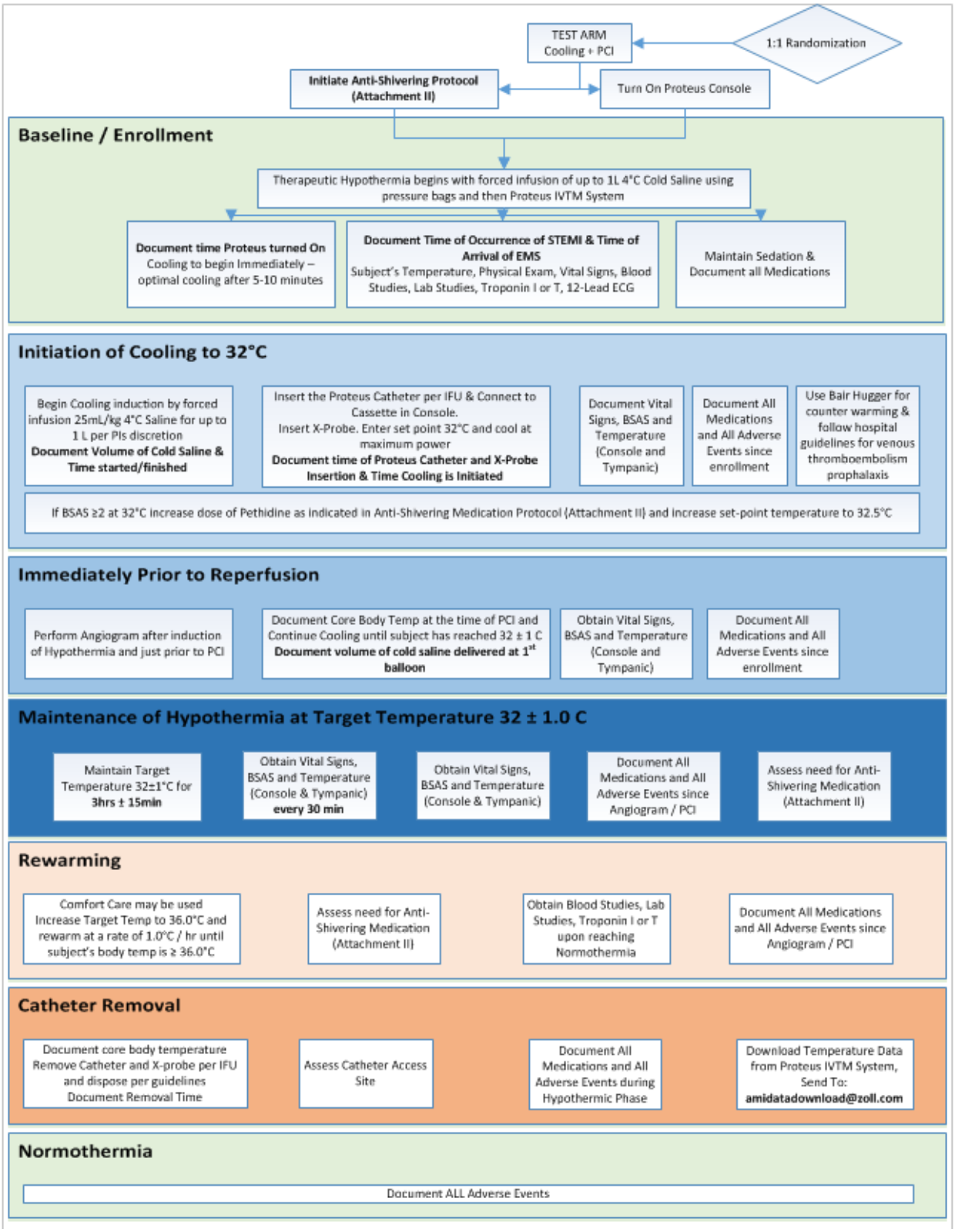
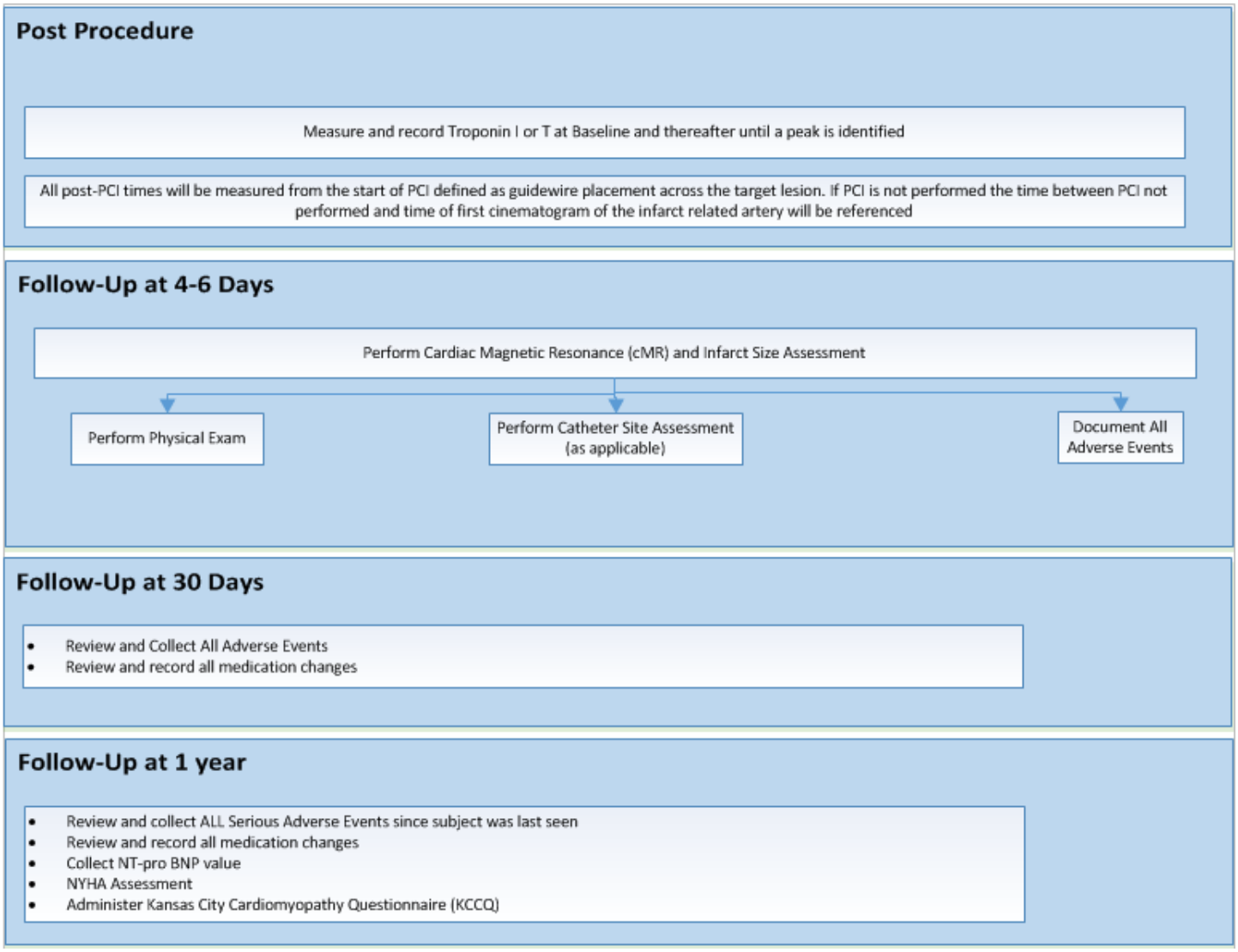


Figure 11 All Patient Procedures



6.8.10 Pre-Cooling Assessment Procedures

All required procedures and data collection from the time of subject screening (presentation at hospital) through the pre-cooling assessment period are given below in **Table 11.**

Table 11: Baseline / Screening and Enrollment Procedures/Evaluations and Data Collection for the Test & Control Arms of the Trial

Procedures/ Evaluations	Data
Trial Eligibility	At admission to the hospital
Informed Consent	Obtain Consent from patient before any trial-related procedure is initiated.
Trial Enrollment	- Follow randomization process to assign patient to Roll-In, Test or Control Arms of the trial - Complete Enrollment Form, document randomization, and FAX or email to ZOLL at +1 800.243.0360 or ami-eu@zoll.com to enter in the eCRF
Temperature	Document subject's temperature using a tympanic thermometer
Vital Signs	Blood Pressure, Heart Rate, Respiratory Rate, BSAS measurement
Physical Exam	Complete Physical Examination
Blood Studies	RBC's, WBC's, Hct, Hgb, Platelets,
Lab Studies	BUN, Creatinine, sodium, potassium, calcium, phosphate, magnesium, chloride, lactic acid, glucose, amylase, lipase
Cardiac Markers	Baseline and peak Troponin I or Troponin T including upper limit of normal
ECG	12-lead baseline
Medications	Document as indicated on Case Report Form since STEMI onset
Adverse Events	Collect all adverse events as soon as patients are enrolled in the trial

6.8.11 Initiation, Maintenance, and Reversal of Cooling with Proteus IVTM System Procedures / Evaluations and Data Collection for Subjects Enrolled in the Test Arm

6.8.12 Test Arm: Temperature Management Protocol and Data Collection Time Points

Treatment with therapeutic hypothermia will begin with a forced infusion of up to 1 L of cold saline (4°C) (according to the guideline) using pressure bags, and at the time of administration of the anti-shivering medication according to the anti-shivering guidelines, then will continue with the Proteus IVTM System as soon as possible. Cooling will be initiated with the Proteus IVTM System set at a temperature of 32.0 °C, and the subject's temperature will be measured with the Proteus IVTM System immediately before PCI has occurred (measured as time the wire crosses the target lesion). Cooling will be maintained for 3 hours and will be followed with active rewarming to attain normothermia 36.0 °C (96.8°F).

Cooling induction, maintenance of hypothermia, and rewarming are described in the following **Table 12.** The data collection schedule for Test Arm subjects is summarized in **Section 6.8.13**.

Table 12: Initiation, Maintenance, and Reversal of Cooling with Proteus IVTM System Procedures / Evaluations and Data Collection for Subjects Enrolled in the Test Arm

Phase	Task
Immediately Upon Arrival to the Hospital	1. **Turn the Proteus Console on** (in preparation for cooling with the device) 2. **Document time of occurrence of STEMI and ECG** 3. **Document time of arrival of Emergency Medical Service EMS (Paramedics)**

Phase	Task
Baseline / Enrollment	4. Immediately after informed consent is obtained and patient is randomized to the Test Arm of the trial, **initiate anti-shivering medication protocol using Guidelines outlined in Attachment II**. 5. Begin cooling induction by forced infusion with 25mL/kg of 4°C cold saline using pressure bags up to 1 L of cold saline (4°C) (according to the guideline) at the physician's discretion. Use Bair Hugger™ (CE marked device) for patient comfort. 6. **Document the time the Proteus console is turned on.** The device will begin cooling the patient immediately; however, optimal cooling is achieved in 5-10 minutes after it is turned on. 7. Perform Physical Examination and obtain Vital Signs. 8. Obtain Blood and Lab studies. 9. Obtain Troponin I or Troponin T . 10. Obtain 12-lead baseline ECG. 11. Document all medication use since STEMI onset. 12. Measure body temperature using an independent tympanic thermometer. The independent measurement is to be used in addition to the core body temperature collected by the Proteus Temperature Probe (X-Probe). 13. Document all Adverse Events.

Phase	Task
Initiation of Cooling	14. Document the volume of cold saline, the time the cold saline infusion is started and the time the cold saline infusion is finished. 15. Following the ZOLL Proteus IVTM System Instructions for Use (IFU), insert the Proteus Catheter into the Inferior Vena Cava via either femoral vein. The Proteus Catheter is then connected to the Cassette that has been inserted into the Proteus Console. 16. Following insertion of the Proteus Catheter, insert the Proteus Temperature Probe (X-Probe). Access site selection may vary by both operator preference and anatomical considerations; however, the function of the system is not dependent on which femoral vein is chosen. 17. Once the Proteus System Catheter & Proteus Temperature Probe (X-Probe) have been inserted, enter set point temperature to 32.0°C on the Proteus Console and perform cooling at maximum power as soon as the console is ready to cool. **18. Document the time of Proteus Catheter & X-Probe (temperature probe) insertion.** **19. Document the time cooling is initiated with the Proteus IVTM System.** **20. Document vital signs (BP, HR, RR), and temperature measurements (Tympanic and Proteus Console measurements).** 21. Document all medication use. 22. Document all adverse events since the time of enrollment. 23. Use Bair Hugger® warming blankets for counter-warming. If choosing to use low dose anticoagulation during the cooling phase, follow hospital's guidelines for venous thromboembolism prophylaxis.

Phase	Task
Immediately Prior to Reperfusion	24. If clinically relevant shivering (Bedside Shivering Assessment Scale (BSAS) of 2 or greater) occurs at 32° (see **Anti-Shivering Guidelines, Attachment II, and BSAS Attachment III),** increase the dose of Pethidine (Meperdine) as indicated in shivering protocol and increase set point temperature on the Proteus IVTM System to 32.5°C. If clinically relevant shivering continues (BSAS ≥2), once again increase dose of Pethidine as indicated in Anti-Shivering Protocol and increase set point temperature on the Proteus IVTM System to 33°C. Continue this process until a temperature is reached where there is no shivering. Follow sedation procedures using **Anti-Shivering Guidelines, Attachment II, and the BSAS Attachment III.** 25. Perform *angiogram after the induction of hypothermia has been initiated and just prior to PCI. **26. Obtain vital signs (BP, HR, RR), BSAS and temperature measurements (Tympanic and Proteus Console measurements) just prior to PCI.** 27. Document all medication use since the initiation of cooling. 28. Document all adverse events since the initiation of cooling. **CAUTION: Anticipate changes in electrolytes and laboratories values secondary to hypothermia.** 29. Document core body temperature at the time of PCI. 30. If subject has not reached 32.0 ± 1.0°C (or temperature where shivering does not occur, as indicated above) at the time of PCI, continue cooling induction until target temperature has been reached. 31. **Document the time wire crossed the target lesion**.

Phase	Task
Maintenance of Hypothermia Target Temperature 32 ±1°C	32. Maintain the patient at the set target temperature of 32.0 (or temperature where shivering does not occur, as indicated above) for 3 hours ± 15 minutes from the initiation of cooling with the Proteus System. **33. Obtain vital signs (BP, HR, RR), BSAS and temperature measurements (Tympanic and Proteus Console measurements) every 30 minutes during the 3 hours of cooling.** 34. Document all medication use since the angiogram/ PCI procedure. 35. Document all adverse events since the angiogram/ PCI procedure. 36. If clinically relevant shivering [Bedside Shivering Assessment Scale (BSAS) of 2 or greater] occurs at 32.0°C (See **Anti-Shivering Guidelines, Attachment II, and BSAS, Attachment III),** increase dose of Pethidine (Meperidine) as indicated in shivering protocol and increase temperature on the Proteus IVTM System console to 32.5°C. 37. If clinically relevant shivering continues (BSAS ≥ 2), once again increase dose of Pethidine as indicated in shivering protocol and increase temperature on the Proteus IVTM System to 33°C. Continue this process until a temperature is reached where there is no shivering. Follow sedation procedures using Anti-Shivering Guidelines outlined in **Attachment II** and BSAS assessment in **Attachment III.**

Phase	Task
Rewarming	38. After 3 hours of cooling with the Proteus IVTM System, begin active rewarming to normothermia. Palliative care such as blankets, Bair Hugger patient warming systems, and warm liquids may be used. 39. Using the Proteus System Console, press **STOP** and Increase target temperature to 36.0°C using the arrow touch buttons and then press **Continue**. 40. Set rewarming rate to 1.0°C/hr using the arrow touch buttons and press **Continue** to start rewarming. 41. Maintain the Pethidine infusion during rewarming using the Anti-Shivering Protocol outlined in Attachment II. 42. Obtain blood studies, lab studies and record peak Troponin I or Troponin T including upper limit of normal for site. 43. Document all medication use during the rewarming phase. 44. Document all adverse events during the rewarming phase. **CAUTION: Anticipate changes in electrolytes and laboratories secondary to re-warming**
Catheter Removal	45. Document core body temperature at time of Proteus Catheter removal. 46. Remove Proteus Catheter and X-Probe per IFU and document time of removal. 47. Dispose of the Proteus Catheter, X-Probe and Proteus Cassette per institution's guidelines (single-use). 48. Assess catheter access site for signs of bleeding, access vessel trauma, or hematoma formation. **49. Download temperature data from the Proteus Console after the cooling phase has been completed. Send downloaded data to amidatadownload@zoll.com immediately upon downloading. Device data must be saved according to Section 16.1, Investigator Records.** 50. Document all medication use during the hypothermic phase. 51. Document all adverse events during the hypothermic phase. **DO NOT DISCARD SPLITTER CABLE (MULTI–USE TEMPERATURE CABLE)**

Phase	Task
Normothermia	52. Document all adverse events until patient is discharged from the hospital.
Post-Procedure	53. If required, provide additional Informed Consent document to patients who were consented with the short consent form (if required by MEC or country-specific regulations).

NOTE: All post-PCI times will be measured from the start of PCI, defined as time the wire crosses the target lesion. In the event that PCI is not performed, the time of the first cineangiogram of the infarct related artery will be referenced. If PCI is staged for the non-culprit lesion, then the PCI will be performed after the 4-6 day cMR

***Angiograms are to be uploaded for all adjudicable events.**

6.8.13 Trial Schedule for Test Arm Subjects

Procedure/ Interval	Baseline / Enrollment	Initiation of Cooling	Immediately prior to reperfusion (PCI)	Maintenance of Target Temp 32 ±1°C	Rewarming to 36°C	Catheter Removal	Discharge	Follow-Up @ 4-6 Days	Follow-Up @ 30 Days (±7 days)	Follow-Up @ 12 months (±14 days)	Unscheduled Visit
Trial Eligibility & Informed Consent	**upon arrival to hospital**										
Physical Exam	**X**						**X**				
Anti-Shivering Protocol	**X**			**X**[α]							
Cold Saline Infusion		**X**									
Catheter Insertion Time		**X**									
Catheter Removal Time						**X**					
Temperature Documented	**X**	**X**	**X**	**every 30 min during 3 hr cooling**	**every 60 min during rewarming**						
Temperature Data Download						**X**					
Vital Signs	**X**	**X**	**X**	**every 30 min**	**every 60 minutes**						
Blood Studies RBC's, WBC's, Hct, Hgb, Platelets,	**X**				**X upon reaching normothermia**						
NT-pro BNP										X	
Lab Studies BUN, Creatinine, Na, K, Ca, Mg, Cl, P, lactic acid, glucose, amylase, lipase	**X**				**upon reaching normothermia**						
Any Medication Use	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Troponin I or T(including ULN) during hospitalization	**X**	**Perform Troponin until peak value identified**									
12 lead ECG	**X**										
Adverse Events		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**SAE only**	**X**[**]
Catheter Access Site Assessment						**X**	**X**	**X**			
Cardiac Magnetic Resonance (cMR) imaging								**X**			
NYHA Assessment										**X**	
KCCQ										**X**	

[α]For persistent clinically relevant shivering (BSAS ≥ 2), increase dose of Pethidine as indicated in shivering protocol and increase temperature on Proteus IVTM System console by 0.5°C. Continue this process until a temperature is reached where there is no shivering. Follow sedation procedure using Anti-Shivering Guidelines outlined in Attachment II and BSAS assessment in Attachment III Include BSAS measurement and temperatures from independent method.

[**]**If unscheduled visit occurred within 30 days follow-up, report all AEs. However, if unscheduled visit occurred after 30 days follow-up within 12 months, report only SAEs.**

6.8.14 Trial Schedule for Control Arm Subjects

Procedure/ Interval	Baseline / Enrollment	Immediately prior to reperfusion (PCI)Post-PCI	Discharge*	Follow-Up @ 4-6 Days	Follow-Up @ 30 Days (±7 days)	Follow-Up @ 12 months (±14 days)	Unscheduled Visit
Trial Eligibility & Informed Consent	**upon arrival to hospital**						
Physical Exam	**X**		**X**				
Catheter Insertion Time	**X**						
Catheter Removal Time							
Temperature Documented	**X**						
Vital Signs	**X**						
Blood Studies RBC's, WBC's, Hct, Hgb, Platelets,	**X**						
NT-pro BNP						**X**	
Lab Studies BUN, Creatinine, Na, K, Ca, Mg, Cl, P, lactic acid, glucose, amylase, lipase	**X**						
Any Medication Use	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Troponin I or T(including ULN)	**X**	**Perform Troponine until peak value identified**					
12 lead ECG	**X**						
Adverse Events		**X**	**X**	**X**	**X**	**SAE only**	**X****
Cardiac Magnetic Resonance (cMR)				**X**			
NYHA Assessment						**X**	
KCCQ						**X**	

**If unscheduled visit occurred within 30 days follow-up, report all AEs. However, if unscheduled visit occurred after 30 days follow-up within 12 months, report only SAEs.

6.8.15 Control Arm Protocol and Data Collection Time Points

The data collection schedule for Control Arm subjects is summarized in **Section 6.8.14**. For patients randomized to the Control Arm, i.e., PCI alone, the following procedures will be performed:

i. Document time of occurrence of the STEMI & ECG results

ii. Document time of arrival of Emergency Medical Service EMS (Paramedics) & time of arrival at hospital

iii. Collect all adverse events as soon as patients are enrolled in the trial

iv. Perform Blood Studies, Labs, and record Baseline and peak Troponin I or T

v. Perform PCI. If PCI is staged for the non-culprit lesion, then the PCI will be performed after the 4-6 day cMR

vi. Monitor and record the patient's vital signs, temperature, blood pressure, heart rate and respiratory rate, at baseline

vii. Obtain 12-lead baseline ECG

viii. Monitor and record all pharmacological agents

ix. Measure and record baselineTroponin I or T including upper limit of normal, and when a peak is identified.

x. Monitor and record all adverse events for the duration of 30 days follow-up and serious adverse events for the duration of 12 month follow-up.

xi. Complete physical exam prior to discharge.

6.8.16 Follow-up at 4-6 days and at 30 days following the PCI Procedure

Subjects enrolled in the Test and Control Arms, and Roll-In patients, will undergo Cardiac Magnetic Resonance (cMR) to assess infarct size at 4-6 days. In addition, the following procedures are to be performed at 4 - 6 days and at 30 days after the index procedure (PCI) for all patients:

i. Monitor and record all adverse events for the duration of 30 days follow-up.
ii. Review and record all medication changes since index.

6.8.17 Follow-up at 12 months following PCI

Following completion of the 30 day follow-up and, all subjects will be followed through 12 months for the incidence of Serious Adverse Events, Death and Heart Failure (as assessed by NYHA and Kansas City Cardiomyopathy Questionnaire (KCCQ))

i. Monitor and record all serious adverse events for the duration of 12 month follow-up.
ii. Collect NT-pro BNP value to assess clinical prognosis of Heart Failure.
iii. Review and record all medication changes
iv. Perform blinded NYHA Assessment. and administer Kansas City Cardiomyopathy Questionnaire (KCCQ).

6.8.18 Use of other Cooling Methods

For the purposes of this trial, no other cooling methods may be used.

6.8.19 Transferring Subject during Cooling

Although interruption during the induction phase of hypothermia is not recommended, if subject transfer is required during any phase of the cooling, follow relevant instructions in the device Instructions for Use.

For additional detail, refer to the Proteus IVTM System Instructions for Use**.** The console screen also provides prompts for entry of user-defined parameters and system start-up.

6.8.20 Patient Withdrawal and Discontinuation

The term "patient withdrawal" refers to the patient deciding to terminate their participation in the trial. The term "discontinuation" refers to the physician deciding that the patient will not continue trial participation as defined below.

A subject has the right to withdraw from the trial at any time and for any reason without prejudice to his or her future medical care by the physician or the institution. Trial withdrawal by a subject specifically means withdrawal of consent from further participation in the trial. Subjects who withdraw consent after enrollment will be evaluated to the time of withdrawal, and withdrawal of consent precludes any further trial related treatment or data collection. If possible, a complete, final physical examination should be performed on all subjects who withdraw from the trial. At a minimum, every effort should be made to document subject outcome at the time of trial withdrawal.

A subject may withdraw from the clinical investigation for the following reason:

- Subjects may choose to withdraw from the clinical investigation under the terms of the Declaration of Helsinki and their consent documentation without having to give a reason;

A subject may be discontinued from the clinical investigation for the following reasons:

- Any unanticipated adverse reaction which is, in the opinion of the Investigator, related to the treatment and will endanger the well-being of the patient if treatment is continued;
- Development of any illness(es), infection or condition(s) that might interfere with the Clinical Investigational Plan;
- Non-compliance with the clinical investigation procedures deemed by the Investigator to be sufficient to cause discontinuation;
- Any problem deemed by the Investigator to be sufficient to cause discontinuation.

- Investigator will treat all subjects discontinued from the investigation due to an unanticipated adverse reaction, directly related to the investigation, until the reaction resolves.

- Investigator will not replace subjects who have withdrawn from the clinical investigation if they have received the investigational device. If possible, Investigator will perform any procedures or assessments planned for the subject at the time of withdrawal.

All subjects are expected to continue in the trial through the final follow-up assessment or until ZOLL notifies the Investigator in writing that further follow-up is no longer required, except in the event of death or upon the subject's request for early withdrawal from the clinical trial.

6.8.21 Patient Lost to Follow-up

The investigator will attempt to contact a subject at least three times prior to designating them as lost-to-follow-up subjects. The investigator will document the date and type of attempted communication. The investigator will complete and sign the Study Exit Form when a subject is lost to follow-up.

6.8.22 Early Termination of a Clinical Investigation

Both the Sponsor and Investigator reserve the right to terminate the clinical investigation at any time. If necessary, and after review and consultation with the Principal Investigator, the Sponsor will make a final determination on whether to terminate the study.

A clinical investigation or Investigator may be terminated at a clinical center for any of the following reasons, or for reasons not listed that affect patient safety or integrity of the trial:

- Unsatisfactory rate of patient enrollment or compliance to eligibility criteria.
- Repeated noncompliance with the investigational plan.
- Inaccurate, incomplete, and/or untimely submission of data.
- Inadequate accountability of the investigational device.

The sponsor may terminate this trial if there are new, previously unknown adverse events related to device or cooling procedure, deaths, SAEs/AEs exceeding those reported as related to device/cooling procedures in previous trials, and/or if recommended by DMC (Data Monitoring Committee) to stop the trial. The sponsor will make the final determination on whether to terminate the study.

The sponsor may terminate the trial for any other unforeseen circumstances. In case of premature termination/suspension, ZOLL will stop the enrollment, inform all investigators at all sites and all regulatory agencies governing the study. ZOLL will perform complete device accountability of all investigational devices and retrieve them from the clinical sites. All study subjects will be followed through the specified follow-up periods. ZOLL will issue a final report of the clinical study.

6.8.23 Amendments and Protocol Deviations

Investigator will not deviate from the CIP without prior written confirmation by Sponsor, or their designee, except as required in a medical emergency. In medical emergencies, Sponsor does not require prior confirmation for protocol deviations, but Investigator will notify Sponsor within 5 days of the incident and will notify the EC according to local requirements. Investigator, or designee, will record deviations with an explanation for the deviation. Investigator will report to Sponsor who will analyze them and assess their significance. Significant deviations from the CIP will be reported to the Competent Authority.

Examples of protocol deviations may include those relating to:

- Eligibility
- Enrollment and randomization
- Informed consent
- Protocol adherence (e.g., tests and assessments done as required in Trial Schedule, etc.)

Routine monitoring will assess Investigator compliance to the protocol.

Investigator must not modify the CIP without the prior and written permission from Sponsor. All modifications to the clinical protocol must be submitted to the Competent Authority (where required) to allow the Competent Authority review and approval.

The Sponsor is responsible for management, processing and approval of any amendment to the Investigational Plan. Should the site consider an amendment necessary, the Sponsor will work with the site to make the appropriate changes. The Sponsor will manage documentation of such changes through the existing document control system. A history of changes and a redline version of the documentation will be maintained per the applicable quality system procedures. The proposed amendment will be submitted to the reviewing MEC/ IRB and government agency as applicable. Any necessary approvals will be received in writing before the requested change is implemented.

This study will be conducted in compliance with ISO 14155, ICH E6 Consolidated Good Clinical Practice Guidance, 21 CFR 812, 21 CFR Part 50, and any requirements imposed by countries with participating clinical sites. The study will not commence until the necessary government and MEC/IRB approvals have been obtained.

6.8.24 Trial Exit

The Trial Exit Form (CRF) should be completed at the time a subject is exited from the trial. A subject will be considered to have exited from the trial for any of the following reasons.

- Subject completes follow-ups required by the investigational plan.
- Subject dies.
- Subject requests to be withdrawn.
- Physician requests that patient be withdrawn to protect the welfare of the patient.
- Patient is lost to follow-up.
- Other (specify)

6.8.25 Subject Confidentiality

Subject confidentiality will be maintained throughout the clinical trial to the extent permitted by law. That is, every attempt will be made to remove patient identifiers from clinical trial documents. For this purpose, a unique subject identification code (site number, subject number and subject initials) will be assigned and used to allow identification of all data reported for each subject. This will also ensure that the information can be traced back to the source data.

Trial data may be made available to third parties, e.g., in the case of an audit performed by regulatory authorities, provided the data are treated confidentially and that the subject's privacy is guaranteed. The identity of a subject will never be disclosed in the event that trial data are published.

Security and Unique usernames and passwords will be utilized by data entry, data verification and other personnel who have database access to insure confidentiality and protection of data.

Trial sites must comply with Health Insurance Portability and Accountability Act (HIPPA) and/or the subject confidentiality provisions and privacy laws of each participating country, local regulations, and institutional requirements, whichever is stricter.

6.8.26 Device Accountability

ZOLL is responsible for the availability and traceability of all investigational products. Documentation is required at each step of the process via a device accountability log. Investigational product will be reconciled on a regular basis.

The investigator also is required to maintain adequate records of the receipt and disposition of all investigational devices. A device accountability log will be provided for this purpose.

All unused product must be returned to ZOLL prior to the close of the trial.

6.8.27 Return of Materials upon Trial Termination

Sponsor will ship investigational devices only to qualified Investigators participating in this clinical investigation. Sponsor will not ship investigational devices to any site until evidence of EC approval has been provided to Sponsor, or designee.
Investigator will control access to investigational devices, and will only use investigational devices in the clinical investigation and according to the CIP.
Sponsor will keep investigational device records to document the physical location of each device. Record(s) will include information documenting devices shipped, devices at investigation sites, devices disposed of, and devices returned.
Investigator, or designee, will keep records documenting the receipt, use, return and disposal of the investigational devices, which will include:

- Date of receipt,
- Identification of each investigational device (serial number or unique code),
- Expiry date, if applicable,
- Date or dates of use,
- Subject identification,
- Date on which the investigational device was returned, or explanted from subject, if applicable, and
- Date of return of unused, expired or malfunctioning investigational devices, if applicable.

After the trial procedures have been completed, all unused devices must be accounted for and returned to ZOLL. Instructions for device return to ZOLL will be reviewed at the site initiation visit.

6.8.28 Trial Closure

Trial closure can occur under the following circumstances:

a. termination of site participation in the trial (i.e., closure that occurs prior to meeting defined endpoints) of the trial
b. upon completion of the trial (i.e., when all patients enrolled have completed the follow-up visits or previously exited the trial, and the CRFs and queries have been completed)

Under any circumstance for closure of the trial at the site, ZOLL and/or its designees will notify the site of this occurrence in writing. Trial closeout visits will be performed once a determination has been made that the trial is closed. All unused trial devices and any unused trial materials and equipment will be collected and returned to ZOLL and/or its designees. The monitors will ensure that the investigator's regulatory files are current and complete and that any outstanding issues from previous visits have been resolved. Other issues that will be reviewed at this visit include: discussing record retention requirements (refer to **Section 14.1**—Investigator Records), device accountability, possibility of site audits, publication policy, and notifying the Medical Ethics Committee and Competent Authorities of trial closure, etc., as applicable.

6.9 Cardiac Magnetic Resonance (cMR) imaging Core Laboratory

Cardiac Magnetic Resonance (cMR) imaging must be collected per the Manual of Operations provided by the sponsor. Images must be submitted to the core laboratory designated by the sponsor for analysis.

7 ADVERSE EVENTS & DEVICE DEFICIENCIES

7.1 Definitions

7.1.1 Adverse Event (AE)

Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.

NOTE 1- This definition includes events related to the investigational medical device or the comparator.

NOTE 2- This definition includes events related to the procedures involved.

NOTE 3- For users or other persons, this definition is restricted to events related to investigational medical devices.

7.1.2 Serious Adverse Event (SAE)

Adverse event that:

a) led to a death, injury or permanent impairment to a body structure or a body function.

b) led to a serious deterioration in health of the subject, that either resulted in:

- a life-threatening illness or injury, or
- a permanent impairment of a body structure or a body function, or
- in-patient hospitalization or prolongation of existing hospitalization, or
- in medical or surgical intervention to prevent life threatening illness

c) led to foetal distress, foetal death or a congenital abnormality or birth defect.

NOTE 1: Planned hospitalization for pre-existing condition, or a procedure required by the Clinical Investigation Plan, without a serious deterioration in health, is not considered a serious adverse event.

7.1.3 Device Deficiency (DD)

Inadequacy of an investigational medical device related to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, use error, or inadequacy in the information supplied by the manufacturer.

7.1.4 Adverse Device Effect (ADE)

Adverse event related to the use of an investigational medical device.

NOTE 1- This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device.

NOTE 2- This includes any event that is a result of a use error or intentional abnormal use of the investigational medical device.

7.1.5 Serious Adverse Device Effect (SADE)

A adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

7.1.6 Unanticipated Serious Adverse Device Effect (USADE)

Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

NOTE: Anticipated SADE (ASADE): an effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report.

7.2 Adverse Event Reporting

7.2.1 Adverse Event Reporting from Site to Sponsor and MEC

The collection of AEs will begin after the informed consent is signed. All AEs that occur through completion of the final follow-up visit, whether observed by the investigator or by the subject, and whether or not thought to be device related, will be reported in detail on the appropriate CRF and followed to resolution or the end of trial participation.

The description of the AE will include the date and time of onset, seriousness, relationship to the device or procedure, the results of any diagnostic procedures or laboratory tests, any treatment recommended, and the outcome of the event. In the circumstance that an AE has not resolved by the time of the subject's completion of the trial, an explanation will be entered on the appropriate CRF.

ZOLL will implement and maintain a system to ensure that the reporting of the reportable events by the investigator to ZOLL occur immediately, but no later than 3 calendar days after investigational site study personnel awareness of the event.

7.2.2 Serious Adverse Event Reporting to Sponsor and MEC

Serious adverse events (SAEs) and device deficiencies should be reported as soon as possible.

Serious adverse events and device deficiencies must be reported no later than 3 calendar days from the site becoming aware of the event or as per the investigative site's local requirements if the requirement is more stringent than those outlined.

The date the site staff became aware of the SAE must be recorded in the source document. The Investigator will further report the event to the IRB/EC according to the institution's IRB/EC reporting requirements.

Serious adverse events that do not occur in the study subject but occur in the user or other persons need to be reported on the fax notification form titled SAE Notification Form. Serious adverse events that occur in the user or other persons other than the study subject should not be entered into the clinical database.

Serious adverse events should be reported on the SAE Notification Form in the occurrence that the clinical database is not available. This does not replace the electronic clinical database. All information must still be entered in the clinical database once the system is back to normal function.

7.2.3 UADE/USADE Reporting to Sponsor and MEC

ZOLL requires the Investigator to report any USADE to the sponsor within 3 calendar days of the investigator's knowledge of the event and to the EC per EC requirements.

7.2.4 Sponsor Reporting to NCAs (National Competent Authority) when European Sites Participate in the Trial

7.2.4.1 What to Report

The following events are considered reportable events:

- any SAE,
- any Device Deficiency that might have led to a SAE if:
    - suitable action had not been taken or
    - intervention had not been made or
    - if circumstances had been less fortunate
- new findings/updates in relation to already reported events.

7.2.4.2 Report to Whom

Reportable events must be reported at the same time to all NCAs where the clinical investigation has commenced using the summary tabulation featured in the of MEDDEV 2.7/3.

7.2.4.3 Reporting Timelines

ZOLL must report to the NCAs where the clinical investigation has commenced:

- for all reportable events as described in section **7.2.4.1** which indicate an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it: immediately, but not later than 2 calendar days after awareness by ZOLL of a new reportable event or of new information in relation with an already reported event.

- any other reportable events as described in section **7.2.4.1** or a new finding/update to it: immediately, but not later than 7 calendar days following the date of awareness by the ZOLL of the new reportable event or of new information in relation with an already reported event.

7.3 Device Relationship

Determination of whether there is a reasonable possibility that an investigational product or device caused or contributed to an AE is to be determined by the Investigator and recorded on the appropriate CRF form. Determination should be based on assessment of temporal relationships, biologic plausibility, association (or lack of association) with underlying disease and presence (or absence) of a more likely cause.

7.3.1.1 Causality Assessment

The relationship between the use of the medical device (including the medical - surgical procedure) and the occurrence of each adverse event shall be assessed and categorized.

The above considerations apply also to the serious adverse events occurring in the comparison group.

The following definitions are used to assess the relationship of the serious adverse event to the investigational medical device or procedures.

1) Not related: relationship to the device or procedures can be excluded when:

- the event is not a known side effect of the product category the device belongs to or of similar devices and procedures;
- the event has no temporal relationship with the use of the investigational device or the procedures;
- the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
- the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event;
- the event involves a body-site or an organ not expected to be affected by the device or procedure;
- the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);
- the event does not depend on a false result given by the investigational device used for diagnosis, when applicable;
- harms to the subject are not clearly due to use error;
- In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

2) Unlikely: the relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.

3) Possible the relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.

4) Probable the relationship with the use of the investigational device seems relevant and/or the event cannot reasonably explained by another cause, but additional information may be obtained.

5) Causal relationship: the serious event is associated with the investigational device or with procedures beyond reasonable doubt when:

- the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
- the event has a temporal relationship with investigational device use/application or procedures;
- the event involves a body-site or organ that
- the investigational device or procedures are applied to;
- the investigational device or procedures have an effect on;
- the serious event follows a known response pattern to the medical device (if the response pattern is previously known);
- the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible);
- other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
- harm to the subject is due to error in use;
- the event depends on a false result given by the investigational device used for diagnosis 17, when applicable;
- In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

ZOLL and the investigators will distinguish between the serious adverse events related to the investigational device and those related to the procedures (any procedure specific to the clinical investigation). An adverse event can be related both to procedures and the investigational device. Complications of procedures are considered not related if the said procedures would have been applied to the patients also in the absence of investigational device use or application.

In some particular cases the event may be not adequately assessed because information is insufficient or contradictory or the data cannot be verified or supplemented. The ZOLL and the

Investigators will make the maximum effort to define and categorize the event and avoid these situations.

Particular attention shall be given to the causality evaluation of unanticipated serious adverse (device) events. The occurrence of unanticipated events related to the use of the device (USADE) could suggest that the clinical investigation places subjects at increased risk of harm than was to be expected beforehand.

8 MONITORING BY DATA MONITORING COMMITTEE

The Data Monitoring Committee (DMC) is used to ensure safety by reviewing cumulative data from the clinical trial at pre-defined intervals for the purpose of safe-guarding the interest of trial participants. The DMC will serve in an advisory role in this trial. The composition, guiding policies, and operating procedures governing the DMC are described in a separate DMC charter. Based on safety data, the DMC may recommend a modification to the protocol or that the sponsor stops the clinical trial/investigation. All final decisions regarding clinical trial/investigation modifications, however, rest with the Sponsor.

9 ADJUDICATION OF EVENTS

The Clinical Events Committee (CEC) is comprised of qualified physicians who are not investigators in the trial. The Clinical Events Committee is responsible for adjudicating specified clinical endpoints based on the specific criteria used for the categorization of clinical events in the trial.

Periprocedural MI will be adjudicated according to the Clinically Relevant Myocardial Infarction After Coronary Revascularization (CRMI) definition.[40] Death, Stent Thrombosis, Spontaneous MI, and Revascularization will be adjudicated per ARC definitions.[27]

Hospitalization due to Heart Failure will be adjudicated per ACC/AHA definition.[48]

The composition, guiding policies, and operating procedures governing the CEC are described in a separate CEC Manual of Operations.

When applicable, sites will provide patients' source documentation per request from the Sponsor and will aploade angiograms into AMBRA website through software service Dicom Grid, Inc., which will de-identify angiograms.

10 RECOMMENDATION FOR DAPT AND STENTS

Control and intervention group patients should receive dual antiplatelet therapy (DAPT) and anticoagulation medication as recommended by the ESC Guideline for the management of acute myocardial infarction in patients presenting with ST-segment elevation.

- This includes aspirin 162 or 325 mg po chewed as soon as feasible.
- This should be followed by loading dose of ticagrelor (preferably crushed or chewed) 180 mg before PCI. If ticagrelor not available, loading dose of prasugrel (60 mg) can be used.
    - Clopidogrel can be used only if the patient cannot take ticagrelor or prasugrel.
- This also includes unfractionated heparin (UFH) given as an intravenous bolus as soon as feasible with subsequent boluses targeted to an activated clotting time of 200 to 250 seconds. If Bivalirudin is used, the infusion should continue for 1-2 hours after PCI is finished.
- Use of an intravenous GP IIb/IIIa inhibitor should be used according to the decision of interventional cardiologist.
- In patients with STEMI in whom clopidogrel was initiated before coronary angiography, it is recommended to switch to either ticagrelor or prasugrel before, or during, or at latest immediately after PCI, if ticagrelor or prasugrel are not contraindicated.
    - Switching from clopidogrel to ticagrelor or prasugrel should include a loading dose of ticagrelor 180 mg (preferably crushed or chewed if before or during PCI) or prasugrel 60 mg if the patient is not at high risk of bleeding, irrespective of the prior dose of clopidogrel.
- Recommended maintenance therapy consists of aspirin 81 mg once daily (or per local practice); ticagrelor 90 mg twice daily for at least 12 months. If ticagrelor not available, prasugrel 5 or 10 mg according to label recommendation can be used.
- If needed, transition to clopidogrel can take place after 30 days post index PCI.
    - The recommended first dose of clopidogrel is 600 mg po 12 h after the last dose of ticagrelor or prasugrel. If maintenance therapy consists of aspirin and clopidogrel, the recommended doses are aspirin 81 mg once daily (or per local practice) and clopidogrel 75 mg once daily.
- Use second or third generation DES. Do not use BMS or BVS or BRS such as Absorb in study patients.

11 RISK ANALYSIS

11.1 Risk Assessment Process

ZOLL has a documented EN ISO 14971:2012 compliant Risk Management process, which includes the identification of risks, risk assessment, identification, implementation and verification of adequate controls (mitigations) to ensure that identified risks have been reduced as low as possible and to ensure the benefits of the intended use as compared to any residual risk is acceptable.

The intent of the Risk Management process is to identify potential hazardous situations related to the design, manufacture, and use of the Proteus IVTM System, evaluate each risk and implement controls to reduce the risks as low as possible.

Risks related to the IVTM System and Sub-Systems (Console, Catheter, Cassette and Temperature Probe) have been evaluated in a number of ways:

- Hazard Analysis – The purpose of the Hazards Analysis is to identify, evaluate and control potential hazards to the patient, user and the environment.
- Software Hazards Analysis - The Software Hazards Analysis is used to investigate potential device Software related hazards and control the potential hazards.
- Design FMECA - The purpose of the Design FMECA is to evaluate failure modes of the device components, or subsystems, to identify potential design failure risk, then evaluate and control potential hazards.
- Process FMECA - The purpose of the Process FMECA is to evaluate failure modes of the device manufacturing process steps to identify process failure risks, then evaluate and control potential hazards.

The results of the Proteus IVTM System Risk Management process was reviewed, and concluded that the risk controls are effective to reduce the risks as low as possible. The ZOLL Proteus IVTM System presents an acceptable risk benefit ratio when used in accordance with its labeling for its proposed intended use: The Proteus IVTM System is intended for use in adult subjects with acute anterior myocardial infarction to induce and maintain hypothermia prior to percutaneous coronary intervention as an adjunctive therapy to reduce anterior infarct size.

Note: See the Investigator Brochure for additional information on the Proteus IVTM System, as applicable.

11.2 Expected Clinical Observations

In subjects who have been treated for myocardial infarction, there are many sequelae of such an event that may be thought to be "normal" effects and not due to the treatment provided. These events may be outside the range of what is considered to be "normal" (e.g., a high lab value such as a shift in potassium), but do not put the patient at risk for harm. These events are therefore expected physiological responses to treatment with therapeutic hypothermia in all patients. Prospectively, these observations may include but are not limited to the following:

- Shift in Potassium levels
- High or low levels of glucose

The expected clinical sequelae of patients treated with hypothermia include, but are not limited to, the following[28]:

- Shivering
- Prolonged ECG intervals
- Bradycardia defined as a heart rate of 40 beats per minute and not requiring treatment (e.g., pacemaker, medications, etc.)
- J wave (also called Osborne wave) can occur at any temperature < 32.3°C
- Blood electrolyte shifts: Calcium, Phosphorus, Magnesium, Chloride
- High or low levels of glucose: Decreased insulin sensitivity and insulin secretion
- Asymptomatic shifts in serum amylase and lipase levels
- Peripheral pulses may be difficult to detect

Cold Diuresis: Increased resistance to ADH or Vasopressin resulting in decreased water or solute reabsorption.

11.3 Potential Clinical Risks

Adverse events that are inherent to a PCI procedure and expected to occur in most subjects for a projected duration according to the opinion of the investigator may be considered unavoidable. Such events include, but are not limited to, those listed in **Table 14**. These adverse events should not be reported during this trial.

Table 14 Expected and unavoidable adverse events related to the PCI procedure

Description of the Event	Time Frame from the Index Procedure (PCI)
Back pain related to laying on Cath lab table	Within 48 hours
Peripheral vasoconstriction	Within 24 hours

Thermal discomfort	Within 24 hours
Incisional pain (pain at access site)	Within 72 hours
Sleep problems or insomnia	Within 72 hours
Mild to moderate bruising or ecchymosis	Within 168 hours

A list of potential (expected) risks that may be associated with use of the Proteus IVTM System is provided below. Since this clinical study utilizes an investigational device, all risks may not be known. However, they are believed to be similar to those associated with the existing intra-vascular temperature management devices in clinical use or commercially available.

The following potential adverse events may occur during the course of the clinical trial.

11.3.1 Potential Adverse Events associated with the Proteus Catheter and Cooling System:

Potential risks related to the Proteus Catheter are reasonably believed to be consistent with the common, known risks of central venous catheters and/or venous introducer sheaths. Potential risks related to cooling, re-warming, and/or the Proteus IVTM System include but are not limited to the following:

- Catheter related injury [embolism (air, thrombus, catheter fragment), clinically significant hematoma, vascular perforation or dissection, arteriovenous fistula, nerve injury, excessive bleeding, pseudoaneurysm]
- Deep vein thrombosis (DVT) requiring treatment
- Infection [local or systemic (pneumonia, sepsis, meningitis, visceral organ)]

11.3.2 Potential Adverse Events associated with the cooling procedure include but are not limited to the following:

- Acute renal failure
- Acute renal insufficiency
- Adverse drug reaction
- Angina
- Blood lysis
- Congestive Heart Failure
- Clinically relevant shivering (BSAS ≥ 2) that cannot be controlled by the antishivering medication regimen

- Dysrhythmia [ventricular tachycardia, ventricular fibrillation or atrial fibrillation requiring intervention, bradycardia (HR ≤ 40 bpm, block)]
- Hyperglycemia / Hypoglycemia
- Hyperkalemia / Hypokalemia
- Hyperphosphatemia / Hypophosphatemia
- Hypotension
- Infection (local, systemic)
- Liver Failure
- Myocardial infarction
- Multi-system organ failure
- Overcooling (temperature <31.0°C for ≥ 20 continuous minutes)
- Overwarming (temperature >38°C for ≥ 20 continuous minutes including dehydration, burns and neurological damage)
- Pancreatitis
- Pulmonary edema
- Peripheral vascular insufficiency
- Thrombocytopenia
- Rebound hyperthermia
- Respiratory failure during cooling or rewarming
- Seizures
- Stroke [Cerebral vascular Accident (CVA)]
- Transient Ischemic Attack (TIA)
- Unstable angina

11.3.3 Risks Associated with Anti-shivering Medications

In order to preserve patient comfort and suppress the shivering response during cooling, a combination of recommended buspirone, where available (or equivalent alternative) and required Pethidine (Meperidine) should be used (see **Attachment II**). As identified in their labeling, the risks associated with the use of these pharmacologic agents in this trial population include the following:

Buspirone (or equivalent alternative)

- Interaction with MAO Inhibitors
- Dizziness
- Nausea
- Headache

- Nervousness
- Lightheadedness
- Excitement

Pethidine (Meperidine)

- CNS Depression
- Hypotension
- Respiratory Depression
- Circulatory Depression
- Respiratory Arrest
- Shock
- Cardiac Arrest

Other reported reactions:

- Lightheadedness
- Dizziness
- Nausea
- Vomiting
- Sweating

11.4 Additional investigations due to the trial

Participation in the clinical trial will involve extra blood sampling for laboratory markers (electrolytes, complete blood count, baseline and peak troponin including upper limit of normal), additional ECGs and the need for cardiac MRI imaging. All of these are standard clinical procedures, and the risks to participants are low. Sites will be carefully monitored for adherence to the protocol. Patients will be screened for appropriateness for MRI prior to enrollment.

11.4.1 Delay in PCI through the use of hypothermia therapy

The probability for potential delay in PCI is considered Occasional. In prior trials of hypothermia for STEMI, the increase in door to balloon time ranged from 9 minutes to 18 minutes. It is noteworthy that this delay was not associated with an increase in infarct size hypothermia patients compared to controls. In fact, patients with anterior STEMI with < 35°C at the time of reperfusion showed smaller infart size. Sites will be trained to incorporate hypothermia into the cath lab workflow while minimizing delay. Feedback will be provided for each case to help maintain efficiency.

11.4.2 Implementation of PCI in patients undergoing hypothermia (patient-related risks).

Potential risks related to the use of hypothermia therapy in patients are outlined in sections 11.2.1 and 11.2.2 above. These risks include: potential adverse events associated with the Proteus Catheter and Cooling System, potential adverse events associated with cooling, and potential risks associated with the anti-shivering medications.

11.4.3 Implementation of PCI with concurrent use of endovascular hypothermia.

The addition of hypothermia as adjunctive treatment of STEMI will potentially lead to more difficult conditions for the Investigator and other users. The ability to integrate hypothermia into the cath lab workflow has been demonstrated successfully in prior clinical trials. Again, thorough training, frequent monitoring, and rapid feedback will help mitigate the challenges of incorporating hypothermia into treatment for STEMI.

11.4.4 The concurrent medication.

Patients who have received medications such as monoamine oxidase inhibitor within a 14 day period will be excluded from the trial to prevent potential interaction with the anti-shivering medications. In patients that receive morphine prior to arrival to the hospital, the pethidine dose will be lowered to decrease the likelihood of respiratory depression.

11.4.5 The supply of 4°C cooled saline solution

The amount of cooled saline solution is limited to 1,000 ml, an amount shown to be well tolerated in the CHILL-MI trial, where the average amount of cooled saline was 1475 ml. Again, careful training and monitoring will help to avoid unnecessary exposure to larger volumes of saline.

11.4.6 Other procedures within the clinical trial

The risk of adverse interaction or influence of other procedures within the clinical trial are deemed to be low. In prior hypothermia trials in STEMI, there was no interference with the stenting procedure, with resuscitation efforts for arrhythmias or cardiogenic shock. Hypothermia does inhibit the absorption and metabolism of clopidogrel, a anti-platelet inhibitor, given to reduce the risk of stent thrombosis. This risk will be mitigated by calling for adherence to ESC guidelines which recommend either prasugrel or ticagrelor, both of which are less affected by hypothermia.

11.5 Potential Clinical Benefits

Although no assurances or guarantees can be made, there is a reasonable expectation that the use of this investigational device is safe within the context of the trial and may be beneficial. Cooling using the device, for instance, may result in improved temperature control relative to the standard techniques already in use at the sites.

The primary benefits of therapeutic hypothermia have been shown to be:

- Improved patient survival
- Improved heart tissue salvage after the ischemic event

Additional potential benefits of therapeutic hypothermia with the Proteus System may include:

- Faster cooling
- More accurate control of the cooling procedure than with surface cooling
- Further improved survival

There is no guarantee that participation in this trial or use of hypothermia will benefit the trial subject. However, collection of such trial data may provide added benefit for future myocardial infarction subjects.

11.6 Methods to Minimize Risk

All efforts will be made to minimize risks by selecting investigators who are experienced and skilled in using minimally invasive catheter-based cardiovascular interventions and who have been adequately trained. Also, risk minimization activities were performed during development and design verification tests of the device. Activities intended to minimize risks include the following.

- Investigator and trial personnel training will be conducted to share information regarding the design of the Proteus IVTM System, its application, pre-clinical results, and clinical trials on comparable intra-vascular cooling devices.
- Adherence to eligibility criteria and screening procedures will ensure that appropriate patients are enrolled.
- Adherence to the Proteus IVTM System Instructions for Use packaged with the device.
- Corrective and preventative actions will be implemented by ZOLL, as necessary, if deviations from recommendations in the protocol or IFU are observed.
- Clinical support by ZOLL representative will be provided during the enrollment in the study and thereafter if needed. ZOLL representatives will only have advisory role.
- The subjects will be carefully monitored throughout the trial period.
- The investigator will evaluate the subject adverse events during the course of the trial.
- Data submitted from the investigative centers will be monitored during the course of the trial.

- Monitoring visits will be conducted to evaluate protocol compliance and data quality.
- Safety and effectiveness data obtained during the course of the trial will be shared with investigators in periodic reports to increase understanding of the device and potential adverse events.
- An independent Data Safety Monitoring Board (DSMB) will monitor safety throughout the clinical trial. Stopping rules will be discussed with the DSMB and applied for subject safety through enrollment.

Detailed trial procedures are provided in **Section 6.8 - Clinical Trial Procedures**.

11.7 Risk – Benefit Assessment

To date, there have been five clinical trials that have reported on the safety and effectiveness of therapeutic hypothermia in AMI and one in Radio-Contrast nephropathy (COOL-RCN Trial), with a total of more than eleven hundred patients being enrolled in total with at least half of those treated with therapeutic hypothermia. The rate of adverse events are well reported in these populations (see section 5, Prior Investigations), and the risks are clearly categorized for these trials. In summary, the number of trials, patients enrolled, and low numbers of safety events reported indicate that therapeutic hypothermia in this patient population is at an acceptable risk level to engage in this trial.

There is significant morbidity and mortality associated with the numerous clinical conditions outlined in this report, and therapeutic hypothermia has shown promise to greatly improve clinical outcomes in these patients. In particular, patients with anterior STEMI have a higher incidence of congestive heart failure, cardiogenic shock, and cardiac mortality. A significant reduction in infarct size in these patients, with therapeutic hypothermia, has the promise to reduce these adverse clinical outcomes. Risks associated with the use of the Proteus IVTM system have been reduced via the Risk Management Process, and are deemed acceptable, considering the potential benefits. We conclude that the use of the Proteus IVTM system for medical practice is justified and warranted.

Risk assessment of the Proteus IVTM System has been performed in accordance with the ISO 14971:2012.[30] The Proteus IVTM System is safe and presents an acceptable risk benefit ratio to provide cooling or warming of patients when:

- Used by and under the supervision of a qualified medical practitioner
- In patients for whom the risks of a central line are acceptable

- In intensive care environments equipped to handle clinical conditions warranting use of the device under this protocol
- Used according to the Instructions For Use (IFU)

12 RECORDS AND REPORTS

Throughout the course of this clinical trial, ZOLL, the investigators, and reviewing MEC are responsible for the records and reports detailed in the following sections.

12.1 Investigator Records

Investigators must retain all trial records required by ZOLL and by the applicable regulations in a secure and safe facility. The investigator must consult a ZOLL representative before disposal of any trial records and must notify ZOLL of any change in the location, disposition, or custody of the trial files.

Trial records are those that individually and collectively permit evaluation of the conduct of the trial and the quality of the data produced. ZOLL's SOP requires that all clinical trial data be kept for a minimum of 15 years and all data used in submissions be kept for the life of the corporation. It is the site's obligation to inform ZOLL if their own policy does not comply with the sponsor's requirement so necessary arrangements can be negotiated. It is ZOLL's responsibility to inform the investigator/institution as to when these documents no longer need to be retained.

The investigator is responsible for the preparation (review and signature) and retention of the records cited below.

- All correspondence with another investigator, MEC, ZOLL, a monitor, or FDA, including required reports and trial documents which pertain to the investigation.
- Records of receipt, use, and final disposition of a device.
- Records of each subject's case history and exposure to the device. Case histories include the Case Report Forms (CRFs) and supporting source data (signed and dated informed consent forms, medical records, e.g., progress notes of the physician, patient's hospital chart, nursing notes).
- The clinical investigational plan, with documents showing the dates of and reasons for each deviation from the protocol.
- Any other records that are required to be maintained by local regulations or by specific regulatory requirements for a category of investigations or a particular investigation.
- Any other record that the reviewing MEC requires to be maintained for the subject investigation.

12.2 Investigator Responsibilities

The participating investigator is responsible for adhering to this Clinical Investigational Plan (CIP), FDA CFR, ISO 14155 and Declaration of Helsinki (Regulatory requirements of his/her country local law).

Specifically, the Principal Investigator at each site shall:

a) indicate his/her acceptance of the CIP in writing,
b) conduct the clinical investigation in compliance with the CIP,
c) create and maintain source documents throughout the clinical investigation and make them available as requested during monitoring visits or audits,
d) ensure that the investigational device is used solely by authorized users as specified in 6.2, and in accordance with the CIP and instructions for use,
e) propose to the sponsor any appropriate modification(s) of the CIP or investigational device or of the use of the investigational device,
f) refrain from implementing any modifications to the CIP without agreement from the sponsor, EC and regulatory authorities, if required,
g) document and explain any deviation from the approved CIP that occurred during the course of the clinical investigation,
h) ensure that an adequate investigation site team and facilities exist and are maintained and documented during the clinical investigation,
i) ensure that maintenance and calibration of the equipment relevant for the assessment of the clinical investigation is appropriately performed and documented, where applicable,
j) ensure the accuracy, completeness, legibility and timeliness of the data reported to the sponsor in the CRFs and in all required reports,
k) maintain the device accountability records,
l) allow and support the sponsor to perform monitoring and auditing activities,
m) be accessible to the monitor and respond to questions during monitoring visits,
n) allow and support regulatory authorities and the EC when performing auditing activities,
o) ensure that all clinical-investigation-related records are retained as required by the applicable regulatory requirement(s), and
p) sign the clinical investigation report, where applicable.

The investigator is responsible for the preparation and submission of the reports cited in **Table 15**. Reports must be prepared in complete, accurate and timely manner. These reports may be subject to regulatory inspection (and ZOLL) and copying, and the retention requirements described above

for Investigator Records. In addition to the reports listed in **Table 15**, the reviewing MEC may request reports pertaining to any aspect of the clinical trial.

Written approval from the Medical Ethics Committee (MEC) with authority for the participating site will be obtained prior to the start of the study. The investigator or if applicable, the Sponsor, is responsible for submitting all required documents to the MEC. At a minimum the following documents will be submitted:

• Clinical Investigational Plan (CIP)

• Patient Informed Consent documents in the local language

• Any other written information to be provided to the subjects in the local language

• Investigator Brochure (IB) (as required)

• Other documents will be submitted as per local requirements

After obtaining MEC approval, the investigator will submit the approval letter indicating the approved version of the CIP, Patient Informed Consent, IB and any other reviewed documentation to ZOLL.

Table 15 Investigator Reporting Responsibilities to Sponsor and MEC

REPORT	SUBMIT TO	DESCRIPTION/CONSTRAINTS
Withdrawal of MEC Approval	Sponsor	The investigator must report a withdrawal of the reviewing authority within **5 working days**.
Case Report Form (CRF)	Sponsor & Monitor	CRFs should be completed as soon as possible after any trial related procedure takes place.
Deviation from Investigation Plan (Emergency)	Sponsor & MEC	Notification must be made within **5 working days** if the deviation was made to protect the life or physical well-being of a subject.
Deviation from Investigation Plan (Other – Non Emergency)	Sponsor & MEC	If the deviation may affect the scientific soundness of the plan or the rights, safety and welfare of the subjects (and is not an emergency), then **the deviation must be approved by ZOLL, the MEC, and the reviewing authority prior to its implementation**. If the deviation does not affect these issues (trial soundness, rights, safety, etc.) then only ZOLL must approve it, (except in cases which are beyond the control of the investigator—see section on Protocol Deviations).
Failure to Obtain Informed Consent	Sponsor & MEC	The Investigator must notify ZOLL and the reviewing authority within **5 working days** after device use. The investigator must submit notification after device use or after the investigator first learns of the absence of informed consent. The report must include a brief description of the circumstances surrounding the failure to obtain informed consent and include written concurrence by a licensed physician not involved in the investigation. Failure to obtain informed consent must be reported to the MEC as required by local regulations.
Final Report	Sponsor & MEC	This report must be submitted within **3 months** after termination or completion of the investigation.

12.3 Sponsor Records

All Sponsor documents and records shall be maintained as indicated by ZOLL's Quality System. ZOLL will maintain the following trial -related records in accordance with ZOLL record retention policies and procedures following the completion of this investigational plan. Clinical data for regulatory submissions and publications will be retained for the life of the corporation.

- All correspondence pertaining to the investigation with the sponsor, a monitor, an investigator, an MEC, regulatory agencies, including required reports.

- Records of shipment and disposition of the investigational device.
- Signed investigator agreements including the financial disclosure information required to be collected and current signed and dated curriculum vitae.
- Records of adverse events and device deficiencies.
- List of participating institutions
- Investigational product accountability reports including record of receipt, use, or disposition of the device(s) that relate to type, quantity, serial numbers of devices, and date of receipt, names of persons who received, used, or disposed of each device and why and how many devices have been returned to ZOLL or otherwise disposed
- All signed and dated case report forms submitted by investigator, samples of patient informed consents, and other information provided to the subjects
- Copies of all MEC approval letters and relevant MEC correspondence
- Names and evidence of the institutions in which the clinical investigation will be conducted
- Insurance certificates
- Forms for reporting adverse events and device deficiencies
- Names/contact addresses of monitors
- Statistical analyses and underlying supporting data
- Final report of the clinical investigation
- The Clinical Investigational Plan, Clinical Monitoring Plan (CMP), Investigator Brochure (as applicable), and study related reports
- Study training records for center personnel and ZOLL personnel participating in the trial
- Any other records that MEC and /or competent authority requires to be maintained by regulation or by specific requirement for a category of investigation or a particular investigation.

12.4 Sponsor Reports

ZOLL Circulation, Inc. is responsible for the classification and reporting of reportable adverse events and device deficiencies and ongoing safety evaluation of the clinical investigation in line with local regulatory requirements.

ZOLL Circulation, Inc. will assure that all Serious Adverse Events and reportable Device Deficiencies are reported to the Competent Authorities in accordance with European Medical Devices directives and all applicable national regulations.

ZOLL Circulation, Inc. is responsible for the reports cited in **Table 16**. These reports are subject to regulatory retention and inspection requirements. Governing Regulatory Agencies or the reviewing MEC may request reports pertaining to any aspect of the clinical trial.

Table 16: ZOLL Reporting Responsibilities

REPORT	SUBMIT TO	DESCRIPTION
Unanticipated Adverse Device Effects; SAEs and Reportable DDs	Relevant authorities and MECs	Reporting timeframe as per local regulatory requirements.
	Investigators	Notification throughout the course of the trial when appropriate (based on perceived risk)
Premature termination or suspension of the Clinical investigation	Investigators, MECs, Relevant Authorities	Provide prompt notification of termination or suspension and reason(s).
Subject enrollment Completed	Investigators, MEC and Relevant regulatory Authorities upon request	ZOLL will notify the investigators within 30 working days of the completion of enrollment. Investigators will, in turn, inform their MECs, when required.
Withdrawal of MEC approval	Investigators, MECs	Notification within five working days.
Final Report	Investigators, MECs, (and other relevant Authorities upon request)	A final report will be submitted to investigators, and MECs within six months after completion or termination of this study. The investigators shall have the opportunity to review and comment on the final report. If a clinical investigator does not agree with the final report, his/her comments shall be communicated to the other investigators. The principal clinical investigator in each center shall sign the report.

13 MONITORING AND AUDITING PROCEDURES

13.1 Clinical Trial Sponsor and Monitors

ZOLL is the Sponsor of the clinical trial. It is the responsibility of the sponsor to ensure that proper monitoring of the investigation is conducted. Clinical trial monitoring and auditing will be done

by appropriately trained personnel appointed by the trial sponsor to ensure that the investigation is conducted in accordance with ZOLL's requirements and applicable laws and regulations.

A monitor is an individual designated by a sponsor or contract research organization to oversee the progress of an investigation. The monitor may be an employee of a sponsor or a consultant to the sponsor, or an employee of or consultant to a contract research organization. The monitor will be trained on the device, investigational plan, informed consent, instructions for use, applicable ZOLL procedures, electronic data capture system, and regulatory requirements. The monitor will periodically check and report on the progress of the clinical trial at an investigational site or other data gathering organization or ZOLL facility.

13.2 Monitoring Methods

Monitoring of the clinical trial will be a continuous, interactive process to ensure that high-quality data is obtained in compliance with the clinical investigational plan and regulatory requirements. Monitoring functions will be conducted by ZOLL, and/ or a contract research organization and/or other designees. Specific monitoring requirements are detailed in the Trial Monitoring Plan (maintained in the ZOLL COOL-AMI clinical trial project files). Frequent communication will be maintained with each investigational site to keep both the clinical center and ZOLL up-to-date and aware of the trial progress. Case Report Forms will be reviewed for completeness and accuracy.

ZOLL will monitor sites in accordance with the monitor's tasks set under Section 8.2.4 of Standard DIN EN ISO 14155:2012-01. These include visits to the clinical trial sites before the start of, during and at the end of the clinical trial. On-site monitoring of all trial centers will be frequent enough (at a minimum annually) to assure continued integrity and acceptability of the data. Accuracy of data reported on case report forms will be verified by comparison to source documents. Reports of monitoring visits will be provided to the clinical trial personnel at each site. Corrective action will be taken to resolve any issues of noncompliance. If ZOLL finds that an investigator is not complying with the executed trial agreements, the investigational plan, the applicable national regulations, or the requirements of the reviewing MEC, then prompt action will be taken to secure compliance. In addition, shipment of the device may be stopped or the participation of the investigator may be terminated. Additional information is provided in **Section 6.30** – **Trial Closure**.

13.3 Monitoring Visits

Scheduled visits to the clinical investigational site will occur at the following times: prior to the start of the clinical trial (pre- trial qualification visit), at initiation of the trial (during first index

procedure or shortly thereafter), interim visits throughout the clinical trial as required, annually, and upon completion of the clinical trial.

13.4 Pre-trial Qualification Visit

A pre- trial visit will be conducted by ZOLL personnel (or designees) to review the clinical investigational plan and regulatory requirements with the investigator and the trial personnel to assure that they:

- Understand the investigational status of the device and the requirements for its use and accountability.
- Understand the clinical investigational plan.
- Understand the requirements for an adequate and well-controlled clinical trial.
- Understand and accept the obligation to conduct the clinical investigation in accordance with the national regulations.
- Understand and accept the obligation to obtain informed consent in accordance with the national regulations.
- Understand and accept the obligation to obtain MEC approval before the clinical trial is initiated, ensure continuing review of the trial by the MEC, and keep ZOLL informed of MEC approval and actions concerning the clinical trial.
- Have access to an adequate number of eligible patients to participate in the trial (at a minimum: 1 patient/center/month).
- Have adequate facilities and resources to conduct the trial. This includes resources appropriate for use of electronic data capture systems.
- Have sufficient time from other obligations to carry out the responsibilities of the clinical trial.
- Sign the Investigator Agreement and trial contracts (prior to enrollment of patients).

A report of the pre- trial qualification visit will be completed. Resolution of any concerns or completion of any appropriate follow-up activities stemming from the pre- trial visit also will be documented.

13.5 Initiation Visit

ZOLL clinical personnel (or designees) will provide assistance for both technical concerns and trial management issues during the initiation visit. Enrollment of the first patient at each clinical site may or may not coincide with this visit. Any observations will be documented and issues requiring follow-up will be identified on a monitoring report. Training of trial personnel also will be documented.

13.6 On-Site Interim Monitoring Visits

On-site monitoring visits will be made on an as-required basis (and at least annually) to assess adherence to the clinical investigation plan, MEC review of trial progress, maintenance of records and reports, and selected review of source documents for accuracy, completeness, legibility, and omissions. The monitors will acquire information to assess the progress of the trial (toward meeting trial objective) and identify any concerns that stem from observation of device performance and/or review of the investigator's patient records, trial management documents, and patient informed consent documents. Monitoring reports will be generated along with communications to the investigator, which document the result of the monitoring visit and any recommended actions. Resolution of concerns and completion of assigned tasks will be documented.

13.7 Audits

An on-site audit may be completed periodically throughout the trial at each clinical site by an independent group. The purpose of the audit will be to ensure compliance to the investigational plan and regulatory requirements, e.g., written informed consent was documented, information recorded on the case report forms is complete and accurate as compared to source documentation, protocol deviations are noted, and device accountability is accurate and complete. A randomly selected number of patient records and other supporting documents will be compared to the case report forms. A record of the findings and recommended actions to correct deficiencies will be documented on the audit report.

13.8 Final Monitoring Review

Depending upon the status of the trial at each center, a close-out or final visit may be conducted. Any ongoing responsibilities will be discussed with the investigator and the trial center coordinator. A final monitoring report, which includes, at a minimum, disposition of any unused devices, will be completed.

14 DATA MANAGEMENT PROCEDURES

ZOLL will oversee all data management functions. ZOLL will be responsible for database development, system maintenance, user training, data queries, and report generation.

14.1 Case Report Forms

ZOLL will use an electronic data capture (EDC) system to collect patient data. The electronic case report forms (eCRFs) are the primary component of EDC and are based on the sample forms that will be provided in a separate document. Training on use of the system will be provided to the trial site personnel. Instructions for completion of the eCRFs also will be provided.

The eCRFs must be completed, saved, and locked via electronic signature by the Investigator using a unique ID and password. This ID and password are for the use of the investigator only and may not be used by any other person. Because of the potential for errors or inaccuracies in transcribing data into eCRFs, source documentation must be maintained in each subject's hospital chart and/or electronic medical record. The eCRFs and source documentation must be available at all times for inspection by the trial monitors or regulatory inspectors.

Changes made to eCRFs will be electronically recorded in a complete audit trail that cannot be changed, but can be accessed by authorized personnel at any time. All data are transmitted via the Internet in an encrypted fashion. When received at the server site, the data are decrypted and stored. Data can be extracted for ZOLL review and analysis at any time.

14.2 Source Documentation

Regulations require that an investigator maintain information in the trial subject's medical records to corroborate data collected on the eCRF. To comply with these regulatory requirements, the following information will be maintained and made available as required by ZOLL and/or its designees and/or regulatory inspectors. Shadow charts are not appropriate or adequate source documentation. Complete medical (clinical and hospital) records include the following documentation.

- Medical history/physical condition of the patient before involvement in the trial sufficient to verify clinical protocol eligibility criteria.
- Description of cooling procedure (material used, drugs administered during the procedure, device identification information and disposition, date, time, angiographic and clinical findings, etc.).
- Electronic data downloaded from the ZOLL Proteus IVTM System.
- Signed notes in the subject's medical record on the enrollment day that identify and include: the subject's date of enrollment, procedure date, the trial sponsor (ZOLL), clinical site name, the subject-assigned identification number, the subject- assigned enrollment number, and documentation and confirmation that the appropriate informed consent was obtained.
- Dated and signed notes for each subject's trial visit.

- Lab results.
- Baseline ECG, angiogram, and MRI reports, etc.
- Dated printouts or reports of special assessments (ECG baseline report, imaging report, etc.).
- Adverse event reporting and follow-up of the adverse events. Information in the medical chart should include at a minimum the following: event description, severity, seriousness, onset date, date site became aware of event, duration, relation to trial device, treatment, and outcome of the adverse event.
- Trial subject's condition upon completion of or withdrawal from the trial.
- Trial subject's medical status, including all SAEs out to 1 year following trial enrollment.
- All notes related to trial subject's KCCQ and the New York Heart Association Functional Class questionnaires.

14.3 Transmission of Data

Required data will be recorded on the appropriate eCRF at the time of or as soon as possible after the patient visit. The eCRFs and any requested supporting source documents must be sent to ZOLL and/or retrieved from the investigator during monitoring visits. Questions about completion of the eCRFs may be directed to the ZOLL COOL AMI clinical team at Clin-safety@zoll.com

14.4 Data Queries

During monitoring visits, the Monitor will perform a 100% review of all variables, i.e., demography, inclusion/exclusion criteria, safety, effectiveness, on the eCRFs with each subject's source documents. Any discrepancies will be queried by ZOLL or its designee and must be resolved by the investigational site staff and investigator in a timely manner. Queries also will be generated by ZOLL data management personnel during routine review of the data on the electronic data capture system.

15 STATISTICAL ANALYSIS PLAN

The objective of this trial is to evaluate the safety and effectiveness of therapeutic hypothermia, using the ZOLL Proteus IVTM System, as an adjunctive therapy for patients presenting with acute anterior myocardial infarction (AMI) and undergoing percutaneous coronary intervention (PCI). An analysis summarizing outcomes for the Primary Effectiveness Endpoint and the Primary Safety Endpoint will be created after the last randomized subject has completed the 30 day follow-up interval. The results of the primary endpoints will be summarized in the final clinical study report.

Two interim analyses are planned to be performed at approximately 50% and 75% of randomization, once subjects have completed 4-6 day cMR follow-up. At the interim stage, the

trial will be stopped to reject the null hypothesis of no difference or continue enrolling. Another report will be issued summarizing all endpoints after all subjects have completed 12 month follow-up.

15.1 Data Analysis

Analysis Data Sets

The Intention-to-Treat (ITT) analysis set will be used for primary statistical analyses and summaries. The ITT population includes subjects who have signed an informed consent and have been randomized to the Test Arm or the Control Arm of the trial. ITT subjects will be evaluated according to the group to which they were randomized.

The Per-Protocol (PP) analysis set will also be evaluated. The PP population includes those subjects who met inclusion and exclusion criteria, were randomized to either the Test or Control arm, received the treatment to which they were randomized, and complied substantially with the treatment timeline and steps of this protocol without major protocol violations.

The Safety Analysis Set will be used to evaluate safety endpoints. These will be all of the subjects included in the study as defined by the ITT analysis set and will include Roll-In subjects. For the safety analysis, subjects will be followed for all adverse events for 30 days post procedure. Additionally, all subjects will be followed for 12 months for the incidence of Serious Adverse Events (SAEs), Death and Heart Failure (as assessed by NYHA and Kansas City Cardiomyopathy Questionnaire (KCCQ)).

Infarction Size (IS) is defined as % Left Ventricular Mass as measured by Cardiac Magnetic Resonance (cMR) imaging. Infarct Size (IS) will be assessed by Cardiac Magnetic Resonance (cMR) at 4 – 6 days following the index procedure. Infarct Size will be assessed in subjects in the ITT analysis set and also in the Per-Protocol analysis set.

The Safety Analysis Set will be used to evaluate safety endpoints. These will be all of the subjects included in the study as defined by the ITT analysis set and will include the following clinical components evaluated at 30 day follow-up visit (30 day ± 7 days):

Secondary Endpoint Analysis:

The following clinical components of MACE will be evaluated at 30 day follow-up visit (30 day ± 7 days):

- Death (Cardiac, Vascular, Non-Cardiovascular)
- Myocardial Infarction (MI)
  - Attributable to target vessel (TV-MI)
  - Not attributable to target vessel (NTV-MI)
- Target Lesion Revascularization (TLR)
  - Clinically-indicated TLR (CI-TLR)
  - Not clinically-indicated TLR (NCI-TLR)
- Target Vessel Revascularization (TVR non TLR,)
  - Clinically-indicated TVR non TLR
  - Not clinically-indicated TVR non TLR
- Non-Target Vessel Revascularization (NTVR,)
  - Clinically-indicated NTVR
  - Not clinically-indicated NTVR
- All coronary revascularization

In addition, Stent Thrombosis will be evaluated at 30 day follow-up visit (30 day ± 7 days):

- Evidence (Definite and Probable)
- Timing (Acute, Sub-acute)

Additional Observational and Descriptive Analysis:

In addition to the secondary endpoint, safety of the trial is also analysed by the following observational and descriptive analysis. These events are not endpoints for the study:

- the following serious adverse events will be evaluated at 30 day follow-up visit (30 day ± 7 days):
  - Stroke
  - Cardiogenic shock
  - Pulmonary embolism
  - Pulmonary edema
  - Atrial fibrillation
  - Ventricular fibrillation
  - Vascular complications requiring intervention
  - Bleeding requiring transfusion of 2 units or greater
  - Cooling catheter access site infection
  - Systemic infection
  - Deep Venous Thrombosis (DVT)
  - Bradycardia
  - Hypotension

- The following serious adverse events will be evaluated at 12 month follow-up visit (12 month ± 14 days):
  - Death (Cardiac, Vascular, Non-Cardiovascular)
  - Stent Thrombosis
    - Timing (Acute, Sub-acute)
    - Evidence (Definite and Probable)
  - Hospitalizations due to Heart Failure

15.2 Statistical Methods

Baseline demographic and clinical characteristics will be summarized for each arm using descriptive statistics. Continuous variables will be reported with mean, standard deviation, median, and range. Discrete variables will be reported as frequency and proportion. A $\chi 2$ test or Fisher exact test (for small frequencies) will be used to compare discrete variables; t-test or Wilcoxon test (for non-normal data) will be used to compare the 2 arms with continuous variables for randomized subjects in the trial.

The primary effectiveness endpoint is to detect a 20% reduction of mean infarct size in the Test Arm compared to Control Arm where infarct size (%LV Mass) is measured by cMR at 4-6 days. The mean, median, standard deviation, and range will be presented for infarct size. A two sample t-test will be used to test the null-hypothesis of no difference in average infarct size test and control arm P-value will be reported with $p<0.05$ considered statistically significant. Infarct size will further be evaluated in subgroups and with ANOVA models.

For the primary safety endpoint of MACE (as defined by CD, All MI, and CI-TLR) at 30 days, all events will be tabulated and reported. Per-patient rate of composite MACE will be compared between the two arms with 1-sided Fisher's exact test.

Two interim analyses are planned to be performed at approximately 50% and 75% of randomization, once subjects have completed 4-6 day cMR follow-up. At the interim stage, the trial will be stopped to reject the null hypothesis of no difference or will continue enrolling. Based on the Lan-DeMets method for group sequential trials using O'Brien-Fleming boundaries, the levels of significance for the interim analyses are alpha=0.00305 (50% information fraction), alpha=0.01832 (75% information fraction), and alpha=0.044 (final analysis).

All analyses for effectiveness will be conducted in intent-to-treat and per-protocol analyses set. All analyses for safety will be conducted in the safety dataset. Imputation will be made for missing infarct size (LV%) in intent-to-treat analyses set per Intention-to-Treat principle; details are described in the Statistical Analysis Plan.

15.3 Sample Size Justification

The primary effectiveness analyses is designed to detect a relative reduction of 20% in mean anterior myocardial infarct size (IS), as determined by Cardiac Magnetic Resonance (cMR) imaging at 4-6 days post infarct in the Test Arm (cooling + PCI) compared to the Control Arm (PCI only). The absolute magnitude of a relative reduction of 20% depends on the mean IS in the control arm, which is assumed to be approximately 17 %LV. Therefore, the treatment effect of interest is an absolute difference of 3.5 %LV.

The hypothesis for the primary effectiveness endpoint is the following for patients randomized 1:1 in Treatment Arm vs Control Arm:

H_0: $\mu_T = \mu_C$
H_A: $\mu_T \neq \mu_C$

Null hypothesis:

The null hypothesis is that the mean infarct size in the Test Arm is equal to the mean IS in the Control Arm.

Alternative hypothesis:

The mean infarct size in the control arm is not equal to mean infarct size of control arm.

This 20% relative reduction is defined as absolute value 3.5 %LV and accounted for in our sample size calculation as minimally detectable effect. This assumption is based on previous studies with anterior infarct size measured with cMR reporting between 17-20% absolute %LV in anterior infarct (***Tables 17 & 18***). Therefore, a relative reduction of 20% can vary depending on the mean infarct size of the control arm. Assuming a representative mean infarct size of ~17% in controls, we assume absolute difference of 3.5 %LV is equivalent to 20% mean anterior infarct size would be an adequate detection limit for effect.

Based on these assumptions--standard deviation of 12.0 %LV, two-tailed t-test of difference between means, a normal distribution, 80% power (beta=0.2), with the final analysis will be conducted using a two-sided test at the alpha=0.044 level of significance (adjusted for the two interim analyses)-- the required total sample to detect a mean difference of 3.5 %LV with 80% power is 384 subjects (192 subjects per group). Assuming 24% loss to follow-up, the trial plans for an enrolment up to 500 randomized subjects (250 in each arm) for 4-6 days cMR imaging follow-up.

Table 17: Clinical trials reporting anterior mean infarct size measured by cMR 4-6 days in PCI trials (Control Group Only) and calculated 20% relative reduction

Study name	Anterior n	Mean infarct size	Standard Deviation	20% relative reduction
APEX-AMI[41]	**60**	**16.6**	**10.7**	**3.3**
LIPSIAABCIXIMAB[42]	**63**	**25.3**	**16.1**	**5.1**
LIPSIA-STEMI[43]	**38**	**18**	**16.0**	**3.6**
CRISP-AMI [44]*	**142**	**37.5**	**20.1**	**7.5**
INFUSE-AMI[45]	**172**	**17.3**	**10.2**	**3.5**
RAPID-MI ICE[1]	**7**	**19.7**	**8.5**	**3.9**
CHILL-MI[37]	**21**	**26.5**	**10.9**	**5.3**
AMI EU PILOT	**21**	**23.3**	**12.0**	**4**

*>60% are large proximal infarcts

A range of standard deviation in the table expected is represented by anterior infarct data measured with cMR from separate and pooled analyses of previous hypothermia trials with AMI patients cooled below 35°C: RAPID-MI ICE (2009), CHILL-MI (2013), AMI EU Pilot (ongoing) as described below in **Table 18.**

Table 18: Hypothermia trials using cMR measured infarct size as primary outcome

	RAPID-MI ICE (2009)	CHILL-MI (2013)	AMI EU Pilot (2017)	Pooled AMI EU Pilot, RAPID-MI-ICE, CHILL-MI
n (Control vs Cooled)	7 vs 5	21 vs 15	21 vs 19	49 vs 39
Control Mean LV%	19.7	26.5	23.3	24.5

	RAPID-MI ICE (2009)	CHILL-MI (2013)	AMI EU Pilot (2017)	Pooled AMI EU Pilot, RAPID-MI-ICE, CHILL-MI
20% reduction in infarct	3.94	5.3	4.7	4.9
Std Dev (control)	8.5	10.9	12.0	10.5
Std Dev (cooled)	6.5	9.3	10.3	11.0

The potential impact of variations in control infarct size and variability is presented in ***Table 19.***

Table 19: Sample size estimates with alternative standard deviation and detection limit

Mean Difference in infarct size for detection (%)	Standard Deviation	Estimated Sample Size	Total Enrollment (with 24% drop-out)
3.0	**9**	**288**	380
3.0	**10**	**355**	468
3.0	**11**	**430**	566
3.0	**12**	**506**	666
3.5	**9**	**212**	280
3.5	**10**	**260**	342
3.5	**11**	**314**	414
3.5	**12**	**374**	500
4.0	**9**	**162**	214
4.0	**10**	**200**	264
4.0	**11**	**240**	316
4.0	**12**	**286**	376

The primary safety endpoint is a composite endpoint. For the sample size calculation, expected incidence is based on a literature review of acute MI hypothermia trials that combined six studies: Dixon et al, COOL MI, ICE-IT, RAPID MI-ICE, CHILL-MI, VELOCITY[46] which resulted in a 30-day MACE rate of 6.6% in the Control patients and 7.5% in treatment patients. Previously, AMIHOT II trial defined 30-day MACE rate comprised of death, reinfarction, target vessel revascularization, and stroke used a non-inferiority hypothesis with a 6% equivalence delta and 7% in the Control patients[47].

The hypothesis for the primary safety endpoint is the following:

$\mathbf{H_0}$: $\pi_T \geq \pi_C + 6\%$

$\mathbf{H_A}$: $\pi_T < \pi_C + 6\%$

π_T and π_C are the underlying proportion of patients having a MACE event.

An enrollment of 500 patients would be able to demonstrate 91% power and 95% 1-sided significance. The safety endpoint will be considered to have been met if there is a high posterior probability of non-inferiority [i.e. P ($\pi t < \pi c + 6\% > 95\%$)]. With a drop-out rate of 20%, the power is calculated to be 86%.

16 PUBLICATION

At the conclusion of the trial, a multi-center manuscript will be prepared for publication. Publications will be managed by the Sponsor, its designee and the Advisory board. Additional publications from any single site will be considered but only after the multi-center publication.

17 INTELLECTUAL PROPERTY

In all documents the company name of ZOLL Circulation® will be referred to in short hand as ZOLL. ZOLL® is a registered trademark of ZOLL Medical Corporation. The Proteus IVTM System is a trademark of ZOLL Circulation, Inc. Proteus Catheters, Cassettes and Temperature Probes (X-Probe) are registered trademarks of ZOLL Circulation, Inc.

18 STATEMENT OF COMPLIANCE

1. Sponsor and Investigator will conduct the clinical investigation in accordance with the ethical principles that have their origin in the Declaration of Helsinki.
2. Sponsor and Investigator will comply with ISO 14155:2011 and any regional or national regulations, as appropriate.
3. Investigator will not begin the clinical investigation until Investigator obtains the required written approval or favorable opinion from the MEC or regulatory authority, if appropriate.
4. Investigator will follow any additional requirements imposed by the MEC or regulatory authority, if appropriate.

ATTACHMENT I – REFERENCES

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ATTACHMENT II – ANTI-SHIVERING PROTOCOL

Shivering Suppression Guidelines

Turn on IVTM System console to initiate system and begin cooling of coldwell

↓

Obtain Informed Consent

↓

Administer Buspirone 60 mg PO/NG x 1 immediately

↓

Place Bair Hugger on upper body; set to "high"; forced-air cover should be adjacent to skin. Put one blanket on top.

↓

Closer to the time of device deployment, **Pethidine 1 mg/kg IV (up to 100 mg)**

***Morphine and/or other sedatives are often administered in the setting of an acute MI Morphine and Pethidine (Demerol) are both opiate narcotics and if possible, morphine should be held as the combination may cause over-sedation. Consider 0.5 mg/kg Pethidine IV, if Morphine has been administered.

↓

At 15 minutes, Pethidine 0.5mg/kg IV should be administered.

Then a 25 mg/hr IV infusion of Pethidine (up to 80 kg patient) or 35mg/hr (> 80 kg patient) should be initiated and maintained for the duration of device deployment.

***Make sure the patient has a respiratory rate ≥ 10 breaths/minute.

What to do if shivering occurs:

First, try **repositioning the Bair Hugger** or changing its settings to increase the heat delivered to the patient's surface.

Second, consider **increasing dose of Pethidine**. Prior to giving additional Pethidine, look for signs of respiratory depression (i.e. decreased Respiratory Rate, decreased O2 Saturation by Pulse Ox.) If it is decided that the patient can tolerate additional Pethidine the following may be tried:

1. An IV dose of 25 mg x 1 may be given
2. If Infusion rate is 25mg/hr, the rate may be increased to a maximum of 35 mg/hr

If the shivering persists following the above measures, **consider raising the target temperature on the Proteus Console by 0.5°C** (i.e. from 32.0°C to 32.5°C). If this does not work after 5-10 minutes at the new target temperature, then the process can be repeated until a temperature where no shivering is obtained.

ATTACHMENT III – BEDSIDE SHIVERING ASSESSMENT SCALE (BSAS)

SCORE	SEVERITY	DEFINITION
0	None	No shivering noted on palpation of the masseter, neck or chest wall
1	Mild	Shivering localized to the neck and/or thorax only
2	Moderate	Shivering involves gross movement of the upper extremities in addition to neck and thorax
3	Severe	Shivering involves gross movements of the trunk, upper and lower extremities

ATTACHMENT IV – SPECIFIC NEW-ONSET ADVERSE EVENT DEFINITIONS

SPECIFIC NEW-ONSET ADVERSE EVENT	DEFINITION
1. All-Cause Mortality	Deaths will be classified as cardiac, vascular or noncardiovascular as defined by the Academic Research Consortium.[27] All deaths are considered cardiac unless an unequivocal non-cardiac cause can be established. Specifically, any unexpected death even in patients with coexisting potentially fatal non-cardiac disease (e.g. cancer, infection) should be classified as cardiac. Cardiac death (CD): Any death due to proximate cardiac cause (e.g. MI, low-output failure, fatal arrhythmia), unwitnessed death and death of unknown cause, all procedure related deaths including those related to concomitant treatment. Vascular death: Death due to non-coronary vascular causes such as cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular cause. Non-cardiovascular death: Any death not covered by the above definitions such as death caused by infection, malignancy, sepsis, pulmonary causes, accident, suicide or trauma.
2. Recurrent MI [27,31]	Recurrent MI or re-infarction may be diagnosed when cardiac biomarker levels are stable on 2 samples that are >6 hours apart or are in decline if a subsequent value 3 to 6 hours after the procedure is increased by ≥ 20% from the baseline sample. If the baseline value is not stable, then insufficient data exists to recommend biomarker criteria for diagnosis, and the Academic Research Consortium[27,31]recommends that the event be considered as pre-procedure MI. Periprocedural MI is that which occurs within the first 48 hrs after PCI or within the first 72 hrs after coronary artery bypass grafting (CABG).

	Q wave MI: Development of new, pathological Q wave on the baseline ECG (≥ 0.04 seconds in duration and ≥ 1 mm in depth) in ≥ 2 contiguous precordial leads or ≥ 2 adjacent limb leads) Non-Q wave MI: Those MIs which are not Q-wave MI.
3. Need for revascularization of the target vessel (TVR)[27]	TVR is defined as any repeat percutaneous intervention or surgical bypass of any segment of the target vessel. The target vessel is defined as the entire major coronary vessel proximal and distal to the target lesion, which includes upstream and downstream branches and the target lesion itself.
4. Stroke	Development of a new neurological deficit that persists > 24 hours, or worsening of previous neurological symptoms that persist > 24 hours.
5. Cardiogenic shock	Systolic blood pressure of less than 90 mmHg for at least 30 minutes which is secondary to myocardial dysfunction, leading to decreased cardiac output and evidence of tissue hypoxia in the presence of adequate intravascular volume.
6. Pulmonary embolism	Sudden onset of pleuritic chest pain, cough, hemoptysis, hypoxia, tachycardia, and a positive ventilation/perfusion scan or a CT scan.
7. Ventricular Fibrillation (V-Fib)	Rapid uncoordinated fluttering contractions of the heart ventricles recognized by the occurrence on the electrocardiogram of coarse and irregular oscillations without discernible QRS complexes or T waves
8. Vascular complications requiring intervention	Complications arising from the use of the Proteus Catheter including the development of a vessel tear, hematoma, pseudoaneurysm, arteriovenous (AV) fistula, or retroperitoneal bleeding which require an additional surgical intervention for treatment.
9. Bleeding requiring transfusion of 2 units or greater	Any periprocedural bleeding which occurs as a result of the PCI and/ or cooling procedure which requires transfusing > 2 units.
10. Systemic Infection	Sepsis with confirmed positive blood cultures.
11. Cooling Catheter Access Site Wound infection	Infection and inflammation of the incision or puncture site requiring drainage and/or debridement in addition to antibiotic therapy, e.g., cellulitis.
12. Pulmonary Edema	Abnormal accumulation of fluid in the lungs

13. Deep Venous Thrombosis (DVT)[32]	Formation of one or more blood clots in one of the body's large veins, most commonly in the lower limbs. The clot(s) can cause partial or complete blocking of circulation in the vein, which in some patients leads to pain, swelling, tenderness, discoloration, or redness of the affected area, and skin that is warm to the touch. As many patients enrolled in the trial will have pre-existing DVT, for the purposes of this trial DVT is defined as the de novo onset of DVT following enrollment which required treatment or worsening of pre-existing DVT.

ATTACHMENT V – ADVERSE EVENT DEFINITIONS

Adverse Event Definitions

In addition to the definitions provided in **Attachment IV– Specific New Onset Serious Adverse Event Definitions**, the following definitions apply to expected adverse events that may occur and must be reported throughout this clinical trial. Events reported should represent a new onset or increase in the severity of the condition from the time of enrollment.

A. CARDIAC COMPLICATIONS	DEFINITION
Recurrent Myocardial ischemia [31]	Recurrent Myocardial Ischemia : is evidenced through baseline ECG changes identified during continuous multilead baseline ECG–ischemia monitoring (or Holter monitoring) which may be accompanied by the development of new clinical symptoms suggesting an ischemic cardiac episode.
Arrhythmias	The development of a new atrial and/or ventricular arrhythmia, significant increase in the severity of a preexisting arrhythmia, or any episode of cardiac arrest.
Congestive Heart Failure[34]	Defined as patients with defined or presumed cardiac disease and one of the following: Class I: without limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea. Class II: slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, or dyspnea. Class III: marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea. Class IV: inability to carry on any physical activity without discomfort. Symptoms are present even at rest or minimal exertion.

B. PULMONARY COMPLICATIONS	DEFINITION
Pneumonia	Clinical evidence as determined by physical, radiographic, and laboratory findings requiring treatment with antibiotics, inhalation therapy, intubation, or suctioning.
Atelectasis	Clinical evidence as determined by physical, radiographic, and laboratory findings requiring treatment with antibiotics, inhalation therapy, intubation, or suctioning.

Respiratory Failure	Need for mechanical ventilation for > 24 hours postoperatively, or reintubation for any reason.

C. RENAL COMPLICATIONS	DEFINITION
Acute Kidney injury (AKI)[35]	AKI is defined as any of the following: Increase in SCr by ≥.3 mg/dl (≥26.5 µmol/l) within 48 hours; or Increase in SCr to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or Urine volume < 0.5 ml/kg/h for 6 hours.

D. VASCULAR COMPLICATIONS	DEFINITION
Arteriovenous Fistula	Formation of an abnormal connection between the lumens of an artery and a vein as documented by CT, ultrasound, angiography, or direct observation.
Embolism	The obstruction of a blood vessel by a blood clot or foreign substance, e.g., air, fat, bacteria.
Vessel perforation	Defined as perforation of the access vessel wall or vena cava confirmed by extravasation of contrast under fluoroscopy, angiography, CT scan, and/ or direct observation at surgery or autopsy.
Hematoma	An abnormal localized collection of blood (clotted or partially clotted) and situated within an organ or a soft tissue space, such as within a muscle. Development of an incisional or retroperitoneal hematoma requiring surgical intervention, evacuation, transfusion or prolonged hospitalization.
Hemorrhage	Post-procedural bleeding requiring transfusion of ≥ 2 units.
Hypotension	Abnormally low systolic blood pressure that is < 80 mm Hg

D. VASCULAR COMPLICATIONS	DEFINITION
Peripheral vascular insufficiency (PVI)	Inadequate peripheral blood flow resulting from the occlusion of vessels by atherosclerotic plaques, thrombi, or emboli; damaged, diseased, or intrinsically weak vascular walls; arteriovenous fistulas; hematologic hypercoagulability; and heavy smoking. Signs of vascular insufficiency include pale, cyanotic, or mottled skin over the affected area; swelling of an extremity; absent or reduced tactile sensation; tingling; diminished sense of temperature; muscle pain, such as intermittent claudication in the calf; and, in advanced disease, ulcers and atrophy of muscles in the involved extremity. As many patients enrolled in the trial will have pre-existing Peripheral Vascular Insufficiency (PVI), for the purposes of this trial PVI is defined as the de novo onset of PVI following enrollment which requires treatment or worsening of pre-existing PVI.
Pseudoaneurysm	Enlargement of the aorta, iliac, or femoral arteries, which contain some or all of the medial layer, the adventitia, and periaortic tissue most commonly associated with previous aortic operative procedures, trauma, and/or infection. Pseudoaneurysms typically present as a well-defined collection of blood outside the vessel wall from contained rupture.
Stenosis	A reduction in the diameter of the vessel lumen when compared to the reference diameter, as documented by angiography, which requires intervention and is related to the procedure, e.g., access vessel.
Thrombosis	Clotting within a blood vessel which may cause infarction of tissues supplied by the vessel; it may be occlusive or attached to the vessel or heart wall without obstructing the lumen.
Transient Ischemic Attack (TIA)	A brief episode of neurological dysfunction caused by focal brain or retinal ischemia with clinical symptoms typically lasting 1 - 24 hours and without evidence of acute infarction.

E. WOUND COMPLICATIONS	DEFINITION

Hematoma	An abnormal localized collection of blood (clotted or partially clotted) and situated within an organ or a soft tissue space, such as within a muscle. Development of an incisional or retroperitoneal hematoma requiring surgical intervention, evacuation, transfusion or prolonged hospitalization.
Arteriovenous Fistula	Formation of an abnormal connection between the lumens of an artery and a vein as documented by CT, ultrasound, angiography, or direct observation.
Nerve Injury/Peripheral Neuropathy	Direct damage to nerves surrounding the access site, operative field, or catheter deployment site, and the resultant signs and/or symptoms of such damage which may include pain and numbness in the affected area associated with muscle weakness and decreased patellar reflex lasting > 1 month after treatment.

F. SYSTEMIC COMPLICATIONS	DEFINITION
Coagulopathy	The development of an abnormal bleeding disorder, e.g., disseminated intravascular coagulopathy or thrombocytopenia, documented by appropriate laboratory studies and requiring therapy with medication or transfusion.
Anesthetic Complications	Reaction or complication caused by administration of an anesthetic.
Liver failure[33]	Acute liver failure is defined as the rapid development of hepatocellular dysfunction, specifically coagulopathy and mental status changes (encephalopathy) in a patient without known prior liver disease.

F. SYSTEMIC COMPLICATIONS	DEFINITION
Pancreatitis[36]	Evidenced on two of the following three conditions: 1) abdominal pain suggestive strongly of acute pancreatitis (epigastric pain often radiating to the back), 2) serum amylase and/or lipase activity at least 3 times greater than the upper limit of normal, (imaging is to be used if the elevated values are <3 times normal); and 3) characteristic findings of acute pancreatitis on transabdominal ultrasound or on Contrast Enhanced Computed Tomography (CECT) [32]

ATTACHMENT VI – INVESTIGATOR LIST

ATTACHMENT VII – LIST OF ABBREVIATIONS

AAR	Area at Risk
ACC	American College of Cardiology
ADE	Adverse Device Effect
AE	Adverse Event
AHA	American Heart Assocation
AKI	Acute Kidney Injury
AMI	Acute Myocardial Infarction
ASADE	Anticipated Serious Adverse Device Effect
AV	Arteriovenous
BSAS	Bedside *Shivering* Assessment *Scale*
CABG	Coronary Artery Bypass Grafting
CD	Cardiac Death
CEC	Clinical Events Committee
CHF	Congestive Heart Failure
CIP	Clinical Investigation Plan
CI-TLR	Clinically-Indicated Target Lesion Revascularization
CMP	Clinical Monitoring Plan
cMR	Cardiac Magnetic Resonance
CNS	Central Nervous System
CRO	Clinincal Research Organization
CRF	Case Report Form
CRMI	Clinically Relevant Myocardial Infarction
CVA	Cerebral Vascular Accident
CVP	Central Venous Pressure
DAPT	Dual Antiplatelet Therapy
DD	Device Deficiency
DES	Drug Eluting Stent
DMC	Data Monitoring Committee
DP	Dorsalis Pedis
DSMB	Data Safety Monitoring Board
DTB	Door-to-Balloon
DVT	Deep Vein Thrombosis
EC	Ethics Committee

ECG	Electrocardiography
EDC	Electronic Data Capture
ED	Emergency Department
ER	Emergency Room
ESC	European Society of Cardiology
EU	European Union
Fr	French
FMECA	Failure Mode, Effects and Criticality Analysis
FEP	Fluorinated Ethylene Propylene
GLP	Good Laboratory Practice
HDPE	High-density Polyethylene
HIPPA	Heath Insurance Portability and Accountability Act
HTN	Hypertension
ICF	Informed Consent Form
IEC	International Electrotechnical Commission
IFU	Instructions for Use
IQR	Interquartile Range
IRB	Institutional Review Board
IRI	Ischemia Reperfusion Injury
IS	Infarct Size
ISO	International Organization for Standardization
ITT	Intention-to-Treat
IVC	Inferior Vena Cava
IVTM	Intravascular Temperature Management
KCCQ	Kansas City Cardiomyopathy Questionnaire
LAL	Limulus Amebocyte Lysate
LED	Light-emitting Diode
LV	Left Ventricular
LVEF	Left Ventricular Ejection Fraction
MACE	Major Adverse Cardiac Events
MAO	*Monoamine Oxidase*
MaR	Myocardium at Risk
MEC	Medical Ethics Committee

MEM	Minimum Essential Medium
MI	Myocardial Infarction
MRI	Magnetic Resonance Imaging
NCA	National Competent Authority
NYHA	New York Health Association
OD	Outer Diameter
PCI	Percutaneous Coronary Intervention
PETG	Polyethylene Terephthalate - Glycol modified
PP	Per-protocol
PVI	Peripheral Vascular Insufficiency
PVP	Polyvinylpyrrolidone
RCN	Radio-Contrast Nephropathy
RF	Radiofrequency
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Events
SBP	Systolic Blood Pressure
SOP	Standard Operating Procedure
SPECT	Single-photon Emission Computed Tomography
STEMI	ST-segment Elevation Myocardial Infarction
SVT	Supraventricular Tachycardia
TIA	Transient Ischemic Attack
TIMI	Thrombolysis In Myocardial Infarction
TH	Therapeutic Hypothermia
TVR	Target Vessel Revascularization
UADE	Unanticipated Adverse Device Effect
UFH	Unfractioned Heparin
USADE	Unanticipated Serious Adverse Device Effect
USP	United States Pharmacopeia
UTI	Urinary Tract Infection

APPENDIX B

COOL-AMI EU Pivotal Trial Clinical Investigational Plan

Germany Protocol (Rev. 6)

(122 pages)

Clinical Investigation Plan

COOL-AMI EU PIVOTAL TRIAL: A MULTICENTER, PROSPECTIVE, RANDOMIZED-CONTROLLED TRIAL TO ASSESS THE SAFETY AND EFFECTIVENESS OF COOLING AS AN ADJUNCTIVE THERAPY TO PERCUTANEOUS INTERVENTION IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

PROTOCOL NO.: EDC-3135

Revision: 6

EFFECTIVE DATE: JUNE 19, 2018

CONFIDENTIAL & PROPRIETARY

CLINICAL INVESTIGATION PLAN APPROVAL PAGE

CLINICAL INVESTIGATION PLAN:	COOL-AMI EU Pivotal Trial: A multicenter, prospective, randomized controlled Trial to assess the safety and effectiveness of cooling as an adjunctive therapy to percutaneous intervention in patients with acute myocardial infarction
PROTOCOL NO.:	EDC-3135
SPONSOR:	ZOLL Circulation, Inc. 2000 Ringwood Avenue San Jose, CA 95131
SPONSOR REPRESENTATIVE:	ZOLL Medical Deutschland GmbH Emil-Hoffmann - Straße 13 50996 Köln, Germany
CLINICAL TRIAL SPONSOR's CONTACT:	Philippa Hill
REVISION NUMBER :	6

Approval of Clinical Investigation Plan by Sponsor:

Philippa Hill — JUNE 19th 2018

Philippa Hill
Senior Director, Clinical Affairs

Date

Signature Page

Clinical Investigation Plan

COOL-AMI EU PIVOTAL TRIAL: A MULTICENTER, PROSPECTIVE, RANDOMIZED-CONTROLLED TRIAL TO ASSESS THE SAFETY AND EFFECTIVENESS OF COOLING AS AN ADJUNCTIVE THERAPY TO PERCUTANEOUS INTERVENTION IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

PROTOCOL NO.: EDC 3135

Revision: 6

Effective Date: JUNE 19, 2018

Signatures of Investigator below constitute their approval of this clinical investigation plan (CIP) and provide necessary assurances that they have read the CIP, understand it, and will work according to all stipulations of it, and to the ethical principles stated in the latest version of the Declaration of Helsinki and the ISO 14155:2011 (Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice).

Investigator Name (Please Print)	
Investigator Signature	**Date**
Institution Name	
Institution Address	
ZOLL Circulation, Inc. **Sponsor Name**	
2000 Ringwood Avenue, San Jose CA 95131 **Sponsor Address**	
ZOLL Medical Deutschland GmbH **Sponsor Representative**	

Table of Contents

1 SYNOPSIS

Clinical Trial Title	**COOL-AMI EU PIVOTAL TRIAL: A MULTICENTER, PROSPECTIVE, RANDOMIZED-CONTROLLED TRIAL TO ASSESS THE SAFETY AND EFFECTIVENESS OF COOLING AS AN ADJUNCTIVE THERAPY TO PERCUTANEOUS INTERVENTION IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION**
Clinical Trial Sponsor	ZOLL® Circulation, Inc.
Clinical Trial Sponsor's Contact	Philippa Hill Senior Director, Clinical Affairs ZOLL Circulation, Inc. 2000 Ringwood Ave. San Jose, CA 95131 Main: +1 (408) 541-2140 Fax: +1 (408) 541-1030 PHill@zoll.com@zoll.com
Trial Number	EDC-3135
Investigational Device	**Proteus™ Intravascular Temperature Management (IVTM) System**
Trial Objective	The objective of this trial is to evaluate the safety and effectiveness of therapeutic hypothermia, using the ZOLL Proteus IVTM System, as an adjunctive therapy for patients presenting with acute anterior myocardial infarction (AMI) and undergoing percutaneous coronary intervention (PCI) in comparison with patients with acute anterior myocardial infarction and undergoing PCI only.
Trial Design	A multicenter, prospective, interventional, randomized-controlled trial. Randomization will be in a 1:1 ratio, Test Arm (PCI + Cooling) or Control Arm (PCI alone) in up to 500 randomized subjects (250 subjects in each arm).
Primary Effectiveness Endpoint	Relative reduction of 20% in mean anterior myocardial infarct size as determined by Cardiac Magnetic Resonance (cMR) imaging at 4-6 days post infarct in the Test Arm (cooling + PCI) relative to the Control Arm (PCI only).

Primary Safety Endpoint	Per-patient rate of composite Major Adverse Cardiac Events (MACE) in randomized subjects, defined as Cardiac Death (CD), All Myocardial Infarction (All MI) and Clinically-Indicated Target Lesion Revascularization (CI-TLR) at 30 day follow-up; non-inferiority to the control.
Investigational Sites	Up to 70 clinical sites in the Europe
Inclusion & Exclusion Criteria	Patients shall be screened to the following inclusion and exclusion criteria. Subjects are qualified for participation only if all Inclusion Criteria have been met and all Exclusion Criteria have been confirmed not present. **Inclusion Criteria** All Inclusion Criteria must be answered YES for subject to satisfy Inclusion Criteria: 1. The patient is ≥ 18 years of age. 2. The patient must have symptoms consistent with AMI (i.e. chest pain, arm pain, etc.) and unresponsive to nitroglycerin, with symptoms beginning greater than 30 minutes <u>but less than 4.5 hours</u> prior to presentation at hospital. 3. Qualifying Infarct location: Evidence of Acute Anterior MI only with ST-segment elevation of ≥ 0.2 mV in two or more anterior contiguous precordial leads (V1 –V4). 4. The patient is eligible for PCI. 5. The patient is willing to provide written informed consent to participate in this clinical trial. **Exclusion Criteria** All Exclusion Criteria must be answered NO for subject to satisfy Exclusion Criteria: 1. The patient has had a previous Myocardial Infarction. 2. The patient is experiencing cardiogenic shock (systolic blood pressure [SBP] <100 mmHg, HR> 100 bpm and arterial oxygen saturation (pulse oximetry) <u>≤</u>92% without additional oxygen The patient is presenting with resuscitated cardiac arrest, atrial fibrillation, or Killip risk stratification class II through IV.

	3. The patient has an aortic dissection or requires an immediate surgical or procedural intervention other than PCI. 4. The patient has known history of Congestive Heart Failure (CHF), hepatic failure, end-stage kidney disease or severe renal failure (clearance < 30ml/min/1.73m²). 5. The patient is febrile (temperature > 37.5 °C) or has experienced an infection with fever in the last 5 days. 6. The patient has a known previous CABG. 7. The patient has a known recent stroke within 90 days of admission. 8. Cardio-pulmonary decompensation that has occurred en route to the hospital or, in the opinion of the physician, that is imminent or likely to occur following presentation to the clinical site. 9. Contraindications to hypothermia, such as patients with known hematologic dyscrasias which affect thrombosis (e.g., cryoglobulinemia, sickle cell disease, serum cold agglutinins) or vasospastic disorders (such as Raynaud's or thromboangitis obliterans).. 10. Any contraindication to cardiac MRI, or any implant in the upper body which may cause artifacts on cardiac MRI imaging. 11. The patient has a known hypersensitivity or contraindication to aspirin, heparin, or sensitivity to contrast media, which cannot be adequately pre-medicated. 12. The patient has a known history of bleeding diathesis, coagulopathy, cryoglobulinemia, sickle cell anemia, or will refuse blood transfusions. 13. The patient has a height of <1.5 meters (4 feet 11 inches). 14. The patient has a known hypersensitivity or contraindication to buspirone hydrochloride or Pethidine (Meperidine) and/or has been treated with a monoamine oxidase inhibitor in the past 14 days. 15. Patient has a known history of severe hepatic or renal impairment, untreated hypothyroidism, Addison's disease, benign prostatic hypertrophy, or urethral stricture that in the opinion of the physician would be incompatible with Pethidine administration. 16. The patient has an Inferior Vena Cava filter in place (IVC). 17. The patient has a pre-MI life expectancy of <1 year due to underlying medical conditions or pre-existing co-morbidities. 18. The patient has a known, unresolved history of drug use or alcohol dependency, or lacks the ability to comprehend or follow instructions.

	19. The patient is currently enrolled in another investigational drug or device trial. 20. The patient is apprehensive about or unwilling to undergo the required MRI imaging at follow-up, has a documented or suspected diagnosis of claustrophobia, or has Gadolinium allergy, or is in permanent Atrial Fibrillation. 21. The patient has received thrombolytic therapy en route to the hospital. 22. The patient shows clinical evidence of spontaneous reperfusion as observed symptomatically and/ or from baseline ECG findings (partial or complete ST resolution in baseline ECG prior to informed consent and randomization). 23. The patient is a vulnerable subject, for instance, a person in detention (i.e., prisoner or ward of the state). 24. The patient is a female who is known to be pregnant.
Clinical Trial Population	Adult male and female patients presenting with an acute myocardial infarction. To qualify, patients must have symptoms consistent with AMI (i.e. chest pain, arm pain, etc.) unresponsive to nitroglycerin, with symptom onset greater than 30 minutes but less than 4.5 hours prior to presentation at hospital and be eligible for PCI. **Randomized subjects** must have evidence of Acute Anterior MI only with ST-segment elevation of ≥ 0.2 mV in two or more anterior contiguous precordial leads (V1 –V4) will be included.
Intervention	Intravascular permissive hypothermia as an adjunct to PCI. Cooling will be initiated prior to PCI with infusion of up to 1 L of cold saline (4°C) (according to the guideline) and with the Proteus Console set at 32.0 degrees Celsius. Total cooling time will be 3 hours (± 15 minutes) and will be followed with active rewarming with the Proteus IVTM System to attain normothermia [36 °C (96.8°F)].
Length of Follow Up	12 months
Enrollment	Initiation of enrollment: January 2017 Completion of Enrollment: June 2019 Follow up completed: June 2020

Summary of Statistical Analysis	Primary efficacy endpoint of infarct size measured as percentage of total LV mass by cMR, the null hypothesis of equal infarct size between two arms will be tested with t-test for the study population. For the safety endpoint, comparison of per patient MACE rate for non-inferiority will be made with Fisher's exact Test.
Planned Interim Analyses	Two interim analyses are planned to be performed at approximately 50% and 75% of randomization, once subjects have completed 4-6 day cMR follow-up. At the interim stage, the trial will be stopped to reject the null hypothesis of no difference or continue enrollment.
Analysis Sets	The **Intention-to-Treat (ITT)** population will be used for primary statistical analyses and summaries for all analyses except for Safety endpoints. The ITT population includes subjects who have signed an informed consent and have been randomized to the Test Arm or the Control Arm of the trial. ITT subjects will be evaluated according to the group to which they were randomized. The **Per-Protocol (PP) population** includes those subjects who met inclusion and exclusion criteria, were randomized to either the Test Arm or Control Arm, received the treatment to which they were randomized, and complied substantially with the treatment timeline and steps of this protocol without major protocol violations. The **Safety Analysis Set** will be used to evaluate safety endpoints. These will be all subjects included in the study as defined by the ITT analysis set. For the safety analysis subjects will be followed for all Adverse Events 12 months post procedure. Additionally, all subjects will be followed through 12 months post procedure for the incidence of Serious Adverse Events (SAEs), Death and Heart Failure (as assessed by NYHA and Kansas City Cardiomyopathy Questionnaire (KCCQ)).
Trial Oversight	Each participating site will dedicate one Principal Investigator to oversee the execution of the clinical trial in accordance with the protocol.

2 INTRODUCTION

Clinical investigations have shown that induction of hypothermia before reperfusion of acute coronary occlusion reduces infarct size. A pilot study from Lund University demonstrated that the induction of mild hypothermia (<35°C) in ST Elevation Myocardial Infarction (STEMI) patients prior to performing Percutaneous Coronary Intervention (PCI) can save (preserve) 38% more cardiac tissue compared with the PCI alone.[1]

Hypothermia has proven to be one of the most potent and consistent adjunctive therapies for infarct size reduction in numerous preclinical studies, when administered prior to reperfusion. This is unlike the well accepted approach for therapeutic hypothermia for cardiac arrest, where cooling is applied after reperfusion. The mechanisms leading to protection are multifactorial. However, unlike the consistent findings in preclinical studies, clinical trials (COOL -MI, ICE-IT, CHILL-MI) have failed to show a decrease in infarct size. The major reason is likely due to the difficulty in achieving adequate cooling prior to reperfusion. As shown in **Table 1** below, none of the clinical trials to date has reached target temperature prior to reperfusion, as has been done in all of the animal studies.

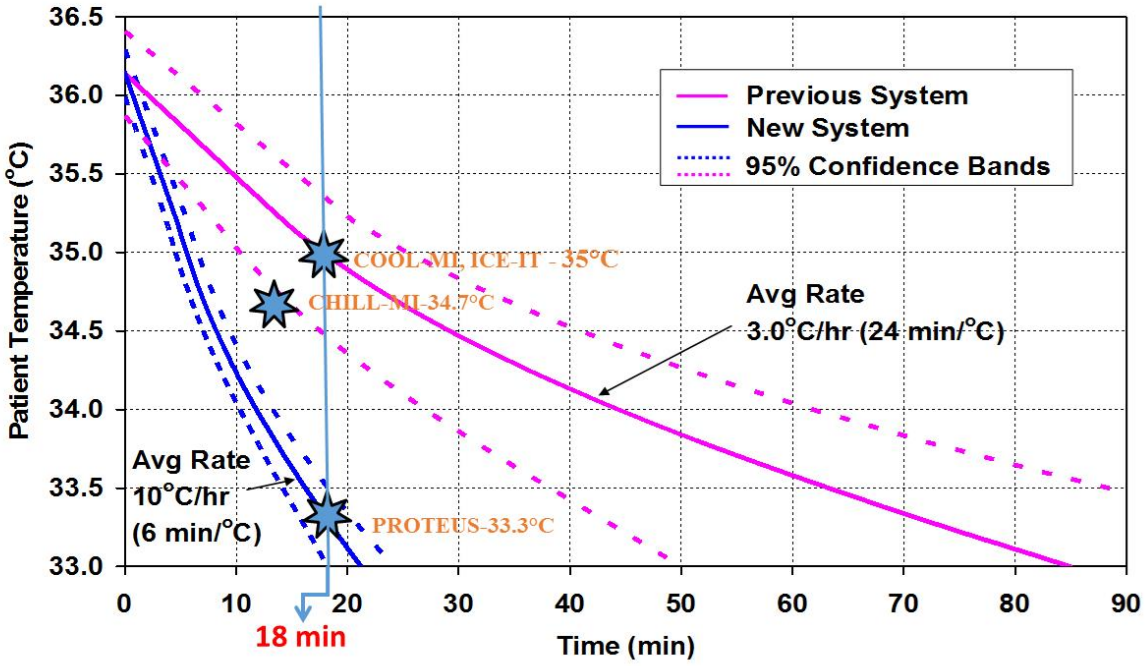
Table 1: Major Cooling Trials in STEMI.

Major Cooling Trials in STEMI					
Trial	**Sample Size**	**Target Temp (°C)**	**Actual Temp at Reperfusion (°C)**	**Temp Miss (°C)**	**Cooling Time before Reperfusion (min)**
COOL -MI	168 – Hyp 157 – Control	33.0	35.0	2.0	18
ICE-IT	105 – Hyp 99 – Control	33.0	35	2.0	16
CHILL-MI	61 – Hyp 59 – Control	33.0	34.7	1.7	13

The target temperature for each trial was 33.0 °C. The actual temperature at the time of reperfusion was 1.7-2.0 °C higher than target. This is a miss in temperature "dose" of around 50% [normal temperature is 37.0 °C, target temperature was 33.0 °C, (37.0 – 35.0) / (37.0 – 33.0) = 50%].

Post hoc analysis of these trials showed that patients with anterior MI that were cooled to less than 35°C at the time of PCI showed a significant reduction in infarct size, supporting the idea of a dose response (**See Figure 1**). Recent preclinical results (Stanford-ZOLL data) have shown that temperature at reperfusion of 32 °C is superior to 35 °C for reducing infarct size, confirming a dose response. Future clinical trials will require more powerful cooling devices, and more consistency in implementing 18 minutes of cooling before reperfusion across all study sites in order to evaluate the actual effectiveness of therapeutic hypothermia as a protection strategy.

Figure 1: Temperature at reperfusion for the Major Therapeutic Hypothermia in AMI Clinical trials.



The Proteus device has a confirmed faster cooling rate. With a duration of cooling of 18 minutes prior to reperfusion, as occurred in the COOL -MI trial, the expected temperature at reperfusion is 33.3°C with the Proteus device. This is significantly better than the 35°C achieved in COOL -MI and ICE-IT, and 34.7°C achieved in CHILL-MI. The relative effectiveness of the Proteus device for cooling, compared to the performance of the prior studies is shown in Figure 1 above. The addition of a bolus infusion of 4°C cold saline is expected to further enhance the temperature achieved at reperfusion with the Proteus System.

This Investigational Plan was developed in accordance with the requirements set forth in the Good Clinical Practices (E6)[2], ISO 14155:2011 Clinical investigation of medical devices for human subjects[3] - Good clinical practice, the Declaration of Helsinki, and the local regulatory requirements an adjunctive therapy to PCI.

3 BACKGROUND

Coronary heart disease complicated by acute myocardial infarction (AMI) remains a leading cause of death and disability worldwide. AMI most commonly occurs when a coronary artery becomes occluded by thrombus following the rupture of an atherosclerotic plaque. Factors that may affect the size of the subsequent infarction include duration of ischemia, size of ischemic territory, collateral blood flow, and myocardial metabolic rate. Long-term sequelae of AMI include ventricular remodeling, loss of ventricular function, congestive heart failure, dysrhythmias, and sudden death.

Although major gains have been made in improving the outcome of patients suffering AMI, and early myocardial reperfusion with the use of thrombolytic therapy or primary percutaneous coronary intervention (PCI) are effective, morbidity and mortality remain substantial. This may be because restoration of blood flow to the ischemic myocardium can itself induce injury through myocardial "ischemia reperfusion injury" (IRI), which can be defined as that portion of the ischemia-reperfusion continuum which is preventable by treatment initiated after restoration of blood flow.[4] It has been proposed that 50% of the final infarct size may be a function of IRI. [4]

Ischemia reperfusion injury is protean in its components, likely including free radical and reactive oxygen species, disordered vasculature, inflammatory injury, programmed cell death, and pathologic remodeling among others.[5] Unfortunately, the cascading nature of these events challenge and, in the end, may defeat the single molecular target pharmacologic model. The long list of failed IRI pharmacologic agents includes antioxidants, calcium channel blockers, anti-inflammatory drugs, sodium hydrogen exchange inhibitors, among others, has led some to question the importance of reperfusion injury in the myocardium.[6] Large infarctions still occur despite timely reperfusion, due to reperfusion injury. Numerous treatments have been studied to reduce reperfusion injury, with little success to date. 7-9

Therapeutic hypothermia (TH) has been studied for many years as a potential therapy for ischemia and reperfusion.[10 -16] The past few years have seen development of a broad literature reporting both laboratory and clinical trials of mild post-reperfusion TH in the treatment of disease entities as diverse as acute cardiac arrest, stroke, and myocardial infarction, among others. Unlike single pharmacologic agents, TH has the potential to modify and ameliorate multiple pathways of injury.

4 INTENDED USE, SYSTEM OVERVIEW, & DEVICE DESCRIPTION

4.1 Intended Use / Indication for Use

The ZOLL® Proteus™ Intravascular Temperature Management (IVTM) System is indicated for use in adult subjects with acute myocardial infarction to induce and maintain hypothermia prior to percutaneous coronary intervention as an adjunctive therapy to reduce anterior infarct size. The Proteus IVTM System is to be used only as part of the clinical investigation.

4.2 System Overview

The Proteus Intravascular Temperature Management (IVTM) System consists of four primary components: a single-use heat exchange catheter; heat exchange cassette; a temperature probe and a reusable microprocessor-driven console. The system is designed to achieve and maintain patient temperatures within the range of 32 - 37°C. Its performance profile includes:

1. Rapid patient cooling and warming

2. Precise achievement and maintenance of a desired patient target temperature

3. Quick and simple deployment: See the catheterization lab, critical care unit, emergency department, and other hospital settings

Reference the Investigator Brochure for additional information on the Proteus IVTM System.

The Proteus IVTM System couples a heat exchange catheter with a dual microprocessor-driven controller to manage patient temperature. The Proteus IVTM System is designed to rapidly cool and warm patients, achieve and precisely maintain a target patient temperature and to be quickly and easily deployed.

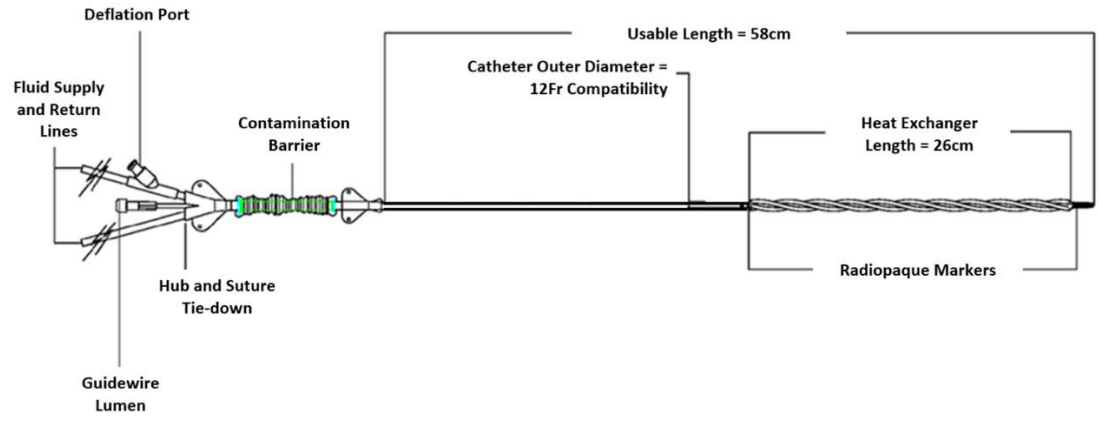
Cool or warm sterile saline is continuously circulated through the catheter, thereby cooling or warming the blood as it flows over the catheter without perfusion of fluids into the body. The saline is transported from the catheter to the cassette (mounted in the console) via extension lines. The cassette has an integral heat exchange element and a pump that couples with the console to cool or warm the saline being pumped through the closed circuit comprised of the cassette and catheter. The Proteus IVTM Console continuously monitors the patient temperature and controls the catheter temperature to cool, warm or maintain the target temperature.

4.3 Device Description

4.3.1 Proteus Catheter

The Proteus Catheter (**Figure 2**) is a single-use, heparin coated, endovascular heat exchange catheter consisting of a triple lobed, helically wound balloon mounted on the distal portion of a multi-lumen shaft. The catheter is designed for placement in the Inferior Vena Cava via the femoral vein using a 12Fr or a 14Fr hemostatic introducer sheath. The catheter has a fluid supply lumen, a fluid return lumen, a guidewire port at the proximal end of the catheter connecting to a guidewire lumen that accommodates guidewires with diameters up to 0.038". The expanded balloon portion of the catheter has an expanded diameter of 17 mm and a length of 26 cm during system operation. The catheter has a radiopaque marker mounted at the distal and proximal end of the balloon portion of the catheter. The distal end of the catheter has a non-traumatic soft tip. The fluid supply and fluid return lumens of the catheter are connected to the cassette via extension lines approximately 2 meters in length, which provide the closed heat transfer fluid circuit. The 0.038", 145-cm. stainless steel guidewire included in the package has a soft atraumatic tip.

Figure 2 Diagram of Proteus Catheter



4.3.2 Proteus Temperature Probe

The Proteus System measures a patient's core body temperature using a heparin-coated endovascular dual output probe (X-Probe) advanced through the guidewire lumen of the Proteus Catheter after the catheter is placed.

4.3.3 Proteus Cassette

The single-use Proteus Cassette consists of a heat exchange element, a pump, a pump coupling to interface with the motor drive in the console and fluid lines to interface with the heat transfer fluid circulated by the console. The cassette is designed to be removed from the portable control console allowing the catheter to remain in the patient to facilitate

moving the patient to another location where temperature management can continue using the same or another control console.

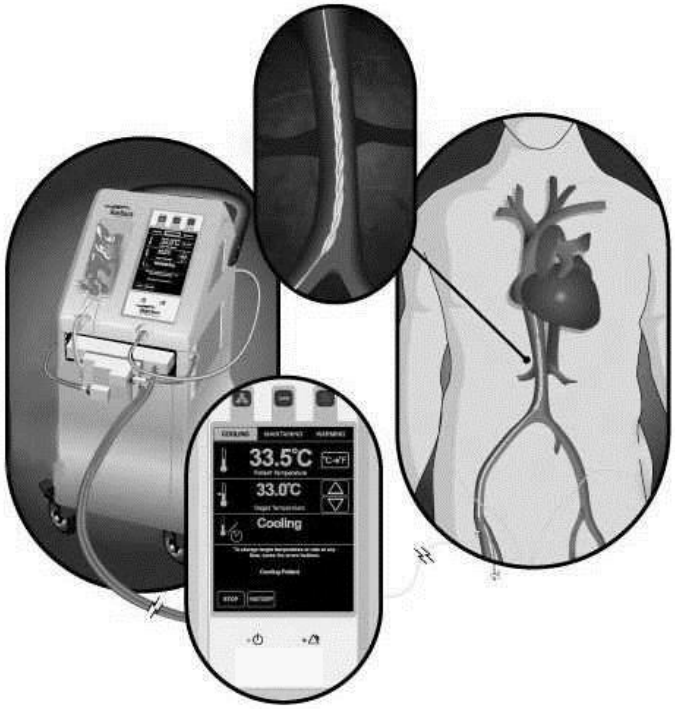
4.3.4 Proteus Console

The Proteus Console **(Figure 3)** consists of solid-state thermoelectric modules, a motor drive, dual fluid level detection systems and dual microprocessors. A dilute polypropylene glycol/water mixture (process fluid) circulates within the console to provide heat exchange with the saline heat transfer fluid loop in the cassette. This technology along with microprocessor proportional control of both the saline and the patient temperature enable the following features:

- Designated patient temperature between 32-37°C is maintained within ± 0.3°C continuous calculation and display, in all ambient lighting conditions, of patient actual temperature, target temperature, and rate of cooling/warming
- Redundant safety system to shut down and warn user of patient overheat or overcool, saline leakage, sensor failure, and electrical or mechanical malfunction
- Control console automatically performs a hardware and software diagnostic check of all functional and safety systems upon startup
- Maximum cooling and heating rates vary from patient to patient depending on the patient's cardiac output, size and weight, room temperature and humidity, and the successful implementation of the anti-shivering medication regimen, type and amount anesthesia, combined use with blankets or active heating/cooling apparatus, body cavity exposure to the environment during surgery and other factors.

Figure 3: Proteus Console

Figure 4: Proteus Catheter and Interconnection between Catheter, Temperature Probe (X-Probe), Cassette and Console.



4.3.5 Device Labeling

Written *Instructions for Use*, *Operation Manual, Quick Reference Guide, and Service Manual* for the Proteus IVTM System will be packaged with product shipped to the investigational sites. The Proteus IVTM System is to be used only as part of the clinical investigation. (See Proteus IVTM System Labeling)

5 PRIOR INVESTIGATIONS

5.1 Pre-Clinical Studies

Hypothermia has been shown to reduce metabolic demand and provide ischemic protection. Recent studies across numerous different animal models have demonstrated a strong direct relationship between myocardial temperature and infarct size.[11,10,14-18] Mild to moderate degrees of hypothermia (32-35°C) have resulted in significant reductions in infarct size when applied either before or after the onset of coronary occlusion in animal studies.

In other studies, in 1996, Duncker et al, and in 1998 Miki et al, both demonstrated a dose response relationship between myocardial temperature and infarct size using a laboratory model of AMI.[11,12] Subsequently, Dae et al in collaboration with Radiant Inc. demonstrated that therapeutic hypothermia can be induced safely and rapidly in animal

models using intravascular cooling.[13] They then showed that hypothermic therapy initiated late during ischemia and continuing for several hours after reperfusion significantly improved reflow and reduced macroscopic zones of no-reflow and necrosis in this model.[15] The study showed:

- A striking reduction of myocardial infarct size. The cooled group had an infarct of 9 ± 6% of the area at risk vs. 45 ± 8% of the area at risk for controls
- Preservation of myocardial perfusion and viability in the cooled group as demonstrated by radionuclide imaging
- No evidence of apoptosis in salvaged myocardium in the cooling arm. Well-preserved cardiac output during the cooling process.

Of particular relevance, Gotberg et al reported in 2008 that hypothermia achieved before reperfusion decreased infarct size, while hypothermia initiated at the time of reperfusion prevented microvascular obstruction, but did not decrease myocardial infarct size. [16]

5.2 Human Clinical Studies

5.2.1 COOL MI Trial

The COOL MI Trial[19] was conducted from September 2001 through April 2003. A total of 421 patients were enrolled (199 Control, 193 Intervention, 29 Roll-In) at 27 investigational sites in the US, Germany and Australia. The primary analysis population included 357 patients (180 Control, 177 Intervention) who received the assigned treatment. The COOL MI Trial evaluated the safety and effectiveness of cooling as an adjunctive therapy to percutaneous coronary intervention (PCI) in patients with acute myocardial infarction. **Table 2** below displays enrollment characteristics.

Table 2: COOL MI Trial Enrollment Characteristics

	Control (N=180)	**Intervention (N=177)**	**p-value**
Anterior Myocardial Infarction	77 (44%)	74 (42%)	0.77
Inferior Myocardial Infarction	99 (56%)	103 (58%)	0.77
Failed thrombolytic therapy prior to enrollment	23 (12.8%)	18 (10.3%)	0.67
Time in minutes – median (interquartile range)			
From symptom onset to hospital presentation	123 (69 – 201)	114 (60 – 190)	0.08
From hospital presentation to PCI	88 (61 – 114)	104 (80 – 134)	<0.0001

5.2.1.1 Procedural and Angiographic Results COOL MI Trial

The Trial demonstrated that endovascular cooling using the Radiant Medical's (now ZOLL's) Reprieve System ™ in the setting of myocardial infarction was safe, well tolerated, and readily integrated into the existing treatment pathway. While the primary effectiveness endpoint of the study was not achieved, the data provided a strong signal indicating that when patients were sufficiently cooled prior to reperfusion, myocardial damage was reduced[19].

The Control and Intervention groups were well matched in terms of culprit vessels, percutaneous coronary intervention (PCI) procedures and treatment success. As expected, cooling did not affect the angiographic success of PCI procedures. Of the 357 patients who underwent primary PCI, the majority were treated with stent implantation and a platelet glycoprotein receptor inhibitor. Approximately 20% of study subjects were determined to have Thrombolysis in Myocardial Infarction (TIMI 3) flow prior to PCI. TIMI Grade Flow is a scoring system from 0-3 referring to levels of coronary blood flow assessed during percutaneous coronary angioplasty:

- TIMI 0 flow (no perfusion) refers to the absence of any antegrade flow beyond a coronary occlusion.
- TIMI 1 flow (penetration without perfusion) is faint antegrade coronary flow beyond the occlusion, with incomplete filling of the distal coronary bed.
- TIMI 2 flow (partial reperfusion) is delayed or sluggish antegrade flow with complete filling of the distal territory.
- TIMI 3 flow (complete perfusion) is normal flow which fills the distal coronary bed completely

After PCI, TIMI 3 flow was achieved in approximately 92% of patients. Only about 30% of patients had TIMI myocardial perfusion grade 3; however the percentage was similar in both treatment groups and is consistent with literature reports of myocardial perfusion. Procedural and angiographic data are presented in **Table 3** below.

Table 3: COOL MI Trial - Procedural and Angiographic Data

	Control (N=180)	Intervention (N=177)	p-value
Infarct related artery, Stent implantation, Glycoprotein & Stenosis Diameter			
Left anterior descending coronary artery	70 (39%)	69 (39%)	0.91
Circumflex artery	13 (7%)	14 (8%)	0.87
Right coronary artery	77 (43%)	74 (42%)	0.93
Stent implanted	153 (92%)	157 (94%)	0.59
Glycoprotein IIb/IIIa receptor inhibitor	140 (78%)	142 (80%)	0.74

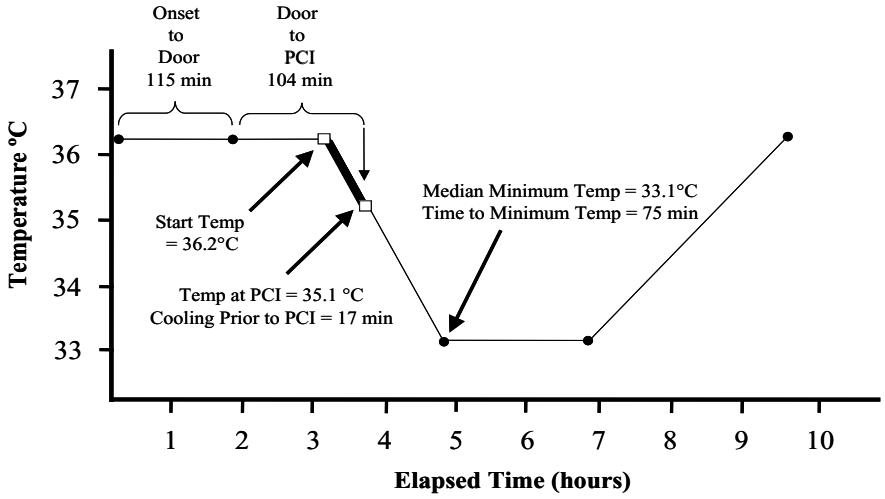
Initial diameter stenosis (mean ± std dev)	92 ± 14%	92 ± 12%	0.93
Initial TIMI flow			
Grade 0/1	126 (71%)	122 (69%)	0.77
Grade 2	14 (8%)	21 (12%)	0.28
Grade 3	38 (21%)	34 (19%)	0.74
Final diameter stenosis	7 ± 9%	8 ± 10%	1.00
Final TIMI* flow			
Grade 0/1	2 (1%)	5 (3%)	0.33
Grade 2	7 (4%)	12 (7%)	0.31
Grade 3	170 (95%)	160 (90%)	0.11
Final myocardial perfusion grade			
Grade 0/1	63 (43%)	76 (53%)	0.11
Grade 2	35 (24%)	26 (18%)	0.27
Grade 3	49 (33%)	41 (29%)	0.54

*Thrombolysis in Myocardial Infarction

5.2.1.2 COOL MI Trial Results

Of the 177 Intervention patients, 11 (6.2%) patients had the Reprieve Catheter placed in the emergency room (ER), one (0.6%) patient had the catheter placed in the cath lab holding area, and 165 (93.2%) patients had the catheter placed in the cath lab. Overall, patients in the Intervention group received a median of 17 minutes (interquartile range (IQR): 10-27) of cooling prior to PCI. During that time, patient temperature was decreased from a median of 36.2°C (IQR: 35.8-36.5) at the initiation of cooling to 35.1°C (IQR: 34.5-35.6) at the time of PCI (**Figure 1**). The median of the minimum temperature reached by each patient was 33.1°C (IQR: 33.0-33.4), which was achieved in 75 minutes (IQR: 50-108). Target patient temperature was set at a 33°C for 3 hours post-PCI. Patients were then re-warmed at 1°C/hr until Investigator-determined normothermia was reached [median=36.5 (IQR: 36.2-36.8]). **Figure 5** below shows patient temperature over time with cooling and time to PCI. The goal to reach target temperature of 33°C at PCI was not achieved in the trial, due to the inadequate cooling power of the Reprieve System. As noted above, target temperature of 33°C was reached after 75 minutes of cooling, long after PCI had occurred.

Figure 5: Median Temperature and Elapsed Times for Intervention Patients



5.2.1.3 COOL MI Trial Tolerability of Cooling

Shivering was managed according to the shivering suppression guidelines recommended for this study by Dr. Daniel Sessler, Chairman of the Department of Anesthesiology at the University of Louisville. The recommended baseline combination of Pethidine, buspirone and skin warming using a forced-air blanket could be supplemented incrementally in the event of shivering or patient discomfort, by additional Pethidine, or by slightly increasing the target temperature. If these steps were unsuccessful, patients could be actively rewarmed to normothermia.

This protocol proved to be quite effective at maintaining patient comfort. Intervention patients received an average of 56 mg of oral buspirone and an average of 267 mg of intravenous Pethidine over the course of the cooling procedure. Of 177 patients in the treatment group, only one patient (0.6%) required premature warming due to intolerability of cooling. Nine patients (5.1%) required a slight increase in target temperature (0.2°C – 0.5°C) to maintain patient comfort. Ninety-eight patients (55.7%) required supplementary dosing of Pethidine, but 60 of these 98 patients (61.2%) had not received the recommended loading dose of the anti-shivering drugs.

COOL MI Trial Safety Results: The primary safety endpoint of the COOL MI study was the incidence, through 30 days, of Major Adverse Cardiac Events (MACE), defined as the composite of death, recurrent myocardial infarction of the target vessel and the need for urgent revascularization of the target vessel. As shown in **Table 4** below, there was no statistical difference in the incidence of MACE in the Intervention group as compared to the Control group. All MACE were adjudicated by an independent Clinical Events Committee and none were attributed to cooling or use of the Reprieve System. **Table 4**

below demonstrates the results of the study with regard to the incidence of Major Adverse Cardiac Events.

Table 4: COOL MI Trial Incidence of MACE

Events through 30 days	Control (N=180)	Intervention (N=177)	p-value
MACE	**7 (3.9%)**	**11 (6.2%)**	**0.45**
Death	4 (2.2%)	6 (3.4%)	0.71
Recurrent MI	3 (1.7%)	1 (0.6%)	0.63
Urgent Revascularization	0 (0%)	4 (2.3%)	0.12

These MACE rates observed in COOL MI compare favorably with those reported for similar patients in recent AMI trials, such as ADMIRAL, CADILLAC, DANAMI and RAPID MI-ICE (**Table 5**).

Table 5 Incidence of MACE for Comparable Patients in Recent AMI Trials

Trial	Death	Reinfarction	Revascularization
COOL MI (Treatment Group) (n=177)	3.4%	0.6%	2.3%
ADMIRAL (n=149)[17]	3.4%	1.3%	4.7%
CADILLAC (n=524)[18]	2.7%	0.8%	1.6%
DANAMI-2 (n=790)[19]	6.6%	1.6%	NA
RAPID MI-ICE (n=20)[1]	0%	0%	0%

5.2.1.4 COOL MI Trial Adverse Events Related to Cooling

Potential adverse events related to cooling (e.g., arrhythmia or hemodynamic complications) and to placement and/or use of the Reprieve Catheter (e.g., vascular or thrombogenic complications) were also evaluated as a secondary endpoint. The incidence of these types of events is presented. It is important to note that these complications are also risks of myocardial infarction and coronary intervention themselves. **Table 6** below reports the incidence of non-MACE complications.

Table 6: Incidence of Other Complications

Events through 30 days	Control (N=180)	Intervention (N=177)	p-value
Bradyarrhythmia	41 (22.8%)	46 (26.0%)	0.56
Ventricular Tachycardia/Fibrillation	36 (20.0%)	31 (17.5%)	0.64
Cardiogenic Shock	11 (6.1%)	22 (12.4%)	0.06
Pulmonary Edema	3 (1.7%)	6 (3.4%)	0.49
Vascular Complications	15 (8.3%)	15 (8.5%)	0.90
Retroperitoneal bleed	2 (1.1%)	1 (0.6%)	0.95
Hematoma >6cm	12 (6.7%)	13 (7.3%)	0.99
Pseudoaneurysm	1 (0.6%)	3 (1.7%)	0.63
AV fistula	1 (0.6%)	0 (0%)	0.95
Bleeding Requiring Transfusion	14 (7.8%)	20 (11.3%)	0.34
Deep Venous Thrombosis	0	3 (1.7%)	0.24
Pulmonary Embolism	3 (1.7%)	0	0.24
Stroke	1 (0.6%)	0	0.95

Arrhythmias are a known risk of moderate to severe hypothermia. In the COOL MI trial, with its mild hypothermia target temperature, arrhythmias were not more common and appeared to be primarily related to ischemia and/or the coronary intervention. Cardiogenic shock requiring treatment with an intra-aortic balloon pump trended toward a higher incidence in the hypothermic group. However, the majority of shock cases appeared to be more related to complicated MIs and/or complex interventions than to cooling. Other potential contributory factors (e.g., age, weight, Pethidine dose) were compared between shock and stable patients; however, no causal relationships were apparent. The majority of the vascular complications reported in the Intervention group were related to the arterial access site for the PCI procedure rather than the venous access site for the cooling catheter. Three cases of deep venous thrombosis (DVT) were reported in the Intervention group.

5.2.1.5 COOL MI Trial Effectiveness Results

The primary effectiveness endpoint in the COOL MI study was infarct size, measured using SPECT imaging at 30 days. Overall, there was no observed difference in infarct size (%LV) between study groups (**Table 7**). The secondary effectiveness endpoints of LV ejection fraction, CK-MB release, and ST-segment resolution, likewise did not demonstrate a difference between the Intervention and Control groups.

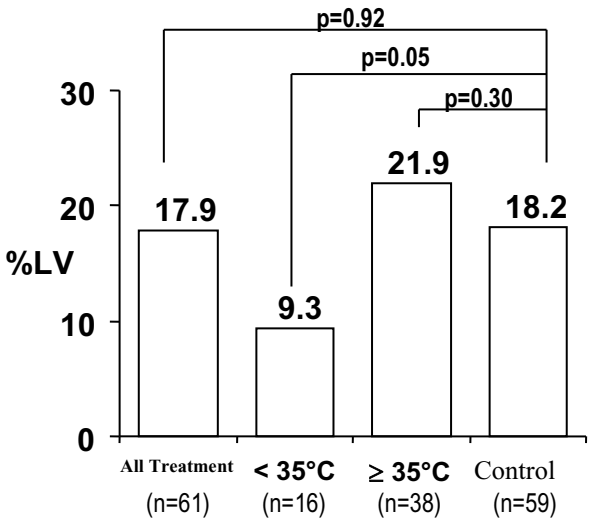
Table 7: COOL MI Results

	Control	Intervention	p-value
% LV Infarct Size (N) mean ± std dev median	157 13.8 ± 15.1 10	168 14.1 ± 14.3 10	 0.83
LV Ejection Fraction (N) mean ± std dev median	104 55.2 ± 11.4 54	115 53.0 ± 12.0 53	 0.17
Peak CK-MB (N) mean ± std dev median	167 42.8 ± 48.1 33.9	168 49.1 ± 50.7 33.6	 0.25
ST-segment resolution - 90 min. post-PCI (N) < 30% 30 - 69% ≥ 70%	90 11.1% 27.8% 53.3%	82 20.7% 35.4% 39.0%	 0.13 0.36 0.09
ST-segment resolution - 180 min. post-PCI (N) < 30% 30 - 69% ≥ 70%	79 10.1% 20.3% 60.8%	80 16.3% 27.5% 51.3%	 0.36 0.38 0.30

In addition, no statistically significant differences were demonstrated when the Intervention and Control patients were compared based on the following stratifications: infarct location, time from onset of symptoms to PCI, prior MI, or TIMI flow prior to PCI. However, subsequent analysis revealed a strong relationship between final infarct size and patient temperature at the time of reperfusion.

The mean temperature at the time of reperfusion, or more specifically, at the time of first balloon inflation, was 35.1°C. As shown in **Figure 6**, in the population of patients with anterior myocardial infarction, those patients who had a temperature <35°C at the time of reperfusion had a statistically significant reduction in final infarct size as compared to both the control group (9.3% vs. 18.2%, p=0.05) and those with a temperature ≥35°C (9.3% vs. 21.9%, p=0.01).

Figure 6: Mean Infarct Sizes (%LV) of Patients with Anterior Infarction



Subject groups:

i) All Intervention patients regardless of temperature at PCI

ii) Intervention patients cooled to < 35°C at PCI

iii) Intervention patients ≥ 35°C at PCI

iv) Control patients

This effect has a strong basis in physiology and was consistent across other clinical measures, i.e., there was a trend toward decreased CK-MB release and increased LV Ejection Fraction in the cooled patients. This effect is not attributable to differences in baseline clinical or angiographic variables. In fact, those patients with a temperature <35°C were more likely to have occlusion of the proximal versus mid left anterior descending coronary artery and a longer time to reperfusion. These factors would be expected to increase infarct size in this group, but the observed reduction in infarct size appears to be the result of cooling.

5.2.2 COOL MI II Trial

Because of the encouraging results in patients with anterior AMI's in whom hypothermia had been achieved at the time of PCI, COOL MI II was initiated. Additionally, COOL MI II Trial was intended to verify the feasibility of initiating cooling earlier in the treatment pathway (e.g., in the emergency department). Only a fraction of the anticipated sample size were enrolled before the trial was ended early because the sponsor became financially insolvent after only 41 patients were enrolled. The study data were submitted by the sites to a Data Management CRO. As a result, the final report is not currently available because the data was not released to ZOLL by the Data Management CRO upon ZOLL acquisition of Radiant Medical.

In COOL MI II, all cooling was initiated in the Cath Lab even though the focus was on earlier cooling. Since earlier initiation of cooling was not accomplished, reaching the goal of a core temperature of 35° C before PCI was dependent on the more powerful GTO System. This was accomplished in 26 of the 27 patients without the intentional delay of PCI. Pivotal data for 23 patients were available and the mean time to reach 35°C was 6.1

minutes (± 3.0), 34°C was 14.5 minutes (± 7.9) and 33°C was 31.3 minutes (± 29.9). Data showed 15 of the patients were cooled to 32°C; the mean time was 36.1 minutes (± 14.0).

Efforts to initiate cooling as early as possible resulted in a median of 39 minutes of cooling time prior to PCI, a significant improvement over the median of 18 minutes of cooling time achieved in the previous study. In addition, the median door-to-balloon time was 106 minutes for these COOL MI II patients, compared to a median of 104 minutes for Test patients in the previous study, indicating that PCI was not delayed by the introduction of cooling. By focusing on cooling earlier in the treatment pathway, additional cooling time can be achieved without significant adverse impact on time to reperfusion.

5.2.2.1 COOL MI II Trial Adverse Events

As with COOL MI, the primary safety endpoint of the COOL MI II study was the incidence, through 30 days, of MACE. Shown below are the adverse events in the COOL MI II trial in the intent to treat (ITT) population. **Table 8** combines the Feasibility and Pilot hypothermia groups for a total of 41 patients (12 Feasibility and 29 Pivotal).

Table 8*:* Incidence of MACE and Other Complications

Events through 30 Days	**Normothermia**	**Hypothermia**
Enrollment	*10*	*41*
UADE	0	0
Cardiac		
Death	0	1 (2.4%)
Repeat MI	0	1 (2.4%)
Repeat PCI	1 (10%)	3 (7.3%)
CABG	0	2 (4.9%)
Hypotension / Shock	1 (10%)	6 (14.6%)
CHF	0	2 (4.9%)
Pericardial Effusion	0	1 (2.4%)
Pericarditis	0	1 (2.4%)
HTN	0	1 (2.4%)
Arrhythmias		
Ventricular Fibrillation	0	4 (9.8%)
Vent. Tachycardia	1 (10%)	7 (17.1%)
Frequent PACs	1 (10%)	0
SVT	0	1 (2.4%)
Atrial Fibrillation	0	11 (26.8%)
Vascular Events		
Bleeding requiring transfusion	0	3 (7.3%)
Thrombocytopenia	0	2 (4.9%)
Anemia	0	2 (4.9%)
Hematoma > 6cm	0	2 (4.9%)
DVT	0	1 (2.4%)
Local Tissue Trauma	0	1 (2.4%)
Epistaxis	1 (10%)	0
Hemoptysis	0	1 (2.4%)
Stroke	0	0
Respiratory Events		
Pulmonary Edema	0	8 (19.5%)
Pulmonary Embolism	0	0
Hypoxia	0	1 (2.4%)
Respiratory Failure	0	1 (2.4%)
Plural Effusion	0	3 (7.3%)
Increased Pulmonary HTN	1 (10%)	0
Pneumonia	1 (10%)	0

Renal		
Renal requiring Treatment	1 (10%)	2 (4.9%)
Hemodialysis	0	0
UTI	0	2 (4.9%)
Hematuria	1 (10%)	0
Other		
Nausea / Vomiting	1 (10%)	15 (36.6%)
Systemic Infection	0	3 (7.3%)
Fever	0	3 (7.3%)
Muscular Pain	1 (10%)	3 (7.3%)
Rhabdomyolysis	1 (10%)	0
Mental Status Changes	0	2 (4.9%)
Hypokalemia	0	1 (2.4%)
Vaginal Infection	0	1 (2.4%)

5.2.3 COOL RCN Trial

The COOL RCN (Radio-Contrast nephropathy) trial was undertaken to evaluate whether endovascular cooling provides more effective protection for patients at high risk of experiencing RCN. The trial was designed as an international, multicenter, 1:1 randomized controlled trial of up to 400 subjects at up to 35 investigational sites. Subjects with a calculated Creatinine clearance of 20 – 50 mL/min and scheduled for a diagnostic or interventional catheterization procedure were enrolled. The trial utilized Radiant Medical's Reprieve System. The study was commenced in March 2006 and was terminated after enrolling only 136 subjects due to the financial insolvency of Radiant Medical.

Table 9: COOL RCN Trial*:* Adverse Events Incidence of Complications In-Hospital

	Normothermia	**Hypothermia**	**P Value**
Enrollment	*70*	*58*	
Nausea/Vomiting	6 / 70 (8.6%)	26 / 58 (44.8%)	<0.01
Bradycardia	2 / 70 (2.9%)	7 / 58 (12.1%)	0.04
Bleeding Requiring Transfusion	7 / 70 (10.0%)	1 / 58 (1.7%)	0.05
Atrial Fibrillation	2 / 70 (2.9%)	3 / 58 (5.2%)	0.5
CABG	4 / 70 (5.7%)	1 / 58 (1.7%)	0.25
Pulmonary Edema	4 / 70 (5.7%)	1 / 58 (1.7%)	0.25
Renal Complication	2 / 70 (2.9%)	3 / 58 (5.2%)	0.5

	Normothermia	Hypothermia	P Value
Acute Renal Failure	2 / 70 (2.9%)	2 / 58 (3.4%)	0.85
Elevated Serum Creatinine	0 / 70 (0%)	1 / 58 (1.7%)	--
Hemodialysis	2 / 70 (2.9%)	0 / 58 (0%)	--
Urinary Tract Infection	3 / 70 (0.4%)	1 / 58 (1.7%)	0.41
Hypotension/Shock	1 / 70 (1.4%)	3 / 58 (5.2%)	0.22
Hematoma >6cm	0 / 70 (0%)	3 / 58 (5.2%)	--
SVT	0 / 70 (0%)	2 / 58 (3.4%)	--
MI	0 / 70 (0%)	1 / 58 (1.7%)	--
Ventricular Tachycardia	1 / 70 (1.4%)	1 / 58 (1.7%)	0.89
Death	0 / 70 (0%)	1 / 58 (1.7%)	--
Repeat PCI	1 / 70 (1.4%)	1 / 58 (1.7%)	0.89
Stroke	0 / 70 (0%)	1 / 58 (1.7%)	--

Table 10: COOL RCN Trial: Incidence of Complications to 30 Days

	Normothermia	Hypothermia	P Value
Enrollment	*70*	*58*	
Renal	7	2	0.15
Acute Renal Failure	5	1	0.15
Renal Stent	2	0	--
Kidney Infection	0	1	--
Cardiac	8	14	0.1
MI	1	1	0.89
CABG	2	3	0.5
PCI	1	3	0.22

	Normothermia	Hypothermia	P Value
PCI or CABG	3	6	0.18
Death - Cardiac	1	2	0.45
Shock	0	3	--
CHF	2	1	0.67
Angina	1	0	--
Hypertension	0	1	--
Arrhythmia	3	3	0.81
Atrial Fibrillation	2	1	0.67
Bradycardia	0	2	--
SVT	1	0	--
Ventricular Fibrillation	0	0	--
Non-Cardiac	3	3	0.81
Stroke	1	0	--
Bleed/Transfusion	2	3	0.5
Dialysis	0	0	--
Vascular Complications Requiring Surgery	0	0	--
Rehospitalization	13	13	0.59
Other	9	12	0.23
Anasarca	1		--
Fatigue	1		--
Ischemic Bowel	1	1	0.89
Hypoglycemia	1		--
Lesion Excision	1		--
Anemia	1		--
Hiatal Hernia	1	1	0.89
Pulmonary Edema	1		--
Knee Injury	1		--
Rash		1	--
Debridement of Sternal Wound		1	--
Leg Weakness		1	--
Nausea/Vomiting		2	--
Dehydration		1	--
Acute Respiratory Failure		1	--
Metabolic Acidosis		1	--
Back Pain		1	--
Systemic Infection		1	--

5.2.3.1 Unanticipated Adverse Events

(i) COOL MI Trial – Unanticipated Adverse Events

There was one Unanticipated Adverse Device Effect (UADE) in the COOL MI Trial; A patient experienced nasopharyngeal trauma and bleeding potentially caused by the nasoesophageal temperature probe used as part of the Reprieve System. This resulted in a modification to the Informed Consent Form to explain the risk of nasal trauma and/or bleeding due to the nasoesophageal probe.

(ii) COOL MI II Trial – Unanticipated Adverse Events

There were no UADE's in the COOL MI II Trial.

(iii) COOL RCN Trial – Unanticipated Adverse Events

There was one UADE in the COOL-RCN Trial. A 73 year old male with chronic renal insufficiency and a history of aortobifemoral bypass scheduled for cardiac catheterization. The patient was randomized to the Hypothermia arm. The Reprieve catheter was placed via the left femoral vein. The angiogram and stenting procedures were performed via right radial arterial access. After approximately 1 hour of cooling, the patient complained that his feet were itching and it was noted that the patient's left foot and leg were cyanotic up to mid-thigh, with no left DP pulse, and the right foot was slightly discolored. He was subsequently rewarmed at the maximum rate for approximately 40 minutes. It was observed that the cyanosis lightened as the patient rewarmed and was apparently resolved with no further sequelae after discontinuation of treatment with the Reprieve catheter, indicating that cooling with the device contributed to the reduced peripheral circulation. The already compromised peripheral vascular circulation is suspected to have been exacerbated by hypothermia induced vasoconstriction. It is known that hypothermia induces superficial vasoconstriction, but this degree of cyanosis had not been observed with previous use of the device. Additionally, after the patient had received Pethidine and versed as part of the anti-shivering protocol, his respiration became depressed, requiring assisted ventilation, Romazicon and Narcan. It is possible that this transient hypoxic event may have also contributed to the cyanosis.

Lower extremity cyanosis in the presence of peripheral vascular insufficiency had not been identified in the protocol or informed consent document as a potential risk of mild hypothermia or use of the Reprieve catheter. The resolution of the cyanosis upon rewarming and removal of the catheter indicated that these may have contributed to the event. The risk section of the protocol and informed consent were subsequently revised.

5.2.4 ICE- IT Trial

The Intravascular Cooling Adjunctive to Percutaneous Coronary Intervention for Acute Myocardial Infarction Trial (ICE-IT) [23] randomized 228 patients presenting with an acute

MI within 6 hours of symptom onset to endovascular cooling concomitant with PCI versus routine PCI. The primary endpoint of infarct size at 30 days as measured by SPECT imaging was similar between the 2 groups (10% for the hypothermia group versus 13% for the control group, p = 0.14). Like the COOL MI trial, ICE-IT was also an overall negative trial. But while TH did not demonstrate any significant decrease in infarct size overall, a trend towards benefit was again observed on post-hoc analysis of the subgroup with anterior infarction who were sufficiently cooled to a temperature of < 35°C at the time of revascularization (infarct size of 12.9% of the left ventricle in the TH population compared to 22.7% in the control group, p = 0.09).[23]

5.2.5 RAPID-MI ICE Trial

Recently, Lund University presented a preliminary report of their RAPID-MI ICE Trial.[1] This trial enrolled 20 patients presenting with acute myocardial infarction, and 10 patients each were randomized to TH by intravascular cooling or a control group. Cooling was accomplished with a combination of 2L of cold saline infusion and the Phillips InnerCool catheter-based cooling system. The endpoint was infarct size normalized to myocardium at risk assessed by cardiac magnetic resonance using T2 weighted imaging and late gadolinium enhancement. Although the sample size is relatively small, the trial produced a number of potentially important results:

- Core body temperature less than for 35°C was achievable before reperfusion without significant delay in the door to balloon time.
- Infarct size normalized to myocardium at risk was reduced by a remarkable 38% in patients receiving hypothermia.
- There were also significant decreases in peak and cumulative Troponin I or T in the hypothermia group.

5.2.6 CHILL-MI Trial

Lund University recently reported the results of the CHILL-MI trial[37], which was a multi-center study of 120 patients with STEMI (< 6 hours) planned to undergo PCI who were randomized to hypothermia induced by rapid infusion of 600 – 2000 ml of cold saline and endovascular cooling, or standard of care. Hypothermia was initiated before PCI and continued for 1 hour after reperfusion. The primary endpoint was infarct size as a percentage of the myocardium at risk (IS/MaR), assessed by cardiac MRI at 4±2 days. The goal to reach target temperature of 33°C at reperfusion was also not achieved in the CHILL-MI trial, due to the inadequate cooling power of the cooling device. Patients randomized to cooling achieved a core body temperature at reperfusion of 34.7°C with a 9 minute longer door-to-balloon time. Hypothermia induced by cold saline infusion and endovascular cooling was feasible and safe, however, there was no significant difference in IS/MaR between the groups. Exploratory analysis of early anterior infarctions (0-4 hrs) showed a significant reduction in IS/AAR of 33% ($p<0.05$). Further, the incidence of

heart failure was lower with hypothermia at 45 days (3% vs 14%, p<0.05). This trial, as the others cited above, shows potential efficacy of cooling in patients with anterior STEMI, supporting further research for confirmation.

5.2.7 Induction of Mild Systemic Hypothermia With Endovascular Cooling During Primary Percutaneous Coronary Intervention for Acute Myocardial Infarction

This multi-center study included 42 patients with acute myocardial infarction (AMI) (onset less than 6hrs) and evaluated the safety and feasibility of endovascular cooling during primary PCI for AMI. [39] Subjects were randomized to PCI with or without endovascular cooling (target core temperature 33°C). Cooling was maintained for 3 h after reperfusion. Skin warming, oral buspirone, and intravenous meperidine were used to reduce the shivering threshold. The primary end point was major adverse cardiac events at 30 days. Infarct size at 30 days was measured using SPECT imaging. All patients successfully cooled did achieved a core temperature below 34°C (mean target temp 33.2 ± 0.9°C). MACE events occurred in 0% vs. 10% (p = NS) of treated versus control patients. The median infarct size was not significantly smaller in patients who received cooling compared with the control group (2% vs. 8% of the left ventricle, p = 0.80).

5.2.8 VELOCITY Trial

The VELOCITY trial[38] randomized 54 STEMI patients at 7 centers in the United States and Canada to emergent PCI with (n = 28) or without (n = 26) hypothermia induced by the Velomedix Automated Peritoneal Lavage System (Velomedix; Menlo Park, CA) between January 2013 and January 2014. Baseline characteristics were similar between the 2 groups, and 46.3% of all infarcts were anterior.

Hypothermia (core temperature at or below 34.9°C) was achieved in 96.3% of patients and PCI was performed in all but 1 patient in each treatment group. Median door-to-balloon time was shorter in the control vs hypothermia group (47 vs 62 minutes; *P* = .007). Among the 46 PCI patients who underwent MRI 3 to 5 days post procedure, the median myocardial infarct size was similar in the control vs hypothermia group (16.1% vs 17.2% of LV mass; *P* = .54).

VELOCITY Investigators observed that prolonged door-to-balloon time in the hypothermia group may have attenuated the effect of hypothermia on infarct size though it is unlikely have been totally responsible for absence of effect as DTB times were short in both groups and within the range wherein further reductions in mortality may not be realized.

At 30-day follow-up, no patients in the control group had a primary composite safety endpoint event, compared with 6 (21.4%) of the patients who underwent hypothermia (P = .01). Further details in Section 5.2.8.1.

In conclusion, the VELOCITY study found that controlled systemic hypothermia through automated peritoneal lavage may be safely and rapidly established in patients with evolving STEMI undergoing primary PCI at the expense of a modest increase in door-to-balloon time. In the VELOCITY randomized trial, peritoneal hypothermia was associated with an increased rate of adverse events (including stent thrombosis) without reducing infarct size. Adequately powered randomized trials (likely limited to patients with anterior MI) are needed to assess the effect of rapidly induced hypothermia on myocardial salvage and clinical outcomes after primary PCI.

5.2.8.1 VELOCITY Trial Adverse Events at 30 Days

At 30-day follow-up, no patients in the control group had a primary composite safety endpoint event (death, reinfarction, ischemia-driven TLR, major bleeding, sepsis, pneumonia, peritonitis, severe arrhythmias, or renal failure), compared with 6 (21.4%) of the patients who underwent hypothermia (P = .01). Four patients (14.3%) experienced MACE (cardiac death, reinfarction, or ischemia-driven TVR), and 3 (11.0%)—all in the hypothermia arm—developed definite stent thrombosis.

Table 11: VELOCITY Trial Clinical Event Rates Within 30 Days

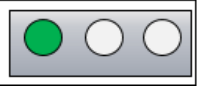
	Control (N=26)	Hypothermia (N=28)	*P* Value
Primary composite safety end point	0% (0)	21.4% (6)	0.01
Cardiac death	0% (0)	3.6% (1)	0.34
Noncardiac death	0% (0)	0% (0)	…
Reinfarction	0% (0)	3.6% (1)	0.34
Ischemia-driven target vessel revascularization	0% (0)	11.0% (3)	0.09
Major bleeding	0% (0)	3.6% (1)	0.34
Ventricular tachycardia or fibrillation	0% (0)	3.6% (1)	0.34
Sepsis	0% (0)	3.6% (1)	0.34
Pneumonia	0% (0)	0% (0)	…
Renal failure	0% (0)	0% (0)	…
Peritonitis	0% (0)	0% (0)	…
Major adverse cardiac events	0% (0)	14.3% (4)	0.047
Stent thrombosis	0% (0)	11.0% (3)	0.09
Acute (≤24 h)	0% (0)	7.1% (2)	0.17
Subacute (1–30 days)	0% (0)	3.6% (1)	0.34
Definite	0% (0)	11.0% (3)	0.09
Probable	0% (0)	0% (0)	…

Data are expressed as Kaplan–Meier estimates, % (n). *P* values are from the log-rank test.

5.2.9 EU AMI Case Series

ZOLL is currently enrolling patients in the COOL-AMI EU Case Series Trials to assess the ability to integrate hypothermia into the current pathway for patients receiving PCI for ST elevation MI. To date, 308 patients have been enrolled at 36 sites in the EU. Both anterior and non-anterior STEMI patients have been enrolled, and cooling is performed using the ZOLL Thermogard XP (TGXP) System or Proteus IVTM system. . A series of six standards has been developed and monitored to enable consistency in the execution of the protocol. The standards include delivery of the antishivering regimen correctly, delivery of 1 L of iced saline before PCI, and at least 18 minutes of cooling delivered prior to wire crossing the lesion. Feedback in the form of a report card (**Figure 7**) is provided to the site after each case as indicated in the following diagram:

Figure 7: Report Card Standards

Standards	Measured	Expected	
1. Anti-shivering Regimen Delivered prior to Iced Saline Delivery	C-B-P-S	Per-protocol C-B-P-S	
2. 1 Liter Iced Saline delivered with pressure bag prior to PCI	1 Liter	1 Liter	
3. At least 18 minutes of cooling delivered prior to PCI	18 min	18 min	
4. Door-to-Balloon Time	59 min	< 90min	
5. Ischemic Time	3 hrs. 9 min	< 6 hrs.	
6. DAPT Agent Administered	Yes	Pre-PCI	

These six standards are consistently achieved at all sites. The 18 minute duration of cooling matches the average duration of cooling in the previous EU COOL AMI trial. The ability to deliver 18 minutes of cooling prior to PCI is consistently achieved in the recent EU Case Series, where the door to balloon (DTB) times, at all sites, were less than 60 minutes (ranging from 38 minutes to 58 minutes). This is far less than the maximum door to balloon time of 90 minutes recommended by the current guidelines for PCI, 2011 ACCF/AHA/SCAI PCI Guideline[24,50]). The experience of one of the sites has been published[26], and notes that the average DTB time for the first 11 patients enrolled in the trial was 38 minutes, compared to a mean DTB time of 37 minutes for all patients presenting with STEMI without cooling. In view of the validation that implementation of hypothermia in the treatment pathway for PCI of STEMI patients is feasible, ZOLL has also conducted the COOL-AMI EU PILOT Trial, following the same standards of implementation, with cooling done by the more powerful Proteus device. The goal is to maximize the dose of cooling prior to PCI.

5.2.10 COOL-AMI EU PILOT Trial

ZOLL has completed enrollment in the COOL-AMI EU PILOT Trial that evaluated the retention of subjects after integrating therapeutic hypothermia using the ZOLL Proteus IVTM System into existing STEMI treatment protocols for subjects who presented with acute anterior myocardial infarction. 50 subjects were randomized at 16 sites in the EU. 22 patients (88%; 95% confidence interval [CI]: 69-97%) in the hypothermia group and 23 patients (92%; 95% CI: 74-99) in the control group completed cardiac magnetic resonance imaging at four to six days and 30-day follow-up. A series of three standards were monitored to enable consistency in the execution of the protocol. The standards included delivery of the antishivering regimen correctly, delivery of up to 1 L of iced saline, and 18 minutes of cooling delivered prior to wire crossing the lesion. Patients with

anterior STEMI were rapidly and safely cooled. Intravascular temperature at coronary guidewire crossing after 20.5 minutes of endovascular cooling decreased to 33.6° C (range 31.9-35.5° C), which is ≥1.1° C lower than in previous cooling studies. There was a 17-minute (95% CI: 4.6-29.8 min) cooling-related delay to reperfusion. In the "per protocol" analysis, median infarct size/left ventricular mass was 16.7% in the hypothermia group versus 23.8% in the control group (absolute reduction 7.1%, relative reduction 30%; p=0.31) and median left ventricular ejection fraction (LVEF) was 42% in the hypothermia group and 40% in the control group (absolute reduction 2.4%, relative reduction 6%; p=0.36). There were no statistically significant differences between the groups, in adverse events or serious adverse events[49].

5.3 Summary and Clinical Trial Rationale

Previous clinical trials in patients experiencing acute myocardial infarction (AMI) have demonstrated that therapeutic hypothermia is safe, well tolerated and showed reductions in infarct size. Additionally, recent preclinical results (Stanford-ZOLL data) have shown that temperature at reperfusion of 32 °C is superior to 35 °C for reducing infarct size, confirming a dose response. Future clinical trials will require more powerful cooling devices, and more consistency in implementing 18 minutes of cooling before reperfusion across all study sites in order anterior infarctions. It is therefore the objective of the COOL-AMI EU PIVOTAL Trial to evaluate the actual effectiveness of therapeutic hypothermia as a protection strategy.

Further clinical trials are needed to evaluate more powerful cooling devices, along with a refined therapeutic hypothermia protocol (target temperature of 32°C + 18 minutes of cooling prior to PCI). It will also be important to understand whether adequate cooling to 32°C + 18 minutes of cooling prior to PCI can be implemented into existing STEMI treatment protocols with no significant delay in door-to-balloon times. This trial aims to address the need for a powered clinical evaluation assessing the safety and effectiveness the Proteus IVTM for this refined therapeutic hypothermia protocol as an adjunct therapy for AMI patients undergoing PCI. Among these refinements are: 1) A larger dose of cooling was achieved with the Proteus System (temp at PCI was 33.6°C as opposed to 35°C for COOL MI), 2) Delivery of at least 18 minutes of cooling prior to PCI was possible (mean 20 minutes in the EU Pilot Study), 3) the anti-shivering protocol was refined and worked successfully, and 4) the use of report cards for every case to track : a) anti-shivering protocol impementation, b) infusion of 1 liter of cold saline prior to PCI, c) 18 minutes of cooling prior to PCI, d) door to balloon time less than 90 minutes, e) total ischemic time less than 6 hours, and f) proper administration of dual antiplatelet therapy (DAPT) are all refinements ready to be implemented.

6 CLINICAL TRIAL PLAN

6.1 Trial Objective

The objective of this randomized clinical trial is to evaluate the safety and effectiveness of therapeutic hypothermia, using the ZOLL Proteus IVTM System, as an adjunctive therapy for patients presenting with acute anterior myocardial infarction and undergoing PCI. in comparison with patients with acute anterior myocardial infarction and undergoing PCI only.

6.2 Trial Endpoints

6.2.1 Primary Effectiveness Endpoint

Relative reduction of 20% in mean anterior myocardial infarct size (IS), as determined by Cardiac Magnetic Resonance (cMR) imaging at 4-6 days post infarct in the Test Arm (cooling + PCI) compared to the Control Arm (PCI only). Infarction Size (IS) is defined as % Left Ventricular Mass as measured by Cardiac Magnetic Resonance (cMR) imaging. Infarct Size (IS) will be assessed by Cardiac Magnetic Resonance (cMR) at 4 – 6 days following the index procedure.

The trial is considered to have met the primary efficacy endpoint if the Test Arm demonstrates a 20% relative reduction in infarct size compared to the Control Arm.

The ITT analysis set will be used for primary statistical analyses and summaries. The ITT population includes those subjects who have signed an informed consent and have been randomized to the Test Arm or the Control Arm of the trial. ITT subjects will be evaluated according to the group to which they were randomized.

The PP analysis set will also be evaluated. The PP population includes those subjects who met inclusion and exclusion criteria, were randomized to either the Test or Control arm, received the treatment to which they were randomized, and complied substantially with the treatment timeline and steps of this protocol without major protocol violations.

6.2.2 Primary Safety Endpoint

Per-patient rate of composite Major Adverse Cardiac Events (MACE) subjects, defined as Cardiac Death (CD), All Myocardial Infarction (All MI) and Clinically-Indicated Target Lesion Revascularization (CI-TLR) at 30 day follow-up; non-inferiority to the control.

6.2.3 Additional Assessments: Demographics and Other Parameters

Subject demographics and various baseline characteristics will also be collected. Additional clinical data collected and evaluated will include the number of patients who can successfully be enrolled and randomized, the timing of subject presentation to hospital, the timing of therapeutic and adjunctive interventions, the timing of reaching the

target temperature zone, temperature at PCI, subsequent maintenance of hypothermia and temperature data from the IVTM System. Observations will be evaluated relating to the use of the ZOLL Proteus IVTM System and how it performs in relation to the induction of therapeutic cooling and follow-up cMR imaging. New York Health Association[24] (NYHA) Functional Class and Kansas City Cardiomyopathy Questionnaire[25] (KCCQ) will be evaluated at12 month follow-up.

6.3 Trial Design

This clinical trial is a multicenter, prospective, interventional, randomized-controlled trial. Randomization will be in a 1:1 ratio, Test Arm (PCI + Cooling) or Control Arm (PCI alone) in up to a total of 500 patients (250 subjects in each arm), at up to 70 clinical sites.

6.4 Patient Population

Subjects will include those who present to the Emergency Department (ED) and / or Cath lab, who meet the trial eligibility requirements and who can provide informed consent for cooling treatment. Subjects considered for enrollment in this trial will include adult patients presenting with an acute anterior myocardial infarction. To qualify, patients must have symptoms consistent with AMI (i.e., chest pain, arm pain, etc.) unresponsive to nitroglycerin, qualifying ST-segment elevation of ≥ 0.2 mV in two or more anterior contiguous precordial leads (V1-V4), with symptom onset greater than 30 minutes, but less than 4.5 hours prior to presentation at hospital, and be eligible for PCI. This ensures that the overall ischemic time from symptom onset to time of wire crossing is less than 6 hours.

Subjects randomized to the Test Arm will receive intravascular cooling with the Proteus IVTM device. While undergoing temperature management, the Anti-shivering Protocol must be followed (see **Attachment II**).

6.5 Selection Criteria

Patients shall be screened to the following inclusion and exclusion criteria. Patients are qualified for participation only if all Inclusion Criteria have been met and all Exclusion Criteria have been confirmed not present.

6.6 Inclusion Criteria

All Inclusion Criteria must be answered YES for subject to satisfy Inclusion Criteria:

1. The patient is ≥ 18 years of age.
2. The patient has symptoms consistent with AMI (i.e. chest pain, arm pain, etc.) and unresponsive to nitroglycerin, with symptoms beginning greater than 30 minutes but less than 4.5 hours prior to presentation at hospital.

3. Qualifying Infarct Location: Evidence of Acute Anterior MI with ST- segment elevation of ≥ 0.2 mV in two or more anterior contiguous precordial leads (V1 –V4).
4. The patient is eligible for PCI.
5. The patient is willing to provide written informed consent to participate in this clinical trial (V1 –V4)..

6.7 Exclusion Criteria

All Exclusion Criteria must be answered NO for subject to satisfy Exclusion Criteria:

1. The patient has had a previous Myocardial Infarction.
2. The patient is experiencing cardiogenic shock (systolic blood pressure [SBP] <100 mmHg, HR > 100 bpm and arterial oxygen saturation (pulse oximetry) ≤92% without additional oxygen. The patient is presenting with resuscitated Cardiac Arrest, Atrial Fibrillation, or Killip risk stratification class II through IV.
3. The patient has an aortic dissection or requires an immediate surgical or procedural intervention other than PCI.
4. The patient has known history of Congestive Heart Failure (CHF), Hepatic Failure, end-stage kidney disease or severe Renal Failure (clearance < 30ml/min/1.73m²).
5. The patient is febrile (temperature > 37.5 °C) or has experienced an Infection with Fever in the last 5 days.
6. The patient has a known previous CABG.
7. The patient has a known recent Stroke within 90 days of admission.
8. Cardio-Pulmonary Decompensation that has occurred en route to the hospital or, in the opinion of the physician, that is imminent or likely to occur following presentation to the clinical site.
9. Contraindications to hypothermia, such as patients with known Hematologic Dyscrasias which affect thrombosis (e.g., cryoglobulinemia, sickle cell disease, serum cold agglutinins) or Vasospastic Disorders (such as Raynaud's or thromboangitis obliterans).
10. Any contraindication to cardiac MRI, or any implants in the upper body which may cause artifacts on cardiac MRI imaging.
11. The patient has a known hypersensitivity or contraindication to aspirin, heparin, or sensitivity to contrast media, which cannot be adequately pre-medicated.
12. The patient has a known history of Bleeding Diathesis, Coagulopathy, Cryoglobulinemia, Sickle Cell Anemia, or will refuse blood transfusions.
13. The patient has a height of <1.5 meters (4 feet 11 inches).
14. The patient has a known hypersensitivity or contraindication to buspirone hydrochloride or Pethidine (Meperidine) and/or has been treated with a monoamine oxidase inhibitor in the past 14 days.

15. Patient has a known history of severe hepatic or renal impairment, untreated hypothyroidism, Addison's disease, benign prostatic hypertrophy, or urethral stricture that in the opinion of the physician would be incompatible with Pethidine administration.
16. The patient has an Inferior Vena Cava filter in place (IVC).
17. The patient has a pre-MI life expectancy of <1 year due to underlying medical conditions or pre-existing co-morbidities.
18. The patient has a known, unresolved history of drug use or alcohol dependency, or lacks the ability to comprehend or follow instructions.
19. The patient is currently enrolled in another investigational drug or device trial.
20. The patient is apprehensive about or unwilling to undergo the required MRI imaging at follow-up, has a documented or suspected diagnosis of claustrophobia, or has Gadolinium allergy, or is in permanent Atrial Fibrillation.
21. The patient has received thrombolytic therapy en route to the hospital
22. The patient shows clinical evidence of spontaneous reperfusion as observed symptomatically and/or from baseline ECG findings (partial or complete ST resolution in ECG prior to informed consent and randomization).
23. The patient is a vulnerable subject, for instance, a person in detention (i.e., prisoner or ward of the state).
24. The patient is a female who is known to be pregnant.

6.8 Clinical Trial Procedures

6.8.1 Patient Screening

Patients presenting at participating centers with clinical signs and symptoms of AMI will be expeditiously triaged and offered the opportunity to participate in this clinical trial without regard to age, gender or ethnicity. To ensure that patients are approached for potential trial participation without bias, patient screening information will be maintained on a patient screening log at each site. This log will track patients that were enrolled in the trial as well as patients who were excluded from participation and the reason(s) for their exclusion. The use of a patient screening log assures that all eligible subjects are given an opportunity to participate or decline participation in the trial.

The subject's eligibility for treatment with the Proteus IVTM System will be evaluated based on the medical and anatomical criteria outlined above in the inclusion/exclusion criteria section. The Investigator will explain the elements of this clinical trial, including the risks, potential benefits and required interventional and follow-up procedures, to each subject prior to obtaining informed consent.

If a subject is found to be ineligible during baseline screening and routine diagnostic tests, the subject shall be considered a screen failure and will be documented on the patient screening log. Randomized subjects are considered enrolled in the trial when all inclusion

and exclusion criteria have been satisfied, informed consent has been signed, and the patient is randomized to either Test or Control Arm of the trial.

6.8.2 Informed Consent

The reviewing Medical Ethics Committee (MEC) must review and approve an Informed Consent Form (ICF) specific to this study. The Sponsor will provide each study center with an example ICF. The study center, to meet specific requirements, may modify this example ICF; however, the ICF to be used for subject consent under this protocol must contain all of the elements required by the study Sponsor and the governing regulatory requirements for informed consent (21 CFR Part 50). Therefore, each investigational site will provide the Sponsor with a copy of the MEC approved ICF - as well as any amendments - for the duration of the study.

Informed consent will be required from each subject. The MEC approved Informed Consent document must be signed by the patient or by the legal authorized representative (LAR) prior to any related procedures (or according to the MEC's approved guidelines), including the collection of data on case report forms (CRFs). Only subjects that have the appropriate informed consent form will be included in the trial.

The informed consent process (including time and date of discussion), should be documented in the subject's medical record and signed/dated by the individual (investigator or designee) who recorded it. The original signed consent form must be filed in the subject's medical record and a copy of the signed informed consent documentation given to the subject.

All subjects must sign, date and note the time on the Institutional Medical Ethics Committee (MEC) approved informed consent prior to any clinical trial/investigation-specific procedures. Obtaining the consent with the documented date and time, and the provision of a copy to the subject will be documented in the subject's medical record.

Due to the emergent nature of treating acute myocardial infarction, patients who have been enrolled in the study may receive a subsequent consent which provides more detailed information about their participation in the trial (based on MEC requirements), which may be reviewed and signed after the acute phase of their treatment has been completed. If the patient decides they no longer want to be included in the study, they will be withdrawn and their data will be included in the analysis up until the time of withdrawal.

If in the course of the pre-study evaluations prior to consent, the patient is found not to be eligible for inclusion in the study, the patient should be notified and the reason for ineligibility documented on the appropriate Screening Log.

All information pertinent to this clinical investigation (including at a minimum the description and purpose of the study, potential benefits, potential risks and

inconveniences, active procedures, confidentiality, compensation, circumstances for termination and site contact persons) will be provided to the subjects in writing and in their native, non-technical, language by Investigator or designee, who has been trained on the protocol.

If new information becomes available that can significantly affect a subject's future health and medical care, this information shall be provided to the affected subject(s) in written form. If relevant, all affected subjects shall be asked to confirm their continuing informed consent in writing.

6.8.3 Simulated Training Program (German centers only)

Germany sites will participate in a simulation training program prior to randomization. The training will include a training mannequin and functional devices (catheters, cassettes, controller, Bair Hugger warming blankets, medication infusion devices). ZOLL will train, test and monitor the sites for times to completion of the various steps to implement cooling, including time to consent, administration of anti-shivering medications, infusion of cold saline, insertion of the cooling catheter, and time of onset of endovascular cooling. Metrics for the successful completion of each step will be developed to provide feedback to the sites. The goal is to ensure the highest level of quality in the execution of the trial protocol and minimize the time from patient contact to institution of cooling.

6.8.4 Approval to Randomize in the Trial

It will be at the discretion of the sponsor to advance a site to Randomization. Based on the site's performance with the Simulated Training Program, as determined by the Sponsor, the site will be notified of authorization to randomize patients in the trial.

6.8.5 Randomization

In the randomization phase, patients who meet eligibility criteria for participation will be randomly assigned to either the Test Arm (PCI + Cooling) or Control Arm (PCI alone) in a 1:1 ratio.

Randomization will be applied using an internet based Interactive Web Response Systems (IWRS). In the trial, randomization will be done using random permuted blocks (based on procedure outlined in Pocock SJ. Clinical Trials: A Practical Approach. Wiley, Chichester, 1983), stratified by site, with 1:1 allocation ratio using a randomization list. At randomization, inclusion and exclusion criteria will be verified, and confirmation of informed consent signature will be done.

Subjects will be considered to be enrolled in the Test Arm and Control Arms of the trial when all inclusion and exclusion criteria have been met, the informed consent form has been signed, and randomization assignment has been completed.

6.8.6 Acute Care and Emergency Room Triage

Prior to the initiation of this trial at each participating institution, training will be conducted by the Sponsor targeted toward the integrated care of each trial subject and emphasizing the shared responsibility between the Departments of Emergency Medicine and Interventional Cardiology, where applicable at each center, with the goal of rapid screening, enrollment and treatment of appropriate patients.

Each center will clearly delineate departmental responsibilities for the following:

- Assessment of patient clinical features, signs and symptoms
- Administration of Informed Consent
- Review of Inclusion/Exclusion Criteria
- Assurance that diagnostic procedures mandated by the protocol are completed prior to randomization into this trial and are appropriately documented
- Patient Randomization
- Administration of pre-treatment medication(s)
- Administration of Anti-shivering medications to subjects randomized to the Test Arm of the trial
- Consensus on location in hospital where cooling using the Proteus IVTM System will be initiated
- Set-up of Proteus IVTM System, including insertion of the Proteus Catheter into the femoral vein induction of cooling, initiation of re-warming, Proteus IVTM System shutdown and catheter extraction for Test Subjects.

6.8.7 Standardized Care Prior to the Cooling Procedure

It is anticipated that subjects may receive one or more of the following therapies as part of current clinical practice in the treatment of acute myocardial infarction:

- Intravenous fluids and electrolytes
- Oxygen
- Antiplatelets and/or antithrombotics
- Vasoactive agents and diuretics

Clinicians will be encouraged to manage the subject in a standardized manner with respect to oxygenation, anti-coagulation and/or anti-platelet medications.

6.8.8 Documentation Procedures

Trial procedures and treatment data will be documented on standardized Case Report Forms (CRFs) which may be on paper or via an electronic data capture system (EDC). The completion of the CRFs may be delegated to a member of the study team (e.g., the study coordinator) as long as that person is listed on the Delegation of Authority Log. However, the Principal Investigator retains responsibility for the accuracy and integrity of

the data entered on the CRF. The CRF will be monitored for accuracy and completeness per the source documents (medical records, charts, interventional systems, worksheets as applicable, etc.) at each clinical center. Temperature data from the Proteus IVTM System will be downloaded and sent to Sponsor. A flow diagram for the Test Arm is represented in **Figure 10**.

It is anticipated that technology and/or techniques such as edit checks and double entry of data may be utilized to minimize the rate of error. Additionally, ZOLL or its assignees may ask for data clarification or re-check of data for accuracy. Monitoring visits and CRF completion logs will be used to track data entry in accordance with trial logistics and expectations.

Any source documentation (procedure reports, imaging studies, lab reports, death certificates, etc.) that is sent to the Sponsor should have all patient identifiers removed and replaced with the subject's trial ID, and processes ensuring patient privacy and clinical data confidentiality will be followed in accordance with local regulations and applicable laws.

6.8.9 Study Flow and Procedures

Figure 8 Screening and Enrollment Flow

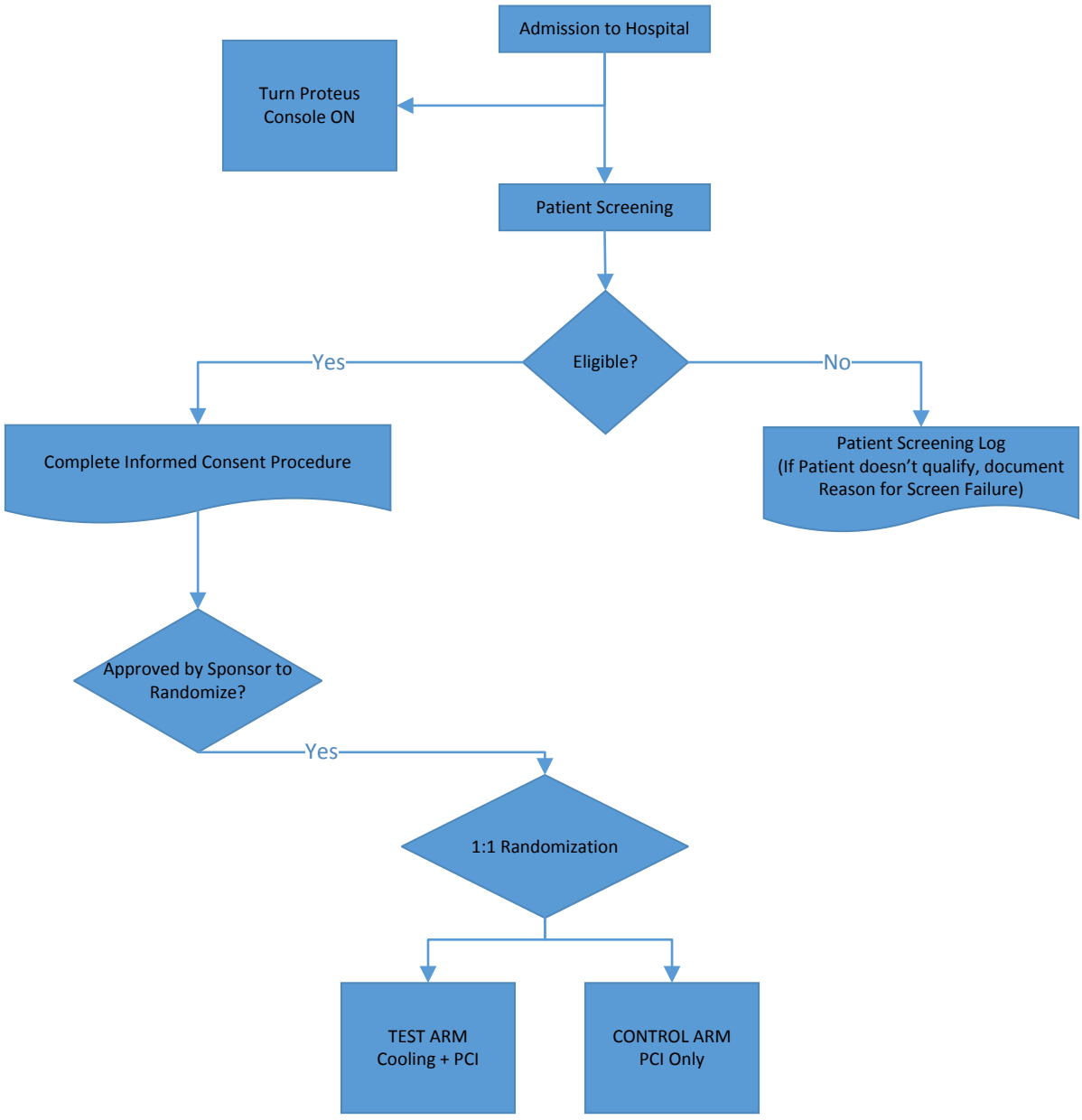


Figure 9 Control Arm Flow

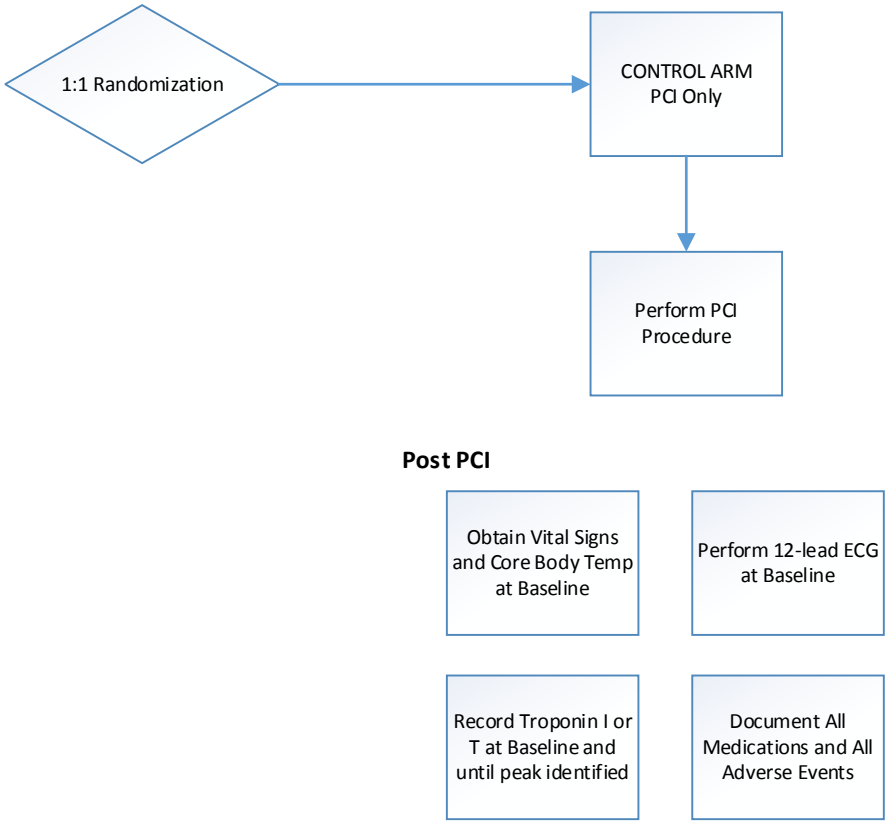


Figure 10 Test Arm Flow

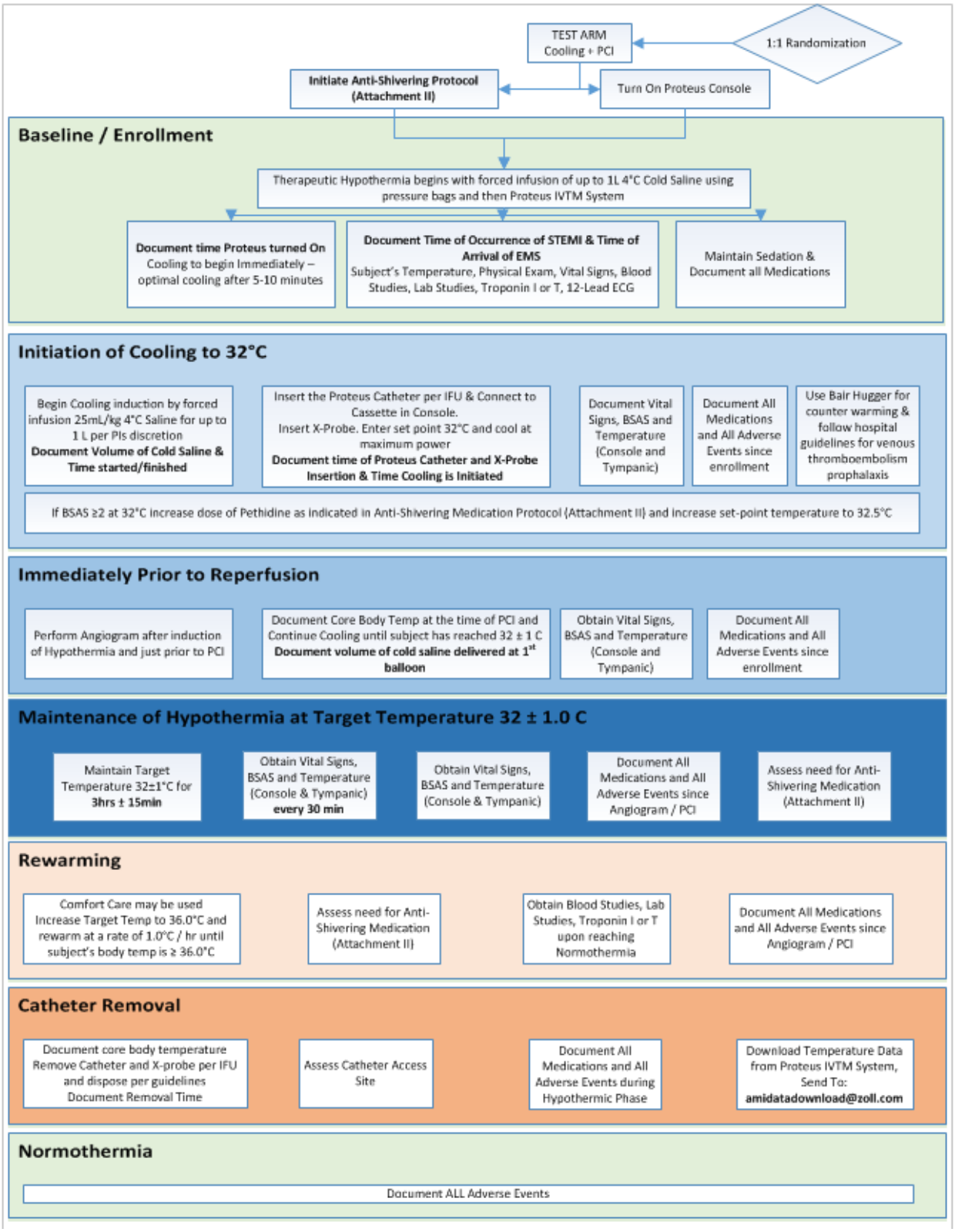
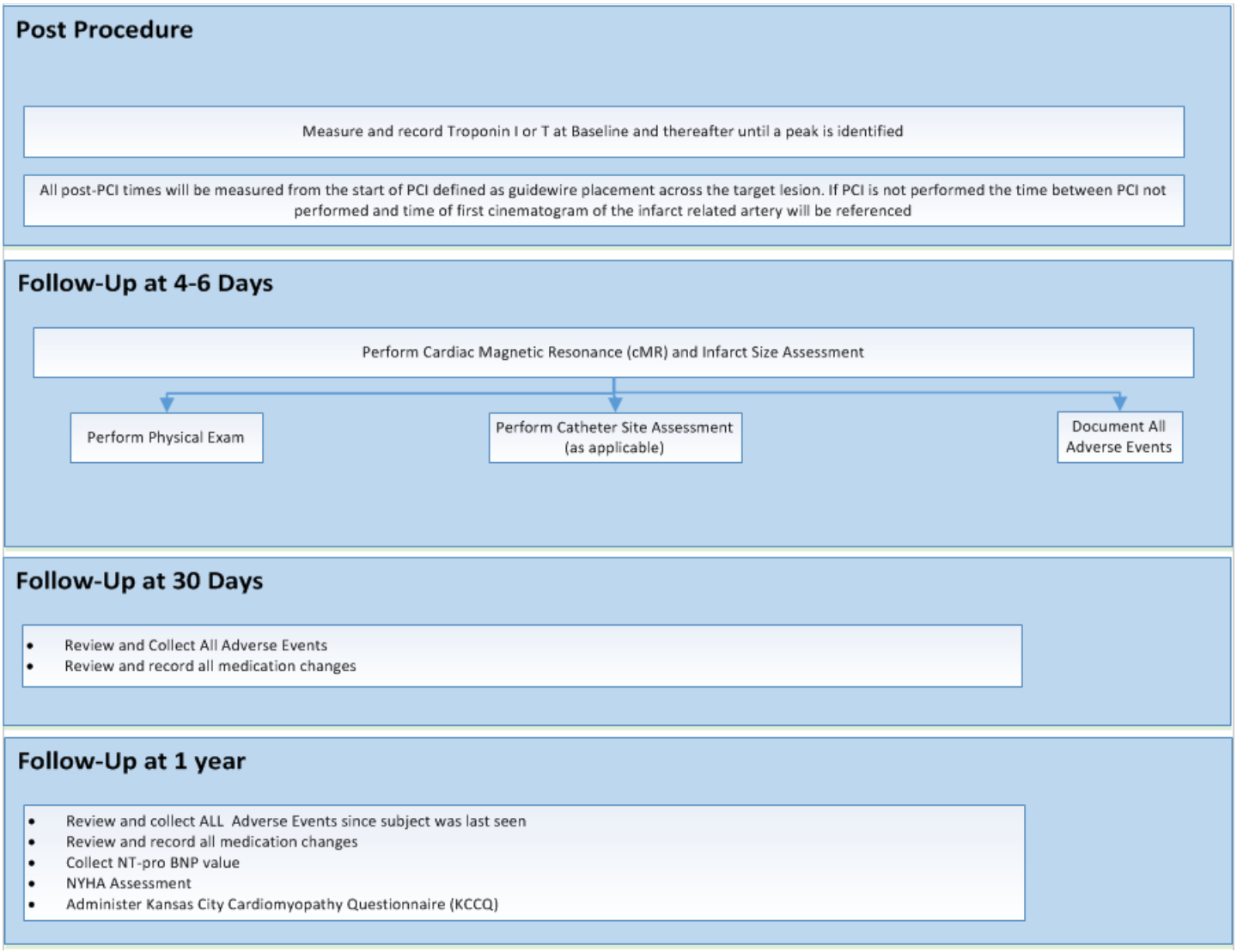


Figure 11 All Patient Procedures



6.8.10 Pre-Cooling Assessment Procedures

All required procedures and data collection from the time of subject screening (presentation at hospital) through the pre-cooling assessment period are given below in **Table 11.**

Table 11: Baseline / Screening and Enrollment Procedures/Evaluations and Data Collection for the Test & Control Arms of the Trial

Procedures/ Evaluations	Data
Trial Eligibility	At admission to the hospital
Informed Consent	Obtain Consent from patient before any trial-related procedure is initiated.
Trial Enrollment	- Follow randomization process to assign patient to Test or Control Arms of the trial - Complete Enrollment Form, document randomization, and FAX or email to ZOLL at +1 800.243.0360 or ami-eu@zoll.com to enter in the eCRF
Temperature	Document subject's temperature using a tympanic thermometer
Vital Signs	Blood Pressure, Heart Rate, Respiratory Rate, BSAS measurement
Physical Exam	Complete Physical Examination
Blood Studies	RBC's, WBC's, Hct, Hgb, Platelets,
Lab Studies	BUN, Creatinine, sodium, potassium, calcium, phosphate, magnesium, chloride, lactic acid, glucose, amylase, lipase
Cardiac Markers	Baseline and peak Troponin I or Troponin T including upper limit of normal
ECG	12-lead baseline
Medications	Document as indicated on Case Report Form since STEMI onset
Adverse Events	Collect all adverse events as soon as patients are enrolled in the trial

6.8.11 Initiation, Maintenance, and Reversal of Cooling with Proteus IVTM System Procedures / Evaluations and Data Collection for Subjects Enrolled in the Test Arm

6.8.12 Test Arm: Temperature Management Protocol and Data Collection Time Points

Treatment with therapeutic hypothermia will begin with a forced infusion of up to 1 L of cold saline (4°C) (according to the guideline) using pressure bags, and at the time of administration of the anti-shivering medication according to the anti-shivering guidelines, then will continue with the Proteus IVTM System as soon as possible. Cooling will be initiated with the Proteus IVTM System set at a temperature of 32.0 °C, and the subject's temperature will be measured with the Proteus IVTM System immediately before PCI has occurred (measured as time the wire crosses the target lesion). Cooling will be maintained for 3 hours and will be followed with active rewarming to attain normothermia 36.0 °C (96.8°F).

Cooling induction, maintenance of hypothermia, and rewarming are described in the following **Table 12.** The data collection schedule for Test Arm subjects is summarized in **Section 6.8.13**.

Table 12: Initiation, Maintenance, and Reversal of Cooling with Proteus IVTM System Procedures / Evaluations and Data Collection for Subjects Enrolled in the Test Arm

Phase	Task
Immediately Upon Arrival to the Hospital	1. **Turn the Proteus Console on** (in preparation for cooling with the device) 2. **Document time of occurrence of STEMI and ECG** 3. **Document time of arrival of Emergency Medical Service EMS (Paramedics)**

Phase	Task
Baseline / Enrollment	4. Immediately after informed consent is obtained and patient is randomized to the Test Arm of the trial, **initiate anti-shivering medication protocol using Guidelines outlined in Attachment II**. 5. Begin cooling induction by forced infusion with 25mL/kg of 4°C cold saline using pressure bags up to 1 L of cold saline (4°C) (according to the guideline) at the physician's discretion. Use Bair Hugger™ (CE marked device) for patient comfort. 6. **Document the time the Proteus console is turned on.** The device will begin cooling the patient immediately; however, optimal cooling is achieved in 5-10 minutes after it is turned on. 7. Perform Physical Examination and obtain Vital Signs. 8. Obtain Blood and Lab studies. 9. Obtain Troponin I or Troponin T . 10. Obtain 12-lead baseline ECG. 11. Document all medication use since STEMI onset. 12. Measure body temperature using an independent tympanic thermometer. The independent measurement is to be used in addition to the core body temperature collected by the Proteus Temperature Probe (X-Probe). 13. Document all Adverse Events.

Phase	Task
Initiation of Cooling	14. Document the volume of cold saline, the time the cold saline infusion is started and the time the cold saline infusion is finished. 15. Following the ZOLL Proteus IVTM System Instructions for Use (IFU), insert the Proteus Catheter into the Inferior Vena Cava via either femoral vein. The Proteus Catheter is then connected to the Cassette that has been inserted into the Proteus Console. 16. Following insertion of the Proteus Catheter, insert the Proteus Temperature Probe (X-Probe). Access site selection may vary by both operator preference and anatomical considerations; however, the function of the system is not dependent on which femoral vein is chosen. 17. Once the Proteus System Catheter & Proteus Temperature Probe (X-Probe) have been inserted, enter set point temperature to 32.0°C on the Proteus Console and perform cooling at maximum power as soon as the console is ready to cool. **18. Document the time of Proteus Catheter & X-Probe (temperature probe) insertion.** **19. Document the time cooling is initiated with the Proteus IVTM System.** 20. Document vital signs (BP, HR, RR), and temperature measurements (Tympanic and Proteus Console measurements). 21. Document all medication use. 22. Document all adverse events since the time of enrollment. 23. Use Bair Hugger™ warming blankets for counter-warming. If choosing to use low dose anticoagulation during the cooling phase, follow hospital's guidelines for venous thromboembolism prophylaxis.

Phase	Task
Immediately Prior to Reperfusion	24. If clinically relevant shivering (Bedside Shivering Assessment Scale (BSAS) of 2 or greater) occurs at 32° (see **Anti-Shivering Guidelines, Attachment II, and BSAS Attachment III),** increase the dose of Pethidine (Meperdine) as indicated in shivering protocol and increase set point temperature on the Proteus IVTM System to 32.5°C. If clinically relevant shivering continues (BSAS ≥2), once again increase dose of Pethidine as indicated in Anti-Shivering Protocol and increase set point temperature on the Proteus IVTM System to 33°C. Continue this process until a temperature is reached where there is no shivering. Follow sedation procedures using **Anti-Shivering Guidelines, Attachment II, and the BSAS Attachment III.** 25. Perform *angiogram after the induction of hypothermia has been initiated and just prior to PCI. **26. Obtain vital signs (BP, HR, RR), BSAS and temperature measurements (Tympanic and Proteus Console measurements) just prior to PCI.** 27. Document all medication use since the initiation of cooling. 28. Document all adverse events since the initiation of cooling. **CAUTION: Anticipate changes in electrolytes and laboratories values secondary to hypothermia.** 29. Document core body temperature at the time of PCI. 30. If subject has not reached 32.0 ± 1.0°C (or temperature where shivering does not occur, as indicated above) at the time of PCI, continue cooling induction until target temperature has been reached. 31. Document the time wire crossed the target lesion.

Phase	Task
Maintenance of Hypothermia Target Temperature 32 ±1°C	32. Maintain the patient at the set target temperature of 32.0 (or temperature where shivering does not occur, as indicated above) for 3 hours ± 15 minutes from the initiation of cooling with the Proteus System. **33. Obtain vital signs (BP, HR, RR), BSAS and temperature measurements (Tympanic and Proteus Console measurements) every 30 minutes during the 3 hours of cooling.** 34. Document all medication use since the angiogram/ PCI procedure. 35. Document all adverse events since the angiogram/ PCI procedure. 36. If clinically relevant shivering [Bedside Shivering Assessment Scale (BSAS) of 2 or greater] occurs at 32.0°C (See **Anti-Shivering Guidelines, Attachment II, and BSAS, Attachment III),** increase dose of Pethidine (Meperidine) as indicated in shivering protocol and increase temperature on the Proteus IVTM System console to 32.5°C. 37. If clinically relevant shivering continues (BSAS ≥ 2), once again increase dose of Pethidine as indicated in shivering protocol and increase temperature on the Proteus IVTM System to 33°C. Continue this process until a temperature is reached where there is no shivering. Follow sedation procedures using Anti-Shivering Guidelines outlined in **Attachment II** and BSAS assessment in **Attachment III.**

Phase	Task
Rewarming	38. After 3 hours of cooling with the Proteus IVTM System, begin active rewarming to normothermia. Palliative care such as blankets, Bair Hugger patient warming systems, and warm liquids may be used. 39. Using the Proteus System Console, press **STOP** and Increase target temperature to 36.0°C using the arrow touch buttons and then press **Continue**. 40. Set rewarming rate to 1.0°C/hr using the arrow touch buttons and press **Continue** to start rewarming. 41. Maintain the Pethidine infusion during rewarming using the Anti-Shivering Protocol outlined in Attachment II. 42. Obtain vital signs (BP, HR, RR), BSAS and temperature measurements (Tympanic and Proteus Console measurements) every hour until normothermia is achieved 43. Obtain blood studies, lab studies and record peak Troponin I or Troponin T including upper limit of normal for site. 44. Document all medication use during the rewarming phase. 45. Document all adverse events during the rewarming phase. **CAUTION: Anticipate changes in electrolytes and laboratories secondary to re-warming**

Phase	Task
Catheter Removal	46. Document core body temperature at time of Proteus Catheter removal. 47. Remove Proteus Catheter and X-Probe per IFU and document time of removal. 48. Dispose of the Proteus Catheter, X-Probe and Proteus Cassette per institution's guidelines (single-use). 49. Assess catheter access site for signs of bleeding, access vessel trauma, or hematoma formation. **50. Download temperature data from the Proteus Console after the cooling phase has been completed. Send downloaded data to amidatadownload@zoll.com immediately upon downloading. Device data must be saved according to Section 16.1, Investigator Records.** 51. Document all medication use during the hypothermic phase. 52. Document all adverse events during the hypothermic phase. **DO NOT DISCARD SPLITTER CABLE (MULTI–USE TEMPERATURE CABLE)**
Normothermia	53. Document all adverse events until patient is discharged from the hospital.
Post-Procedure	54. If required, provide additional Informed Consent document to patients who were consented with the short consent form (if required by MEC or country-specific regulations).

NOTE: All post-PCI times will be measured from the start of PCI, defined as time the wire crosses the target lesion. In the event that PCI is not performed, the time of the first cineangiogram of the infarct related artery will be referenced. If PCI is staged for the non-culprit lesion, then the PCI will be performed after the 4-6 day cMR

***Angiograms are to be uploaded for all adjudicable events.**

6.8.13 Trial Schedule for Test Arm Subjects

Procedure/ Interval	Baseline / Enrollment	Initiation of Cooling	Immediately prior to reperfusion (PCI)	Maintenance of Target Temp 32 ±1°C	Rewarming to 36°C	Catheter Removal	Discharge	Follow-Up @ 4-6 Days	Follow-Up @ 30 Days (±7 days)	Follow-Up @ 12 months (±14 days)	Unscheduled Visit
Trial Eligibility & Informed Consent	**upon arrival to hospital**										
Physical Exam	**X**						**X**				
Anti-Shivering Protocol	**X**			**X**[a]							
Cold Saline Infusion		**X**									
Catheter Insertion Time		**X**									
Catheter Removal Time						**X**					
Temperature Documented	**X**	**X**	**X**	**every 60 min during 3 hr cooling**	**every 60 min during rewarming**						
Temperature Data Download						**X**					
Vital Signs	**X**	**X**	**X**	**every 60 min**	**every 60 min**						
Blood Studies RBC's, WBC's, Hct, Hgb, Platelets,	**X**				**upon reaching normothermia**						
NT-pro BNP										X	
Lab Studies BUN, Creatinine, Na, K, Ca, Mg, Cl, P, lactic acid, glucose, amylase, lipase	**X**				**upon reaching normothermia**						
Any Medication Use	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Troponin I or T(including ULN) during hospitalization	**X**	**Perform Troponin until peak value identified**									
12 lead ECG	**X**										
Adverse Events		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Catheter Access Site Assessment						**X**	**X**	**X**			
Cardiac Magnetic Resonance (cMR) imaging								**X**			
NYHA Assessment										**X**	
KCCQ										**X**	

[a] **For persistent clinically relevant shivering (BSAS ≥ 2), increase dose of Pethidine as indicated in shivering protocol and increase temperature on Proteus IVTM System console by 0.5°C. Continue this process until a temperature is reached where there is no shivering. Follow sedation procedure using Anti-Shivering Guidelines outlined in Attachment II and BSAS assessment in Attachment III Include BSAS measurement and temperatures from independent method.**

6.8.14 Trial Schedule for Control Arm Subjects

Procedure/ Interval	Baseline / Enrollment	Immediately prior to reperfusion (PCI)Post-PCI	Discharge*	Follow-Up @ 4-6 Days	Follow-Up @ 30 Days (±7 days)	Follow-Up @ 12 months (±14 days)	Unscheduled Visit
Trial Eligibility & Informed Consent	**upon arrival to hospital**						
Physical Exam	**X**		**X**				
Catheter Insertion Time	**X**						
Catheter Removal Time							
Temperature Documented	**X**						
Vital Signs	**X**						
Blood Studies RBC's, WBC's, Hct, Hgb, Platelets,	**X**						
NT-pro BNP						X	
Lab Studies BUN, Creatinine, Na, K, Ca, Mg, Cl, P, lactic acid, glucose, amylase, lipase	**X**						
Any Medication Use	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Troponin I or T(including ULN)	**X**	**Perform Troponine until peak value identified**					
12 lead ECG	**X**						
Adverse Events		**X**	**X**	**X**	**X**	**X**	**X**
Cardiac Magnetic Resonance (cMR)				**X**			
NYHA Assessment						**X**	
KCCQ						**X**	

6.8.15 Control Arm Protocol and Data Collection Time Points

The data collection schedule for Control Arm subjects is summarized in **Section 6.8.14**. For patients randomized to the Control Arm, i.e., PCI alone, the following procedures will be performed:

i. Document time of occurrence of the STEMI & ECG results

ii. Document time of arrival of Emergency Medical Service EMS (Paramedics) & time of arrival at hospital

iii. Collect all adverse events as soon as patients are enrolled in the trial

iv. Perform Blood Studies, Labs, and record Baseline and peak Troponin I or T

v. Perform PCI. If PCI is staged for the non-culprit lesion, then the PCI will be performed after the 4-6 day cMR

vi. Monitor and record the patient's vital signs, temperature, blood pressure, heart rate and respiratory rate at baseline.

vii. Obtain 12-lead baseline ECG .

viii. Monitor and record all pharmacological agents

ix. Measure and record Baseline Troponin I or T, including upper limit of normal, and when a peak is identified.

x. Monitor and record all adverse events for the duration of 12 month follow-up.

xi. Complete physical exam prior to discharge.

6.8.16 Follow-up at 4-6 days and at 30 days following the PCI Procedure

Subjects enrolled in the Test and Control Arms will undergo Cardiac Magnetic Resonance (cMR) to assess infarct size at 4-6 days.

In addition, the following procedures are to be performed at 4 - 6 days and at 30 days after the index procedure (PCI) for **both** Test Arm and Control Arm patients:

i. Monitor and record all adverse events for the duration of 12 month follow-up.
ii. Review and record all medication changes since index.

6.8.17 Follow-up at 12 months following PCI

Following completion of the 30 day follow-up, all subjects will be followed through 12 months for the incidence of Adverse Events, Serious Adverse Events, Death and Heart Failure (as assessed by NYHA and Kansas City Cardiomyopathy Questionnaire (KCCQ)

i. Monitor and record all adverse events for the duration of 12 month follow-up.
ii. Collect NT-pro BNP value to assess clinical prognosis of Heart Failure.
iii. Review and record all medication changes
iv. Perform blinded NYHA Assessment andadminister Kansas City Cardiomyopathy Questionnaire (KCCQ).

6.8.18 Use of other Cooling Methods

For the purposes of this trial, no other cooling methods may be used.

6.8.19 Transferring Subject during Cooling

Although interruption during the induction phase of hypothermia is not recommended, if subject transfer is required during any phase of the cooling, follow relevant instructions in the device Instructions for Use.

For additional detail, refer to the Proteus IVTM System Instructions for Use**.** The console screen also provides prompts for entry of user-defined parameters and system start-up.

6.8.20 Patient Withdrawal and Discontinuation

The term "patient withdrawal" refers to the patient deciding to terminate their participation in the trial. The term "discontinuation" refers to the physician deciding that the patient will not continue trial participation as defined below.

A subject has the right to withdraw from the trial at any time and for any reason without prejudice to his or her future medical care by the physician or the institution. Trial withdrawal by a subject specifically means withdrawal of consent from further participation in the trial. Subjects who withdraw consent after enrollment will be evaluated to the time of withdrawal, and withdrawal of consent precludes any further trial related treatment or data collection. If possible, a complete, final physical examination should be performed on all subjects who withdraw from the trial. At a minimum, every effort should be made to document subject outcome at the time of trial withdrawal.

A subject may withdraw from the clinical investigation for the following reason:

- Subjects may choose to withdraw from the clinical investigation under the terms of the Declaration of Helsinki and their consent documentation without having to give a reason;

A subject may be discontinued from the clinical investigation for the following reasons:

- Any unanticipated adverse reaction which is, in the opinion of the Investigator, related to the treatment and will endanger the well-being of the patient if treatment is continued;
- Development of any illness(es), infection or condition(s) that might interfere with the Clinical Investigational Plan;
- Non-compliance with the clinical investigation procedures deemed by the Investigator to be sufficient to cause discontinuation;
- Any problem deemed by the Investigator to be sufficient to cause discontinuation.

- Investigator will treat all subjects discontinued from the investigation due to an unanticipated adverse reaction, directly related to the investigation, until the reaction resolves.

- Investigator will not replace subjects who have withdrawn from the clinical investigation if they have received the investigational device. If possible, Investigator will perform any procedures or assessments planned for the subject at the time of withdrawal.

All subjects are expected to continue in the trial through the final follow-up assessment or until ZOLL notifies the Investigator in writing that further follow-up is no longer required, except in the event of death or upon the subject's request for early withdrawal from the clinical trial.

6.8.21 Patient Lost to Follow-up

The investigator will attempt to contact a subject at least three times prior to designating them as lost-to-follow-up subjects. The investigator will document the date and type of attempted communication. The investigator will complete and sign the Study Exit Form when a subject is lost to follow-up.

6.8.22 Early Termination of a Clinical Investigation

Both the Sponsor and Investigator reserve the right to terminate the clinical investigation at any time. If necessary, and after review and consultation with Principal Investigator, Sponsor will make a final determination on whether to terminate the study.

A clinical investigation or Investigator may be terminated at a clinical center for any of the following reasons, or for reasons not listed that affect patient safety or integrity of the trial:

- Unsatisfactory rate of patient enrollment or compliance to eligibility criteria.
- Repeated noncompliance with the investigational plan.
- Inaccurate, incomplete, and/or untimely submission of data.
- Inadequate accountability of the investigational device.

The sponsor may terminate this trial if there are new, previously unknown adverse events related to device or cooling procedure, deaths, SAEs/AEs exceeding those reported as related to device/cooling procedures in previous trials, and/or if recommended by DMC (Data Monitoring Committee) to stop the trial. The sponsor will make the final determination on whether to terminate the study.

The sponsor may terminate the trial for any other unforeseen circumstances. In case of premature termination/suspension, ZOLL will stop the enrollment, inform all investigators at all sites and all

regulatory agencies governing the study. ZOLL will perform complete device accountability of all investigational devices and retrieve them from the clinical sites. All study subjects will be followed through the specified follow-up periods. ZOLL will issue a final report of the clinical study.

6.8.23 Amendments and Protocol Deviations

Investigator will not deviate from the CIP without prior written confirmation by Sponsor, or their designee, except as required in a medical emergency. In medical emergencies, Sponsor does not require prior confirmation for protocol deviations, but Investigator will notify Sponsor within 5 days of the incident and will notify the EC according to local requirements. Investigator, or designee, will record deviations with an explanation for the deviation. Investigator will report to Sponsor who will analyze them and assess their significance. Significant deviations from the CIP will be reported to the Competent Authority.

Examples of protocol deviations may include those relating to:

- Eligibility
- Enrollment and randomization
- Informed consent
- Protocol adherence (e.g., tests and assessments done as required in Trial Schedule, etc.)

Routine monitoring will assess Investigator compliance to the protocol.

Investigator must not modify the CIP without the prior and written permission from Sponsor. All modifications to the clinical protocol must be submitted to the Competent Authority (where required) to allow the Competent Authority review and approval.

The Sponsor is responsible for management, processing and approval of any amendment to the Investigational Plan. Should the site consider an amendment necessary, the Sponsor will work with the site to make the appropriate changes. The Sponsor will manage documentation of such changes through the existing document control system. A history of changes and a redline version of the documentation will be maintained per the applicable quality system procedures. The proposed amendment will be submitted to the reviewing MEC and government agency as applicable. Any necessary approvals will be received in writing before the requested change is implemented.

This study will be conducted in compliance with ISO 14155, ICH E6 Consolidated Good Clinical Practice Guidance, 21 CFR 812, 21 CFR Part 50, and any requirements imposed by countries with participating clinical sites. The study will not commence until the necessary government and MEC approvals have been obtained.

6.8.24 Trial Exit

The Trial Exit Form (CRF) should be completed at the time a subject is exited from the trial. A subject will be considered to have exited from the trial for any of the following reasons.

- Subject completes follow-ups required by the investigational plan.
- Subject dies.
- Subject requests to be withdrawn.
- Physician requests that patient be withdrawn to protect the welfare of the patient.
- Patient is lost to follow-up.
- Other (specify)

6.8.25 Subject Confidentiality

Subject confidentiality will be maintained throughout the clinical trial to the extent permitted by law. That is, every attempt will be made to remove patient identifiers from clinical trial documents. For this purpose, a unique subject identification code (site number, subject number and subject initials) will be assigned and used to allow identification of all data reported for each subject. This will also ensure that the information can be traced back to the source data.

Trial data may be made available to third parties, e.g., in the case of an audit performed by regulatory authorities, provided the data are treated confidentially and that the subject's privacy is guaranteed. The identity of a subject will never be disclosed in the event that trial data are published.

Security and Unique usernames and passwords will be utilized by data entry, data verification and other personnel who have database access to insure confidentiality and protection of data.

Trial sites must comply with Health Insurance Portability and Accountability Act (HIPPA) and/or the subject confidentiality provisions and privacy laws of each participating country, local regulations, and institutional requirements, whichever is stricter.

6.8.26 Device Accountability

ZOLL is responsible for the availability and traceability of all investigational products. Documentation is required at each step of the process via a device accountability log. Investigational product will be reconciled on a regular basis.

The investigator also is required to maintain adequate records of the receipt and disposition of all investigational devices. A device accountability log will be provided for this purpose.

All unused product must be returned to ZOLL prior to the close of the trial.

6.8.27 Return of Materials upon Trial Termination

Sponsor will ship investigational devices only to qualified Investigators participating in this clinical investigation. Sponsor will not ship investigational devices to any site until evidence of EC approval has been provided to Sponsor, or designee.

Investigator will control access to investigational devices, and will only use investigational devices in the clinical investigation and according to the CIP.

Sponsor will keep investigational device records to document the physical location of each device. Record(s) will include information documenting devices shipped, devices at investigation sites, devices disposed of, and devices returned.

Investigator, or designee, will keep records documenting the receipt, use, return and disposal of the investigational devices, which will include:

- Date of receipt,
- Identification of each investigational device (serial number or unique code),
- Expiry date, if applicable,
- Date or dates of use,
- Subject identification,
- Date on which the investigational device was returned, or explanted from subject, if applicable, and
- Date of return of unused, expired or malfunctioning investigational devices, if applicable.

After the trial procedures have been completed, all unused devices must be accounted for and returned to ZOLL. Instructions for device return to ZOLL will be reviewed at the site initiation visit.

6.8.28 Trial Closure

Trial closure can occur under the following circumstances:

a. termination of site participation in the trial (i.e., closure that occurs prior to meeting defined endpoints) of the trial
b. upon completion of the trial (i.e., when all patients enrolled have completed the follow-up visits or previously exited the trial, and the CRFs and queries have been completed)

Under any circumstance for closure of the trial at the site, ZOLL and/or its designees will notify the site of this occurrence in writing. Trial closeout visits will be performed once a determination has been made that the trial is closed. All unused trial devices and any unused trial materials and equipment will be collected and returned to ZOLL and/or its designees. The monitors will ensure that the investigator's regulatory files are current and complete and that any outstanding issues from previous visits have been resolved. Other issues that will be reviewed at

this visit include: discussing record retention requirements (refer to **Section 14.1**—Investigator Records), device accountability, possibility of site audits, publication policy, and notifying the Medical Ethics Committee and Competent Authorities of trial closure, etc., as applicable.

6.9 Cardiac Magnetic Resonance (cMR) imaging Core Laboratory

Cardiac Magnetic Resonance (cMR) imaging must be collected per the Manual of Operations provided by the sponsor. Images must be submitted to the core laboratory designated by the sponsor for analysis.

7 ADVERSE EVENTS & DEVICE DEFICIENCIES

7.1 Definitions

7.1.1 Adverse Event (AE)

Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.

NOTE 1 This definition includes events related to the investigational medical device or the comparator.

NOTE 2 This definition includes events related to the procedures involved.

NOTE 3 For users or other persons, this definition is restricted to events related to investigational medical devices.

7.1.2 Serious Adverse Event (SAE)

Adverse event that:

a) led to a death, injury or permanent impairment to a body structure or a body function.

b) led to a serious deterioration in health of the subject, that either resulted in:

- a life-threatening illness or injury, or
- a permanent impairment of a body structure or a body function, or
- in-patient hospitalization or prolongation of existing hospitalization, or
- in medical or surgical intervention to prevent life threatening illness

c) led to foetal distress, foetal death or a congenital abnormality or birth defect.

NOTE 1: Planned hospitalization for pre-existing condition, or a procedure required by the Clinical Investigation Plan, without a serious deterioration in health, is not considered a serious adverse event.

7.1.3 Device Deficiency (DD)

Inadequacy of an investigational medical device related to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, use error, or inadequacy in the information supplied by the manufacturer.

7.1.4 Adverse Device Effect (ADE)

Adverse event related to the use of an investigational medical device.

NOTE 1- This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device.

NOTE 2- This includes any event that is a result of a use error or intentional abnormal use of the investigational medical device.

7.1.5 Serious Adverse Device Effect (SADE)

A adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

7.1.6 Unanticipated Serious Adverse Device Effect (USADE)

Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

NOTE: Anticipated SADE (ASADE): an effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report.

7.2 Adverse Event Reporting

7.2.1 Adverse Event Reporting from Site to Sponsor and MEC

The collection of AEs will begin after the informed consent is signed. All AEs that occur through completion of the final follow-up visit, whether observed by the investigator or by the subject, and whether or not thought to be device related, will be reported in detail on the appropriate CRF and followed to resolution or the end of trial participation.

The description of the AE will include the date and time of onset, seriousness, relationship to the device or procedure, the results of any diagnostic procedures or laboratory tests, any treatment recommended, and the outcome of the event. In the circumstance that an AE has not resolved by

the time of the subject's completion of the trial, an explanation will be entered on the appropriate CRF.

ZOLL will implement and maintain a system to ensure that the reporting of the reportable events by the investigator to ZOLL occur immediately, but no later than 3 calendar days after investigational site study personnel awareness of the event.

7.2.2 Serious Adverse Event Reporting to Sponsor and MEC

Serious adverse events (SAEs) and device deficiencies should be reported as soon as possible.

Serious adverse events and device deficiencies must be reported no later than 3 calendar days from the site becoming aware of the event or as per the investigative site's local requirements if the requirement is more stringent than those outlined.

The date the site staff became aware of the SAE must be recorded in the source document. The Investigator will further report the event to the IRB/EC according to the institution's IRB/EC reporting requirements.

Serious adverse events that do not occur in the study subject but occur in the user or other persons need to be reported on the fax notification form titled SAE Notification Form. Serious adverse events that occur in the user or other persons other than the study subject should not be entered into the clinical database.

Serious adverse events should be reported on the SAE Notification Form in the occurrence that the clinical database is not available. This does not replace the electronic clinical database. All information must still be entered in the clinical database once the system is back to normal function.

7.2.3 UADE/USADE Reporting to Sponsor and MEC

ZOLL requires the Investigator to report any USADE to the sponsor within 3 calendar days of the investigator's knowledge of the event and to the EC per EC requirements.

7.2.4 Sponsor Reporting to NCAs (National Competent Authority) when European Sites Participate in the Trial

7.2.4.1 What to Report

The following events are considered reportable events:

- any SAE,
- any Device Deficiency that might have led to a SAE if:
    - suitable action had not been taken or

    - intervention had not been made or
    - if circumstances had been less fortunate
- new findings/updates in relation to already reported events.

7.2.4.2 Report to Whom

Reportable events must be reported at the same time to all NCAs where the clinical investigation has commenced using the summary tabulation featured in the of MEDDEV 2.7/3.

7.2.4.3 Reporting Timelines

ZOLL must report to the NCAs where the clinical investigation has commenced:

- for all reportable events as described in section **7.2.4.1** which indicate an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it: immediately, but not later than 2 calendar days after awareness by ZOLL of a new reportable event or of new information in relation with an already reported event.

- any other reportable events as described in section **7.2.4.1** or a new finding/update to it: immediately, but not later than 7 calendar days following the date of awareness by the ZOLL of the new reportable event or of new information in relation with an already reported event.

7.3 Device Relationship

Determination of whether there is a reasonable possibility that an investigational product or device caused or contributed to an AE is to be determined by the Investigator and recorded on the appropriate CRF form. Determination should be based on assessment of temporal relationships, biologic plausibility, association (or lack of association) with underlying disease and presence (or absence) of a more likely cause.

7.3.1.1 Causality Assessment

The relationship between the use of the medical device (including the medical - surgical procedure) and the occurrence of each adverse event shall be assessed and categorized.

The above considerations apply also to the serious adverse events occurring in the comparison group.

The following definitions are used to assess the relationship of the serious adverse event to the investigational medical device or procedures.

1) Not related: relationship to the device or procedures can be excluded when:

- the event is not a known side effect of the product category the device belongs to or of similar devices and procedures;
- the event has no temporal relationship with the use of the investigational device or the procedures;
- the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
- the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event;
- the event involves a body-site or an organ not expected to be affected by the device or procedure;
- the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);
- the event does not depend on a false result given by the investigational device used for diagnosis, when applicable;
- harms to the subject are not clearly due to use error;
- In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

2) Unlikely: the relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.

3) Possible the relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.

4) Probable the relationship with the use of the investigational device seems relevant and/or the event cannot reasonably explained by another cause, but additional information may be obtained.

5) Causal relationship: the serious event is associated with the investigational device or with procedures beyond reasonable doubt when:

- the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
- the event has a temporal relationship with investigational device use/application or procedures;
- the event involves a body-site or organ that
- the investigational device or procedures are applied to;

- the investigational device or procedures have an effect on;
- the serious event follows a known response pattern to the medical device (if the response pattern is previously known);
- the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible);
- other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
- harm to the subject is due to error in use;
- the event depends on a false result given by the investigational device used for diagnosis 17, when applicable;
- In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

ZOLL and the investigators will distinguish between the serious adverse events related to the investigational device and those related to the procedures (any procedure specific to the clinical investigation). An adverse event can be related both to procedures and the investigational device. Complications of procedures are considered not related if the said procedures would have been applied to the patients also in the absence of investigational device use or application.

In some particular cases the event may be not adequately assessed because information is insufficient or contradictory or the data cannot be verified or supplemented. The ZOLL and the Investigators will make the maximum effort to define and categorize the event and avoid these situations.

Particular attention shall be given to the causality evaluation of unanticipated serious adverse (device) events. The occurrence of unanticipated events related to the use of the device (USADE) could suggest that the clinical investigation places subjects at increased risk of harm than was to be expected beforehand.

8 MONITORING BY DATA MONITORING COMMITTEE

The Data Monitoring Committee (DMC) is used to ensure safety by reviewing cumulative data from the clinical trial at pre-defined intervals for the purpose of safe-guarding the interest of trial participants. The DMC will serve in an advisory role in this trial. The composition, guiding policies, and operating procedures governing the DMC are described in a separate DMC charter. Based on safety data, the DMC may recommend a modification to the protocol or that the sponsor

stops the clinical trial/investigation. All final decisions regarding clinical trial/investigation modifications, however, rest with the Sponsor.

9 ADJUDICATION OF EVENTS

The Clinical Events Committee (CEC) is comprised of qualified physicians who are not investigators in the trial. The Clinical Events Committee is responsible for adjudicating specified clinical endpoints based on the specific criteria used for the categorization of clinical events in the trial.

Periprocedural MI will be adjudicated according to the Clinically Relevant Myocardial Infarction After Coronary Revascularization (CRMI) definition.[40] Death, Stent Thrombosis, Spontaneous MI, and Revascularization will be adjudicated per ARC definitions.[27]

Hospitalization due to Heart Failure will be adjudicated per ACC/AHA definition.[48]

The composition, guiding policies, and operating procedures governing the CEC are described in a separate CEC Manual of Operations.

When applicable, sites will provide patients' source documentation per request from the Sponsor and will aploade angiograms into AMBRA website through software service Dicom Grid, Inc., which will de-identify angiograms.

10 RECOMMENDATION FOR DAPT AND STENTS

Control and intervention group patients should receive dual antiplatelet therapy (DAPT) and anticoagulation medication as recommended by the ESC Guideline for the management of acute myocardial infarction in patients presenting with ST-segment elevation.

- This includes aspirin 162 or 325 mg po chewed as soon as feasible.
- This should be followed by loading dose of ticagrelor (preferably crushed or chewed) 180 mg before PCI. If ticagrelor not available, loading dose of prasugrel (60 mg) can be used.
    - Clopidogrel can be used only if the patient cannot take ticagrelor or prasugrel.
- This also includes unfractionated heparin (UFH) given as an intravenous bolus as soon as feasible with subsequent boluses targeted to an activated clotting time of 200 to 250 seconds. If Bivalirudin is used, the infusion should continue after finished PCI for 1-2 hours.
- Use of an intravenous GP IIb/IIIa inhibitor should be used according to the decision of interventional cardiologist.

- In patients with STEMI in whom clopidogrel was initiated before coronary angiography, it is recommended to switch to either ticagrelor or prasugrel before, or during, or at latest immediately after PCI, if ticagrelor or prasugrel are not contraindicated.
    - Switching from clopidogrel to ticagrelor or prasugrel should include a loading dose of ticagrelor 180 mg (preferably crushed or chewed if before or during PCI) or prasugrel 60 mg if the patient is not at high risk of bleeding, irrespective of the prior dose of clopidogrel.
- Recommended maintenance therapy consists of aspirin 81 mg once daily (or per local practice); ticagrelor 90 mg twice daily for at least 12 months. If ticagrelor not available, prasugrel 5 or 10 mg according to label recommendation can be used.
- If needed, transition to clopidogrel can take place after 30 days post index PCI.
    - The recommended first dose of clopidogrel is 600 mg po 12 h after the last dose of ticagrelor or prasugrel. If maintenance therapy consists of aspirin and clopidogrel, the recommended doses are aspirin 81 mg once daily (or per local practice) and clopidogrel 75 mg once daily.
- Use second or third generation DES. Do not use BMS or BVS or BRS such as Absorb in study patients.

11 RISK ANALYSIS

11.1 Risk Assessment Process

ZOLL has a documented EN ISO 14971:2012 compliant Risk Management process, which includes the identification of risks, risk assessment, identification, implementation and verification of adequate controls (mitigations) to ensure that identified risks have been reduced as low as possible and to ensure the benefits of the intended use as compared to any residual risk is acceptable.

The intent of the Risk Management process is to identify potential hazardous situations related to the design, manufacture, and use of the Proteus IVTM System, evaluate each risk and implement controls to reduce the risks as low as possible.

Risks related to the IVTM System and Sub-Systems (Console, Catheter, Cassette and Temperature Probe) have been evaluated in a number of ways:

- Hazard Analysis – The purpose of the Hazards Analysis is to identify, evaluate and control potential hazards to the patient, user and the environment.

- Software Hazards Analysis - The Software Hazards Analysis is used to investigate potential device Software related hazards and control the potential hazards.

- Design FMECA - The purpose of the Design FMECA is to evaluate failure modes of the device components, or subsystems to identify potential design failure risk, then evaluate and control potential hazards.

- Process FMECA - The purpose of the Process FMECA is to evaluate failure modes of the device manufacturing process steps to identify process failure risks, then evaluate and control potential hazards.

The results of the Proteus IVTM System Risk Management process was reviewed, and concluded that the risk controls are effective to reduce the risks as low as possible. The ZOLL Proteus IVTM System presents an acceptable risk benefit ratio when used in accordance with its labeling for its proposed intended use: The Proteus IVTM System is intended for use in adult subjects with acute anterior myocardial infarction to induce and maintain hypothermia prior to percutaneous coronary intervention as an adjunctive therapy to reduce anterior infarct size.

Note: See the Investigator Brochure for additional information on the Proteus IVTM System, as applicable.

11.2 Expected Clinical Observations

In subjects who have been treated for myocardial infarction, there are many sequelae of such an event that may be thought to be "normal" effects and not due to the treatment provided. These events may be outside the range of what is considered to be "normal" (e.g., a high lab value such as a shift in potassium), but do not put the patient at risk for harm. These events are therefore expected physiological responses to treatment with therapeutic hypothermia in all patients. Prospectively, these observations may include but are not limited to the following:

- Shift in Potassium levels
- High or low levels of glucose

The expected clinical sequelae of patients treated with hypothermia include, but are not limited to, the following[28]:

- Shivering
- Prolonged ECG intervals
- Bradycardia defined as a heart rate of 40 beats per minute and not requiring treatment (e.g., pacemaker, medications, etc.)

- J wave (also called Osborne wave) can occur at any temperature < 32.3°C
- Blood electrolyte shifts: Calcium, Phosphorus, Magnesium, Chloride
- High or low levels of glucose: Decreased insulin sensitivity and insulin secretion
- Asymptomatic shifts in serum amylase and lipase levels
- Peripheral pulses may be difficult to detect

Cold Diuresis: Increased resistance to ADH or Vasopressin resulting in decreased water or solute reabsorption.

11.3 Potential Clinical Risks

Adverse events that are inherent to a PCI procedure and expected to occur in most subjects for a projected duration according to the opinion of the investigator may be considered unavoidable. Such events include, but are not limited to, those listed in **Table 14**. These adverse events should not be reported during this trial.

Table *14* Expected and unavoidable adverse events related to the PCI procedure

Description of the Event	Time Frame from the Index Procedure (PCI)
Back pain related to laying on Cathlab table	Within 48 hours
Peripheral vasoconstriction	Within 24 hours
Thermal discomfort	Within 24 hours
Incisional pain (pain at access site)	Within 72 hours
Sleep problems or insomnia	Within 72 hours
Mild to moderate bruising or ecchymosis	Within 168 hours

A list of potential (expected) risks that may be associated with use of the Proteus IVTM System is provided below. Since this clinical study utilizes an investigational device, all risks may not be known. However, they are believed to be similar to those associated with the existing intra-vascular temperature management devices in clinical use or commercially available.

The following potential adverse events may occur during the course of the clinical trial.

11.3.1 Potential Adverse Events associated with the Proteus Catheter and Cooling System:

Potential risks related to the Proteus Catheter are reasonably believed to be consistent with the common, known risks of central venous catheters and/or venous introducer sheaths. Potential risks related to cooling, re-warming, and/or the Proteus IVTM System include but are not limited to the following:

- Catheter related injury [embolism (air, thrombus, catheter fragment), clinically significant hematoma, vascular perforation or dissection, arteriovenous fistula, nerve injury, excessive bleeding, pseudoaneurysm
- Deep vein thrombosis (DVT) requiring treatment
- Infection [local or systemic (pneumonia, sepsis, meningitis, visceral organ)]

11.3.2 Potential Adverse Events associated with the cooling procedure include but are not limited to the following:

- Acute renal failure
- Acute renal insufficiency
- Adverse drug reaction
- Angina
- Blood lysis
- Congestive Heart Failure
- Clinically relevant shivering (BSAS ≥ 2) that cannot be controlled by the antishivering medication regimen
- Dysrhythmia [ventricular tachycardia, ventricular fibrillation or atrial fibrillation requiring intervention, bradycardia (HR ≤ 40 bpm, block)]
- Hyperglycemia / Hypoglycemia
- Hyperkalemia / Hypokalemia
- Hyperphosphatemia / Hypophosphatemia
- Hypotension
- Infection (local, systemic)
- Liver Failure
- Myocardial infarction
- Multi-system organ failure
- Overcooling (temperature <31.0°C for ≥ 20 continuous minutes)
- Overwarming (temperature >38°C for ≥ 20 continuous minutes including dehydration, burns and neurological damage)
- Pancreatitis
- Pulmonary edema
- Peripheral vascular insufficiency
- Thrombocytopenia
- Rebound hyperthermia
- Respiratory failure during cooling or rewarming
- Seizures

- Stroke [Cerebral vascular Accident (CVA)]
- Transient Ischemic Attack (TIA)
- Unstable angina

11.3.3 Risks Associated with Anti-shivering Medications

In order to preserve patient comfort and suppress the shivering response during cooling, a combination of recommended buspirone, where available (or equivalent alternative) and required Pethidine (Meperidine) should be used (see **Attachment II**). As identified in their labeling, the risks associated with the use of these pharmacologic agents in this trial population include the following:

Buspirone (or equivalent alternative)

- Interaction with MAO Inhibitors
- Dizziness
- Nausea
- Headache
- Nervousness
- Lightheadedness
- Excitement

Pethidine (Meperidine)

- CNS Depression
- Hypotension
- Respiratory Depression
- Circulatory Depression
- Respiratory Arrest
- Shock
- Cardiac Arrest

Other reported reactions:

- Lightheadedness
- Dizziness
- Nausea
- Vomiting
- Sweating

11.4 Additional investigations due to the trial

Participation in the clinical trial will involve extra blood sampling for laboratory markers (electrolytes, complete blood count, baseline and peak troponin including upper limit of normal), additional ECGs, and the need for cardiac MRI imaging. All of these are standard clinical procedures, and the risks to participants are low. Sites will be carefully monitored for adherence to the protocol. Patients will be screened for appropriateness for MRI prior to enrollment.

11.4.1 Delay in PCI through the use of hypothermia therapy

The probability for potential delay in PCI is considered Occasional. In prior trials of hypothermia for STEMI, the increase in door to balloon time ranged from 9 minutes to 18 minutes. It is noteworthy that this delay was not associated with an increase in infarct size hypothermia patients compared to controls. In fact, patients with anterior STEMI with < 35°C at the time of reperfusion showed smaller infart size. Sites will be trained to incorporate hypothermia into the cath lab workflow while minimizing delay. Feedback will be provided for each case to help maintain efficiency.

11.4.2 Implementation of PCI in patients undergoing hypothermia (patient-related risks).

Potential risks related to the use of hypothermia therapy in patients are outlined in sections 11.2.1 and 11.2.2 above. These risks include: potential adverse events associated with the Proteus Catheter and Cooling System, potential adverse events associated with cooling, and potential risks associated with the anti-shivering medications.

11.4.3 Implementation of PCI with concurrent use of endovascular hypothermia.

The addition of hypothermia as adjunctive treatment of STEMI will potentially lead to more difficult conditions for the Investigator and other users. The ability to integrate hypothermia into the cath lab workflow has been demonstrated successfully in prior clinical trials. Again, thorough training, frequent monitoring, and rapid feedback will help mitigate the challenges of incorporating hypothermia into treatment for STEMI.

11.4.4 The concurrent medication.

Patients who have received medications such as monoamine oxidase inhibitor within a 14 day period will be excluded from the trial to prevent potential interaction with the anti-shivering medications. In patients that receive morphine prior to arrival to the hospital, the pethidine dose will be lowered to decrease the likelihood of respiratory depression.

11.4.5 The supply of 4°C cooled saline solution

The amount of cooled saline solution is limited to 1,000 ml, an amount shown to be well tolerated in the CHILL-MI trial, where the average amount of cooled saline was 1475 ml. Again, careful training and monitoring will help to avoid unnecessary exposure to larger volumes of saline.

11.4.6 Other procedures within the clinical trial

The risk of adverse interaction or influence of other procedures within the clinical trial are deemed to be low. In prior hypothermia trials in STEMI, there was no interference with the stenting procedure, with resuscitation efforts for arrhythmias or cardiogenic shock. Hypothermia does inhibit the absorption and metabolism of clopidogrel, a anti-platelet inhibitor, given to reduce the risk of stent thrombosis. This risk will be mitigated by calling for adherence to ESC guidelines which recommend either prasugrel or ticagrelor, both of which are less affected by hypothermia.

11.5 Potential Clinical Benefits

Although no assurances or guarantees can be made, there is a reasonable expectation that the use of this investigational device is safe within the context of the trial and may be beneficial. Cooling using the device, for instance, may result in improved temperature control relative to the standard techniques already in use at the sites.
The primary benefits of therapeutic hypothermia have been shown to be:

- Improved patient survival
- Improved heart tissue salvage after the ischemic event

Additional potential benefits of therapeutic hypothermia with the Proteus System may include:

- Faster cooling
- More accurate control of the cooling procedure than with surface cooling
- Further improved survival

There is no guarantee that participation in this trial or use of hypothermia will benefit the trial subject. However, collection of such trial data may provide added benefit for future myocardial infarction subjects.

11.6 Methods to Minimize Risk

All efforts will be made to minimize risks by selecting investigators who are experienced and skilled in using minimally invasive catheter-based cardiovascular interventions and who have been adequately trained. Also, risk minimization activities were performed during development and design verification tests of the device. Activities intended to minimize risks include the following.

- Investigator and trial personnel training will be conducted to share information regarding the design of the Proteus IVTM System, its application, pre-clinical results, and clinical trials on comparable intra-vascular cooling devices.
- Adherence to eligibility criteria and screening procedures will ensure that appropriate patients are enrolled.
- Adherence to the Proteus IVTM System Instructions for Use packaged with the device.
- Corrective and preventative actions will be implemented by ZOLL, as necessary, if deviations from recommendations in the protocol or IFU are observed.
- Clinical support by ZOLL representative will be provided during the enrollment in the study and thereafter if needed. ZOLL representatives will only have advisory role.
- The subjects will be carefully monitored throughout the trial period.
- The investigator will evaluate the subject adverse events during the course of the trial.
- Data submitted from the investigative centers will be monitored during the course of the trial.
- Monitoring visits will be conducted to evaluate protocol compliance and data quality.
- Safety and effectiveness data obtained during the course of the trial will be shared with investigators in periodic reports to increase understanding of the device and potential adverse events.
- An independent Data Safety Monitoring Board (DSMB) will monitor safety throughout the clinical trial. Stopping rules will be discussed with the DSMB and applied for subject safety through enrollment.

Detailed trial procedures are provided in **Section 6.8 - Clinical Trial Procedures**.

11.7 Risk – Benefit Assessment

To date, there have been five clinical trials that have reported on the safety and effectiveness of therapeutic hypothermia in AMI and one in Radio-Contrast nephropathy (COOL-RCN Trial), with a total of more than eleven hundred patients being enrolled in total with at least half of those treated with therapeutic hypothermia. The rate of adverse events are well reported in these populations (see section 5, Prior Investigations), and the risks are clearly categorized for these trials. In summary, the number of trials, patients enrolled, and low numbers of safety events reported indicate that therapeutic hypothermia in this patient population is at an acceptable risk level to engage in this trial.

There is significant morbidity and mortality associated with the numerous clinical conditions outlined in this report, and therapeutic hypothermia has shown promise to greatly improve clinical outcomes in these patients. In particular, patients with anterior STEMI have a higher incidence of

congestive heart failure, cardiogenic shock, and cardiac mortality. A significant reduction in infarct size in these patients, with therapeutic hypothermia, has the promise to reduce these adverse clinical outcomes. Risks associated with the use of the Proteus IVTM system have been reduced via the Risk Management Process, and are deemed acceptable, considering the potential benefits. We conclude that the use of the Proteus IVTM system for medical practice is justified and warranted.

Risk assessment of the Proteus IVTM System has been performed in accordance with the ISO 14971:2012.[30] The Proteus IVTM System is safe and presents an acceptable risk benefit ratio to provide cooling or warming of patients when:

- Used by and under the supervision of a qualified medical practitioner
- In patients for whom the risks of a central line are acceptable
- In intensive care environments equipped to handle clinical conditions warranting use of the device under this protocol
- Used according to the Instructions For Use (IFU)

12 RECORDS AND REPORTS

Throughout the course of this clinical trial, ZOLL, the investigators, and reviewing MEC are responsible for the records and reports detailed in the following sections.

12.1 Investigator Records

Investigators must retain all trial records required by ZOLL and by the applicable regulations in a secure and safe facility. The investigator must consult a ZOLL representative before disposal of any trial records and must notify ZOLL of any change in the location, disposition, or custody of the trial files.

Trial records are those that individually and collectively permit evaluation of the conduct of the trial and the quality of the data produced. ZOLL's SOP requires that all clinical trial data be kept for a minimum of 15 years and all data used in submissions be kept for the life of the corporation. It is the site's obligation to inform ZOLL if their own policy does not comply with the sponsor's requirement so necessary arrangements can be negotiated. It is ZOLL's responsibility to inform the investigator/institution as to when these documents no longer need to be retained.

The investigator is responsible for the preparation (review and signature) and retention of the records cited below.

- All correspondence with another investigator, MEC, ZOLL, a monitor, or FDA, including required reports and trial documents which pertain to the investigation.
- Records of receipt, use, and final disposition of a device.
- Records of each subject's case history and exposure to the device. Case histories include the Case Report Forms (CRFs) and supporting source data (signed and dated informed consent forms, medical records, e.g., progress notes of the physician, patient's hospital chart, nursing notes).
- The clinical investigational plan, with documents showing the dates of and reasons for each deviation from the protocol.
- Any other records that are required to be maintained by local regulations or by specific regulatory requirements for a category of investigations or a particular investigation.
- Any other record that the reviewing MEC requires to be maintained for the subject investigation.

12.2 Investigator Responsibilities

The participating investigator is responsible for adhering to this Clinical Investigational Plan (CIP), FDA CFR, ISO 14155 and Declaration of Helsinki (Regulatory requirements of his/her country local law).

Specifically, the Principal Investigator at each site shall:

a) indicate his/her acceptance of the CIP in writing,
b) conduct the clinical investigation in compliance with the CIP,
c) create and maintain source documents throughout the clinical investigation and make them available as requested during monitoring visits or audits,
d) ensure that the investigational device is used solely by authorized users as specified in 6.2, and in accordance with the CIP and instructions for use,
e) propose to the sponsor any appropriate modification(s) of the CIP or investigational device or of the use of the investigational device,
f) refrain from implementing any modifications to the CIP without agreement from the sponsor, EC and regulatory authorities, if required,
g) document and explain any deviation from the approved CIP that occurred during the course of the clinical investigation,
h) ensure that an adequate investigation site team and facilities exist and are maintained and documented during the clinical investigation,
i) ensure that maintenance and calibration of the equipment relevant for the assessment of the clinical investigation is appropriately performed and documented, where applicable,

j) ensure the accuracy, completeness, legibility and timeliness of the data reported to the sponsor in the CRFs and in all required reports,
k) maintain the device accountability records,
l) allow and support the sponsor to perform monitoring and auditing activities,
m) be accessible to the monitor and respond to questions during monitoring visits,
n) allow and support regulatory authorities and the EC when performing auditing activities,
o) ensure that all clinical-investigation-related records are retained as required by the applicable regulatory requirement(s), and
p) sign the clinical investigation report, where applicable.

The investigator is responsible for the preparation and submission of the reports cited in **Table 15**. Reports must be prepared in complete, accurate and timely manner. These reports may be subject to regulatory inspection (and ZOLL) and copying, and the retention requirements described above for Investigator Records. In addition to the reports listed in **Table 15**, the reviewing MEC may request reports pertaining to any aspect of the clinical trial.

Written approval Medical Ethics Committee (MEC) with authority for the participating site will be obtained prior to the start of the study. The investigator or if applicable the Sponsor is responsible for submitting all required documents to the MEC. At a minimum the following documents will be submitted:

• Clinical Investigational Plan (CIP)

• Patient Informed Consent documents in the local language

• Any other written information to be provided to the subjects in the local language

• Investigator Brochure (IB) (as required)

• Other documents will be submitted as per local requirements

After obtaining MEC approval, the investigator will submit the approval letter indicating the approved version of the CIP, Patient Informed Consent, IB and any other reviewed documentation to ZOLL.

Table 15 Investigator Reporting Responsibilities to Sponsor and MEC

REPORT	SUBMIT TO	DESCRIPTION/CONSTRAINTS
Withdrawal of MEC Approval	Sponsor	The investigator must report a withdrawal of the reviewing authority within **5 working days**.
Case Report Form (CRF)	Sponsor & Monitor	CRFs should be completed as soon as possible after any trial related procedure takes place.
Deviation from Investigation Plan (Emergency)	Sponsor & MEC	Notification must be made within **5 working days** if the deviation was made to protect the life or physical well-being of a subject.
Deviation from Investigation Plan (Other – Non Emergency)	Sponsor & MEC	If the deviation may affect the scientific soundness of the plan or the rights, safety and welfare of the subjects (and is not an emergency), then **the deviation must be approved by ZOLL, the MEC, and the reviewing authority prior to its implementation**. If the deviation does not affect these issues (trial soundness, rights, safety, etc.) then only ZOLL must approve it, (except in cases which are beyond the control of the investigator—see section on Protocol Deviations).
Failure to Obtain Informed Consent	Sponsor & MEC	The Investigator must notify ZOLL and the reviewing authority within **5 working days** after device use The investigator must submit notification after device use or after the investigator first learns of the absence of informed consent. The report must include a brief description of the circumstances surrounding the failure to obtain informed consent and include written concurrence by a licensed physician not involved in the investigation. Failure to obtain informed consent must be reported to the MEC as required by local regulations.
Final Report	Sponsor & MEC	This report must be submitted within **3 months** after termination or completion of the investigation.

12.3 Sponsor Records

All Sponsor documents and records shall be maintained as indicated by ZOLL's Quality System. ZOLL will maintain the following trial -related records in accordance with ZOLL record retention policies and procedures following the completion of this investigational plan. Clinical data for regulatory submissions and publications will be retained for the life of the corporation.

- All correspondence pertaining to the investigation with the sponsor, a monitor, an investigator, an MEC, regulatory agencies, including required reports.

- Records of shipment and disposition of the investigational device.
- Signed investigator agreements including the financial disclosure information required to be collected and current signed and dated curriculum vitae.
- Records of adverse events and device deficiencies.
- List of participating institutions
- Investigational product accountability reports including record of receipt, use, or disposition of the device(s) that relate to type, quantity, serial numbers of devices, and date of receipt, names of persons who received, used, or disposed of each device and why and how many devices have been returned to ZOLL or otherwise disposed
- All signed and dated case report forms submitted by investigator, samples of patient informed consents, and other information provided to the subjects
- Copies of all MEC approval letters and relevant MEC correspondence
- Names and evidence of the institutions in which the clinical investigation will be conducted
- Insurance certificates
- Forms for reporting adverse events and device deficiencies
- Names/contact addresses of monitors
- Statistical analyses and underlying supporting data
- Final report of the clinical investigation
- The Clinical Investigational Plan, Clinical Monitoring Plan (CMP), Investigator Brochure (as applicable), and study related reports
- Study training records for center personnel and ZOLL personnel participating in the trial
- Any other records that MEC and /or competent authority requires to be maintained by regulation or by specific requirement for a category of investigation or a particular investigation.

12.4 Sponsor Reports

ZOLL Circulation, Inc. is responsible for the classification and reporting of reportable adverse events and device deficiencies and ongoing safety evaluation of the clinical investigation in line with local regulatory requirements.

ZOLL Circulation, Inc. will assure that all Serious Adverse Events and reportable Device Deficiencies are reported to the Competent Authorities in accordance with European Medical Devices directives and all applicable national regulations.

ZOLL Circulation, Inc. is responsible for the reports cited in **Table 16**. These reports are subject to regulatory retention and inspection requirements. Governing Regulatory Agencies or the reviewing MEC may request reports pertaining to any aspect of the clinical trial.

Table 16: ZOLL Reporting Responsibilities

REPORT	SUBMIT TO	DESCRIPTION
Unanticipated Adverse Device Effects; SAEs and Reportable DDs	Relevant authorities and MECs	Reporting timeframe as per local regulatory requirements.
	Investigators	Notification throughout the course of the trial when appropriate (based on perceived risk)
Premature termination or suspension of the Clinical investigation	Investigators, MECs, Relevant Authorities	Provide prompt notification of termination or suspension and reason(s).
Subject enrollment Completed	Investigators. MEC and Relevant regulatory Authorities upon request	ZOLL will notify the investigators within 30 working days of the completion of enrollment. Investigators will, in turn, inform their MECs, when required.
Withdrawal of MEC approval	Investigators, MECs	Notification within five working days.
Final Report	Investigators, MECs, BfArM (and other relevant Authorities upon request)	A final report will be submitted within six months after completion or termination of this study. The investigators shall have the opportunity to review and comment on the final report. If a clinical investigator does not agree with the final report, his/her comments shall be communicated to the other investigators. The principal clinical investigator in each center shall sign the report.

13 MONITORING AND AUDITING PROCEDURES

13.1 Clinical Trial Sponsor and Monitors

ZOLL is the Sponsor of the clinical trial. It is the responsibility of the sponsor to ensure that proper monitoring of the investigation is conducted. Clinical trial monitoring and auditing will

be done by appropriately trained personnel appointed by the trial sponsor to ensure that the investigation is conducted in accordance with ZOLL's requirements and applicable laws and regulations.

A monitor is an individual designated by a sponsor or contract research organization to oversee the progress of an investigation. The monitor may be an employee of a sponsor or a consultant to the sponsor, or an employee of or consultant to a contract research organization. The monitor will be trained on the device, investigational plan, informed consent, instructions for use, applicable ZOLL procedures, electronic data capture system, and regulatory requirements. The monitor will periodically check and report on the progress of the clinical trial at an investigational site or other data gathering organization or ZOLL facility.

13.2 Monitoring Methods

Monitoring of the clinical trial will be a continuous, interactive process to ensure that high-quality data is obtained in compliance with the clinical investigational plan and regulatory requirements. Monitoring functions will be conducted by ZOLL, and/ or a contract research organization and/or other designees. Specific monitoring requirements are detailed in the Trial Monitoring Plan (maintained in the ZOLL COOL-AMI clinical trial project files). Frequent communication will be maintained with each investigational site to keep both the clinical center and ZOLL up-to-date and aware of the trial progress. Case Report Forms will be reviewed for completeness and accuracy.

ZOLL will monitor sites in accordance with the monitor's tasks set under Section 8.2.4 of Standard DIN EN ISO 14155:2012-01. These include visits to the clinical trial sites before the start of, during and at the end of the clinical trial. On-site monitoring of all trial centers will be frequent enough (at a minimum annually) to assure continued integrity and acceptability of the data. Accuracy of data reported on case report forms will be verified by comparison to source documents. Reports of monitoring visits will be provided to the clinical trial personnel at each site. Corrective action will be taken to resolve any issues of noncompliance. If ZOLL finds that an investigator is not complying with the executed trial agreements, the investigational plan, the applicable national regulations, or the requirements of the reviewing MEC, then prompt action will be taken to secure compliance. In addition, shipment of the device may be stopped or the participation of the investigator may be terminated. Additional information is provided in **Section 6.30** – **Trial Closure**.

13.3 Monitoring Visits

Scheduled visits to the clinical investigational site will occur at the following times: prior to the start of the clinical trial (pre- trial qualification visit), at initiation of the trial (during first index

procedure or shortly thereafter), interim visits throughout the clinical trial as required, annually, and upon completion of the clinical trial.

13.4 Pre-trial Qualification Visit

A pre- trial visit will be conducted by ZOLL personnel (or designees) to review the clinical investigational plan and regulatory requirements with the investigator and the trial personnel to assure that they:

- Understand the investigational status of the device and the requirements for its use and accountability.
- Understand the clinical investigational plan.
- Understand the requirements for an adequate and well-controlled clinical trial.
- Understand and accept the obligation to conduct the clinical investigation in accordance with the national regulations.
- Understand and accept the obligation to obtain informed consent in accordance with the national regulations.
- Understand and accept the obligation to obtain MEC approval before the clinical trial is initiated, ensure continuing review of the trial by the MEC, and keep ZOLL informed of MEC approval and actions concerning the clinical trial.
- Have access to an adequate number of eligible patients to participate in the trial (at a minimum: 1 patient/center/month).
- Have adequate facilities and resources to conduct the trial. This includes resources appropriate for use of electronic data capture systems.
- Have sufficient time from other obligations to carry out the responsibilities of the clinical trial.
- Sign the Investigator Agreement and trial contracts (prior to enrollment of patients).

A report of the pre- trial qualification visit will be completed. Resolution of any concerns or completion of any appropriate follow-up activities stemming from the pre- trial visit also will be documented.

13.5 Initiation Visit

ZOLL clinical personnel (or designees) will provide assistance for both technical concerns and trial management issues during the initiation visit. Enrollment of the first patient at each clinical site may or may not coincide with this visit. Any observations will be documented and issues requiring follow-up will be identified on a monitoring report. Training of trial personnel also will be documented.

13.6 On-Site Interim Monitoring Visits

On-site monitoring visits will be made on an as-required basis (and at least annually) to assess adherence to the clinical investigation plan, MEC review of trial progress, maintenance of records and reports, and selected review of source documents for accuracy, completeness, legibility, and omissions. The monitors will acquire information to assess the progress of the trial (toward meeting trial objective) and identify any concerns that stem from observation of device performance and/or review of the investigator's patient records, trial management documents, and patient informed consent documents. Monitoring reports will be generated along with communications to the investigator, which document the result of the monitoring visit and any recommended actions. Resolution of concerns and completion of assigned tasks will be documented.

13.7 Audits

An on-site audit may be completed periodically throughout the trial at each clinical site by an independent group. The purpose of the audit will be to ensure compliance to the investigational plan and regulatory requirements, e.g., written informed consent was documented, information recorded on the case report forms is complete and accurate as compared to source documentation, protocol deviations are noted, and device accountability is accurate and complete. A randomly selected number of patient records and other supporting documents will be compared to the case report forms. A record of the findings and recommended actions to correct deficiencies will be documented on the audit report.

13.8 Final Monitoring Review

Depending upon the status of the trial at each center, a close-out or final visit may be conducted. Any ongoing responsibilities will be discussed with the investigator and the trial center coordinator. A final monitoring report, which includes, at a minimum, disposition of any unused devices, will be completed.

14 DATA MANAGEMENT PROCEDURES

ZOLL will oversee all data management functions. ZOLL will be responsible for database development, system maintenance, user training, data queries, and report generation.

14.1 Case Report Forms

ZOLL will use an electronic data capture (EDC) system to collect patient data. The electronic case report forms (eCRFs) are the primary component of EDC and are based on the sample forms that will be provided in a separate document. Training on use of the system will be provided to the trial site personnel. Instructions for completion of the eCRFs also will be provided.

The eCRFs must be completed, saved, and locked via electronic signature by the Investigator using a unique ID and password. This ID and password are for the use of the investigator only and may not be used by any other person. Because of the potential for errors or inaccuracies in transcribing data into eCRFs, source documentation must be maintained in each subject's hospital chart and/or electronic medical record. The eCRFs and source documentation must be available at all times for inspection by the trial monitors or regulatory inspectors.

Changes made to eCRFs will be electronically recorded in a complete audit trail that cannot be changed, but can be accessed by authorized personnel at any time. All data are transmitted via the Internet in an encrypted fashion. When received at the server site, the data are decrypted and stored. Data can be extracted for ZOLL review and analysis at any time.

14.2 Source Documentation

Regulations require that an investigator maintain information in the trial subject's medical records to corroborate data collected on the eCRF. To comply with these regulatory requirements, the following information will be maintained and made available as required by ZOLL and/or its designees and/or regulatory inspectors. Shadow charts are not appropriate or adequate source documentation. Complete medical (clinical and hospital) records include the following documentation.

- Medical history/physical condition of the patient before involvement in the trial sufficient to verify clinical protocol eligibility criteria.
- Description of cooling procedure (material used, drugs administered during the procedure, device identification information and disposition, date, time, angiographic and clinical findings, etc.).
- Electronic data downloaded from the ZOLL Proteus IVTM System.
- Signed notes in the subject's medical record on the enrollment day that identify and include: the subject's date of enrollment, procedure date, the trial sponsor (ZOLL), clinical site name, the subject-assigned identification number, the subject- assigned enrollment number, and documentation and confirmation that the appropriate informed consent was obtained.
- Dated and signed notes for each subject's trial visit.

- Lab results.
- Baseline ECG, angiogram, and MRI reports, etc.
- Dated printouts or reports of special assessments (ECG baseline report, imaging report, etc.).
- Adverse event reporting and follow-up of the adverse events. Information in the medical chart should include at a minimum the following: event description, severity, seriousness, onset date, date site became aware of event, duration, relation to trial device, treatment, and outcome of the adverse event.
- Trial subject's condition upon completion of or withdrawal from the trial.
- Trial subject's medical status, including all SAEs out to 1 year following trial enrollment.
- All notes related to trial subject's KCCQ and the New York Heart Association Functional Class questionnaires.

14.3 Transmission of Data

Required data will be recorded on the appropriate eCRF at the time of or as soon as possible after the patient visit. The eCRFs and any requested supporting source documents must be sent to ZOLL and/or retrieved from the investigator during monitoring visits. Questions about completion of the eCRFs may be directed to the ZOLL COOL AMI clinical team at Clin-safety@zoll.com

14.4 Data Queries

During monitoring visits, the Monitor will perform a 100% review of all variables, i.e., demography, inclusion/exclusion criteria, safety, effectiveness, on the eCRFs with each subject's source documents. Any discrepancies will be queried by ZOLL or its designee and must be resolved by the investigational site staff and investigator in a timely manner. Queries also will be generated by ZOLL data management personnel during routine review of the data on the electronic data capture system.

15 STATISTICAL ANALYSIS PLAN

The objective of this trial is to evaluate the safety and effectiveness of therapeutic hypothermia, using the ZOLL Proteus IVTM System, as an adjunctive therapy for patients presenting with acute anterior myocardial infarction (AMI) and undergoing percutaneous coronary intervention (PCI). An analysis summarizing outcomes for the Primary Effectiveness Endpoint and the Primary Safety Endpoint will be created after the last randomized subject has completed the 30 day follow-up interval. The results of the primary endpoints will be summarized in the final clinical study report.

Two interim analyses are planned to be performed at approximately 50% and 75% of randomization, once subjects have completed 4-6 day cMR follow-up. At the interim stage, the

trial will be stopped to reject the null hypothesis of no difference or continue enrolling. Another report will be issued summarizing all endpoints after all subjects have completed 12 month follow-up.

15.1 Data Analysis

Analysis Data Sets

The Intention-to-Treat (ITT) analysis set will be used for primary statistical analyses and summaries. The ITT population includes subjects who have signed an informed consent and have been randomized to the Test Arm or the Control Arm of the trial. ITT subjects will be evaluated according to the group to which they were randomized.

The Per-Protocol (PP) analysis set will also be evaluated. The PP population includes those subjects who met inclusion and exclusion criteria, were randomized to either the Test or Control arm, received the treatment to which they were randomized, and complied substantially with the treatment timeline and steps of this protocol without major protocol violations.

The Safety Analysis Set will be used to evaluate safety endpoints. These will be all of the subjects included in the study as defined by the ITT analysis set and will include Roll-In subjects. For the safety analysis, subjects will be followed for all adverse events for 12 months post procedure. Additionally, all subjects will be followed for 12 months for the incidence of Adverse Events (AEs), Serious Adverse Events (SAEs), Death and Heart Failure (as assessed by NYHA and Kansas City Cardiomyopathy Questionnaire (KCCQ)).

Infarction Size (IS) is defined as % Left Ventricular Mass as measured by Cardiac Magnetic Resonance (cMR) imaging. Infarct Size (IS) will be assessed by Cardiac Magnetic Resonance (cMR) at 4 – 6 days following the index procedure. Infarct Size will be assessed in subjects in the ITT analysis set and also in the Per-Protocol analysis set.

The Safety Analysis Set will be used to evaluate safety endpoints. These will be all of the subjects included in the study as defined by the ITT analysis set and will include the following clinical components evaluated at 30 day follow-up visit (30 day ± 7 days):

Secondary Endpoint Analysis:

The following clinical components of MACE will be evaluated at 30 day follow-up visit (30 day ± 7 days):

- Death (Cardiac, Vascular, Non-Cardiovascular)
- Myocardial Infarction (MI)

        - Attributable to target vessel (TV-MI)
        - Not attributable to target vessel (NTV-MI)
    - Target Lesion Revascularization (TLR)
        - Clinically-indicated TLR (CI-TLR)
        - Not clinically-indicated TLR (NCI-TLR)
    - Target Vessel Revascularization (TVR non TLR,)
        - Clinically-indicated TVR non TLR
        - Not clinically-indicated TVR non TLR
    - Non-Target Vessel Revascularization (NTVR,)
        - Clinically-indicated NTVR
        - Not clinically-indicated NTVR
    - All coronary revascularization

In addition, Stent Thrombosis will be evaluated at 30 day follow-up visit (30 day ± 7 days):

- Evidence (Definite and Probable)
-
- Timing (Acute, Sub-acute)

Additional Observational and Descriptive Analysis:

In addition to the secondary endpoint, safety of the trial is also analyzed by the following observational and descriptive analysis. These events are not endpoints for the study:

- the following serious adverse events will be evaluated at 30 day follow-up visit (30 day ± 7 days):
    - Stroke
    - Cardiogenic shock
    - Pulmonary embolism
    - Pulmonary edema
    - Atrial fibrillation
    - Ventricular fibrillation
    - Vascular complications requiring intervention
    - Bleeding requiring transfusion of 2 units or greater
    - Cooling catheter access site infection
    - Systemic infection
    - Deep Venous Thrombosis (DVT)
    - Bradycardia
    - Hypotension
- The following serious adverse events will be evaluated at 12 month follow-up visit (12 month ± 14 days):

- Death (Cardiac, Vascular, Non-Cardiovascular)
- Stent Thrombosis
    - Timing (Acute, Sub-acute)
    - Evidence (Definite and Probable)
- Hospitalizations due to Heart Failure

15.2 Statistical Methods

Baseline demographic and clinical characteristics will be summarized for each arm using descriptive statistics. Continuous variables will be reported with mean, standard deviation, median, and range. Discrete variables will be reported as frequency and proportion. A $\chi 2$ test or Fisher exact test (for small frequencies) will be used to compare discrete variables; t-test or Wilcoxon test (for non-normal data) will be used to compare the 2 arms with continuous variables for randomized subjects in the trial.

The primary effectiveness endpoint is to detect a 20% reduction of mean infarct size in the Test Arm compared to Control Arm where infarct size (%LV Mass) is measured by cMR at 4-6 days. The mean, median, standard deviation, and range will be presented for infarct size. A two sample t-test will be used to test the null-hypothesis of no difference in average infarct size test and control arm P-value will be reported with $p<0.05$ considered statistically significant. Infarct size will further be evaluated in subgroups and with ANOVA models.

For the primary safety endpoint of MACE (as defined by CD, All MI, and CI-TLR) at 30 days, all events will be tabulated and reported. Per-patient rate of composite MACE will be compared between the two arms with 1-sided Fisher's exact test.

Two interim analyses are planned to be performed at approximately 50% and 75% of randomization, once subjects have completed 4-6 day cMR follow-up. At the interim stage, the trial will be stopped to reject the null hypothesis of no difference or will continue enrolling. Based on the Lan-DeMets method for group sequential trials using O'Brien-Fleming boundaries, the levels of significance for the interim analyses are alpha=0.00305 (50% information fraction), alpha=0.01832 (75% information fraction), and alpha=0.044 (final analysis).

All analyses for effectiveness will be conducted in intent-to-treat and per-protocol analyses set. All analyses for safety will be conducted in the safety dataset. Imputation will be made for missing infarct size (LV%) in intent-to-treat analyses set per Intention-to-Treat principle; details are described in the Statistical Analysis Plan.

15.3 Sample Size Justification

The primary effectiveness analyses is designed to detect a relative reduction of 20% in mean anterior myocardial infarct size (IS), as determined by Cardiac Magnetic Resonance (cMR) imaging at 4-6 days post infarct in the Test Arm (cooling + PCI) compared to the Control Arm (PCI only). The absolute magnitude of a relative reduction of 20% depends on the mean IS in the control arm, which is assumed to be approximately 17 %LV. Therefore, the treatment effect of interest is an absolute difference of 3.5 %LV.

The hypothesis for the primary effectiveness endpoint is the following for patients randomized 1:1 in Treatment Arm vs Control Arm:

H_0: $\mu_T = \mu_C$
H_A: $\mu_T \neq \mu_C$

Null hypothesis:

The null hypothesis is that the mean infarct sizein the Test Arm is equal to the mean IS in the Control Arm.

Alternative hypothesis:

The mean infarct size in the control arm is not equal to mean infarct size of control arm.

This 20% relative reduction is defined as absolute value 3.5 %LV and accounted for in our sample size calculation as minimally detectable effect. This assumption is based on previous studies with anterior infarct size measured with cMR reporting between 17-20% absolute %LV in anterior infarct (***Tables 17 & 18***). Therefore, a relative reduction of 20% can vary depending on the mean infarct size of the control arm. Assuming a representative mean infarct size of ~17% in controls, we assume absolute difference of 3.5 %LV is equivalent to 20% mean anterior infarct size would be an adequate detection limit for effect.

Based on these assumptions--standard deviation of 12.0 %LV, two-tailed t-test of difference between means, a normal distribution, 80% power (beta=0.2), with the final analysis will be conducted using a two-sided test at the alpha=0.044 level of significance (adjusted for the two interim analyses)-- the required total sample to detect a mean difference of 3.5 %LV with 80% power is 384 subjects (192 subjects per group). Assuming 24% loss to follow-up, the trial plans for an enrolment up to 500 randomized subjects (250 in each arm) for 4-6 days cMR imaging follow-up.

Table 17: Clinical trials reporting anterior mean infarct size measured by cMR 4-6 days in PCI trials (Control Group Only) and calculated 20% relative reduction

Study name	Anterior n	Mean infarct size	Standard Deviation	20% relative reduction
APEX-AMI[41]	**60**	**16.6**	**10.7**	**3.3**
LIPSIAABCIXIMAB[42]	**63**	**25.3**	**16.1**	**5.1**
LIPSIA-STEMI[43]	**38**	**18**	**16.0**	**3.6**
CRISP-AMI [44]*	**142**	**37.5**	**20.1**	**7.5**
INFUSE-AMI[45]	**172**	**17.3**	**10.2**	**3.5**
RAPID-MI ICE[1]	**7**	**19.7**	**8.5**	**3.9**
CHILL-MI[37]	**21**	**26.5**	**10.9**	**5.3**
AMI EU PILOT	**21**	**23.3**	**12.0**	**4**

*>60% are large proximal infarcts

A range of standard deviation in the table expected is represented by anterior infarct data measured with cMR from separate and pooled analyses of previous hypothermia trials with AMI patients cooled below 35°C: RAPID-MI ICE (2009), CHILL-MI (2013), AMI EU Pilot (ongoing) as described below in **Table 18.**

Table 18: Hypothermia trials using cMR measured infarct size as primary outcome

	RAPID-MI ICE (2009)	CHILL-MI (2013)	AMI EU Pilot (2017)	Pooled AMI EU Pilot, RAPID-MI-ICE, CHILL-MI
n (Control vs Cooled)	7 vs 5	21 vs 15	21 vs 19	49 vs 39
Control Mean LV%	19.7	26.5	23.3	24.5

	RAPID-MI ICE (2009)	CHILL-MI (2013)	AMI EU Pilot (2017)	Pooled AMI EU Pilot, RAPID-MI-ICE, CHILL-MI
20% reduction in infarct	3.94	5.3	4.7	4.9
Std Dev (control)	8.5	10.9	12.0	10.5
Std Dev (cooled)	6.5	9.3	10.3	11.0

The potential impact of variations in control infarct size and variability is presented in ***Table 19.***

Table 19: Sample size estimates with alternative standard deviation and detection limit

Mean Difference in infarct size for detection (%)	Standard Deviation	Estimated Sample Size	Total Enrolment (with24% drop-out)
3.0	**9**	**288**	380
3.0	**10**	**355**	468
3.0	**11**	**430**	566
3.0	**12**	**506**	666
3.5	**9**	**212**	280
3.5	**10**	**260**	342
3.5	**11**	**314**	414
3.5	**12**	**374**	500
4.0	**9**	**162**	214
4.0	**10**	**200**	264
4.0	**11**	**240**	316
4.0	**12**	**286**	376

The primary safety endpoint is a composite endpoint. For the sample size calculation, expected incidence is based on a literature review of acute MI hypothermia trials that combined six studies: Dixon et al, COOL MI, ICE-IT, RAPID MI-ICE, CHILL-MI, VELOCITY[46] which resulted in a 30-day MACE rate of 6.6% in the Control patients and 7.5% in treatment patients. Previously, AMIHOT II trial defined 30-day MACE rate comprised of death, reinfarction, target vessel revascularization, and stroke used a non-inferiority hypothesis with a 6% equivalence delta and 7% in the Control patients[47].

The hypothesis for the primary safety endpoint is the following:

$\mathbf{H_0}: \pi_T \geq \pi_C + 6\%$

$\mathbf{H_A}: \pi_T < \pi_C + 6\%$

π_T and π_C are the underlying proportion of patients having a MACE event.

An enrollment of 500 patients would be able to demonstrate 91% power and 95% 1-sided significance. The safety endpoint will be considered to have been met if there is a high posterior probability of non-inferiority [i.e. P ($\pi t < \pi c + 6\% > 95\%$)]. With a drop-out rate of 20%, the power is calculated to be 86%.

16 PUBLICATION

At the conclusion of the trial, a multi-center manuscript will be prepared for publication. Publications will be managed by the Sponsor, its designee and the Advisory board. Additional publications from any single site will be considered but only after the multi-center publication.

17 INTELLECTUAL PROPERTY

In all documents the company name of ZOLL Circulation® will be referred to in short hand as ZOLL. ZOLL® is a registered trademark of ZOLL Medical Corporation. The Proteus IVTM System is a trademark of ZOLL Circulation, Inc. Proteus Catheters, Cassettes and Temperature Probes (X-Probe) are registered trademarks of ZOLL Circulation, Inc.

18 STATEMENT OF COMPLIANCE

1. Sponsor and Investigator will conduct the clinical investigation in accordance with the ethical principles that have their origin in the Declaration of Helsinki.
2. Sponsor and Investigator will comply with ISO 14155:2011 and any regional or national regulations, as appropriate.
3. Investigator will not begin the clinical investigation until Investigator obtains the required written approval or favorable opinion from the MEC or regulatory authority, if appropriate.
4. Investigator will follow any additional requirements imposed by the MEC or regulatory authority, if appropriate.

ATTACHMENT I – REFERENCES

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ATTACHMENT II – ANTI-SHIVERING PROTOCOL

Shivering Suppression Guidelines

Turn on IVTM System console to initiate system and begin cooling of coldwell

↓

Obtain Informed Consent

↓

Administer Buspirone 60 mg PO/NG x 1 immediately

↓

Place Bair Hugger on upper body; set to "high"; forced-air cover should be adjacent to skin. Put one blanket on top.

↓

Closer to the time of device deployment, **Pethidine 1 mg/kg IV (up to 100 mg)**

***Morphine and/or other sedatives are often administered in the setting of an acute MI Morphine and Pethidine (Demerol) are both opiate narcotics and if possible, morphine should be held as the combination may cause over-sedation. Consider 0.5 mg/kg Pethidine IV, if Morphine has been administered.

↓

At 15 minutes, Pethidine 0.5mg/kg IV should be administered.

Then a 25 mg/hr IV infusion of Pethidine (up to 80 kg patient) or 35mg/hr (> 80 kg patient) should be initiated and maintained for the duration of device deployment.

***Make sure the patient has a respiratory rate ≥ 10 breaths/minute.

What to do if shivering occurs:

First, try **repositioning the Bair Hugger** or changing its settings to increase the heat delivered to the patient's surface.

Second, consider **increasing dose of Pethidine**. Prior to giving additional Pethidine, look for signs of respiratory depression (i.e. decreased Respiratory Rate, decreased O2 Saturation by Pulse Ox.) If it is decided that the patient can tolerate additional Pethidine the following may be tried:

1. An IV dose of 25 mg x 1 may be given
2. If Infusion rate is 25mg/hr, the rate may be increased to a maximum of 35 mg/hr

If the shivering persists following the above measures, **consider raising the target temperature on the Proteus Console by 0.5°C** (i.e. from 32.0°C to 32.5°C). If this does not work after 5-10 minutes at the new target temperature, then the process can be repeated until a temperature where no shivering is obtained.

ATTACHMENT III – BEDSIDE SHIVERING ASSESSMENT SCALE (BSAS)

SCORE	SEVERITY	DEFINITION
0	None	No shivering noted on palpation of the masseter, neck or chest wall
1	Mild	Shivering localized to the neck and/or thorax only
2	Moderate	Shivering involves gross movement of the upper extremities in addition to neck and thorax
3	Severe	Shivering involves gross movements of the trunk, upper and lower extremities

ATTACHMENT IV – SPECIFIC NEW-ONSET ADVERSE EVENT DEFINITIONS

SPECIFIC NEW-ONSET ADVERSE EVENT	DEFINITION
1. All-Cause Mortality	Deaths will be classified as cardiac, vascular or noncardiovascular as defined by the Academic Research Consortium.[27] All deaths are considered cardiac unless an unequivocal non-cardiac cause can be established. Specifically, any unexpected death even in patients with coexisting potentially fatal non-cardiac disease (e.g. cancer, infection) should be classified as cardiac. <u>Cardiac death (CD):</u> Any death due to proximate cardiac cause (e.g. MI, low-output failure, fatal arrhythmia), unwitnessed death and death of unknown cause, all procedure related deaths including those related to concomitant treatment. <u>Vascular death:</u> Death due to non-coronary vascular causes such as cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular cause. <u>Non-cardiovascular death</u>: Any death not covered by the above definitions such as death caused by infection, malignancy, sepsis, pulmonary causes, accident, suicide or trauma.
2. Recurrent MI [27,31]	Recurrent MI or re-infarction may be diagnosed when cardiac biomarker levels are stable on 2 samples that are >6 hours apart or are in decline if a subsequent value 3 to 6 hours after the procedure is increased by $\geq$ 20% from the baseline sample. If the baseline value is not stable, then insufficient data exist to recommend biomarker criteria for diagnosis, and the Academic Research Consortium[27,31] recommends that the event be considered as pre-procedure MI. Periprocedural MI is that which occurs within the first 48 hrs after PCI or within the first 72 hrs after coronary artery bypass grafting (CABG).

	Q wave MI: Development of new, pathological Q wave on the baseline ECG (≥ 0.04 seconds in duration and ≥ 1 mm in depth) in ≥ 2 contiguous precordial leads or ≥ 2 adjacent limb leads) Non-Q wave MI: Those MIs which are not Q-wave MI.
3. Need for revascularization of the target vessel (TVR)[27]	TVR is defined as any repeat percutaneous intervention or surgical bypass of any segment of the target vessel. The target vessel is defined as the entire major coronary vessel proximal and distal to the target lesion, which includes upstream and downstream branches and the target lesion itself.
4. Stroke	Development of a new neurological deficit that persists > 24 hours, or worsening of previous neurological symptoms that persist > 24 hours.
5. Cardiogenic shock	Systolic blood pressure of less than 90 mmHg for at least 30 minutes which is secondary to myocardial dysfunction, leading to decreased cardiac output and evidence of tissue hypoxia in the presence of adequate intravascular volume.
6. Pulmonary embolism	Sudden onset of pleuritic chest pain, cough, hemoptysis, hypoxia, tachycardia, and a positive ventilation/perfusion scan or a CT scan.
7. Ventricular Fibrillation (V-Fib)	Rapid uncoordinated fluttering contractions of the heart ventricles recognized by the occurrence on the electrocardiogram of coarse and irregular oscillations without discernible QRS complexes or T waves
8. Vascular complications requiring intervention	Complications arising from the use of the Proteus Catheter including the development of a vessel tear, hematoma, pseudoaneurysm, arteriovenous (AV) fistula, or retroperitoneal bleeding which require an additional surgical intervention for treatment.
9. Bleeding requiring transfusion of 2 units or greater	Any periprocedural bleeding which occurs as a result of the PCI and/ or cooling procedure which requires transfusing > 2 units.
10. Systemic Infection	Sepsis with confirmed positive blood cultures.
11. Cooling Catheter Access Site Wound infection	Infection and inflammation of the incision or puncture site requiring drainage and/or debridement in addition to antibiotic therapy, e.g., cellulitis.
12. Pulmonary Edema	Abnormal accumulation of fluid in the lungs

13. Deep Venous Thrombosis (DVT)[32]	Formation of one or more blood clots in one of the body's large veins, most commonly in the lower limbs. The clot(s) can cause partial or complete blocking of circulation in the vein, which in some patients leads to pain, swelling, tenderness, discoloration, or redness of the affected area, and skin that is warm to the touch. As many patients enrolled in the trial will have pre-existing DVT, for the purposes of this trial DVT is defined as the de novo onset of DVT following enrollment which required treatment or worsening of pre-existing DVT.

ATTACHMENT V – ADVERSE EVENT DEFINITIONS

Adverse Event Definitions

In addition to the definitions provided in **Attachment IV– Specific New Onset Serious Adverse Event Definitions**, the following definitions apply to expected adverse events that may occur and must be reported throughout this clinical trial. Events reported should represent a new onset or increase in the severity of the condition from the time of enrollment.

A. CARDIAC COMPLICATIONS	DEFINITION
Recurrent Myocardial ischemia [31]	Recurrent Myocardial Ischemia : is evidenced through baseline ECG changes identified during continuous multilead baseline ECG–ischemia monitoring (or Holter monitoring) which may be accompanied by the development of new clinical symptoms suggesting an ischemic cardiac episode.
Arrhythmias	The development of a new atrial and/or ventricular arrhythmia, significant increase in the severity of a preexisting arrhythmia, or any episode of cardiac arrest.
Congestive Heart Failure[34]	Defined as patients with defined or presumed cardiac disease and one of the following: Class I: without limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea. Class II: slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, or dyspnea. Class III: marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea. Class IV: inability to carry on any physical activity without discomfort. Symptoms are present even at rest or minimal exertion.

B. PULMONARY COMPLICATIONS	DEFINITION
Pneumonia	Clinical evidence as determined by physical, radiographic, and laboratory findings requiring treatment with antibiotics, inhalation therapy, intubation, or suctioning.
Atelectasis	Clinical evidence as determined by physical, radiographic, and laboratory findings requiring treatment with antibiotics, inhalation therapy, intubation, or suctioning.

Respiratory Failure	Need for mechanical ventilation for > 24 hours postoperatively, or reintubation for any reason.

C. RENAL COMPLICATIONS	DEFINITION
Acute Kidney injury (AKI)[35]	AKI is defined as any of the following: Increase in SCr by ≥.3 mg/dl (≥26.5 µmol/l) within 48 hours; or Increase in SCr to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or Urine volume < 0.5 ml/kg/h for 6 hours.

D. VASCULAR COMPLICATIONS	DEFINITION
Arteriovenous Fistula	Formation of an abnormal connection between the lumens of an artery and a vein as documented by CT, ultrasound, angiography, or direct observation.
Embolism	The obstruction of a blood vessel by a blood clot or foreign substance, e.g., air, fat, bacteria.
Vessel perforation	Defined as perforation of the access vessel wall or vena cava confirmed by extravasation of contrast under fluoroscopy, angiography, CT scan, and/ or direct observation at surgery or autopsy.
Hematoma	An abnormal localized collection of blood (clotted or partially clotted) and situated within an organ or a soft tissue space, such as within a muscle. Development of an incisional or retroperitoneal hematoma requiring surgical intervention, evacuation, transfusion or prolonged hospitalization.
Hemorrhage	Post-procedural bleeding requiring transfusion of ≥ 2 units.
Hypotension	Abnormally low systolic blood pressure that is < 80 mm Hg

D. VASCULAR COMPLICATIONS	DEFINITION
Peripheral vascular insufficiency (PVI)	Inadequate peripheral blood flow resulting from the occlusion of vessels by atherosclerotic plaques, thrombi, or emboli; damaged, diseased, or intrinsically weak vascular walls; arteriovenous fistulas; hematologic hypercoagulability; and heavy smoking. Signs of vascular insufficiency include pale, cyanotic, or mottled skin over the affected area; swelling of an extremity; absent or reduced tactile sensation; tingling; diminished sense of temperature; muscle pain, such as intermittent claudication in the calf; and, in advanced disease, ulcers and atrophy of muscles in the involved extremity. As many patients enrolled in the trial will have pre-existing Peripheral Vascular Insufficiency (PVI), for the purposes of this trial PVI is defined as the de novo onset of PVI following enrollment which requires treatment or worsening of pre-existing PVI.
Pseudoaneurysm	Enlargement of the aorta, iliac, or femoral arteries, which contain some or all of the medial layer, the adventitia, and periaortic tissue most commonly associated with previous aortic operative procedures, trauma, and/or infection. Pseudoaneurysms typically present as a well-defined collection of blood outside the vessel wall from contained rupture.
Stenosis	A reduction in the diameter of the vessel lumen when compared to the reference diameter, as documented by angiography, which requires intervention and is related to the procedure, e.g., access vessel.
Thrombosis	Clotting within a blood vessel which may cause infarction of tissues supplied by the vessel; it may be occlusive or attached to the vessel or heart wall without obstructing the lumen.
Transient Ischemic Attack (TIA)	A brief episode of neurological dysfunction caused by focal brain or retinal ischemia with clinical symptoms typically lasting 1 - 24 hours and without evidence of acute infarction.

E. WOUND COMPLICATIONS	DEFINITION
Hematoma	An abnormal localized collection of blood (clotted or partially clotted) and situated within an organ or a soft tissue

	space, such as within a muscle. Development of an incisional or retroperitoneal hematoma requiring surgical intervention, evacuation, transfusion or prolonged hospitalization.
Arteriovenous Fistula	Formation of an abnormal connection between the lumens of an artery and a vein as documented by CT, ultrasound, angiography, or direct observation.
Nerve Injury/Peripheral Neuropathy	Direct damage to nerves surrounding the access site, operative field, or catheter deployment site, and the resultant signs and/or symptoms of such damage which may include pain and numbness in the affected area associated with muscle weakness and decreased patellar reflex lasting > 1 month after treatment.

F. SYSTEMIC COMPLICATIONS	DEFINITION
Coagulopathy	The development of an abnormal bleeding disorder, e.g., disseminated intravascular coagulopathy or thrombocytopenia, documented by appropriate laboratory studies and requiring therapy with medication or transfusion.
Anesthetic Complications	Reaction or complication caused by administration of an anesthetic.
Liver failure[33]	Acute liver failure is defined as the rapid development of hepatocellular dysfunction, specifically coagulopathy and mental status changes (encephalopathy) in a patient without known prior liver disease.

F. SYSTEMIC COMPLICATIONS	DEFINITION
Pancreatitis[36]	Evidenced on two of the following three conditions: 1) abdominal pain suggestive strongly of acute pancreatitis (epigastric pain often radiating to the back), 2) serum amylase and/or lipase activity at least 3 times greater than the upper limit of normal, (imaging is to be used if the elevated values are <3 times normal); and 3) characteristic findings of acute pancreatitis on transabdominal ultrasound or on Contrast Enhanced Computed Tomography (CECT) [32]

ATTACHMENT VI – INVESTIGATOR LIST

ATTACHMENT VII – LIST OF ABBREVIATIONS

AAR	Area at Risk
ACC	American College of Cardiology
ADE	Adverse Device Effect
AE	Adverse Event
AHA	American Heart Assocation
AKI	Acute Kidney Injury
AMI	Acute Myocardial Infarction
ASADE	Anticipated Serious Adverse Device Effect
AV	Arteriovenous
BSAS	Bedside *Shivering* Assessment *Scale*
CABG	Coronary Artery Bypass Grafting
CD	Cardiac Death
CEC	Clinical Events Committee
CHF	Congestive Heart Failure
CIP	Clinical Investigation Plan
CI-TLR	Clinically-Indicated Target Lesion Revascularization
CMP	Clinical Monitoring Plan
cMR	Cardiac Magnetic Resonance
CNS	Central Nervous System
CRO	Clinincal Research Organization
CRF	Case Report Form

CRMI	Clinically Relevant Myocardial Infarction
CVA	Cerebral Vascular Accident
CVP	Central Venous Pressure
DAPT	Dual Antiplatelet Therapy
DD	Device Deficiency
DES	Drug Eluting Stent
DMC	Data Monitoring Committee
DP	Dorsalis Pedis
DSMB	Data Safety Monitoring Board
DTB	Door-to-Balloon
DVT	Deep Vein Thrombosis
EC	Ethics Committee
ECG	Electrocardiography
EDC	Electronic Data Capture
ED	Emergency Department
ER	Emergency Room
ESC	European Society of Cardiology
EU	European Union
Fr	French
FMECA	Failure Mode, Effects and Criticality Analysis
FEP	Fluorinated Ethylene Propylene
GLP	Good Laboratory Practice

HDPE	High-density Polyethylene
HIPPA	Heath Insurance Portability and Accountability Act
HTN	Hypertension
ICF	Informed Consent Form
IEC	International Electrotechnical Commission
IFU	Instructions for Use
IQR	Interquartile Range
IRB	Institutional Review Board
IRI	Ischemia Reperfusion Injury
IS	Infarct Size
ISO	International Organization for Standardization
ITT	Intention-to-Treat
IVC	Inferior Vena Cava
IVTM	Intravascular Temperature Management
KCCQ	Kansas City Cardiomyopathy Questionnaire
LAL	Limulus Amebocyte Lysate
LED	Light-emitting Diode
LV	Left Ventricular
LVEF	Left Ventricular Ejection Fraction
MACE	Major Adverse Cardiac Events
MAO	*Monoamine Oxidase*

APPENDIX C

COOL-AMI EU Pivotal Trial Clinical Investigational Plan

Specific DAPT Protocol (For sites that require specific Dual Anti-Platelet Therapy details) (Rev. 6)

(124 pages)

Clinical Investigation Plan

COOL-AMI EU PIVOTAL TRIAL: A MULTICENTER, PROSPECTIVE, RANDOMIZED-CONTROLLED TRIAL TO ASSESS THE SAFETY AND EFFECTIVENESS OF COOLING AS AN ADJUNCTIVE THERAPY TO PERCUTANEOUS INTERVENTION IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

PROTOCOL NO.: EDC-3135

Revision: 6

EFFECTIVE DATE: JUNE 19, 2018

CONFIDENTIAL & PROPRIETARY

CLINICAL INVESTIGATION PLAN APPROVAL PAGE

CLINICAL INVESTIGATION PLAN:	COOL-AMI EU Pivotal Trial: A multicenter, prospective, randomized controlled Trial to assess the safety and effectiveness of cooling as an adjunctive therapy to percutaneous intervention in patients with acute myocardial infarction
PROTOCOL NO.:	EDC-3135
SPONSOR:	ZOLL Circulation, Inc. 2000 Ringwood Avenue San Jose, CA 95131
SPONSOR REPRESENTATIVE:	ZOLL Medical Deutschland GmbH Emil-Hoffmann - Straße 13 50996 Köln, Germany
CLINICAL TRIAL SPONSOR's CONTACT:	Philippa Hill
REVISION NUMBER:	6

Approval of Clinical Investigation Plan by Sponsor:

Philippa Hill
Senior Director, Clinical Affairs

JUNE 19th 2018
Date

Signature Page

Clinical Investigation Plan

COOL-AMI EU PIVOTAL TRIAL: A MULTICENTER, PROSPECTIVE, RANDOMIZED-CONTROLLED TRIAL TO ASSESS THE SAFETY AND EFFECTIVENESS OF COOLING AS AN ADJUNCTIVE THERAPY TO PERCUTANEOUS INTERVENTION IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

PROTOCOL NO.: EDC-3135

Revision: 6

Effective Date: JUNE 19, 2018

Signatures of Investigator below constitute their approval of this clinical investigation plan (CIP) and provide necessary assurances that they have read the CIP, understand it, and will work according to all stipulations of it, and to the ethical principles stated in the latest version of the Declaration of Helsinki and the ISO 14155:2011 (Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice).

Investigator Name (Please Print)	
Investigator Signature	**Date**
Institution Name	
Institution Address	
ZOLL Circulation, Inc. **Sponsor Name**	
2000 Ringwood Avenue, San Jose CA 95131 **Sponsor Address**	
ZOLL Medical Deutschland GmbH **Sponsor Representative**	

Table of Contents

1 SYNOPSIS

Clinical Trial Title	**COOL-AMI EU PIVOTAL TRIAL: A MULTICENTER, PROSPECTIVE, RANDOMIZED-CONTROLLED TRIAL TO ASSESS THE SAFETY AND EFFECTIVENESS OF COOLING AS AN ADJUNCTIVE THERAPY TO PERCUTANEOUS INTERVENTION IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION**
Clinical Trial Sponsor	ZOLL® Circulation, Inc.
Clinical Trial Sponsor's Contact	Philippa Hill Senior Director, Clinical Affairs ZOLL Circulation, Inc. 2000 Ringwood Ave. San Jose, CA 95131 Main: +1 (408) 541-2140 Fax: +1 (408) 541-1030 PHill@zoll.com@zoll.com
Trial Number	EDC-3135
Investigational Device	**Proteus™ Intravascular Temperature Management (IVTM) System**
Trial Objective	The objective of this trial is to evaluate the safety and effectiveness of therapeutic hypothermia, using the ZOLL Proteus IVTM System, as an adjunctive therapy for patients presenting with acute anterior myocardial infarction (AMI) and undergoing percutaneous coronary intervention (PCI) in comparison with patients with acute anterior myocardial infarction and undergoing PCI only.
Trial Design	A multicenter, prospective, interventional, randomized-controlled trial. Randomization will be in a 1:1 ratio, Test Arm (PCI + Cooling) or Control Arm (PCI alone) in up to 500 randomized subjects (250 subjects in each arm). **Roll-In Subjects**: To enhance each site's ability to successfully integrate steps of the protocol and for training purposes prior to randomizing subjects in the trial, each site may enroll up to 4 Roll-In subjects in a non-randomized fashion. Roll-In subjects will be treated and followed in the same manner as subjects in the Test Arm of the

	protocol (PCI + Cooling). Up to a total of 280 Roll-In subjects (up to 4 per site) may be enrolled. Due to limited cMR data available in patients with inferior MI who received an adequate dose of cooling prior to revascularization, Inferior MI subjects will be allowed to be included as Roll-Ins to further evaluate inferior MI infarct size by cMR imaging. Evaluation of infarct size will be performed by cMR imaging at 4-6 days.
Primary Effectiveness Endpoint	Relative reduction of 20% in mean anterior myocardial infarct size as determined by Cardiac Magnetic Resonance (cMR) imaging at 4-6 days post infarct in the Test Arm (cooling + PCI) relative to the Control Arm (PCI only).
Primary Safety Endpoint	Per-patient rate of composite Major Adverse Cardiac Events (MACE) in randomized subjects, defined as Cardiac Death (CD), All Myocardial Infarction (All MI) and Clinically-Indicated Target Lesion Revascularization (CI-TLR) at 30 day follow-up; non-inferiority to the control.
Investigational Sites	Up to 70 clinical sites in the Europe
Inclusion & Exclusion Criteria	Patients shall be screened to the following inclusion and exclusion criteria. Subjects are qualified for participation only if all Inclusion Criteria have been met and all Exclusion Criteria have been confirmed not present. **Inclusion Criteria** All Inclusion Criteria must be answered YES for subject to satisfy Inclusion Criteria: 1. The patient is ≥ 18 years of age. 2. The patient must have symptoms consistent with AMI (i.e. chest pain, arm pain, etc.) and unresponsive to nitroglycerin, with symptoms beginning greater than 30 minutes but less than 4.5 hours prior to presentation at hospital. 3. Qualifying Infarct location: a. **Roll-In subjects**: Evidence of Acute Anterior or Inferior MI with ST-segment elevation of ≥ 0.2 mV in two or more anterior or inferior contiguous precordial leads.(VI-V4)

	b. **Randomized subjects**: Evidence of Acute Anterior MI only with ST-segment elevation of ≥ 0.2 mV in two or more anterior contiguous precordial leads. (V1-V4) 4. The patient is eligible for PCI. 5. The patient is willing to provide written informed consent to participate in this clinical trial. **Exclusion Criteria** All Exclusion Criteria must be answered NO for subject to satisfy Exclusion Criteria: The patient has had a previous myocardial infarction. 1. The patient has had a previous Myocardial Infarction. 2. The patient is experiencing cardiogenic shock, (systolic blood pressure [SBP] <100 mmHg, HR >100 bpm and arterial oxygen saturation (pulse oximetry) ≤92% without additional oxygen. 3. The patient is presenting with resuscitated cardiac arrest, atrial fibrillation, or Killip risk stratification class II through IV. 4. The patient has an aortic dissection or requires an immediate surgical or procedural intervention other than PCI. 5. The patient has known history of Congestive Heart Failure (CHF), hepatic failure, end-stage kidney disease or severe renal failure (clearance < 30ml/min/1.73m²). 6. The patient is febrile (temperature > 37.5 °C) or has experienced an infection with fever in the last 5 days. 7. The patient has a known previous CABG. 8. The patient has a known recent stroke within 90 days of admission. 9. Cardio-pulmonary decompensation that has occurred en route to the hospital or, in the opinion of the physician, that is imminent or likely to occur following presentation to the clinical site. 10. Contraindications to hypothermia, such as patients with known hematologic dyscrasias which affect thrombosis (e.g., cryoglobulinemia, sickle cell disease, serum cold agglutinins) or vasospastic disorders (such as Raynaud's or thromboangitis obliterans). 11. Any contraindication to cardiac MRI, or any implant in the upper body which may cause artifacts on cardiac MRI imaging. 12. The patient has a known hypersensitivity or contraindication to aspirin, heparin, or sensitivity to contrast media, which cannot be adequately pre-medicated.

	13. The patient has a known history of bleeding diathesis, coagulopathy, cryoglobulinemia, sickle cell anemia, or will refuse blood transfusions. 14. The patient has a height of <1.5 meters (4 feet 11 inches). 15. The patient has a known hypersensitivity or contraindication to buspirone hydrochloride or Pethidine (Meperidine) and/or has been treated with a monoamine oxidase inhibitor in the past 14 days. 16. Patient has a known history of severe hepatic or renal impairment, untreated hypothyroidism, Addison's disease, benign prostatic hypertrophy, or urethral stricture that in the opinion of the physician would be incompatible with Pethidine administration. 17. The patient has an Inferior Vena Cava filter in place (IVC). 18. The patient has a pre-MI life expectancy of <1 year due to underlying medical conditions or pre-existing co-morbidities. 19. The patient has a known, unresolved history of drug use or alcohol dependency, or lacks the ability to comprehend or follow instructions. 20. The patient is currently enrolled in another investigational drug or device trial. 21. The patient is apprehensive about or unwilling to undergo the required MRI imaging at follow-up, has a documented or suspected diagnosis of claustrophobia, or has Gadolinium allergy, or is in permanent Atrial Fibrillation. 22. The patient has received thrombolytic therapy en route to the hospital. 23. The patient shows clinical evidence of spontaneous reperfusion as observed symptomatically and/ or from baseline ECG findings (partial or complete ST resolution in baseline ECG prior to informed consent and randomization). 24. The patient is a vulnerable subject, for instance, a person in detention (i.e., prisoner or ward of the state). 25. The patient is a female who is known to be pregnant.
Clinical Trial Population	Adult male and female patients presenting with an acute myocardial infarction. To qualify, patients must have symptoms consistent with AMI (i.e. chest pain, arm pain, etc.) unresponsive to nitroglycerin, with symptom onset greater than 30 minutes <u>but less than 4.5 hours</u> prior to presentation at hospital and be eligible for PCI.

	Randomized subjects must have evidence of Acute Anterior MI only with ST-segment elevation of ≥ 0.2 mV in two or more anterior contiguous precordial leads will be included. (V1-V4) **Roll-In subjects** with evidence of Acute Anterior or Inferior MI with ST-segment elevation of ≥ 0.2 mV in two or more anterior or inferior contiguous precordial leads will be included. (V1-V4)
Intervention	Intravascular permissive hypothermia as an adjunct to PCI. Cooling will be initiated prior to PCI with infusion of up to 1 L of cold saline (4°C) (according to the guideline) and with the Proteus Console set at 32.0 degrees Celsius. Total cooling time will be 3 hours (± 15 minutes) and will be followed with active rewarming with the Proteus IVTM System to attain normothermia [36 °C (96.8°F)].
Length of Follow Up	12 months
Enrollment	Initiation of enrollment: January 2017 Completion of Enrollment: June 2019 Follow up completed: June 2020
Summary of Statistical Analysis	Primary efficacy endpoint of infarct size measured as percentage of total LV mass by cMR, the null hypothesis of equal infarct size between two arms will be tested with t-test for the study population. For the safety endpoint, comparison of per patient MACE rate for non-inferiority will be made with Fisher's exact Test.
Planned Interim Analyses	Two interim analyses are planned to be performed at approximately 50% and 75% of randomization, once subjects have completed 4-6 day cMR follow-up. At the interim stage, the trial will be stopped to reject the null hypothesis of no difference or continue enrollment.
Analysis Sets	The **Intention-to-Treat (ITT)** population will be used for primary statistical analyses and summaries for all analyses except for Safety endpoints. The ITT population includes subjects who have signed an informed consent and have been randomized to the Test Arm or the Control Arm of the trial. ITT subjects will be evaluated according to the group to which they were randomized. The **Per-Protocol (PP) population** includes those subjects who met inclusion and exclusion criteria, were randomized to either the Test Arm or Control Arm, received the treatment to which they were

	randomized, and complied substantially with the treatment timeline and steps of this protocol without major protocol violations. The **Safety Analysis Set** will be used to evaluate safety endpoints. These will be all subjects included in the study as defined by the ITT analysis set and Roll-In subjects. For the safety analysis subjects will be followed for all Adverse Events 30days post procedure. Additionally, all subjects will be followed through 12 months post procedure for the incidence of Serious Adverse Events (SAEs), Death and Heart Failure (as assessed by NYHA and Kansas City Cardiomyopathy Questionnaire (KCCQ),).
Trial Oversight	Each participating site will dedicate one Principal Investigator to oversee the execution of the clinical trial in accordance with the protocol.

2 INTRODUCTION

Clinical investigations have shown that induction of hypothermia before reperfusion of acute coronary occlusion reduces infarct size. A pilot study from Lund University demonstrated that the induction of mild hypothermia (<35°C) in ST Elevation Myocardial Infarction (STEMI) patients prior to performing Percutaneous Coronary Intervention (PCI) can save (preserve) 38% more cardiac tissue compared with the PCI alone.[1]

Hypothermia has proven to be one of the most potent and consistent adjunctive therapies for infarct size reduction in numerous preclinical studies, when administered prior to reperfusion. This is unlike the well accepted approach for therapeutic hypothermia for cardiac arrest, where cooling is applied after reperfusion. The mechanisms leading to protection are multifactorial. However, unlike the consistent findings in preclinical studies, clinical trials (COOL -MI, ICE-IT, CHILL-MI) have failed to show a decrease in infarct size. The major reason is likely due to the difficulty in achieving adequate cooling prior to reperfusion. As shown in **Table 1** below, none of the clinical trials to date has reached target temperature prior to reperfusion, as has been done in all of the animal studies.

Table 1: Major Cooling Trials in STEMI.

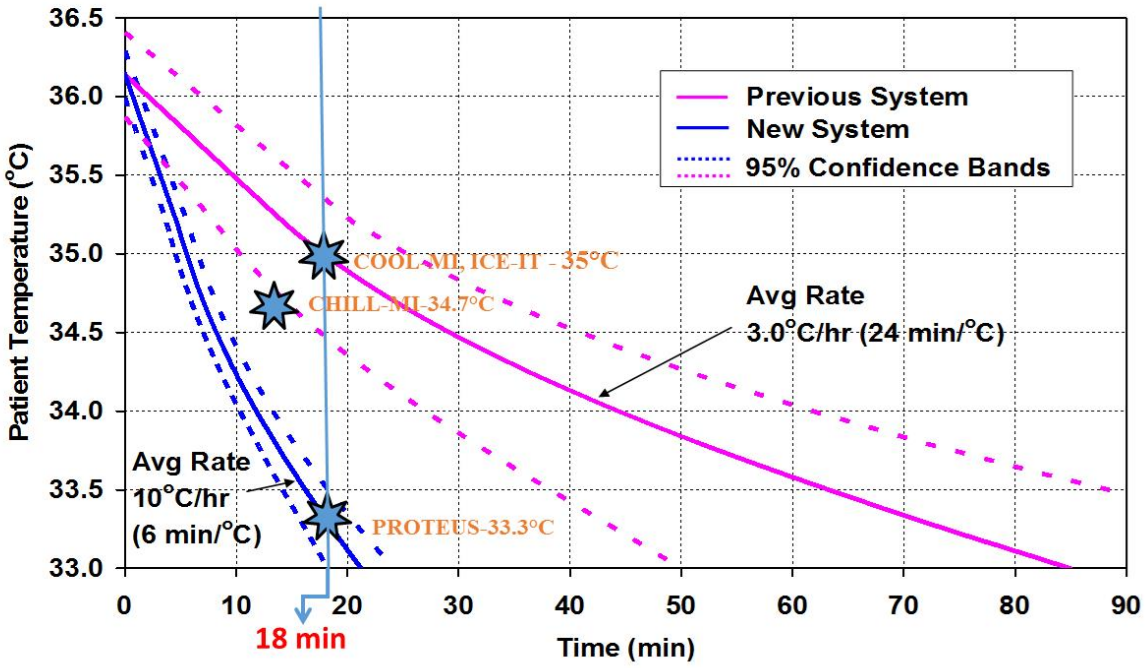
Major Cooling Trials in STEMI					
Trial	**Sample Size**	**Target Temp (°C)**	**Actual Temp at Reperfusion (°C)**	**Temp Miss (°C)**	**Cooling Time before Reperfusion (min)**
COOL -MI	168 – Hyp 157 – Control	33.0	35.0	2.0	18
ICE-IT	105 – Hyp 99 – Control	33.0	35	2.0	16
CHILL-MI	61 – Hyp 59 – Control	33.0	34.7	1.7	13

The target temperature for each trial was 33.0 °C. The actual temperature at the time of reperfusion was 1.7-2.0 °C higher than target. This is a miss in temperature "dose" of

around 50% [normal temperature is 37.0 °C, target temperature was 33.0 °C, (37.0 – 35.0) / (37.0 – 33.0) = 50%].

Post hoc analysis of these trials showed that patients with anterior MI that were cooled to less than 35°C at the time of PCI showed a significant reduction in infarct size, supporting the idea of a dose response (**See Figure 1**). Recent preclinical results (Stanford-ZOLL data) have shown that temperature at reperfusion of 32 °C is superior to 35 °C for reducing infarct size, confirming a dose response. Future clinical trials will require more powerful cooling devices, and more consistency in implementing 18 minutes of cooling before reperfusion across all study sites in order to evaluate the actual effectiveness of therapeutic hypothermia as a protection strategy.

Figure 1: Temperature at reperfusion for the Major Therapeutic Hypothermia in AMI Clinical trials.



The Proteus device has a confirmed faster cooling rate. With a duration of cooling of 18 minutes prior to reperfusion, as occurred in the COOL -MI trial, the expected temperature at reperfusion is 33.3°C with the Proteus device. This is significantly better than the 35°C achieved in COOL -MI and ICE-IT, and 34.7°C achieved in CHILL-MI. The relative effectiveness of the Proteus device for cooling, compared to the performance of the prior studies is shown in Figure 1 above. The addition of a bolus

infusion of 4°C cold saline is expected to further enhance the temperature achieved at reperfusion with the Proteus System.

This Investigational Plan was developed in accordance with the requirements set forth in the Good Clinical Practices (E6)[2], ISO 14155:2011 Clinical investigation of medical devices for human subjects[3] - Good clinical practice, the Declaration of Helsinki, and the local regulatory requirements an adjunctive therapy to PCI.

3 BACKGROUND

Coronary heart disease complicated by acute myocardial infarction (AMI) remains a leading cause of death and disability worldwide. AMI most commonly occurs when a coronary artery becomes occluded by thrombus following the rupture of an atherosclerotic plaque. Factors that may affect the size of the subsequent infarction include duration of ischemia, size of ischemic territory, collateral blood flow, and myocardial metabolic rate. Long-term sequelae of AMI include ventricular remodeling, loss of ventricular function, congestive heart failure, dysrhythmias, and sudden death.

Although major gains have been made in improving the outcome of patients suffering AMI, and early myocardial reperfusion with the use of thrombolytic therapy or primary percutaneous coronary intervention (PCI) are effective, morbidity and mortality remain substantial. This may be because restoration of blood flow to the ischemic myocardium can itself induce injury through myocardial "ischemia reperfusion injury" (IRI), which can be defined as that portion of the ischemia-reperfusion continuum which is preventable by treatment initiated after restoration of blood flow.[4] It has been proposed that 50% of the final infarct size may be a function of IRI. [4]

Ischemia reperfusion injury is protean in its components, likely including free radical and reactive oxygen species, disordered vasculature, inflammatory injury, programmed cell death, and pathologic remodeling among others.[5] Unfortunately, the cascading nature of these events challenge and, in the end, may defeat the single molecular target pharmacologic model. The long list of failed IRI pharmacologic agents includes antioxidants, calcium channel blockers, anti-inflammatory drugs, sodium hydrogen exchange inhibitors, among others, has led some to question the importance of reperfusion injury in the myocardium.[6] Large infarctions still occur despite timely reperfusion, due to reperfusion injury. Numerous treatments have been studied to reduce reperfusion injury, with little success to date. [7-9]

Therapeutic hypothermia (TH) has been studied for many years as a potential therapy for ischemia and reperfusion.[10-16] The past few years have seen development of a broad literature reporting both laboratory and clinical trials of mild post-reperfusion TH in the treatment of disease entities as diverse as acute cardiac arrest, stroke, and myocardial

infarction, among others. Unlike single pharmacologic agents, TH has the potential to modify and ameliorate multiple pathways of injury.

4 INTENDED USE, SYSTEM OVERVIEW, & DEVICE DESCRIPTION

4.1 Intended Use / Indication for Use

The ZOLL® Proteus™ Intravascular Temperature Management (IVTM) System is indicated for use in adult subjects with acute myocardial infarction to induce and maintain hypothermia prior to percutaneous coronary intervention as an adjunctive therapy to reduce anterior infarct size. The Proteus IVTM System is to be used only as part of the clinical investigation.

4.2 System Overview

The Proteus Intravascular Temperature Management (IVTM) System consists of four primary components: a single-use heat exchange catheter; heat exchange cassette; a temperature probe and a reusable microprocessor-driven console. The system is designed to achieve and maintain patient temperatures within the range of 32 - 37°C. Its performance profile includes:

1. Rapid patient cooling and warming

2. Precise achievement and maintenance of a desired patient target temperature

3. Quick and simple deployment: See the catheterization lab, critical care unit, emergency department, and other hospital settings

Reference the Investigator Brochure for additional information on the Proteus IVTM System.

The Proteus IVTM System couples a heat exchange catheter with a dual microprocessor-driven controller to manage patient temperature. The Proteus IVTM System is designed to rapidly cool and warm patients, achieve and precisely maintain a target patient temperature and to be quickly and easily deployed.

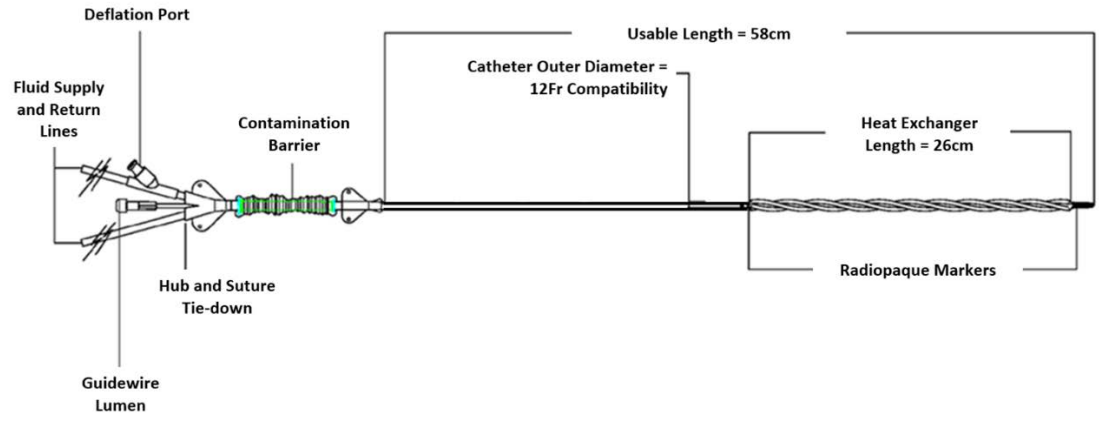
Cool or warm sterile saline is continuously circulated through the catheter, thereby cooling or warming the blood as it flows over the catheter without perfusion of fluids into the body. The saline is transported from the catheter to the cassette (mounted in the console) via extension lines. The cassette has an integral heat exchange element and a pump that couples with the console to cool or warm the saline being pumped through the closed circuit comprised of the cassette and catheter. The Proteus IVTM Console continuously monitors the patient temperature and controls the catheter temperature to cool, warm or maintain the target temperature.

4.3 Device Description

4.3.1 Proteus Catheter

The Proteus Catheter (**Figure 2**) is a single-use, heparin coated, endovascular heat exchange catheter consisting of a triple lobed, helically wound balloon mounted on the distal portion of a multi-lumen shaft. The catheter is designed for placement in the Inferior Vena Cava via the femoral vein using a 12Fr or a 14 Fr hemostatic introducer sheath. The catheter has a fluid supply lumen, a fluid return lumen, a guidewire port at the proximal end of the catheter connecting to a guidewire lumen that accommodates guidewires with diameters up to 0.038". The expanded balloon portion of the catheter has an expanded diameter of 17 mm and a length of 26 cm during system operation. The catheter has a radiopaque marker mounted at the distal and proximal end of the balloon portion of the catheter. The distal end of the catheter has a non-traumatic soft tip. The fluid supply and fluid return lumens of the catheter are connected to the cassette via extension lines approximately 2 meters in length, which provide the closed heat transfer fluid circuit. The 0.038", 145-cm. stainless steel guidewire included in the package has a soft atraumatic tip.

Figure 2 Diagram of Proteus Catheter



4.3.2 Proteus Temperature Probe

The Proteus System measures a patient's core body temperature using a heparin-coated endovascular dual output probe (X-Probe) advanced through the guidewire lumen of the Proteus Catheter after the catheter is placed.

4.3.3 Proteus Cassette

The single-use Proteus Cassette consists of a heat exchange element, a pump, a pump coupling to interface with the motor drive in the console and fluid lines to interface with the heat transfer fluid circulated by the console. The cassette is designed to be removed from the portable control console allowing the catheter to remain in the patient to

facilitate moving the patient to another location where temperature management can continue using the same or another control console.

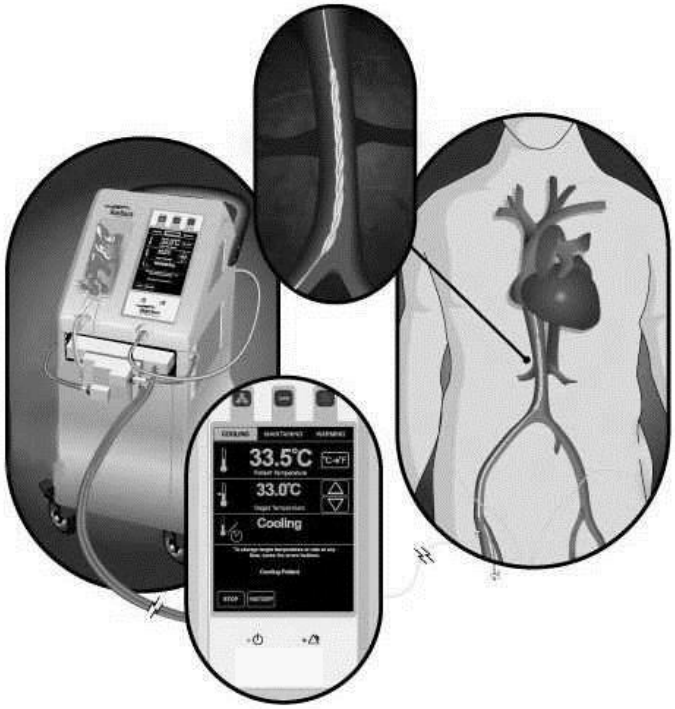
4.3.4 Proteus Console

The Proteus Console **(Figure 3)** consists of solid-state thermoelectric modules, a motor drive, dual fluid level detection systems and dual microprocessors. A dilute polypropylene glycol/water mixture (process fluid) circulates within the console to provide heat exchange with the saline heat transfer fluid loop in the cassette. This technology along with microprocessor proportional control of both the saline and the patient temperature enable the following features:

- Designated patient temperature between 32-37°C is maintained within ± 0.3°C continuous calculation and display, in all ambient lighting conditions, of patient actual temperature, target temperature, and rate of cooling/warming
- Redundant safety system to shut down and warn user of patient overheat or overcool, saline leakage, sensor failure, and electrical or mechanical malfunction
- Control console automatically performs a hardware and software diagnostic check of all functional and safety systems upon startup
- Maximum cooling and heating rates vary from patient to patient depending on the patient's cardiac output, size and weight, room temperature and humidity, and the successful implementation of the anti-shivering medication regimen, type and amount anesthesia, combined use with blankets or active heating/cooling apparatus, body cavity exposure to the environment during surgery and other factors.

Figure 3: Proteus Console

Figure 4: Proteus Catheter and Interconnection between Catheter, Temperature Probe (X-Probe), Cassette and Console.



4.3.5 Device Labeling

Written *Instructions for Use*, *Operation Manual, Quick Reference Guide, and Service Manual* for the Proteus IVTM System will be packaged with product shipped to the investigational sites. The Proteus IVTM System is to be used only as part of the clinical investigation. (See Proteus IVTM System Labeling)

5 PRIOR INVESTIGATIONS

5.1 Pre-Clinical Studies

Hypothermia has been shown to reduce metabolic demand and provide ischemic protection. Recent studies across numerous different animal models have demonstrated a strong direct relationship between myocardial temperature and infarct size.[11,12,14,18] Mild to moderate degrees of hypothermia (32-35°C) have resulted in significant reductions in infarct size when applied either before or after the onset of coronary occlusion in animal studies.

In other studies, in 1996, Duncker et al, and in 1998 Miki et al, both demonstrated a dose response relationship between myocardial temperature and infarct size using a laboratory model of AMI.[11,12] Subsequently, Dae et al in collaboration with Radiant Inc. demonstrated that therapeutic hypothermia can be induced safely and rapidly in animal

models using intravascular cooling.[13] They then showed that hypothermic therapy initiated late during ischemia and continuing for several hours after reperfusion significantly improved reflow and reduced macroscopic zones of no-reflow and necrosis in this model.[15] The study showed:

- A striking reduction of myocardial infarct size. The cooled group had an infarct of 9 ± 6% of the area at risk vs. 45 ± 8% of the area at risk for controls
- Preservation of myocardial perfusion and viability in the cooled group as demonstrated by radionuclide imaging
- No evidence of apoptosis in salvaged myocardium in the cooling arm. Well-preserved cardiac output during the cooling process.

Of particular relevance, Gotberg et al reported in 2008 that hypothermia achieved before reperfusion decreased infarct size, while hypothermia initiated at the time of reperfusion prevented microvascular obstruction, but did not decrease myocardial infarct size. [16]

5.2 Human Clinical Studies

5.2.1 COOL MI Trial

The COOL MI Trial[19] was conducted from September 2001 through April 2003. A total of 421 patients were enrolled (199 Control, 193 Intervention, 29 Roll-In) at 27 investigational sites in the US, Germany and Australia. The primary analysis population included 357 patients (180 Control, 177 Intervention) who received the assigned treatment. The COOL MI Trial evaluated the safety and effectiveness of cooling as an adjunctive therapy to percutaneous coronary intervention (PCI) in patients with acute myocardial infarction. **Table 2** below displays enrollment characteristics.

Table 2: COOL MI Trial Enrollment Characteristics

	Control (N=180)	**Intervention (N=177)**	**p-value**
Anterior Myocardial Infarction	77 (44%)	74 (42%)	0.77
Inferior Myocardial Infarction	99 (56%)	103 (58%)	0.77
Failed thrombolytic therapy prior to enrollment	23 (12.8%)	18 (10.3%)	0.67
Time in minutes – median (interquartile range)			
From symptom onset to hospital presentation	123 (69 – 201)	114 (60 – 190)	0.08
From hospital presentation to PCI	88 (61 – 114)	104 (80 – 134)	<0.0001

5.2.1.1 Procedural and Angiographic Results COOL MI Trial

The Trial demonstrated that endovascular cooling using the Radiant Medical's (now ZOLL's) Reprieve System ™ in the setting of myocardial infarction was safe, well tolerated, and readily integrated into the existing treatment pathway. While the primary effectiveness endpoint of the study was not achieved, the data provided a strong signal indicating that when patients were sufficiently cooled prior to reperfusion, myocardial damage was reduced.[19]

The Control and Intervention groups were well matched in terms of culprit vessels, percutaneous coronary intervention (PCI) procedures and treatment success. As expected, cooling did not affect the angiographic success of PCI procedures. Of the 357 patients who underwent primary PCI, the majority were treated with stent implantation and a platelet glycoprotein receptor inhibitor. Approximately 20% of study subjects were determined to have Thrombolysis in Myocardial Infarction (TIMI 3) flow prior to PCI. TIMI Grade Flow is a scoring system from 0-3 referring to levels of coronary blood flow assessed during percutaneous coronary angioplasty:

- TIMI 0 flow (no perfusion) refers to the absence of any antegrade flow beyond a coronary occlusion.
- TIMI 1 flow (penetration without perfusion) is faint antegrade coronary flow beyond the occlusion, with incomplete filling of the distal coronary bed.
- TIMI 2 flow (partial reperfusion) is delayed or sluggish antegrade flow with complete filling of the distal territory.
- TIMI 3 flow (complete perfusion) is normal flow which fills the distal coronary bed completely

After PCI, TIMI 3 flow was achieved in approximately 92% of patients. Only about 30% of patients had TIMI myocardial perfusion grade 3; however the percentage was similar in both treatment groups and is consistent with literature reports of myocardial perfusion. Procedural and angiographic data are presented in **Table 3** below.

Table 3: COOL MI Trial - Procedural and Angiographic Data

	Control (N=180)	Intervention (N=177)	p-value
Infarct related artery, Stent implantation, Glycoprotein & Stenosis Diameter			
Left anterior descending coronary artery	70 (39%)	69 (39%)	0.91
Circumflex artery	13 (7%)	14 (8%)	0.87
Right coronary artery	77 (43%)	74 (42%)	0.93

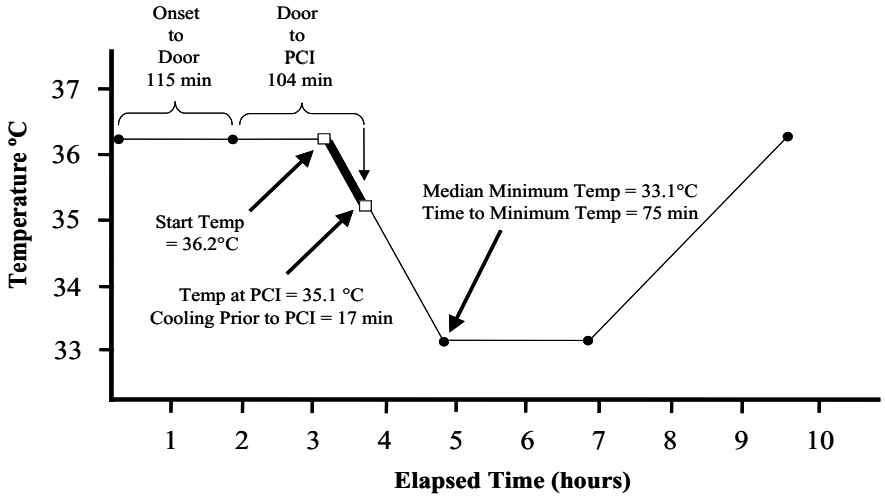
Stent implanted	153 (92%)	157 (94%)	0.59
Glycoprotein IIb/IIIa receptor inhibitor	140 (78%)	142 (80%)	0.74
Initial diameter stenosis (mean ± std dev)	92 ± 14%	92 ± 12%	0.93
Initial TIMI flow			
Grade 0/1	126 (71%)	122 (69%)	0.77
Grade 2	14 (8%)	21 (12%)	0.28
Grade 3	38 (21%)	34 (19%)	0.74
Final diameter stenosis	7 ± 9%	8 ± 10%	1.00
Final TIMI* flow			
Grade 0/1	2 (1%)	5 (3%)	0.33
Grade 2	7 (4%)	12 (7%)	0.31
Grade 3	170 (95%)	160 (90%)	0.11
Final myocardial perfusion grade			
Grade 0/1	63 (43%)	76 (53%)	0.11
Grade 2	35 (24%)	26 (18%)	0.27
Grade 3	49 (33%)	41 (29%)	0.54

*Thrombolysis in Myocardial Infarction

5.2.1.2 COOL MI Trial Results

Of the 177 Intervention patients, 11 (6.2%) patients had the Reprieve Catheter placed in the emergency room (ER), one (0.6%) patient had the catheter placed in the cath lab holding area, and 165 (93.2%) patients had the catheter placed in the cath lab. Overall, patients in the Intervention group received a median of 17 minutes (interquartile range (IQR): 10-27) of cooling prior to PCI. During that time, patient temperature was decreased from a median of 36.2°C (IQR: 35.8-36.5) at the initiation of cooling to 35.1°C (IQR: 34.5-35.6) at the time of PCI (**Figure 1**). The median of the minimum temperature reached by each patient was 33.1°C (IQR: 33.0-33.4), which was achieved in 75 minutes (IQR: 50-108). Target patient temperature was set at a 33°C for 3 hours post-PCI. Patients were then re-warmed at 1°C/hr until Investigator-determined normothermia was reached [median=36.5 (IQR: 36.2-36.8]). **Figure 5** below shows patient temperature over time with cooling and time to PCI. The goal to reach target temperature of 33°C at PCI was not achieved in the trial, due to the inadequate cooling power of the Reprieve System. As noted above, target temperature of 33°C was reached after 75 minutes of cooling, long after PCI had occurred.

Figure 5: Median Temperature and Elapsed Times for Intervention Patients



5.2.1.3 COOL MI Trial Tolerability of Cooling

Shivering was managed according to the shivering suppression guidelines recommended for this study by Dr. Daniel Sessler, Chairman of the Department of Anesthesiology at the University of Louisville. The recommended baseline combination of Pethidine, buspirone and skin warming using a forced-air blanket could be supplemented incrementally in the event of shivering or patient discomfort, by additional Pethidine, or by slightly increasing the target temperature. If these steps were unsuccessful, patients could be actively rewarmed to normothermia.

This protocol proved to be quite effective at maintaining patient comfort. Intervention patients received an average of 56 mg of oral buspirone and an average of 267 mg of intravenous Pethidine over the course of the cooling procedure. Of 177 patients in the treatment group, only one patient (0.6%) required premature warming due to intolerability of cooling. Nine patients (5.1%) required a slight increase in target temperature (0.2°C – 0.5°C) to maintain patient comfort. Ninety-eight patients (55.7%) required supplementary dosing of Pethidine, but 60 of these 98 patients (61.2%) had not received the recommended loading dose of the anti-shivering drugs.

COOL MI Trial Safety Results: The primary safety endpoint of the COOL MI study was the incidence, through 30 days, of Major Adverse Cardiac Events (MACE), defined as the composite of death, recurrent myocardial infarction of the target vessel and the need for urgent revascularization of the target vessel. As shown in **Table 4** below, there was no statistical difference in the incidence of MACE in the Intervention group as compared to the Control group. All MACE were adjudicated by an independent Clinical Events Committee and none were attributed to cooling or use of the Reprieve System. **Table 4**

below demonstrates the results of the study with regard to the incidence of Major Adverse Cardiac Events.

Table 4: COOL MI Trial Incidence of MACE

Events through 30 days	Control (N=180)	Intervention (N=177)	p-value
MACE	**7 (3.9%)**	**11 (6.2%)**	**0.45**
Death	4 (2.2%)	6 (3.4%)	0.71
Recurrent MI	3 (1.7%)	1 (0.6%)	0.63
Urgent Revascularization	0 (0%)	4 (2.3%)	0.12

These MACE rates observed in COOL MI compare favorably with those reported for similar patients in recent AMI trials, such as ADMIRAL, CADILLAC, DANAMI and RAPID MI-ICE (**Table 5**).

Table 5 Incidence of MACE for Comparable Patients in Recent AMI Trials

Trial	Death	Reinfarction	Revascularization
COOL MI (Treatment Group) (n=177)	3.4%	0.6%	2.3%
ADMIRAL (n=149)[17]	3.4%	1.3%	4.7%
CADILLAC (n=524)[18]	2.7%	0.8%	1.6%
DANAMI-2 (n=790)[19]	6.6%	1.6%	NA
RAPID MI-ICE (n=20)[1]	0%	0%	0%

5.2.1.4 COOL MI Trial Adverse Events Related to Cooling

Potential adverse events related to cooling (e.g., arrhythmia or hemodynamic complications) and to placement and/or use of the Reprieve Catheter (e.g., vascular or thrombogenic complications) were also evaluated as a secondary endpoint. The incidence of these types of events is presented. It is important to note that these complications are also risks of myocardial infarction and coronary intervention themselves. **Table 6** below reports the incidence of non-MACE complications.

Table 6: Incidence of Other Complications

Events through 30 days	Control (N=180)	Intervention (N=177)	p-value
Bradyarrhythmia	41 (22.8%)	46 (26.0%)	0.56
Ventricular Tachycardia/Fibrillation	36 (20.0%)	31 (17.5%)	0.64
Cardiogenic Shock	11 (6.1%)	22 (12.4%)	0.06
Pulmonary Edema	3 (1.7%)	6 (3.4%)	0.49
Vascular Complications	15 (8.3%)	15 (8.5%)	0.90
Retroperitoneal bleed	2 (1.1%)	1 (0.6%)	0.95
Hematoma >6cm	12 (6.7%)	13 (7.3%)	0.99
Pseudoaneurysm	1 (0.6%)	3 (1.7%)	0.63
AV fistula	1 (0.6%)	0 (0%)	0.95
Bleeding Requiring Transfusion	14 (7.8%)	20 (11.3%)	0.34
Deep Venous Thrombosis	0	3 (1.7%)	0.24
Pulmonary Embolism	3 (1.7%)	0	0.24
Stroke	1 (0.6%)	0	0.95

Arrhythmias are a known risk of moderate to severe hypothermia. In the COOL MI trial, with its mild hypothermia target temperature, arrhythmias were not more common and appeared to be primarily related to ischemia and/or the coronary intervention. Cardiogenic shock requiring treatment with an intra-aortic balloon pump trended toward a higher incidence in the hypothermic group. However, the majority of shock cases appeared to be more related to complicated MIs and/or complex interventions than to cooling. Other potential contributory factors (e.g., age, weight, Pethidine dose) were compared between shock and stable patients; however, no causal relationships were apparent. The majority of the vascular complications reported in the Intervention group were related to the arterial access site for the PCI procedure rather than the venous access site for the cooling catheter. Three cases of deep venous thrombosis (DVT) were reported in the Intervention group.

5.2.1.5 COOL MI Trial Effectiveness Results

The primary effectiveness endpoint in the COOL MI study was infarct size, measured using SPECT imaging at 30 days. Overall, there was no observed difference in infarct size (%LV) between study groups (**Table 7**). The secondary effectiveness endpoints of LV ejection fraction, CK-MB release, and ST-segment resolution, likewise did not demonstrate a difference between the Intervention and Control groups.

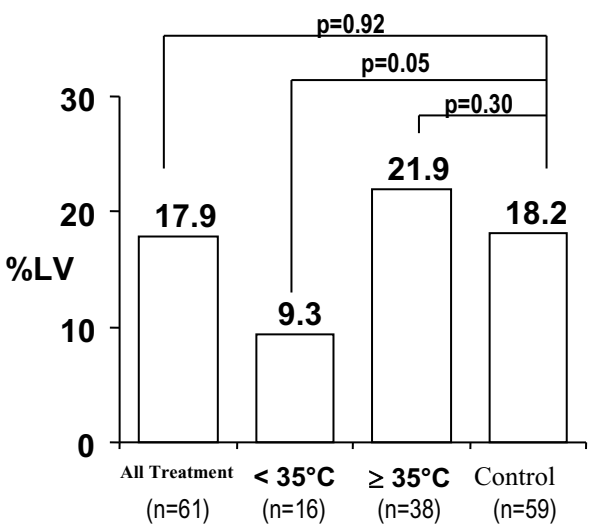
Table 7: COOL MI Results

	Control	Intervention	p-value
% LV Infarct Size (N) mean ± std dev median	157 13.8 ± 15.1 10	168 14.1 ± 14.3 10	 0.83
LV Ejection Fraction (N) mean ± std dev median	104 55.2 ± 11.4 54	115 53.0 ± 12.0 53	 0.17
Peak CK-MB (N) mean ± std dev median	167 42.8 ± 48.1 33.9	168 49.1 ± 50.7 33.6	 0.25
ST-segment resolution - 90 min. post-PCI (N) < 30% 30 - 69% ≥ 70%	90 11.1% 27.8% 53.3%	82 20.7% 35.4% 39.0%	 0.13 0.36 0.09
ST-segment resolution - 180 min. post-PCI (N) < 30% 30 - 69% ≥ 70%	79 10.1% 20.3% 60.8%	80 16.3% 27.5% 51.3%	 0.36 0.38 0.30

In addition, no statistically significant differences were demonstrated when the Intervention and Control patients were compared based on the following stratifications: infarct location, time from onset of symptoms to PCI, prior MI, or TIMI flow prior to PCI. However, subsequent analysis revealed a strong relationship between final infarct size and patient temperature at the time of reperfusion.

The mean temperature at the time of reperfusion, or more specifically, at the time of first balloon inflation, was 35.1°C. As shown in **Figure 6**, in the population of patients with anterior myocardial infarction, those patients who had a temperature <35°C at the time of reperfusion had a statistically significant reduction in final infarct size as compared to both the control group (9.3% vs. 18.2%, p=0.05) and those with a temperature ≥35°C (9.3% vs. 21.9%, p=0.01).

Figure 6: Mean Infarct Sizes (%LV) of Patients with Anterior Infarction



Subject groups:

i) All Intervention patients regardless of temperature at PCI

ii) Intervention patients cooled to < 35°C at PCI

iii) Intervention patients ≥ 35°C at PCI

iv) Control patients

This effect has a strong basis in physiology and was consistent across other clinical measures, i.e., there was a trend toward decreased CK-MB release and increased LV Ejection Fraction in the cooled patients. This effect is not attributable to differences in baseline clinical or angiographic variables. In fact, those patients with a temperature <35°C were more likely to have occlusion of the proximal versus mid left anterior descending coronary artery and a longer time to reperfusion. These factors would be expected to increase infarct size in this group, but the observed reduction in infarct size appears to be the result of cooling.

5.2.2 COOL MI II Trial

Because of the encouraging results in patients with anterior AMI's in whom hypothermia had been achieved at the time of PCI, COOL MI II was initiated. Additionally, COOL MI II Trial was intended to verify the feasibility of initiating cooling earlier in the treatment pathway (e.g., in the emergency department). Only a fraction of the anticipated sample size were enrolled before the trial was ended early because the sponsor became financially insolvent after only 41 patients were enrolled. The study data were submitted by the sites to a Data Management CRO. As a result, the final report is not currently available because the data was not released to ZOLL by the Data Management CRO upon ZOLL acquisition of Radiant Medical.

In COOL MI II, all cooling was initiated in the Cath Lab even though the focus was on earlier cooling. Since earlier initiation of cooling was not accomplished, reaching the goal of a core temperature of 35° C before PCI was dependent on the more powerful GTO System. This was accomplished in 26 of the 27 patients without the intentional delay of PCI. Pivotal data for 23 patients were available and the mean time to reach 35°C was 6.1

minutes (± 3.0), 34°C was 14.5 minutes (± 7.9) and 33°C was 31.3 minutes (± 29.9). Data showed 15 of the patients were cooled to 32°C; the mean time was 36.1 minutes (± 14.0).

Efforts to initiate cooling as early as possible resulted in a median of 39 minutes of cooling time prior to PCI, a significant improvement over the median of 18 minutes of cooling time achieved in the previous study. In addition, the median door-to-balloon time was 106 minutes for these COOL MI II patients, compared to a median of 104 minutes for Test patients in the previous study, indicating that PCI was not delayed by the introduction of cooling. By focusing on cooling earlier in the treatment pathway, additional cooling time can be achieved without significant adverse impact on time to reperfusion.

5.2.2.1 COOL MI II Trial Adverse Events

As with COOL MI, the primary safety endpoint of the COOL MI II study was the incidence, through 30 days, of MACE. Shown below are the adverse events in the COOL MI II trial in the intent to treat (ITT) population. **Table 8** combines the Feasibility and Pilot hypothermia groups for a total of 41 patients (12 Feasibility and 29 Pivotal).

Table 8*:* Incidence of MACE and Other Complications

Events through 30 Days	**Normothermia**	**Hypothermia**
Enrollment	*10*	*41*
UADE	0	0
Cardiac		
Death	0	1 (2.4%)
Repeat MI	0	1 (2.4%)
Repeat PCI	1 (10%)	3 (7.3%)
CABG	0	2 (4.9%)
Hypotension / Shock	1 (10%)	6 (14.6%)
CHF	0	2 (4.9%)
Pericardial Effusion	0	1 (2.4%)
Pericarditis	0	1 (2.4%)
HTN	0	1 (2.4%)
Arrhythmias		
Ventricular Fibrillation	0	4 (9.8%)
Vent. Tachycardia	1 (10%)	7 (17.1%)
Frequent PACs	1 (10%)	0
SVT	0	1 (2.4%)
Atrial Fibrillation	0	11 (26.8%)
Vascular Events		
Bleeding requiring transfusion	0	3 (7.3%)
Thrombocytopenia	0	2 (4.9%)
Anemia	0	2 (4.9%)
Hematoma > 6cm	0	2 (4.9%)
DVT	0	1 (2.4%)
Local Tissue Trauma	0	1 (2.4%)
Epistaxis	1 (10%)	0
Hemoptysis	0	1 (2.4%)
Stroke	0	0
Respiratory Events		
Pulmonary Edema	0	8 (19.5%)
Pulmonary Embolism	0	0
Hypoxia	0	1 (2.4%)
Respiratory Failure	0	1 (2.4%)
Plural Effusion	0	3 (7.3%)
Increased Pulmonary HTN	1 (10%)	0
Pneumonia	1 (10%)	0

Renal		
Renal requiring Treatment	1 (10%)	2 (4.9%)
Hemodialysis	0	0
UTI	0	2 (4.9%)
Hematuria	1 (10%)	0
Other		
Nausea / Vomiting	1 (10%)	15 (36.6%)
Systemic Infection	0	3 (7.3%)
Fever	0	3 (7.3%)
Muscular Pain	1 (10%)	3 (7.3%)
Rhabdomyolysis	1 (10%)	0
Mental Status Changes	0	2 (4.9%)
Hypokalemia	0	1 (2.4%)
Vaginal Infection	0	1 (2.4%)

5.2.3 COOL RCN Trial

The COOL RCN (Radio-Contrast nephropathy) trial was undertaken to evaluate whether endovascular cooling provides more effective protection for patients at high risk of experiencing RCN. The trial was designed as an international, multicenter, 1:1 randomized controlled trial of up to 400 subjects at up to 35 investigational sites. Subjects with a calculated Creatinine clearance of 20 – 50 mL/min and scheduled for a diagnostic or interventional catheterization procedure were enrolled. The trial utilized Radiant Medical's Reprieve System. The study was commenced in March 2006 and was terminated after enrolling only 136 subjects due to the financial insolvency of Radiant Medical.

Table 9: COOL RCN Trial*:* Adverse Events Incidence of Complications In-Hospital

	Normothermia	**Hypothermia**	**P Value**
Enrollment	*70*	*58*	
Nausea/Vomiting	6 / 70 (8.6%)	26 / 58 (44.8%)	<0.01
Bradycardia	2 / 70 (2.9%)	7 / 58 (12.1%)	0.04
Bleeding Requiring Transfusion	7 / 70 (10.0%)	1 / 58 (1.7%)	0.05
Atrial Fibrillation	2 / 70 (2.9%)	3 / 58 (5.2%)	0.5
CABG	4 / 70 (5.7%)	1 / 58 (1.7%)	0.25
Pulmonary Edema	4 / 70 (5.7%)	1 / 58 (1.7%)	0.25
Renal Complication	2 / 70 (2.9%)	3 / 58 (5.2%)	0.5

	Normothermia	Hypothermia	P Value
Acute Renal Failure	2 / 70 (2.9%)	2 / 58 (3.4%)	0.85
Elevated Serum Creatinine	0 / 70 (0%)	1 / 58 (1.7%)	--
Hemodialysis	2 / 70 (2.9%)	0 / 58 (0%)	--
Urinary Tract Infection	3 / 70 (0.4%)	1 / 58 (1.7%)	0.41
Hypotension/Shock	1 / 70 (1.4%)	3 / 58 (5.2%)	0.22
Hematoma >6cm	0 / 70 (0%)	3 / 58 (5.2%)	--
SVT	0 / 70 (0%)	2 / 58 (3.4%)	--
MI	0 / 70 (0%)	1 / 58 (1.7%)	--
Ventricular Tachycardia	1 / 70 (1.4%)	1 / 58 (1.7%)	0.89
Death	0 / 70 (0%)	1 / 58 (1.7%)	--
Repeat PCI	1 / 70 (1.4%)	1 / 58 (1.7%)	0.89
Stroke	0 / 70 (0%)	1 / 58 (1.7%)	--

Table 10: COOL RCN Trial: Incidence of Complications to 30 Days

	Normothermia	Hypothermia	P Value
Enrollment	*70*	*58*	
Renal	7	2	0.15
Acute Renal Failure	5	1	0.15
Renal Stent	2	0	--
Kidney Infection	0	1	--
Cardiac	8	14	0.1
MI	1	1	0.89
CABG	2	3	0.5
PCI	1	3	0.22

	Normothermia	Hypothermia	P Value
PCI or CABG	3	6	0.18
Death - Cardiac	1	2	0.45
Shock	0	3	--
CHF	2	1	0.67
Angina	1	0	--
Hypertension	0	1	--
Arrhythmia	3	3	0.81
Atrial Fibrillation	2	1	0.67
Bradycardia	0	2	--
SVT	1	0	--
Ventricular Fibrillation	0	0	--
Non-Cardiac	3	3	0.81
Stroke	1	0	--
Bleed/Transfusion	2	3	0.5
Dialysis	0	0	--
Vascular Complications Requiring Surgery	0	0	--
Rehospitalization	13	13	0.59
Other	9	12	0.23
Anasarca	1		--
Fatigue	1		--
Ischemic Bowel	1	1	0.89
Hypoglycemia	1		--
Lesion Excision	1		--
Anemia	1		--
Hiatal Hernia	1	1	0.89
Pulmonary Edema	1		--
Knee Injury	1		--
Rash		1	--
Debridement of Sternal Wound		1	--
Leg Weakness		1	--
Nausea/Vomiting		2	--
Dehydration		1	--
Acute Respiratory Failure		1	--
Metabolic Acidosis		1	--
Back Pain		1	--
Systemic Infection		1	--

5.2.3.1 Unanticipated Adverse Events

(i) COOL MI Trial – Unanticipated Adverse Events

There was one Unanticipated Adverse Device Effect (UADE) in the COOL MI Trial; A patient experienced nasopharyngeal trauma and bleeding potentially caused by the nasoesophageal temperature probe used as part of the Reprieve System. This resulted in a modification to the Informed Consent Form to explain the risk of nasal trauma and/or bleeding due to the nasoesophageal probe.

(ii) COOL MI II Trial – Unanticipated Adverse Events

There were no UADE's in the COOL MI II Trial.

(iii) COOL RCN Trial – Unanticipated Adverse Events

There was one UADE in the COOL-RCN Trial. A 73 year old male with chronic renal insufficiency and a history of aortobifemoral bypass scheduled for cardiac catheterization. The patient was randomized to the Hypothermia arm. The Reprieve catheter was placed via the left femoral vein. The angiogram and stenting procedures were performed via right radial arterial access. After approximately 1 hour of cooling, the patient complained that his feet were itching and it was noted that the patient's left foot and leg were cyanotic up to mid-thigh, with no left DP pulse, and the right foot was slightly discolored. He was subsequently rewarmed at the maximum rate for approximately 40 minutes. It was observed that the cyanosis lightened as the patient rewarmed and was apparently resolved with no further sequelae after discontinuation of treatment with the Reprieve catheter, indicating that cooling with the device contributed to the reduced peripheral circulation. The already compromised peripheral vascular circulation is suspected to have been exacerbated by hypothermia induced vasoconstriction. It is known that hypothermia induces superficial vasoconstriction, but this degree of cyanosis had not been observed with previous use of the device. Additionally, after the patient had received Pethidine and versed as part of the anti-shivering protocol, his respiration became depressed, requiring assisted ventilation, Romazicon and Narcan. It is possible that this transient hypoxic event may have also contributed to the cyanosis.

Lower extremity cyanosis in the presence of peripheral vascular insufficiency had not been identified in the protocol or informed consent document as a potential risk of mild hypothermia or use of the Reprieve catheter. The resolution of the cyanosis upon rewarming and removal of the catheter indicated that these may have contributed to the event. The risk section of the protocol and informed consent were subsequently revised.

5.2.4 ICE- IT Trial

The Intravascular Cooling Adjunctive to Percutaneous Coronary Intervention for Acute Myocardial Infarction Trial (ICE-IT) [23] randomized 228 patients presenting with an acute

MI within 6 hours of symptom onset to endovascular cooling concomitant with PCI versus routine PCI. The primary endpoint of infarct size at 30 days as measured by SPECT imaging was similar between the 2 groups (10% for the hypothermia group versus 13% for the control group, p = 0.14). Like the COOL MI trial, ICE-IT was also an overall negative trial. But while TH did not demonstrate any significant decrease in infarct size overall, a trend towards benefit was again observed on post-hoc analysis of the subgroup with anterior infarction who were sufficiently cooled to a temperature of < 35°C at the time of revascularization (infarct size of 12.9% of the left ventricle in the TH population compared to 22.7% in the control group, p = 0.09).[23]

5.2.5 RAPID-MI ICE Trial

Recently, Lund University presented a preliminary report of their RAPID-MI ICE Trial.[1] This trial enrolled 20 patients presenting with acute myocardial infarction, and 10 patients each were randomized to TH by intravascular cooling or a control group. Cooling was accomplished with a combination of 2L of cold saline infusion and the Phillips InnerCool catheter-based cooling system. The endpoint was infarct size normalized to myocardium at risk assessed by cardiac magnetic resonance using T2 weighted imaging and late gadolinium enhancement. Although the sample size is relatively small, the trial produced a number of potentially important results:

- Core body temperature less than for 35°C was achievable before reperfusion without significant delay in the door to balloon time.
- Infarct size normalized to myocardium at risk was reduced by a remarkable 38% in patients receiving hypothermia.
- There were also significant decreases in peak and cumulative Troponin I or T in the hypothermia group.

5.2.6 CHILL-MI Trial

Lund University recently reported the results of the CHILL-MI trial[37], which was a multi-center study of 120 patients with STEMI (< 6 hours) planned to undergo PCI who were randomized to hypothermia induced by rapid infusion of 600 – 2000 ml of cold saline and endovascular cooling, or standard of care. Hypothermia was initiated before PCI and continued for 1 hour after reperfusion. The primary endpoint was infarct size as a percentage of the myocardium at risk (IS/MaR), assessed by cardiac MRI at 4±2 days. The goal to reach target temperature of 33°C at reperfusion was also not achieved in the CHILL-MI trial, due to the inadequate cooling power of the cooling device. Patients randomized to cooling achieved a core body temperature at reperfusion of 34.7°C with a 9 minute longer door-to-balloon time. Hypothermia induced by cold saline infusion and endovascular cooling was feasible and safe, however, there was no significant difference in IS/MaR between the groups. Exploratory analysis of early anterior infarctions (0-4 hrs) showed a significant reduction in IS/AAR of 33% ($p<0.05$). Further, the incidence of

heart failure was lower with hypothermia at 45 days (3% vs 14%, p<0.05). This trial, as the others cited above, shows potential efficacy of cooling in patients with anterior STEMI, supporting further research for confirmation.

5.2.7 Induction of Mild Systemic Hypothermia With Endovascular Cooling During Primary Percutaneous Coronary Intervention for Acute Myocardial Infarction

This multi-center study included 42 patients with acute myocardial infarction (AMI) (onset less than 6hrs) and evaluated the safety and feasibility of endovascular cooling during primary PCI for AMI. [39] Subjects were randomized to PCI with or without endovascular cooling (target core temperature 33°C). Cooling was maintained for 3 h after reperfusion. Skin warming, oral buspirone, and intravenous meperidine were used to reduce the shivering threshold. The primary end point was major adverse cardiac events at 30 days. Infarct size at 30 days was measured using SPECT imaging. All patients successfully cooled did achieved a core temperature below 34°C (mean target temp 33.2 ± 0.9°C). MACE events occurred in 0% vs. 10% (p = NS) of treated versus control patients. The median infarct size was not significantly smaller in patients who received cooling compared with the control group (2% vs. 8% of the left ventricle, p = 0.80).

5.2.8 VELOCITY Trial

The VELOCITY trial[38] randomized 54 STEMI patients at 7 centers in the United States and Canada to emergent PCI with (n = 28) or without (n = 26) hypothermia induced by the Velomedix Automated Peritoneal Lavage System (Velomedix; Menlo Park, CA) between January 2013 and January 2014. Baseline characteristics were similar between the 2 groups, and 46.3% of all infarcts were anterior.

Hypothermia (core temperature at or below 34.9°C) was achieved in 96.3% of patients and PCI was performed in all but 1 patient in each treatment group. Median door-to-balloon time was shorter in the control vs hypothermia group (47 vs 62 minutes; *P* = .007). Among the 46 PCI patients who underwent MRI 3 to 5 days post procedure, the median myocardial infarct size was similar in the control vs hypothermia group (16.1% vs 17.2% of LV mass; *P* = .54).

VELOCITY Investigators observed that prolonged door-to-balloon time in the hypothermia group may have attenuated the effect of hypothermia on infarct size though it is unlikely to have been totally responsible for absence of effect as DTB times were short in both groups and within the range wherein further reductions in mortality may not be realized.

At 30-day follow-up, no patients in the control group had a primary composite safety endpoint event, compared with 6 (21.4%) of the patients who underwent hypothermia (P = .01). Further details in Section 5.2.8.1.

In conclusion, the VELOCITY study found that controlled systemic hypothermia through automated peritoneal lavage may be safely and rapidly established in patients with evolving STEMI undergoing primary PCI at the expense of a modest increase in door-to-balloon time. In the VELOCITY randomized trial, peritoneal hypothermia was associated with an increased rate of adverse events (including stent thrombosis) without reducing infarct size. Adequately powered randomized trials (likely limited to patients with anterior MI) are needed to assess the effect of rapidly induced hypothermia on myocardial salvage and clinical outcomes after primary PCI.

5.2.8.1 VELOCITY Trial Adverse Events at 30 Days

At 30-day follow-up, no patients in the control group had a primary composite safety endpoint event (death, reinfarction, ischemia-driven TLR, major bleeding, sepsis, pneumonia, peritonitis, severe arrhythmias, or renal failure), compared with 6 (21.4%) of the patients who underwent hypothermia (P = .01). Four patients (14.3%) experienced MACE (cardiac death, reinfarction, or ischemia-driven TVR), and 3 (11.0%)—all in the hypothermia arm—developed definite stent thrombosis.

Table 11: VELOCITY Trial Clinical Event Rates Within 30 Days

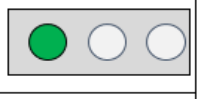
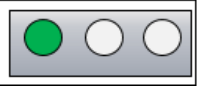
	Control (N=26)	Hypothermia (N=28)	*P* Value
Primary composite safety end point	0% (0)	21.4% (6)	0.01
Cardiac death	0% (0)	3.6% (1)	0.34
Noncardiac death	0% (0)	0% (0)	…
Reinfarction	0% (0)	3.6% (1)	0.34
Ischemia-driven target vessel revascularization	0% (0)	11.0% (3)	0.09
Major bleeding	0% (0)	3.6% (1)	0.34
Ventricular tachycardia or fibrillation	0% (0)	3.6% (1)	0.34
Sepsis	0% (0)	3.6% (1)	0.34
Pneumonia	0% (0)	0% (0)	…
Renal failure	0% (0)	0% (0)	…
Peritonitis	0% (0)	0% (0)	…
Major adverse cardiac events	0% (0)	14.3% (4)	0.047
Stent thrombosis	0% (0)	11.0% (3)	0.09
Acute (≤24 h)	0% (0)	7.1% (2)	0.17
Subacute (1–30 days)	0% (0)	3.6% (1)	0.34
Definite	0% (0)	11.0% (3)	0.09
Probable	0% (0)	0% (0)	…

Data are expressed as Kaplan–Meier estimates, % (n). *P* values are from the log-rank test.

5.2.9 EU AMI Case Series

ZOLL is currently enrolling patients in the COOL-AMI EU Case Series Trials to assess the ability to integrate hypothermia into the current pathway for patients receiving PCI for ST elevation MI. To date, 308 patients have been enrolled at 36 sites in the EU. Both anterior and non-anterior STEMI patients have been enrolled, and cooling is performed using the ZOLL Thermogard XP (TGXP) System or Proteus IVTM system. A series of six standards has been developed and monitored to enable consistency in the execution of the protocol. The standards include delivery of the antishivering regimen correctly, delivery of 1 L of iced saline before PCI, and at least 18 minutes of cooling delivered prior to wire crossing the lesion. Feedback in the form of a report card (**Figure 7**) is provided to the site after each case as indicated in the following diagram:

Figure 7: Report Card Standards

Standards	Measured	Expected	
1. Anti-shivering Regimen Delivered prior to Iced Saline Delivery	C-B-P-S	Per-protocol C-B-P-S	
2. 1 Liter Iced Saline delivered with pressure bag prior to PCI	1 Liter	1 Liter	
3. At least 18 minutes of cooling delivered prior to PCI	18 min	18 min	
4. Door-to-Balloon Time	59 min	< 90min	
5. Ischemic Time	3 hrs. 9 min	< 6 hrs.	
6. DAPT Agent Administered	Yes	Pre-PCI	

These six standards are consistently achieved at all sites. The 18 minute duration of cooling matches the average duration of cooling in the previous EU COOL AMI trial. The ability to deliver 18 minutes of cooling prior to PCI is consistently achieved in the recent EU Case Series, where the door to balloon (DTB) times, at all sites, were less than 60 minutes (ranging from 38 minutes to 58 minutes). This is far less than the maximum door to balloon time of 90 minutes recommended by the current guidelines for PCI, 2011 ACCF/AHA/SCAI PCI Guideline[24,50]). The experience of one of the sites has been published[26], and notes that the average DTB time for the first 11 patients enrolled in the trial was 38 minutes, compared to a mean DTB time of 37 minutes for all patients presenting with STEMI without cooling. In view of the validation that implementation of hypothermia in the treatment pathway for PCI of STEMI patients is feasible, ZOLLhas also conducted the COOL-AMI EU PILOT Trial, following the same standards of implementation, with cooling done by the more powerful Proteus device. The goal is to maximize the dose of cooling prior to PCI.

5.2.10 COOL-AMI EU PILOT Trial

ZOLL has completed enrollment in the COOL-AMI EU PILOT Trial that evaluated the retention of subjects after integrating therapeutic hypothermia using the ZOLL Proteus IVTM System into existing STEMI treatment protocols for subjects who presented with acute anterior myocardial infarction. 50 subjects were randomized at 16 sites in the EU. 22 patients (88%; 95% confidence interval [CI]: 69-97%) in the hypothermia group and 23 patients (92%; 95% CI: 74-99) in the control group completed cardiac magnetic resonance imaging at four to six days and 30-day follow-up. A series of three standards were monitored to enable consistency in the execution of the protocol. The standards included delivery of the antishivering regimen correctly, delivery of up to 1 L of iced saline, and 18 minutes of cooling delivered prior to wire crossing the lesion. Patients with

anterior STEMI were rapidly and safely cooled. Intravascular temperature at coronary guidewire crossing after 20.5 minutes of endovascular cooling decreased to 33.6° C (range 31.9-35.5° C), which is ≥1.1° C lower than in previous cooling studies. There was a 17-minute (95% CI: 4.6-29.8 min) cooling-related delay to reperfusion. In the "per protocol" analysis, median infarct size/left ventricular mass was 16.7% in the hypothermia group versus 23.8% in the control group (absolute reduction 7.1%, relative reduction 30%; p=0.31) and median left ventricular ejection fraction (LVEF) was 42% in the hypothermia group and 40% in the control group (absolute reduction 2.4%, relative reduction 6%; p=0.36). There were no statistically significant differences between the groups, in adverse events or serious adverse events.[49]

5.3 Summary and Clinical Trial Rationale

Previous clinical trials in patients experiencing acute myocardial infarction (AMI) have demonstrated that therapeutic hypothermia is safe, well tolerated and showed reductions in infarct size[19]. Additionally, recent preclinical results (Stanford-ZOLL data) have shown that temperature at reperfusion of 32 °C is superior to 35 °C for reducing infarct size, confirming a dose response. Future clinical trials will require more powerful cooling devices, and more consistency in implementing 18 minutes of cooling before reperfusion across all study sites in order anterior infarctions. It is therefore the objective of the COOL-AMI EU PIVOTAL Trial to evaluate the actual effectiveness of therapeutic hypothermia as a protection strategy.

Further clinical trials are needed to evaluate more powerful cooling devices, along with a refined therapeutic hypothermia protocol (target temperature of 32°C + 18 minutes of cooling prior to PCI). It will also be important to understand whether adequate cooling to 32°C + 18 minutes of cooling prior to PCI can be implemented into existing STEMI treatment protocols with no significant delay in door-to-balloon times. This trial aims to address the need for a powered clinical evaluation assessing the safety and effectiveness of the Proteus IVTM for this refined therapeutic hypothermia protocol as an adjunct therapy for AMI patients undergoing PCI. Among these refinements are: 1) A larger dose of cooling was achieved with the Proteus System (temp at PCI was 33.6°C as opposed to 35°C for COOL MI), 2) Delivery of at least 18 minutes of cooling prior to PCI was possible (mean 20 minutes in the EU Pilot Study), 3) the anti-shivering protocol was refined and worked successfully, and 4) the use of report cards for every case to track : a) anti-shivering protocol impementation, b) infusion of 1 liter of cold saline prior to PCI, c) 18 minutes of cooling prior to PCI, d) door to balloon time less than 90 minutes, e) total ischemic time less than 6 hours, and f) proper administration of dual antiplatelet therapy (DAPT) are all refinements ready to be implemented.

6 CLINICAL TRIAL PLAN

6.1 Trial Objective

The objective of this randomized clinical trial is to evaluate the safety and effectiveness of therapeutic hypothermia, using the ZOLL Proteus IVTM System, as an adjunctive therapy for patients presenting with acute anterior myocardial infarction and undergoing PCI in comparison with patients with acute anterior myocardial infarction and undergoing PCI only.

6.2 Trial Endpoints

6.2.1 Primary Effectiveness Endpoint

Relative reduction of 20% in mean anterior myocardial infarct size (IS), as determined by Cardiac Magnetic Resonance (cMR) imaging at 4-6 days post-infarct in the Test Arm (cooling + PCI) compared to the Control Arm (PCI only). Infarction Size (IS) is defined as % Left Ventricular Mass as measured by Cardiac Magnetic Resonance (cMR) imaging. Infarct Size (IS) will be assessed by Cardiac Magnetic Resonance (cMR) at 4 – 6 days following the index procedure. The trial is considered to have met the primary efficacy endpoint if the Test Arm demonstrates a 20% relative reduction in infarct size compared to the Control Arm.

The ITT analysis set will be used for primary statistical analyses and summaries. The ITT population includes those subjects who have signed an informed consent and have been randomized to the Test Arm or the Control Arm of the trial. ITT subjects will be evaluated according to the group to which they were randomized.

The PP analysis set will also be evaluated. The PP population includes those subjects who met inclusion and exclusion criteria, were randomized to either the Test or Control arm, received the treatment to which they were randomized, and complied substantially with the treatment timeline and steps of this protocol without major protocol violations.

6.2.2 Primary Safety Endpoint

Per-patient rate of composite Major Adverse Cardiac Events (MACE) subjects, defined as Cardiac Death (CD), All Myocardial Infarction (All MI) and Clinically-Indicated Target Lesion Revascularization (CI-TLR) at 30 day follow-up; non-inferiority to the control.

6.2.3 Additional Assessments: Demographics and Other Parameters

Subject demographics and various baseline characteristics will also be collected. Additional clinical data collected and evaluated will include the number of patients who can successfully be enrolled and randomized, the timing of subject presentation to hospital, the timing of therapeutic and adjunctive interventions, the timing of reaching the target temperature zone, temperature at PCI, subsequent maintenance of hypothermia and

temperature data from the IVTM System. Observations will be evaluated relating to the use of the ZOLL Proteus IVTM System and how it performs in relation to the induction of therapeutic cooling and follow-up cMR imaging. New York Health Association[24] (NYHA) Functional Class and Kansas City Cardiomyopathy Questionnaire[25] (KCCQ) will be evaluated at12 month follow-up..

6.3 Trial Design

This clinical trial is a multicenter, prospective, interventional, randomized-controlled trial. Randomization will be in a 1:1 ratio, Test Arm (PCI + Cooling) or Control Arm (PCI alone) in up to a total of 500 patients (250 subjects in each arm), at up to 70 clinical sites.

To enhance each site's ability to successfully integrate steps of the protocol and for training purposes prior to randomization, each site may enroll up to 4 Roll-In subjects in a non-randomized fashion. Roll-In subjects will be treated and followed as subjects in the Test Arm of the protocol (PCI + Cooling). Up to a total of 280 Roll-In subjects (up to 4 per site) may be enrolled. Due to limited cMR data in patients with inferior MI who received an adequate dose of cooling prior to revascularization, Inferior MI subjects will be allowed to be included as Roll-Ins to further evaluate inferior MI infarct size by cMR imaging. Evaluation will be done of cMR imaging at 4-6 days. ZOLL will provide financial support for staff if cMRs are performed on weekends.

6.4 Patient Population

Subjects will include those who present to the Emergency Department (ED) and / or Cath lab, who meet the trial eligibility requirements and who can provide informed consent for cooling treatment. Subjects considered for enrollment in this trial will include adult patients presenting with an acute anterior myocardial infarction. To qualify, patients must have symptoms consistent with AMI (i.e., chest pain, arm pain, etc.) unresponsive to nitroglycerin, qualifying ST-segment elevation of ≥ 0.2 mV in two or more anterior contiguous precordial leads(V1-V4), with symptom onset greater than 30 minutes, but less than 4.5 hours prior to presentation at hospital, and be eligible for PCI. This ensures that the overall ischemic time from symptom onset to time of wire crossing is less than 6 hours.

Subjects randomized to the Test Arm, as well as all Roll-In subjects, will receive intravascular cooling with the Proteus IVTM device. While undergoing temperature management, the Anti-shivering Protocol must be followed (see **Attachment II**).

6.5 Selection Criteria

Patients shall be screened to the following inclusion and exclusion criteria. Patients are qualified for participation only if all Inclusion Criteria have been met and all Exclusion Criteria have been confirmed not present.

6.6 Inclusion Criteria

All Inclusion Criteria must be answered YES for subject to satisfy Inclusion Criteria:

1. The patient is ≥ 18 years of age.
2. The patient has symptoms consistent with AMI (i.e. chest pain, arm pain, etc.) and unresponsive to nitroglycerin, with symptoms beginning greater than 30 minutes but less than 4.5 hours prior to presentation at hospital.
3. Qualifying Infarct Location:
    a. **Roll-In subjects**: Evidence of Acute Anterior or Inferior MI with ST-segment elevation of ≥ 0.2 mV in two or more anterior or inferior contiguous precordial leads (V1-V4).
    b. **Randomized subjects**: Evidence of Acute Anterior MI only with ST-segment elevation of ≥ 0.2 mV in two or more anterior contiguous precordial leads (v1-V4).
4. The patient is eligible for PCI.
5. The patient is willing to provide written informed consent to participate in this clinical trial.

6.7 Exclusion Criteria

All Exclusion Criteria must be answered NO for subject to satisfy Exclusion Criteria:

1. The patient has had a previous Myocardial Infarction.
2. The patient is experiencing cardiogenic shock. systolic blood pressure [SBP] <100 mmHg, HR> 100 bpm and arterial oxygen saturation (pulse oximetry) ≤92% without additional oxygen.
3. The patient is presenting with resuscitated Cardiac Arrest, Atrial Fibrillation, or Killip risk stratification class II through IV.
4. The patient has an aortic dissection or requires an immediate surgical or procedural intervention other than PCI.
5. The patient has known history of Congestive Heart Failure (CHF), Hepatic Failure, end-stage kidney disease or severe Renal Failure (clearance < 30ml/min/1.73m²).
6. The patient is febrile (temperature > 37.5 °C) or has experienced an Infection with Fever in the last 5 days.
7. The patient has a known previous CABG.
8. The patient has a known recent Stroke within 90 days of admission.
9. Cardio-Pulmonary Decompensation that has occurred en route to the hospital or, in the opinion of the physician, that is imminent or likely to occur following presentation to the clinical site.
10. Contraindications to hypothermia, such as patients with known Hematologic Dyscrasias which affect thrombosis (e.g., cryoglobulinemia, sickle cell disease, serum

cold agglutinins) or Vasospastic Disorders (such as Raynaud's or thromboangitis obliterans).

11. Any contraindication to cardiac MRI, or any implants in the upper body which may cause artifacts on cardiac MRI imaging.
12. The patient has a known hypersensitivity or contraindication to aspirin, heparin, or sensitivity to contrast media, which cannot be adequately pre-medicated.
13. The patient has a known history of Bleeding Diathesis, Coagulopathy, Cryoglobulinemia, Sickle Cell Anemia, or will refuse blood transfusions.
14. The patient has a height of <1.5 meters (4 feet 11 inches).
15. The patient has a known hypersensitivity or contraindication to buspirone hydrochloride or Pethidine (Meperidine) and/or has been treated with a monoamine oxidase inhibitor in the past 14 days.
16. Patient has a known history of severe hepatic or renal impairment, untreated hypothyroidism, Addison's disease, benign prostatic hypertrophy, or urethral stricture that in the opinion of the physician would be incompatible with Pethidine administration.
17. The patient has an Inferior Vena Cava filter in place (IVC).
18. The patient has a pre-MI life expectancy of <1 year due to underlying medical conditions or pre-existing co-morbidities.
19. The patient has a known, unresolved history of drug use or alcohol dependency, or lacks the ability to comprehend or follow instructions.
20. The patient is currently enrolled in another investigational drug or device trial.
21. The patient is apprehensive about or unwilling to undergo the required MRI imaging at follow-up, has a documented or suspected diagnosis of claustrophobia, or has Gadolinium allergy, or is in permanent Atrial Fibrillation.
22. The patient has received thrombolytic therapy en route to the hospital
23. The patient shows clinical evidence of spontaneous reperfusion as observed symptomatically and/or from baseline ECG findings (partial or complete ST resolution in ECG prior to informed consent and randomization).
24. The patient is a vulnerable subject, for instance, a person in detention (i.e., prisoner or ward of the state).
25. The patient is a female who is known to be pregnant.

6.8 Clinical Trial Procedures

6.8.1 Patient Screening

Patients presenting at participating centers with clinical signs and symptoms of AMI will be expeditiously triaged and offered the opportunity to participate in this clinical trial without regard to age, gender or ethnicity. To ensure that patients are approached for potential trial participation without bias, patient screening information will be maintained on a patient screening log at each site. This log will track patients that were enrolled in

the trial as well as patients who were excluded from participation and the reason(s) for their exclusion. The use of a patient screening log assures that all eligible subjects are given an opportunity to participate or decline participation in the trial.

The subject's eligibility for treatment with the Proteus IVTM System will be evaluated based on the medical and anatomical criteria outlined above in the inclusion/exclusion criteria section. The Investigator will explain the elements of this clinical trial, including the risks, potential benefits and required interventional and follow-up procedures, to each subject prior to obtaining informed consent.

If a subject is found to be ineligible during baseline screening and routine diagnostic tests, the subject shall be considered a screen failure and will be documented on the patient screening log. Roll-In subjects are considered enrolled in the trial when all inclusion and exclusion criteria have been satisfied, and informed consent has been signed. Randomized subjects are considered enrolled in the trial when all inclusion and exclusion criteria have been satisfied, informed consent has been signed, and the patient is randomized to either Test or Control Arm of the trial.

6.8.2 Informed Consent

The reviewing Medical Ethics Committee (MEC) must review and approve an Informed Consent Form (ICF) specific to this study. The Sponsor will provide each study center with an example ICF. The study center, to meet specific requirements, may modify this example ICF; however, the ICF to be used for subject consent under this protocol must contain all of the elements required by the study Sponsor and the governing regulatory requirements for informed consent (21 CFR Part 50). Therefore, each investigational site will provide the Sponsor with a copy of the MEC approved ICF - as well as any amendments - for the duration of the study.

Informed consent will be required from each subject. The MEC approved Informed Consent document must be signed by the patient or by the legal authorized representative (LAR) prior to any related procedures (or according to the MEC's approved guidelines), including the collection of data on case report forms (CRFs). Only subjects that have the appropriate informed consent form will be included in the trial.

The informed consent process (including time and date of discussion), should be documented in the subject's medical record and signed/dated by the individual (investigator or designee) who recorded it. The original signed consent form must be filed in the subject's medical record and a copy of the signed informed consent documentation given to the subject.

All subjects must sign, date and note the time on the Institutional Medical Ethics Committee (MEC) approved informed consent prior to any clinical trial/investigation-

specific procedures. Obtaining the consent with the documented date and time, and the provision of a copy to the subject will be documented in the subject's medical record.

Due to the emergent nature of treating acute myocardial infarction, patients who have been enrolled in the study may receive a subsequent consent which provides more detailed information about their participation in the trial (based on MEC requirements), which may be reviewed and signed after the acute phase of their treatment has been completed. If the patient decides they no longer want to be included in the study, they will be withdrawn and their data will be included in the analysis up until the time of withdrawal.

If in the course of the pre-study evaluations prior to consent, the patient is found not to be eligible for inclusion in the study, the patient should be notified and the reason for ineligibility documented on the appropriate Screening Log.

All information pertinent to this clinical investigation (including at a minimum the description and purpose of the study, potential benefits, potential risks and inconveniences, active procedures, confidentiality, compensation, circumstances for termination and site contact persons) will be provided to the subjects in writing and in their native, non-technical, language by Investigator or designee, who has been trained on the protocol.

If new information becomes available that can significantly affect a subject's future health and medical care, this information shall be provided to the affected subject(s) in written form. If relevant, all affected subjects shall be asked to confirm their continuing informed consent in writing.

6.8.3 Roll-In Enrollment

Prior to randomizing patients, each participating center (except German centers) may enroll up to 4 patients Roll-In subjects in a non-randomized fashion. Roll-In subjects are treated and followed as patients in the Test Arm (PCI + Cooling) for training purposes. The justification for the number Roll-In patients in this study is based on ZOLL's previous clinical trial experience in relationship to a site's ability to successfully incorporate the cooling protocol including consent, anti-shivering regimen and an adequate dose of cooling without significantly delaying door-to-balloon time. Successful implementation takes teamwork and often several cases to assure the cooling protocol is adhered to with consistent accuracy.

In light of the fact that previous clinical trials (e.g., COOL-MI[19], ICE-IT[23] and CHILL-MI[37]) have failed to provide an adequate dose of cooling prior to reperfusion, ZOLL has implemented a tool called a "Report Card". This Report Card notes the site's success in achieving critical aspects of the protocol, called "Standards", and is provided to the site after every patient is enrolled into the trial. The objective of the Report Card is to report back to the site their success in implementing a set of standards according to the protocol,

and to encourage continuous improvement following each enrollment. The Standards, as noted on the Report Card, include but are not limited to accuracy of antishivering regimen administration and 18 minutes of cooling delivered prior to the wire crossing the lesion. The Standard of 18 minutes of cooling has been demonstrated in previous ZOLL trials to be the amount of time required to deliver an optimal dose of cooling so the patient's core body temperature is as close to target temperature as possible prior to reperfusion without significantly delaying door-to-balloon time.

Consistent achievement of each standard allows sites to move from Roll-In to randomization and enables consistency in execution of the protocol. Feedback will be provided to the site after each enrollment to assure the standards have been met and an adequate dose of cooling has been achieved. Use of the Report Card and Standards is intended to assist sites in ascending their learning curve as rapidly as possible. All centers will transition from Roll-In to Randomization as soon as possible once they have demonstrated their ability to enroll patients while consistently meeting the standards, thereby minimizing the number of Roll-In patients but ensuring accurate, precise adherence to the investigational protocol. Based on the site's performance with the Roll-In patients, as determined by the Sponsor, the site will be notified of authorization to randomize patients in the trial.

Additionally, Roll-In patients will undergo cMR as part of the cMR training process at each site. This will allow the site to train and qualify acquisition of cMR images per cMR protocol and ensure high quality and consistent imaging throughout the study across sites. Roll-In patients will not be included in the primary endpoint analysis; however, they will be included in the safety endpoint analysis. All performed activities on Roll-In subjects will be recorded as if performed in the Test Arm of the trial and hence documented in the Case Report Forms (CRF) for training and evaluation.

Roll-In subjects will be considered to be enrolled when all inclusion and exclusion criteria have been met and the informed consent form has been signed.

6.8.4 Approval to Randomize in the Trial

It will be at the discretion of the sponsor to advance a site to Randomization. Based on the site's performance with the Roll-In patients, as determined by the Sponsor, the site will be notified of authorization to randomize patients in the trial.

6.8.5 Randomization

In the randomization phase, patients who meet eligibility criteria for participation will be randomly assigned to either the Test Arm (PCI + Cooling) or Control Arm (PCI alone) in a 1:1 ratio.

Randomization will be applied using an internet based Interactive Web Response Systems (IWRS). In the trial, randomization will be done using random permuted blocks (based on

procedure outlined in Pocock SJ. Clinical Trials: A Practical Approach. Wiley, Chichester, 1983), stratified by site, with 1:1 allocation ratio using a randomization list. At randomization, inclusion and exclusion criteria will be verified, and confirmation of informed consent signature will be done.

Subjects will be considered to be enrolled in the Test Arm and Control Arms of the trial when all inclusion and exclusion criteria have been met, the informed consent form has been signed, and randomization assignment has been completed.

6.8.6 Acute Care and Emergency Room Triage

Prior to the initiation of this trial at each participating institution, training will be conducted by the Sponsor targeted toward the integrated care of each trial subject and emphasizing the shared responsibility between the Departments of Emergency Medicine and Interventional Cardiology, where applicable at each center, with the goal of rapid screening, enrollment and treatment of appropriate patients.

Each center will clearly delineate departmental responsibilities for the following:

- Assessment of patient clinical features, signs and symptoms
- Administration of Informed Consent
- Review of Inclusion/Exclusion Criteria
- Assurance that diagnostic procedures mandated by the protocol are completed prior to randomization into this trial and are appropriately documented
- Patient Randomization
- Administration of pre-treatment medication(s)
- Administration of Anti-shivering medications to subjects randomized to the Test Arm of the trial
- Consensus on location in hospital where cooling using the Proteus IVTM System will be initiated
- Set-up of Proteus IVTM System, including insertion of the Proteus Catheter into the femoral vein induction of cooling, initiation of re-warming, Proteus IVTM System shutdown and catheter extraction for Test Subjects.

6.8.7 Standardized Care Prior to the Cooling Procedure

It is anticipated that subjects may receive one or more of the following therapies as part of current clinical practice in the treatment of acute myocardial infarction:

- Intravenous fluids and electrolytes
- Oxygen
- Antiplatelets and/or antithrombotics
- Vasoactive agents and diuretics

Clinicians will be encouraged to manage the subject in a standardized manner with respect to oxygenation, anti-coagulation and/or anti-platelet medications.

6.8.8 Documentation Procedures

Trial procedures and treatment data will be documented on standardized Case Report Forms (CRFs) which may be on paper or via an electronic data capture system (EDC). The completion of the CRFs may be delegated to a member of the study team (e.g., the study coordinator) as long as that person is listed on the Delegation of Authority Log. However, the Principal Investigator retains responsibility for the accuracy and integrity of the data entered on the CRF. The CRF will be monitored for accuracy and completeness per the source documents (medical records, charts, interventional systems, worksheets as applicable, etc.) at each clinical center. Temperature data from the Proteus IVTM System will be downloaded and sent to Sponsor. A flow diagram for the Test Arm is represented in **Figure 10**.

It is anticipated that technology and/or techniques such as edit checks and double entry of data may be utilized to minimize the rate of error. Additionally, ZOLL or its assignees may ask for data clarification or re-check of data for accuracy. Monitoring visits and CRF completion logs will be used to track data entry in accordance with trial logistics and expectations.

Any source documentation (procedure reports, imaging studies, lab reports, death certificates, etc.) that is sent to the Sponsor should have all patient identifiers removed and replaced with the subject's trial ID, and processes ensuring patient privacy and clinical data confidentiality will be followed in accordance with local regulations and applicable laws.

6.8.9 Study Flow and Procedures

Figure 8 Screening and Enrollment Flow

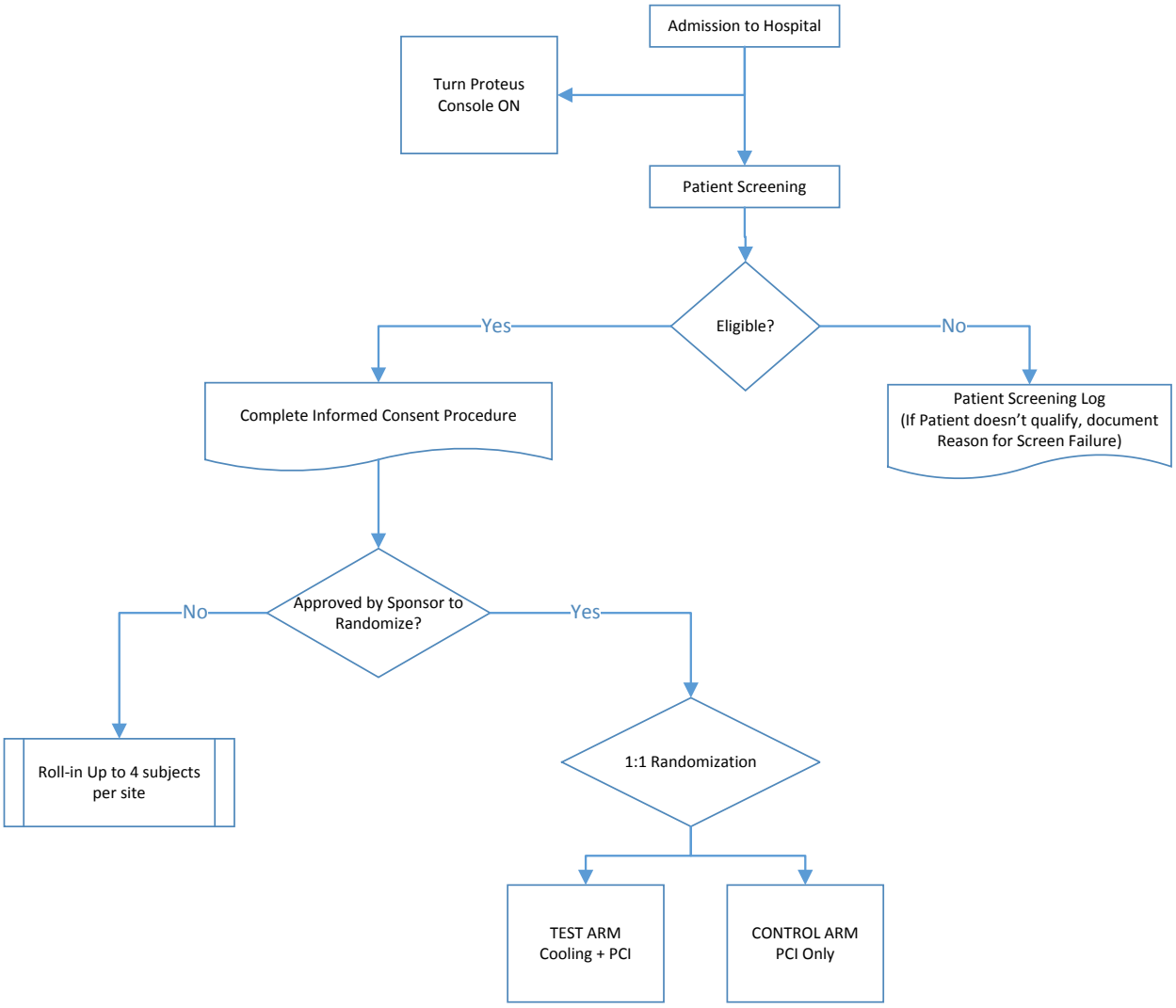


Figure 9 Control Arm Flow

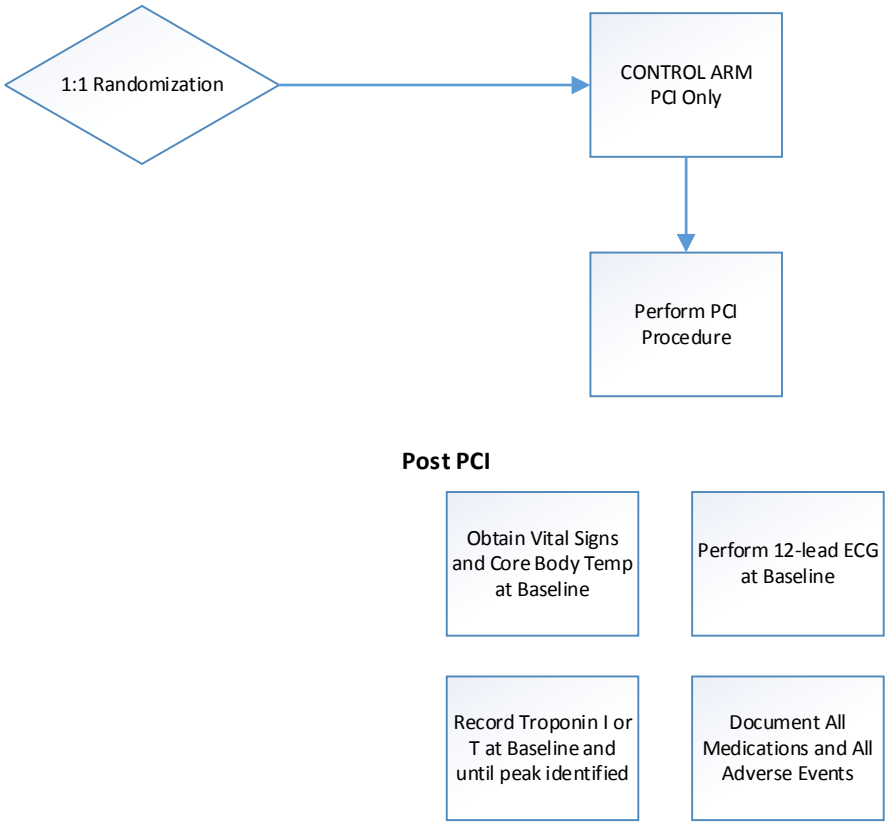


Figure 10 Test Arm Flow

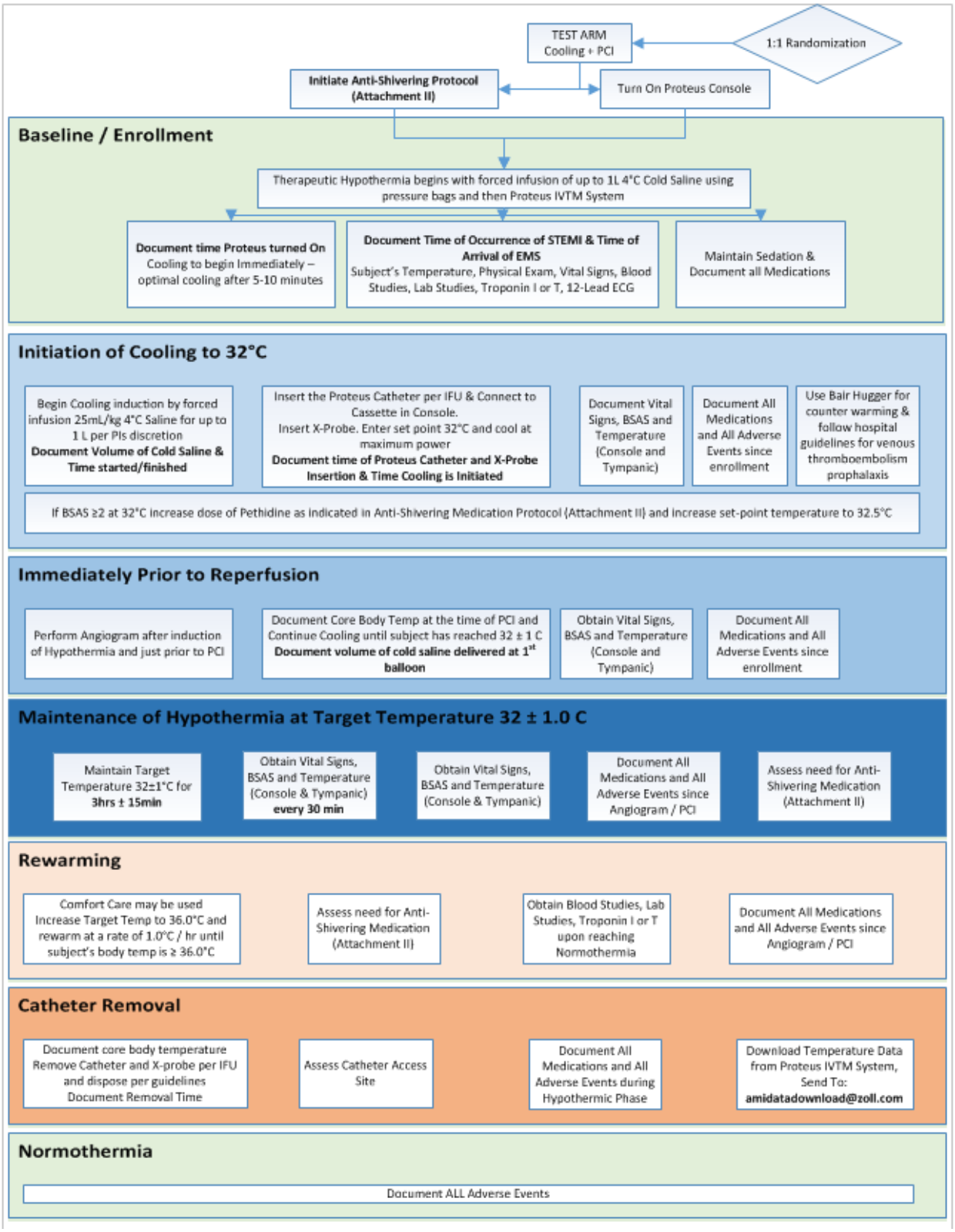
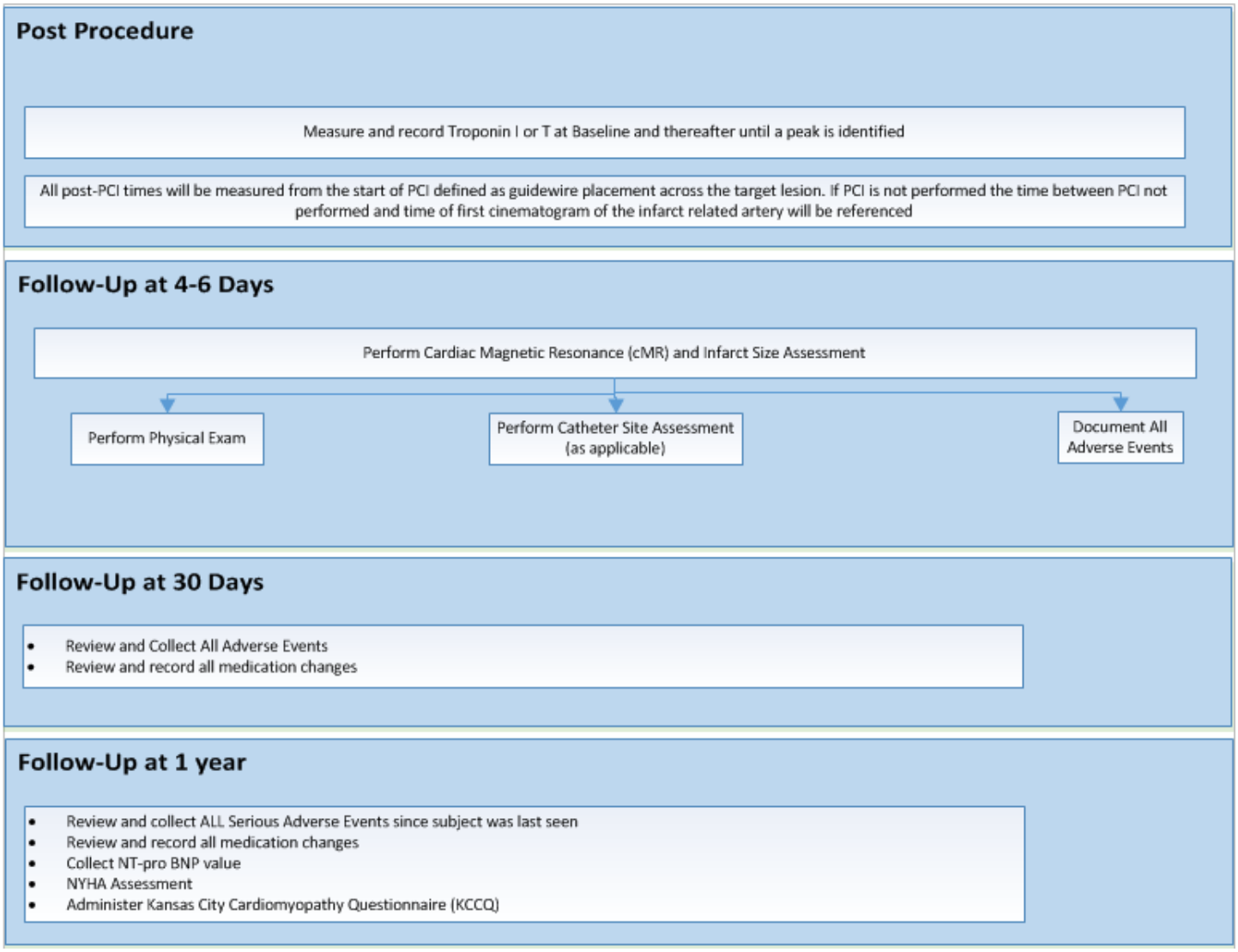


Figure 11 All Patient Procedures



6.8.10 Pre-Cooling Assessment Procedures

All required procedures and data collection from the time of subject screening (presentation at hospital) through the pre-cooling assessment period are given below in **Table 11.**

Table 11: Baseline / Screening and Enrollment Procedures/Evaluations and Data Collection for the Test & Control Arms of the Trial

Procedures/ Evaluations	Data
Trial Eligibility	At admission to the hospital
Informed Consent	Obtain Consent from patient before any trial-related procedure is initiated.
Trial Enrollment	- Follow randomization process to assign patient to Roll-In, Test or Control Arms of the trial - Complete Enrollment Form, document randomization, and FAX or email to ZOLL at +1 800.243.0360 or ami-eu@zoll.com to enter in the eCRF
Temperature	Document subject's temperature using a tympanic thermometer
Vital Signs	Blood Pressure, Heart Rate, Respiratory Rate, BSAS measurement
Physical Exam	Complete Physical Examination
Blood Studies	RBC's, WBC's, Hct, Hgb, Platelets
Lab Studies	BUN, Creatinine, sodium, potassium, calcium, phosphate, magnesium, chloride, lactic acid, glucose, amylase, lipase
Cardiac Markers	Baseline and peak Troponin I or Troponin T including upper limit of normal
ECG	12-lead baseline
Medications	Document as indicated on Case Report Form since STEMI onset
Adverse Events	Collect all adverse events as soon as patients are enrolled in the trial

6.8.11 Initiation, Maintenance, and Reversal of Cooling with Proteus IVTM System Procedures / Evaluations and Data Collection for Subjects Enrolled in the Test Arm

6.8.12 Test Arm: Temperature Management Protocol and Data Collection Time Points

Treatment with therapeutic hypothermia will begin with a forced infusion of up to 1 L of cold saline (4°C) (according to the guideline) using pressure bags, and at the time of administration of the anti-shivering medication according to the anti-shivering guidelines, then will continue with the Proteus IVTM System as soon as possible. Cooling will be initiated with the Proteus IVTM System set at a temperature of 32.0 °C, and the subject's temperature will be measured with the Proteus IVTM System immediately before PCI has occurred (measured as time the wire crosses the target lesion). Cooling will be maintained for 3 hours and will be followed with active rewarming to attain normothermia 36.0 °C (96.8°F).

Cooling induction, maintenance of hypothermia, and rewarming are described in the following **Table 12.** The data collection schedule for Test Arm subjects is summarized in **Section 6.8.13**.

Table 12: Initiation, Maintenance, and Reversal of Cooling with Proteus IVTM System Procedures / Evaluations and Data Collection for Subjects Enrolled in the Test Arm

Phase	Task
Immediately Upon Arrival to the Hospital	1. **Turn the Proteus Console on** (in preparation for cooling with the device) 2. **Document time of occurrence of STEMI and ECG** 3. **Document time of arrival of Emergency Medical Service EMS (Paramedics)**

Phase	Task
Baseline / Enrollment	4. Immediately after informed consent is obtained and patient is randomized to the Test Arm of the trial, **initiate anti-shivering medication protocol using Guidelines outlined in Attachment II**. 5. Begin cooling induction by forced infusion with 25mL/kg of 4°C cold saline using pressure bags up to 1 L of cold saline (4°C) (according to the guideline) at the physician's discretion. Use Bair Hugger™ (CE marked device) for patient comfort. 6. **Document the time the Proteus console is turned on.** The device will begin cooling the patient immediately; however, optimal cooling is achieved in 5-10 minutes after it is turned on. 7. Perform Physical Examination and obtain Vital Signs. 8. Obtain Blood and Lab studies. 9. Obtain Troponin I or Troponin T . 10. Obtain 12-lead baseline ECG. 11. Document all medication use since STEMI onset. 12. Measure body temperature using an independent tympanic thermometer. The independent measurement is to be used in addition to the core body temperature collected by the Proteus Temperature Probe (X-Probe). 13. Document all Adverse Events.

Phase	Task
Initiation of Cooling	14. Document the volume of cold saline, the time the cold saline infusion is started and the time the cold saline infusion is finished. 15. Following the ZOLL Proteus IVTM System Instructions for Use (IFU), insert the Proteus Catheter into the Inferior Vena Cava via either femoral vein. The Proteus Catheter is then connected to the Cassette that has been inserted into the Proteus Console. 16. Following insertion of the Proteus Catheter, insert the Proteus Temperature Probe (X-Probe). Access site selection may vary by both operator preference and anatomical considerations; however, the function of the system is not dependent on which femoral vein is chosen. 17. Once the Proteus System Catheter & Proteus Temperature Probe (X-Probe) have been inserted, enter set point temperature to 32.0°C on the Proteus Console and perform cooling at maximum power as soon as the console is ready to cool. **18. Document the time of Proteus Catheter & X-Probe (temperature probe) insertion.** **19. Document the time cooling is initiated with the Proteus IVTM System.** 20. Document vital signs (BP, HR, RR), and temperature measurements (Tympanic and Proteus Console measurements). 21. Document all medication use. 22. Document all adverse events since the time of enrollment. 23. Use Bair Hugger™ warming blankets for counter-warming. If choosing to use low dose anticoagulation during the cooling phase, follow hospital's guidelines for venous thromboembolism prophylaxis.

Phase	Task
Immediately Prior to Reperfusion	24. If clinically relevant shivering (Bedside Shivering Assessment Scale (BSAS) of 2 or greater) occurs at 32° (see **Anti-Shivering Guidelines, Attachment II, and BSAS Attachment III),** increase the dose of Pethidine (Meperdine) as indicated in shivering protocol and increase set point temperature on the Proteus IVTM System to 32.5°C. If clinically relevant shivering continues (BSAS ≥2), once again increase dose of Pethidine as indicated in Anti-Shivering Protocol and increase set point temperature on the Proteus IVTM System to 33°C. Continue this process until a temperature is reached where there is no shivering. Follow sedation procedures using **Anti-Shivering Guidelines, Attachment II, and the BSAS Attachment III.** 25. Perform * angiogram after the induction of hypothermia has been initiated and just prior to PCI. **26. Obtain vital signs (BP, HR, RR), BSAS and temperature measurements (Tympanic and Proteus Console measurements) just prior to PCI.** 27. Document all medication use since the initiation of cooling. 28. Document all adverse events since the initiation of cooling. **CAUTION: Anticipate changes in electrolytes and laboratories values secondary to hypothermia.** 29. Document core body temperature at the time of PCI. 30. If subject has not reached 32.0 ± 1.0°C (or temperature where shivering does not occur, as indicated above) at the time of PCI, continue cooling induction until target temperature has been reached. **31. Document the time wire crossed the target lesion.**

Phase	Task
Maintenance of Hypothermia Target Temperature 32 ±1°C	32. Maintain the patient at the set target temperature of 32.0 (or temperature where shivering does not occur, as indicated above) for 3 hours ± 15 minutes from the initiation of cooling with the Proteus System. **33. Obtain vital signs (BP, HR, RR), BSAS and temperature measurements (Tympanic and Proteus Console measurements) every 30 minutes during the 3 hours of cooling.** 34. Document all medication use since the angiogram/ PCI procedure. 35. Document all adverse events since the angiogram/ PCI procedure. 36. If clinically relevant shivering [Bedside Shivering Assessment Scale (BSAS) of 2 or greater] occurs at 32.0°C (See **Anti-Shivering Guidelines, Attachment II, and BSAS, Attachment III),** increase dose of Pethidine (Meperidine) as indicated in shivering protocol and increase temperature on the Proteus IVTM System console to 32.5°C. 37. If clinically relevant shivering continues (BSAS ≥ 2), once again increase dose of Pethidine as indicated in shivering protocol and increase temperature on the Proteus IVTM System to 33°C. Continue this process until a temperature is reached where there is no shivering. Follow sedation procedures using Anti-Shivering Guidelines outlined in **Attachment II** and BSAS assessment in **Attachment III.**

Phase	Task
Rewarming	38. After 3 hours of cooling with the Proteus IVTM System, begin active rewarming to normothermia. Palliative care such as blankets, Bair Hugger patient warming systems, and warm liquids may be used. 39. Using the Proteus System Console, press **STOP** and Increase target temperature to 36.0°C using the arrow touch buttons and then press **Continue**. 40. Set rewarming rate to 1.0°C/hr using the arrow touch buttons and press **Continue** to start rewarming. 41. Maintain the Pethidine infusion during rewarming using the Anti-Shivering Protocol outlined in Attachment II. 42. Obtain blood studies, lab studies and record peak Troponin I or Troponin T including upper limit of normal for site. 43. Document all medication use during the rewarming phase. 44. Document all adverse events during the rewarming phase. **CAUTION: Anticipate changes in electrolytes and laboratories secondary to re-warming**

Phase	Task
Catheter Removal	45. Document core body temperature at time of Proteus Catheter removal. 46. Remove Proteus Catheter and X-Probe per IFU and document time of removal. 47. Dispose of the Proteus Catheter, X-Probe and Proteus Cassette per institution's guidelines (single-use). 48. Assess catheter access site for signs of bleeding, access vessel trauma, or hematoma formation. **49. Download temperature data from the Proteus Console after the cooling phase has been completed. Send downloaded data to amidatadownload@zoll.com immediately upon downloading. Device data must be saved according to Section 16.1, Investigator Records.** 50. Document all medication use during the hypothermic phase. 51. Document all adverse events during the hypothermic phase. **DO NOT DISCARD SPLITTER CABLE (MULTI–USE TEMPERATURE CABLE)**
Normothermia	52. Document all adverse events until patient is discharged from the hospital.
Post-Procedure	53. If required, provide additional Informed Consent document to patients who were consented with the short consent form (if required by MEC or country-specific regulations).

NOTE: All post-PCI times will be measured from the start of PCI, defined as time the wire crosses the target lesion. In the event that PCI is not performed, the time of the first cineangiogram of the infarct related artery will be referenced. If PCI is staged for the non-culprit lesion, then the PCI will be performed after the 4-6 day cMR

***Angiograms are to be uploaded for all heart failure patients.**

6.8.13 Trial Schedule for Test Arm Subjects

Procedure/ Interval	Baseline / Enrollment	Initiation of Cooling	Immediately prior to reperfusion (PCI)	Maintenance of Target Temp 32 ±1°C	Rewarming to 36°C	Catheter Removal	Discharge	Follow-Up @ 4-6 Days	Follow-Up @ 30 Days (±7 days)	Follow-Up @ 12 months (±14 days)	Unscheduled Visit
Trial Eligibility & Informed Consent	**upon arrival to hospital**										
Physical Exam	**X**						**X**				
Anti-Shivering Protocol	**X**			**X**[α]							
Cold Saline Infusion		**X**									
Catheter Insertion Time		**X**									
Catheter Removal Time						**X**					
Temperature Documented	**X**	**X**	**X**	**every 30 min during 3 hr cooling**	**every 60 min during rewarming**						
Temperature Data Download						**X**					
Vital Signs	**X**	**X**	**X**	**every 30 min**	every 60 minutes						
Blood Studies RBC's, WBC's, Hct, Hgb, Platelets	**X**				**X upon reaching normothermia**						
NT-pro BNP										X	
Lab Studies BUN, Creatinine, Na, K, Ca, Mg, Cl, P, lactic acid, glucose, amylase, lipase	**X**				**upon reaching normothermia**						
Any Medication Use	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Troponin I or T(including ULN) during hospitalization	**X**	**Perform Troponin unitl peak value identified.**									
12 lead ECG	**X**										
Adverse Events		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**SAE only**	**X**[**]
Catheter Access Site Assessment						**X**	**X**	**X**			
Cardiac Magnetic Resonance (cMR) imaging								**X**			
NYHA Assessment										**X**	
KCCQ										**X**	

[α]For persistent clinically relevant shivering (BSAS ≥ 2), increase dose of Pethidine as indicated in shivering protocol and increase temperature on Proteus IVTM System console by 0.5°C. Continue this process until a temperature is reached where there is no shivering. Follow sedation procedure using Anti-Shivering Guidelines outlined in Attachment II and BSAS assessment in Attachment III Include BSAS measurement and temperatures from independent method.

[**]**If unscheduled visit occurred within 30 days follow-up, report all AEs. However, if unscheduled visit occurred after 30 days follow-up within 12 months, report only SAEs.**

6.8.14 Trial Schedule for Control Arm Subjects

Procedure/ Interval	Baseline / Enrollment	Immediately prior to reperfusion (PCI)Post-PCI	Discharge*	Follow-Up @ 4-6 Days	Follow-Up @ 30 Days (±7 days)	Follow-Up @ 12 months (±14 days)	Unscheduled Visit
Trial Eligibility & Informed Consent	**upon arrival to hospital**						
Physical Exam	**X**		**X**				
Catheter Insertion Time	**X**						
Catheter Removal Time							
Temperature Documented	**X**						
Vital Signs	**X**						
Blood Studies RBC's, WBC's, Hct, Hgb, Platelets	**X**						
NT-pro BNP						X	
Lab Studies BUN, Creatinine, Na, K, Ca, Mg, Cl, P, lactic acid, glucose, amylase, lipase	**X**						
Any Medication Use	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Troponin I or T(including ULN)	**X**	**Perform Troponine until peak value identified**					
12 lead ECG	**X**						
Adverse Events		**X**	**X**	**X**	**X**	**SAE only**	
Cardiac Magnetic Resonance (cMR)				**X**			
NYHA Assessment						**X**	
KCCQ						**X**	

If unscheduled visit occurred within 30 days follow-up, report all AEs. However, if unscheduled visit occurred after 30 days follow-up within 12 months, report only SAEs.

6.8.15 Control Arm Protocol and Data Collection Time Points

The data collection schedule for Control Arm subjects is summarized in **Section 6.8.14**. For patients randomized to the Control Arm, i.e., PCI alone, the following procedures will be performed:

i. Document time of occurrence of the STEMI & ECG results

ii. Document time of arrival of Emergency Medical Service EMS (Paramedics) & time of arrival at hospital

iii. Collect all adverse events as soon as patients are enrolled in the trial

iv. Perform Blood Studies, Labs, and record Baseline and PeakTroponin I or T

v. Perform PCI. If PCI is staged for the non-culprit lesion, then the PCI will be performed after the 4-6 day cMR

vi. Monitor and record the patient's vital signs, temperature, blood pressure, heart rate and respiratory rate, at baseline

vii. Obtain 12-lead baseline ECG

viii. Monitor and record all pharmacological agents

ix. Measure and record baseline Troponin I or T including upper limit of normal, and when a peak is identified.

x. Monitor and record all adverse events for the duration of 30 days follow-up and serious adverse events for the duration of 12 month follow-up.

xi. Complete physical exam prior to discharge.

6.8.16 Follow-up at 4-6 days and at 30 days following the PCI Procedure

Subjects enrolled in the Test and Control Arms, and Roll-In patients, will undergo Cardiac Magnetic Resonance (cMR) to assess infarct size at 4-6 days In addition, the following procedures are to be performed at 4 - 6 days and at 30 days after the index procedure (PCI) for all patients:

i. Monitor and record all adverse events for the duration of 30 days follow-up.
ii. Review and record all medication changes since index.

6.8.17 Follow-up at 12 months following PCI

Following completion of the 30 day follow-up and, all subjects will be followed through 12 months for the incidence of Serious Adverse Events, Death and Heart Failure (as assessed by NYHA and Kansas City Cardiomyopathy Questionnaire (KCCQ)

i. Monitor and record all serious adverse events for the duration of 12 month follow-up.
ii. Collect NT-pro BNP value to assess clinical prognosis of Heart Failure.
iii. Review and record all medication changes
iv. Perform blinded NYHA Assessmentand administer Kansas City Cardiomyopathy Questionnaire (KCCQ).

6.8.18 Use of other Cooling Methods

For the purposes of this trial, no other cooling methods may be used.

6.8.19 Transferring Subject during Cooling

Although interruption during the induction phase of hypothermia is not recommended, if subject transfer is required during any phase of the cooling, follow relevant instructions in the device Instructions for Use.

For additional detail, refer to the Proteus IVTM System Instructions for Use**.** The console screen also provides prompts for entry of user-defined parameters and system start-up.

6.8.20 Patient Withdrawal and Discontinuation

The term “patient withdrawal” refers to the patient deciding to terminate their participation in the trial. The term “discontinuation” refers to the physician deciding that the patient will not continue trial participation as defined below.

A subject has the right to withdraw from the trial at any time and for any reason without prejudice to his or her future medical care by the physician or the institution. Trial withdrawal by a subject specifically means withdrawal of consent from further participation in the trial. Subjects who withdraw consent after enrollment will be evaluated to the time of withdrawal, and withdrawal of consent precludes any further trial related treatment or data collection. If possible, a complete, final physical examination should be performed on all subjects who withdraw from the trial. At a minimum, every effort should be made to document subject outcome at the time of trial withdrawal.

A subject may withdraw from the clinical investigation for the following reason:

- Subjects may choose to withdraw from the clinical investigation under the terms of the Declaration of Helsinki and their consent documentation without having to give a reason;

A subject may be discontinued from the clinical investigation for the following reasons:

- Any unanticipated adverse reaction which is, in the opinion of the Investigator, related to the treatment and will endanger the well-being of the patient if treatment is continued;
- Development of any illness(es), infection or condition(s) that might interfere with the Clinical Investigational Plan;
- Non-compliance with the clinical investigation procedures deemed by the Investigator to be sufficient to cause discontinuation;
- Any problem deemed by the Investigator to be sufficient to cause discontinuation.

- Investigator will treat all subjects discontinued from the investigation due to an unanticipated adverse reaction, directly related to the investigation, until the reaction resolves.

- Investigator will not replace subjects who have withdrawn from the clinical investigation if they have received the investigational device. If possible, Investigator will perform any procedures or assessments planned for the subject at the time of withdrawal.

All subjects are expected to continue in the trial through the final follow-up assessment or until ZOLL notifies the Investigator in writing that further follow-up is no longer required, except in the event of death or upon the subject's request for early withdrawal from the clinical trial.

6.8.21 Patient Lost to Follow-up

The investigator will attempt to contact a subject at least three times prior to designating them as lost-to-follow-up subjects. The investigator will document the date and type of attempted communication. The investigator will complete and sign the Study Exit Form when a subject is lost to follow-up.

6.8.22 Early Termination of a Clinical Investigation

Both the Sponsor and Investigator reserve the right to terminate the clinical investigation at any time. If necessary, and after review and consultation with the Principal Investigator, the Sponsor will make a final determination on whether to terminate the study.

A clinical investigation or Investigator may be terminated at a clinical center for any of the following reasons, or for reasons not listed that affect patient safety or integrity of the trial:

- Unsatisfactory rate of patient enrollment or compliance to eligibility criteria.
- Repeated noncompliance with the investigational plan.
- Inaccurate, incomplete, and/or untimely submission of data.
- Inadequate accountability of the investigational device.

The sponsor may terminate this trial if there are new, previously unknown adverse events related to device or cooling procedure, deaths, SAEs/AEs exceeding those reported as related to device/cooling procedures in previous trials, and/or if recommended by Data Monitoriubg Committee (DMC)to stop the trial. The sponsor will make the final determination on whether to terminate the study.

The sponsor may terminate the trial for any other unforeseen circumstances. In case of premature termination/suspension, ZOLL will stop the enrollment, inform all investigators at all sites and all regulatory agencies governing the study. ZOLL will perform complete device accountability of all investigational devices and retrieve them from the clinical sites. All study subjects will be followed through the specified follow-up periods. ZOLL will issue a final report of the clinical study.

6.8.23 Amendments and Protocol Deviations

Investigator will not deviate from the CIP without prior written confirmation by Sponsor, or their designee, except as required in a medical emergency. In medical emergencies, Sponsor does not require prior confirmation for protocol deviations, but Investigator will notify Sponsor within 5 days of the incident and will notify the EC according to local requirements. Investigator, or designee, will record deviations with an explanation for the deviation. Investigator will report to Sponsor who will analyze them and assess their significance. Significant deviations from the CIP will be reported to the Competent Authority.

Examples of protocol deviations may include those relating to:

- Eligibility
- Enrollment and randomization
- Informed consent
- Protocol adherence (e.g., tests and assessments done as required in Trial Schedule, etc.)

Routine monitoring will assess Investigator compliance to the protocol.

Investigator must not modify the CIP without the prior and written permission from Sponsor. All modifications to the clinical protocol must be submitted to the Competent Authority (where required) to allow the Competent Authority review and approval.

The Sponsor is responsible for management, processing and approval of any amendment to the Investigational Plan. Should the site consider an amendment necessary, the Sponsor will work with the site to make the appropriate changes. The Sponsor will manage documentation of such changes through the existing document control system. A history of changes and a redline version of the documentation will be maintained per the applicable quality system procedures. The proposed amendment will be submitted to the reviewing MEC and government agency as applicable. Any necessary approvals will be received in writing before the requested change is implemented.

This study will be conducted in compliance with ISO 14155, ICH E6 Consolidated Good Clinical Practice Guidance, 21 CFR 812, 21 CFR Part 50, and any requirements imposed by countries with participating clinical sites. The study will not commence until the necessary government and MEC approvals have been obtained.

6.8.24 Trial Exit

The Trial Exit Form (CRF) should be completed at the time a subject is exited from the trial. A subject will be considered to have exited from the trial for any of the following reasons.

- Subject completes follow-ups required by the investigational plan.
- Subject dies.
- Subject requests to be withdrawn.
- Physician requests that patient be withdrawn to protect the welfare of the patient.
- Patient is lost to follow-up.
- Other (specify)

6.8.25 Subject Confidentiality

Subject confidentiality will be maintained throughout the clinical trial to the extent permitted by law. That is, every attempt will be made to remove patient identifiers from clinical trial documents. For this purpose, a unique subject identification code (site number, subject number and subject initials) will be assigned and used to allow identification of all data reported for each subject. This will also ensure that the information can be traced back to the source data.

Trial data may be made available to third parties, e.g., in the case of an audit performed by regulatory authorities, provided the data are treated confidentially and that the subject's privacy is guaranteed. The identity of a subject will never be disclosed in the event that trial data are published.

Security and Unique usernames and passwords will be utilized by data entry, data verification and other personnel who have database access to insure confidentiality and protection of data.

Trial sites must comply with Health Insurance Portability and Accountability Act (HIPPA) and/or the subject confidentiality provisions and privacy laws of each participating country, local regulations, and institutional requirements, whichever is stricter.

6.8.26 Device Accountability

ZOLL is responsible for the availability and traceability of all investigational products. Documentation is required at each step of the process via a device accountability log. Investigational product will be reconciled on a regular basis.

The investigator also is required to maintain adequate records of the receipt and disposition of all investigational devices. A device accountability log will be provided for this purpose.

All unused product must be returned to ZOLL prior to the close of the trial.

6.8.27 Return of Materials upon Trial Termination

Sponsor will ship investigational devices only to qualified Investigators participating in this clinical investigation. Sponsor will not ship investigational devices to any site until evidence of EC approval has been provided to Sponsor, or designee.
Investigator will control access to investigational devices, and will only use investigational devices in the clinical investigation and according to the CIP.
Sponsor will keep investigational device records to document the physical location of each device. Record(s) will include information documenting devices shipped, devices at investigation sites, devices disposed of, and devices returned.
Investigator, or designee, will keep records documenting the receipt, use, return and disposal of the investigational devices, which will include:

- Date of receipt,
- Identification of each investigational device (serial number or unique code),
- Expiry date, if applicable,
- Date or dates of use,
- Subject identification,
- Date on which the investigational device was returned, or explanted from subject, if applicable, and
- Date of return of unused, expired or malfunctioning investigational devices, if applicable.

After the trial procedures have been completed, all unused devices must be accounted for and returned to ZOLL. Instructions for device return to ZOLL will be reviewed at the site initiation visit.

6.8.28 Trial Closure

Trial closure can occur under the following circumstances:

a. termination of site participation in the trial (i.e., closure that occurs prior to meeting defined endpoints) of the trial
b. upon completion of the trial (i.e., when all patients enrolled have completed the follow-up visits or previously exited the trial, and the CRFs and queries have been completed)

Under any circumstance for closure of the trial at the site, ZOLL and/or its designees will notify the site of this occurrence in writing. Trial closeout visits will be performed once a determination has been made that the trial is closed. All unused trial devices and any unused trial materials and equipment will be collected and returned to ZOLL and/or its designees. The monitors will ensure that the investigator's regulatory files are current and complete and that any outstanding issues from previous visits have been resolved. Other issues that will be reviewed at this visit include: discussing record retention requirements (refer to **Section 14.1**—Investigator Records), device accountability, possibility of site audits, publication policy, and notifying the Medical Ethics Committee and Competent Authorities of trial closure, etc., as applicable.

6.9 Cardiac Magnetic Resonance (cMR) imaging Core Laboratory

Cardiac Magnetic Resonance (cMR) imaging must be collected per the Manual of Operations provided by the sponsor. Images must be submitted to the core laboratory designated by the sponsor for analysis.

7 ADVERSE EVENTS & DEVICE DEFICIENCIES

7.1 Definitions

7.1.1 Adverse Event (AE)

Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.

NOTE 1 This definition includes events related to the investigational medical device or the comparator.
NOTE 2 This definition includes events related to the procedures involved.
NOTE 3 For users or other persons, this definition is restricted to events related to investigational medical devices.

7.1.2 Serious Adverse Event (SAE)

Adverse event that:

a) led to a death, injury or permanent impairment to a body structure or a body function.

b) led to a serious deterioration in health of the subject, that either resulted in:

- a life-threatening illness or injury, or
- a permanent impairment of a body structure or a body function, or
- in-patient hospitalization or prolongation of existing hospitalization, or
- in medical or surgical intervention to prevent life threatening illness

c) led to foetal distress, foetal death or a congenital abnormality or birth defect.

NOTE 1: Planned hospitalization for pre-existing condition, or a procedure required by the Clinical Investigation Plan, without a serious deterioration in health, is not considered a serious adverse event.

7.1.3 Device Deficiency (DD)

Inadequacy of an investigational medical device related to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, use error, or inadequacy in the information supplied by the manufacturer.

7.1.4 Adverse Device Effect (ADE)

Adverse event related to the use of an investigational medical device.

NOTE 1- This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device.
NOTE 2- This includes any event that is a result of a use error or intentional abnormal use of the investigational medical device.

7.1.5 Serious Adverse Device Effect (SADE)

Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

7.1.6 Unanticipated Serious Adverse Device Effect (USADE)

Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.
NOTE: Anticipated SADE (ASADE): an effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report

7.2 Adverse Event Reporting

7.2.1 Adverse Event Reporting from Site to Sponsor and MEC

The collection of AEs will begin after the informed consent is signed. All AEs that occur through completion of the final follow-up visit, whether observed by the investigator or by the subject, and whether or not thought to be device related, will be reported in detail on the appropriate CRF and followed to resolution or the end of trial participation.

The description of the AE will include the date and time of onset, seriousness, relationship to the device or procedure, the results of any diagnostic procedures or laboratory tests, any treatment recommended, and the outcome of the event. In the circumstance that an AE has not resolved by the time of the subject's completion of the trial, an explanation will be entered on the appropriate CRF.

ZOLL will implement and maintain a system to ensure that the reporting of the reportable events by the investigator to ZOLL occur immediately, but no later than 3 calendar days after investigational site study personnel awareness of the event.

7.2.2 Serious Adverse Event Reporting to Sponsor and MEC

Serious adverse events (SAEs) and device deficiencies should be reported as soon as possible.

Serious adverse events and device deficiencies must be reported no later than 3 calendar days from the site becoming aware of the event or as per the investigative site's local requirements if the requirement is more stringent than those outlined.

The date the site staff became aware of the SAE must be recorded in the source document. The Investigator will further report the event to the EC according to the institution's EC reporting requirements.

Serious adverse events that do not occur in the study subject but occur in the user or other persons need to be reported on the fax notification form titled SAE Notification Form. Serious adverse events that occur in the user or other persons other than the study subject should not be entered into the clinical database.

Serious adverse events should be reported on the SAE Notification Form in the occurrence that the clinical database is not available. This does not replace the electronic clinical database. All information must still be entered in the clinical database once the system is back to normal function.

7.2.3 UADE/USADE Reporting to Sponsor and MEC

ZOLL requires the Investigator to report any USADE to the sponsor within 3 calendar days of the investigator's knowledge of the event and to the EC per EC requirements.

7.2.4 Sponsor Reporting to National Competent Authorities (NCA) when European Sites Participate in the Trial

7.2.4.1 What to Report

The following events are considered reportable events:

- any SAE,
- any Device Deficiency that might have led to a SAE if:
  - suitable action had not been taken or
  - intervention had not been made or
  - if circumstances had been less fortunate
- new findings/updates in relation to already reported events.

7.2.4.2 Report to Whom

Reportable events must be reported at the same time to all NCAs where the clinical investigation has commenced using the summary tabulation featured in the of MEDDEV 2.7/3.

7.2.4.3 Reporting Timelines

ZOLL must report to the NCAs where the clinical investigation has commenced:
- for all reportable events as described in section **7.2.4.1** which indicate an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it: immediately, but not later than 2 calendar days after awareness by ZOLL of a new reportable event or of new information in relation with an already reported event.
- any other reportable events as described in section **7.2.4.1** or a new finding/update to it: immediately, but not later than 7 calendar days following the date of awareness by the ZOLL of the new reportable event or of new information in relation with an already reported event.

7.3 Device Relationship

Determination of whether there is a reasonable possibility that an investigational product or device caused or contributed to an AE is to be determined by the Investigator and recorded on the appropriate CRF form. Determination should be based on assessment of temporal relationships, biologic plausibility, association (or lack of association) with underlying disease and presence (or absence) of a more likely cause.

7.3.1.1 Causality Assessment

The relationship between the use of the medical device (including the medical - surgical procedure) and the occurrence of each adverse event shall be assessed and categorized.

The above considerations apply also to the serious adverse events occurring in the comparison group.

The following definitions are used to assess the relationship of the serious adverse event to the investigational medical device or procedures.

1) Not related: relationship to the device or procedures can be excluded when:

- the event is not a known side effect of the product category the device belongs to or of similar devices and procedures;
- the event has no temporal relationship with the use of the investigational device or the procedures;
- the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
- the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event;
- the event involves a body-site or an organ not expected to be affected by the device or procedure;
- the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);
- the event does not depend on a false result given by the investigational device used for diagnosis, when applicable;
- harms to the subject are not clearly due to use error;
- In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

2) Unlikely: the relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.

3) Possible the relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.

4) Probable the relationship with the use of the investigational device seems relevant and/or the event cannot reasonably explained by another cause, but additional information may be obtained.

5) Causal relationship: the serious event is associated with the investigational device or with procedures beyond reasonable doubt when:

- the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
- the event has a temporal relationship with investigational device use/application or procedures;
- the event involves a body-site or organ that
- the investigational device or procedures are applied to;
- the investigational device or procedures have an effect on;
- the serious event follows a known response pattern to the medical device (if the response pattern is previously known);

- the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible);
- other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
- harm to the subject is due to error in use;
- the event depends on a false result given by the investigational device used for diagnosis 17, when applicable;
- In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

ZOLL and the investigators will distinguish between the serious adverse events related to the investigational device and those related to the procedures (any procedure specific to the clinical investigation). An adverse event can be related both to procedures and the investigational device. Complications of procedures are considered not related if the said procedures would have been applied to the patients also in the absence of investigational device use or application.

In some particular cases the event may be not adequately assessed because information is insufficient or contradictory or the data cannot be verified or supplemented. The ZOLL and the Investigators will make the maximum effort to define and categorize the event and avoid these situations.

Particular attention shall be given to the causality evaluation of unanticipated serious adverse (device) events. The occurrence of unanticipated events related to the use of the device (USADE) could suggest that the clinical investigation places subjects at increased risk of harm than was to be expected beforehand.

8 MONITORING BY DATA MONITORING COMMITTEE

The Data Monitoring Committee (DMC) is used to ensure safety by reviewing cumulative data from the clinical trial at pre-defined intervals for the purpose of safe-guarding the interest of trial participants. The DMC will serve in an advisory role in this trial. The composition, guiding policies, and operating procedures governing the DMC are described in a separate DMC charter. Based on safety data, the DMC may recommend a modification to the protocol or that the sponsor stops the clinical trial/investigation. All final decisions regarding clinical trial/investigation modifications, however, rest with the Sponsor.

9 ADJUDICATION OF EVENTS

The Clinical Events Committee (CEC) is comprised of qualified physicians who are not investigators in the trial. The Clinical Events Committee is responsible for adjudicating specified clinical endpoints based on the specific criteria used for the categorization of clinical events in the trial.

Periprocedural MI will be adjudicated according to the Clinically Relevant Myocardial Infarction After Coronary Revascularization (CRMI) definition.[40] Death, Stent Thrombosis, Spontaneous MI, and Revascularization will be adjudicated per ARC definitions.[27]
Hospitalization due to Heart Failure will be adjudicated per ACC/AHA definition. [48]

The composition, guiding policies, and operating procedures governing the CEC are described in a separate CEC Manual of Operations.

When applicable, sites will provide patients' source documentation per request from the Sponsor and will aploade angiograms into AMBRA website through software service Dicom Grid, Inc., which will de-identify angiograms.

10 RECOMMENDATION FOR DAPT AND STENTS

Control and intervention group patients should receive dual antiplatelet therapy (DAPT) and anticoagulation medication as recommended by the ESC Guideline for the management of acute myocardial infarction in patients presenting with ST-segment elevation.

- This includes aspirin 162 or 325 mg po chewed as soon as feasible.
- This should be followed by loading dose of ticagrelor (preferably crushed or chewed) 180 mg before PCI. If ticagrelor not available, loading dose of prasugrel (60 mg) can be used.
    - Clopidogrel can be used only if the patient cannot take ticagrelor or prasugrel.
- This also includes unfractionateded heparin (UFH) given as an intravenous bolus as soon as feasible with subsequent boluses targeted to an activated clotting time of 200 to 250 seconds. If Bivalirudin is used, the infusion should continue for 1-2 hours after PCI is finished .
- Use of an intravenous GP IIb/IIIa inhibitor should be used according to the decision of interventional cardiologist.
- In patients with STEMI in whom clopidogrel was initiated before coronary angiography, it is recommended to switch to either ticagrelor or prasugrel before, or during, or early after PCI, if ticagrelor or prasugrel are not contraindicated.
    - Switching from clopidogrel to ticagrelor or prasugrel should include a loading dose of ticagrelor 180 mg (preferably crushed or chewed if before

or during PCI) or prasugrel 60 mg if the patient is not at high risk of bleeding, irrespective of the prior dose of clopidogrel.

- Recommended maintenance therapy consists of aspirin 81 mg once daily; ticagrelor 90 mg twice daily for at least 12 months. If ticagrelor not available, prasugrel 5 or 10 mg according to label recommendation can be used.
- If needed, transition to clopidogrel can take place after 30 days post index PCI.
    - The recommended first dose of clopidogrel is 600 mg po 12 h after the last dose of ticagrelor or prasugrel. If maintenance therapy consists of aspirin and clopidogrel, the recommended doses are aspirin per local practice and clopidogrel 75 mg once daily.
    - Use second or third generation DES. Do not use BMS or BVS or BRS such as Absorb in study patients.

ZOLL will pay for Ticagrelor for first 30 days in countries where it is not reimbursed

11 RISK ANALYSIS

11.1 Risk Assessment Process

ZOLL has a documented EN ISO 14971:2012 compliant Risk Management process, which includes the identification of risks, risk assessment, identification, implementation and verification of adequate controls (mitigations) to ensure that identified risks have been reduced as low as possible and to ensure the benefits of the intended use as compared to any residual risk is acceptable.

The intent of the Risk Management process is to identify potential hazardous situations related to the design, manufacture, and use of the Proteus IVTM System, evaluate each risk and implement controls to reduce the risks as low as possible.

Risks related to the IVTM System and Sub-Systems (Console, Catheter, Cassette and Temperature Probe) have been evaluated in a number of ways:

- Hazard Analysis – The purpose of the Hazards Analysis is to identify, evaluate and control potential hazards to the patient, user and the environment.

- Software Hazards Analysis - The Software Hazards Analysis is used to investigate potential device Software related hazards and control the potential hazards.

- Design FMECA - The purpose of the Design FMECA is to evaluate failure modes of the device components, or subsystems, to identify potential design failure risk, then evaluate and control potential hazards.

- Process FMECA - The purpose of the Process FMECA is to evaluate failure modes of the device manufacturing process steps to identify process failure risks, then evaluate and control potential hazards.

The results of the Proteus IVTM System Risk Management process was reviewed, and concluded that the risk controls are effective to reduce the risks as low as possible. The ZOLL Proteus IVTM System presents an acceptable risk benefit ratio when used in accordance with its labeling for its proposed intended use: The Proteus IVTM System is intended for use in adult subjects with acute anterior myocardial infarction to induce and maintain hypothermia prior to percutaneous coronary intervention as an adjunctive therapy to reduce anterior infarct size.

Note: See the Investigator Brochure for additional information on the Proteus IVTM System, as applicable.

11.2 Expected Clinical Observations

In subjects who have been treated for myocardial infarction, there are many sequelae of such an event that may be thought to be "normal" effects and not due to the treatment provided. These events may be outside the range of what is considered to be "normal" (e.g., a high lab value such as a shift in potassium), but do not put the patient at risk for harm. These events are therefore expected physiological responses to treatment with therapeutic hypothermia in all patients. Prospectively, these observations may include but are not limited to the following:

- Shift in Potassium levels
- High or low levels of glucose

The expected clinical sequelae of patients treated with hypothermia include, but are not limited to, the following[28]:

- Shivering
- Prolonged ECG intervals
- Bradycardia defined as a heart rate of 40 beats per minute and not requiring treatment (e.g., pacemaker, medications, etc.)
- J wave (also called Osborne wave) can occur at any temperature < 32.3°C

- Blood electrolyte shifts: Calcium, Phosphorus, Magnesium, Chloride
- High or low levels of glucose: Decreased insulin sensitivity and insulin secretion
- Asymptomatic shifts in serum amylase and lipase levels
- Peripheral pulses may be difficult to detect

Cold Diuresis: Increased resistance to ADH or Vasopressin resulting in decreased water or solute reabsorption.

11.3 Potential Clinical Risks

Adverse events that are inherent to a PCI procedure and expected to occur in most subjects for a projected duration according to the opinion of the investigator may be considered unavoidable. Such events include, but are not limited to, those listed in **Table 14**. These adverse events should not be reported during this trial.

Table *14* Expected and unavoidable adverse events related to the PCI procedure

Description of the Event	Time Frame from the Index Procedure (PCI)
Back pain related to laying on Cath-lab table	Within 48 hours
Peripheral vasoconstriction	Within 24 hours
Thermal discomfort	Within 24 hours
Incisional pain (pain at access site)	Within 72 hours
Sleep problems or insomnia	Within 72 hours
Mild to moderate bruising or ecchymosis	Within 168 hours

A list of potential (expected) risks that may be associated with use of the Proteus IVTM System is provided below. Since this clinical study utilizes an investigational device, all risks may not be known. However, they are believed to be similar to those associated with the existing intra-vascular temperature management devices in clinical use or commercially available.

The following potential adverse events may occur during the course of the clinical trial.

11.3.1 Potential Adverse Events associated with the Proteus Catheter and Cooling System:

Potential risks related to the Proteus Catheter are reasonably believed to be consistent with the common, known risks of central venous catheters and/or venous introducer sheaths. Potential risks related to cooling, re-warming, and/or the Proteus IVTM System include but are not limited to the following:

- Catheter related injury [embolism (air, thrombus, catheter fragment), clinically significant hematoma, vascular perforation or dissection, arteriovenous fistula, nerve injury, excessive bleeding, pseudoaneurysm)
- Deep vein thrombosis (DVT) requiring treatment
- Infection [local or systemic (pneumonia, sepsis, meningitis, visceral organ)]

11.3.2 Potential Adverse Events associated with the cooling procedure include but are not limited to the following:

- Acute renal failure
- Acute renal insufficiency
- Adverse drug reaction
- Angina
- Blood lysis
- Congestive Heart Failure
- Clinically relevant shivering (BSAS $\geq$ 2) that cannot be controlled by the antishivering medication regimen
- Dysrhythmia [ventricular tachycardia, ventricular fibrillation or atrial fibrillation requiring intervention, bradycardia (HR $\leq$ 40 bpm, block)]
- Hyperglycemia / Hypoglycemia
- Hyperkalemia / Hypokalemia
- Hyperphosphatemia / Hypophosphatemia
- Hypotension
- Infection (local, systemic)
- Liver Failure
- Myocardial infarction
- Multi-system organ failure
- Overcooling (temperature <31.0°C for $\geq$ 20 continuous minutes)
- Overwarming (temperature >38°C for $\geq$ 20 continuous minutes including dehydration, burns and neurological damage)
- Pancreatitis
- Pulmonary edema
- Peripheral vascular insufficiency
- Thrombocytopenia
- Rebound hyperthermia
- Respiratory failure during cooling or rewarming
- Seizures

- Stroke [Cerebral vascular Accident (CVA)]
- Transient Ischemic Attack (TIA)
- Unstable angina

11.3.3 Risks Associated with Anti-shivering Medications

In order to preserve patient comfort and suppress the shivering response during cooling, a combination of recommended buspirone, where available (or equivalent alternative) and required Pethidine (Meperidine) should be used (see **Attachment II**). As identified in their labeling, the risks associated with the use of these pharmacologic agents in this trial population include the following:

Buspirone (or equivalent alternative)

- Interaction with MAO Inhibitors
- Dizziness
- Nausea
- Headache
- Nervousness
- Lightheadedness
- Excitement

Pethidine (Meperidine)

- CNS Depression
- Hypotension
- Respiratory Depression
- Circulatory Depression
- Respiratory Arrest
- Shock
- Cardiac Arrest

Other reported reactions:

- Lightheadedness
- Dizziness
- Nausea
- Vomiting
- Sweating

11.4 Additional investigations due to the trial

Participation in the clinical trial will involve extra blood sampling for laboratory markers (electrolytes, complete blood count, baseline and peak troponin including upper limit of normal), additional ECGs, and the need for cardiac MRI imaging. All of these are standard clinical procedures, and the risks to participants are low. Sites will be carefully monitored for adherence to the protocol. Patients will be screened for appropriateness for MRI prior to enrollment.

11.4.1 Delay in PCI through the use of hypothermia therapy

The probability for potential delay in PCI is considered Occasional. In prior trials of hypothermia for STEMI, the increase in door to balloon time ranged from 9 minutes to 18 minutes. It is noteworthy that this delay was not associated with an increase in infarct size hypothermia patients compared to controls. In fact, patients with anterior STEMI with < 35°C at the time of reperfusion showed smaller infart size. Sites will be trained to incorporate hypothermia into the cath lab workflow while minimizing delay. Feedback will be provided for each case to help maintain efficiency.

11.4.2 Implementation of PCI in patients undergoing hypothermia (patient-related risks).

Potential risks related to the use of hypothermia therapy in patients are outlined in sections 11.2.1 and 11.2.2 above. These risks include: potential adverse events associated with the Proteus Catheter and Cooling System, potential adverse events associated with cooling, and potential risks associated with the anti-shivering medications.

11.4.3 Implementation of PCI with concurrent use of endovascular hypothermia.

The addition of hypothermia as adjunctive treatment of STEMI will potentially lead to more difficult conditions for the Investigator and other users. The ability to integrate hypothermia into the cath lab workflow has been demonstrated successfully in prior clinical trials. Again, thorough training, frequent monitoring, and rapid feedback will help mitigate the challenges of incorporating hypothermia into treatment for STEMI.

11.4.4 The concurrent medication.

Patients who have received medications such as monoamine oxidase inhibitor within a 14 day period will be excluded from the trial to prevent potential interaction with the anti-shivering medications. In patients that receive morphine prior to arrival to the hospital, the pethidine dose will be lowered to decrease the likelihood of respiratory depression.

11.4.5 The supply of 4°C cooled saline solution

The amount of cooled saline solution is limited to 1,000 ml, an amount shown to be well tolerated in the CHILL-MI trial, where the average amount of cooled saline was 1475 ml. Again, careful training and monitoring will help to avoid unnecessary exposure to larger volumes of saline.

11.4.6 Other procedures within the clinical trial

The risk of adverse interaction or influence of other procedures within the clinical trial are deemed to be low. In prior hypothermia trials in STEMI, there was no interference with the stenting procedure, with resuscitation efforts for arrhythmias or cardiogenic shock. Hypothermia does inhibit the absorption and metabolism of clopidogrel, a anti-platelet inhibitor, given to reduce the risk of stent thrombosis. This risk will be mitigated by calling for adherence to ESC guidelines which recommend either prasugrel or ticagrelor, both of which are less affected by hypothermia.

11.5 Potential Clinical Benefits

Although no assurances or guarantees can be made, there is a reasonable expectation that the use of this investigational device is safe within the context of the trial and may be beneficial. Cooling using the device, for instance, may result in improved temperature control relative to the standard techniques already in use at the sites.
The primary benefits of therapeutic hypothermia have been shown to be:

- Improved patient survival
- Improved heart tissue salvage after the ischemic event

Additional potential benefits of therapeutic hypothermia with the Proteus System may include:

- Faster cooling
- More accurate control of the cooling procedure than with surface cooling
- Further improved survival

There is no guarantee that participation in this trial or use of hypothermia will benefit the trial subject. However, collection of such trial data may provide added benefit for future myocardial infarction subjects.

11.6 Methods to Minimize Risk

All efforts will be made to minimize risks by selecting investigators who are experienced and skilled in using minimally invasive catheter-based cardiovascular interventions and who have been adequately trained. Also, risk minimization activities were performed during development and design verification tests of the device. Activities intended to minimize risks include the following.

- Investigator and trial personnel training will be conducted to share information regarding the design of the Proteus IVTM System, its application, pre-clinical results, and clinical trials on comparable intra-vascular cooling devices.
- Adherence to eligibility criteria and screening procedures will ensure that appropriate patients are enrolled.
- Adherence to the Proteus IVTM System Instructions for Use packaged with the device.
- Corrective and preventative actions will be implemented by ZOLL, as necessary, if deviations from recommendations in the protocol or IFU are observed.
- Clinical support by ZOLL representative will be provided during the enrollment in the study and thereafter if needed. ZOLL representatives will only have advisory role.
- The subjects will be carefully monitored throughout the trial period.
- The investigator will evaluate the subject adverse events during the course of the trial.
- Data submitted from the investigative centers will be monitored during the course of the trial.
- Monitoring visits will be conducted to evaluate protocol compliance and data quality.
- Safety and effectiveness data obtained during the course of the trial will be shared with investigators in periodic reports to increase understanding of the device and potential adverse events.
- An independent Data Safety Monitoring Board (DSMB) will monitor safety throughout the clinical trial. Stopping rules will be discussed with the DSMB and applied for subject safety through enrollment.

Detailed trial procedures are provided in **Section 6.8 - Clinical Trial Procedures**.

11.7 Risk – Benefit Assessment

To date, there have been five clinical trials that have reported on the safety and effectiveness of therapeutic hypothermia in AMI and one in Radio-Contrast nephropathy (COOL-RCN Trial), with a total of more than eleven hundred patients being enrolled in total with at least half of those treated with therapeutic hypothermia. The rate of adverse events are well reported in these populations (see section 5, Prior Investigations), and the risks are clearly categorized for these trials. In summary, the number of trials, patients enrolled, and low numbers of safety events reported indicate that therapeutic hypothermia in this patient population is at an acceptable risk level to engage in this trial.

There is significant morbidity and mortality associated with the numerous clinical conditions outlined in this report, and therapeutic hypothermia has shown promise to greatly improve clinical outcomes in these patients. In particular, patients with anterior STEMI have a higher incidence of congestive heart failure, cardiogenic shock, and cardiac mortality. A significant reduction in

infarct size in these patients, with therapeutic hypothermia, has the promise to reduce these adverse clinical outcomes. Risks associated with the use of the Proteus IVTM system have been reduced via the Risk Management Process, and are deemed acceptable, considering the potential benefits. We conclude that the use of the Proteus IVTM system for medical practice is justified and warranted.

Risk assessment of the Proteus IVTM System has been performed in accordance with the ISO 14971:2012.[306] The Proteus IVTM System is safe and presents an acceptable risk benefit ratio to provide cooling or warming of patients when:

- Used by and under the supervision of a qualified medical practitioner
- In patients for whom the risks of a central line are acceptable
- In intensive care environments equipped to handle clinical conditions warranting use of the device under this protocol
- Used according to the Instructions For Use (IFU)

12 RECORDS AND REPORTS

Throughout the course of this clinical trial, ZOLL, the investigators, and reviewing MEC are responsible for the records and reports detailed in the following sections.

12.1 Investigator Records

Investigators must retain all trial records required by ZOLL and by the applicable regulations in a secure and safe facility. The investigator must consult a ZOLL representative before disposal of any trial records and must notify ZOLL of any change in the location, disposition, or custody of the trial files.

Trial records are those that individually and collectively permit evaluation of the conduct of the trial and the quality of the data produced. ZOLL's SOP requires that all clinical trial data be kept for a minimum of 15 years and all data used in submissions be kept for the life of the corporation. It is the site's obligation to inform ZOLL if their own policy does not comply with the sponsor's requirement so necessary arrangements can be negotiated. It is ZOLL's responsibility to inform the investigator/institution as to when these documents no longer need to be retained.

The investigator is responsible for the preparation (review and signature) and retention of the records cited below.

- All correspondence with another investigator, MEC, ZOLL, a monitor, or FDA, including required reports and trial documents which pertain to the investigation.

- Records of receipt, use, and final disposition of a device.
- Records of each subject's case history and exposure to the device. Case histories include the Case Report Forms (CRFs) and supporting source data (signed and dated informed consent forms, medical records, e.g., progress notes of the physician, patient's hospital chart, nursing notes).
- The clinical investigational plan, with documents showing the dates of and reasons for each deviation from the protocol.
- Any other records that are required to be maintained by local regulations or by specific regulatory requirements for a category of investigations or a particular investigation.
- Any other record that the reviewing MEC requires to be maintained for the subject investigation.

12.2 Investigator Responsibilities

The participating investigator is responsible for adhering to this Clinical Investigational Plan (CIP), FDA CFR, ISO 14155 and Declaration of Helsinki (Regulatory requirements of his/her country local law).

Specifically, the Principal Investigator at each site shall:

a) indicate his/her acceptance of the CIP in writing,
b) conduct the clinical investigation in compliance with the CIP,
c) create and maintain source documents throughout the clinical investigation and make them available as requested during monitoring visits or audits,
d) ensure that the investigational device is used solely by authorized users as specified in 6.2, and in accordance with the CIP and instructions for use,
e) propose to the sponsor any appropriate modification(s) of the CIP or investigational device or of the use of the investigational device,
f) refrain from implementing any modifications to the CIP without agreement from the sponsor, EC and regulatory authorities, if required,
g) document and explain any deviation from the approved CIP that occurred during the course of the clinical investigation,
h) ensure that an adequate investigation site team and facilities exist and are maintained and documented during the clinical investigation,
i) ensure that maintenance and calibration of the equipment relevant for the assessment of the clinical investigation is appropriately performed and documented, where applicable,
j) ensure the accuracy, completeness, legibility and timeliness of the data reported to the sponsor in the CRFs and in all required reports,
k) maintain the device accountability records,
l) allow and support the sponsor to perform monitoring and auditing activities,

m) be accessible to the monitor and respond to questions during monitoring visits,
n) allow and support regulatory authorities and the EC when performing auditing activities,
o) ensure that all clinical-investigation-related records are retained as required by the applicable regulatory requirement(s), and
p) sign the clinical investigation report, where applicable.

The investigator is responsible for the preparation and submission of the reports cited in **Table 15**. Reports must be prepared in complete, accurate and timely manner. These reports may be subject to regulatory inspection (and ZOLL) and copying, and the retention requirements described above for Investigator Records. In addition to the reports listed in **Table 15**, the reviewing MEC may request reports pertaining to any aspect of the clinical trial.

Written approval from the Medical Ethics Committee (MEC) with authority for the participating site will be obtained prior to the start of the study. The investigator or if applicable, the Sponsor, is responsible for submitting all required documents to the MEC. At a minimum the following documents will be submitted:

• Clinical Investigational Plan (CIP)

• Patient Informed Consent documents in the local language

• Any other written information to be provided to the subjects in the local language

• Investigator Brochure (IB) (as required)

• Other documents will be submitted as per local requirements

After obtaining MEC approval, the investigator will submit the approval letter indicating the approved version of the CIP, Patient Informed Consent, IB and any other reviewed documentation to ZOLL.

Table 15 Investigator Reporting Responsibilities to Sponsor and MEC

REPORT	SUBMIT TO	DESCRIPTION/CONSTRAINTS
Withdrawal of MEC Approval	Sponsor	The investigator must report a withdrawal of the reviewing authority within **5 working days**.
Case Report Form (CRF)	Sponsor & Monitor	CRFs should be completed as soon as possible after any trial related procedure takes place.
Deviation from Investigation Plan (Emergency)	Sponsor & MEC	Notification must be made within **5 working days** if the deviation was made to protect the life or physical well-being of a subject.
Deviation from Investigation Plan (Other – Non Emergency)	Sponsor & MEC	If the deviation may affect the scientific soundness of the plan or the rights, safety and welfare of the subjects (and is not an emergency), then **the deviation must be approved by ZOLL, the MEC, and the reviewing authority prior to its implementation**. If the deviation does not affect these issues (trial soundness, rights, safety, etc.) then only ZOLL must approve it, (except in cases which are beyond the control of the investigator—see section on Protocol Deviations).
Failure to Obtain Informed Consent	Sponsor & MEC	The Investigator must notify ZOLL and the reviewing authority within **5 working days** after device use. The investigator must submit notification after device use or after the investigator first learns of the absence of informed consent. The report must include a brief description of the circumstances surrounding the failure to obtain informed consent and include written concurrence by a licensed physician not involved in the investigation. Failure to obtain informed consent must be reported to the MEC as required by local regulations.
Final Report	Sponsor & MEC	This report must be submitted within **3 months** after termination or completion of the investigation.

12.3 Sponsor Records

All Sponsor documents and records shall be maintained as indicated by ZOLL's Quality System. ZOLL will maintain the following trial -related records in accordance with ZOLL record retention policies and procedures following the completion of this investigational plan. Clinical data for regulatory submissions and publications will be retained for the life of the corporation.

- All correspondence pertaining to the investigation with the sponsor, a monitor, an investigator, an MEC, regulatory agencies, including required reports.
- Records of shipment and disposition of the investigational device.

- Signed investigator agreements including the financial disclosure information required to be collected and current signed and dated curriculum vitae.
- Records of adverse events and device deficiencies.
- List of participating institutions
- Investigational product accountability reports including record of receipt, use, or disposition of the device(s) that relate to type, quantity, serial numbers of devices, and date of receipt, names of persons who received, used, or disposed of each device and why and how many devices have been returned to ZOLL or otherwise disposed
- All signed and dated case report forms submitted by investigator, samples of patient informed consents, and other information provided to the subjects
- Copies of all MEC approval letters and relevant MEC correspondence
- Names and evidence of the institutions in which the clinical investigation will be conducted
- Insurance certificates
- Forms for reporting adverse events and device deficiencies
- Names/contact addresses of monitors
- Statistical analyses and underlying supporting data
- Final report of the clinical investigation
- The Clinical Investigational Plan, Clinical Monitoring Plan (CMP), Investigator Brochure (as applicable), and study related reports
- Study training records for center personnel and ZOLL personnel participating in the trial
- Any other records that MEC and /or competent authority requires to be maintained by regulation or by specific requirement for a category of investigation or a particular investigation.

12.4 Sponsor Reports

ZOLL Circulation, Inc. is responsible for the classification and reporting of reportable adverse events and device deficiencies and ongoing safety evaluation of the clinical investigation in line with local regulatory requirements.

ZOLL Circulation, Inc. will assure that all Serious Adverse Events and reportable Device Deficiencies are reported to the Competent Authorities in accordance with European Medical Devices directives and all applicable national regulations.

ZOLL Circulation, Inc. is responsible for the reports cited in **Table 16**. These reports are subject to regulatory retention and inspection requirements. Governing Regulatory Agencies or the reviewing MEC may request reports pertaining to any aspect of the clinical trial.

Table 16: ZOLL Reporting Responsibilities

REPORT	SUBMIT TO	DESCRIPTION
Unanticipated Adverse Device Effects; SAEs and Reportable DDs	Relevant authorities and MECs	Reporting timeframe as per local regulatory requirements.
	Investigators	Notification throughout the course of the trial when appropriate (based on perceived risk)
Premature termination or suspension of the Clinical investigation	Investigators, MECs, Relevant Authorities	Provide prompt notification of termination or suspension and reason(s).
Subject enrollment Completed	Investigators, MEC and Relevant regulatory Authorities upon request	ZOLL will notify the investigators within 30 working days of the completion of enrollment. Investigators will, in turn, inform their MECs, when required.
Withdrawal of MEC approval	Investigators, MECs	Notification within five working days.
Final Report	Investigators, MECs, (and other relevant Authorities upon request)	A final report will be submitted to investigators, and MECs within six months after completion or termination of this study. The investigators shall have the opportunity to review and comment on the final report. If a clinical investigator does not agree with the final report, his/her comments shall be communicated to the other investigators. The principal clinical investigator in each center shall sign the report.

13 MONITORING AND AUDITING PROCEDURES

13.1 Clinical Trial Sponsor and Monitors

ZOLL is the Sponsor of the clinical trial. It is the responsibility of the sponsor to ensure that proper monitoring of the investigation is conducted. Clinical trial monitoring and auditing will be done

by appropriately trained personnel appointed by the trial sponsor to ensure that the investigation is conducted in accordance with ZOLL's requirements and applicable laws and regulations.

A monitor is an individual designated by a sponsor or contract research organization to oversee the progress of an investigation. The monitor may be an employee of a sponsor or a consultant to the sponsor, or an employee of or consultant to a contract research organization. The monitor will be trained on the device, investigational plan, informed consent, instructions for use, applicable ZOLL procedures, electronic data capture system, and regulatory requirements. The monitor will periodically check and report on the progress of the clinical trial at an investigational site or other data gathering organization or ZOLL facility.

13.2 Monitoring Methods

Monitoring of the clinical trial will be a continuous, interactive process to ensure that high-quality data is obtained in compliance with the clinical investigational plan and regulatory requirements. Monitoring functions will be conducted by ZOLL, and/ or a contract research organization and/or other designees. Specific monitoring requirements are detailed in the Trial Monitoring Plan (maintained in the ZOLL COOL-AMI clinical trial project files). Frequent communication will be maintained with each investigational site to keep both the clinical center and ZOLL up-to-date and aware of the trial progress. Case Report Forms will be reviewed for completeness and accuracy.

ZOLL will monitor sites in accordance with the monitor's tasks set under Section 8.2.4 of Standard DIN EN ISO 14155:2012-01. These include visits to the clinical trial sites before the start of, during and at the end of the clinical trial. On-site monitoring of all trial centers will be frequent enough (at a minimum annually) to assure continued integrity and acceptability of the data. Accuracy of data reported on case report forms will be verified by comparison to source documents. Reports of monitoring visits will be provided to the clinical trial personnel at each site. Corrective action will be taken to resolve any issues of noncompliance. If ZOLL finds that an investigator is not complying with the executed trial agreements, the investigational plan, the applicable national regulations, or the requirements of the reviewing MEC, then prompt action will be taken to secure compliance. In addition, shipment of the device may be stopped or the participation of the investigator may be terminated. Additional information is provided in **Section 6.30** – **Trial Closure**.

13.3 Monitoring Visits

Scheduled visits to the clinical investigational site will occur at the following times: prior to the start of the clinical trial (pre- trial qualification visit), at initiation of the trial (during first index

procedure or shortly thereafter), interim visits throughout the clinical trial as required, annually, and upon completion of the clinical trial.

13.4 Pre-trial Qualification Visit

A pre- trial visit will be conducted by ZOLL personnel (or designees) to review the clinical investigational plan and regulatory requirements with the investigator and the trial personnel to assure that they:

- Understand the investigational status of the device and the requirements for its use and accountability.
- Understand the clinical investigational plan.
- Understand the requirements for an adequate and well-controlled clinical trial.
- Understand and accept the obligation to conduct the clinical investigation in accordance with the national regulations.
- Understand and accept the obligation to obtain informed consent in accordance with the national regulations.
- Understand and accept the obligation to obtain MEC approval before the clinical trial is initiated, ensure continuing review of the trial by the MEC, and keep ZOLL informed of MEC approval and actions concerning the clinical trial.
- Have access to an adequate number of eligible patients to participate in the trial (at a minimum: 1 patient/center/month).
- Have adequate facilities and resources to conduct the trial. This includes resources appropriate for use of electronic data capture systems.
- Have sufficient time from other obligations to carry out the responsibilities of the clinical trial.
- Sign the Investigator Agreement and trial contracts (prior to enrollment of patients).

A report of the pre- trial qualification visit will be completed. Resolution of any concerns or completion of any appropriate follow-up activities stemming from the pre- trial visit also will be documented.

13.5 Initiation Visit

ZOLL clinical personnel (or designees) will provide assistance for both technical concerns and trial management issues during the initiation visit. Enrollment of the first patient at each clinical site may or may not coincide with this visit. Any observations will be documented and issues requiring follow-up will be identified on a monitoring report. Training of trial personnel also will be documented.

13.6 On-Site Interim Monitoring Visits

On-site monitoring visits will be made on an as-required basis (and at least annually) to assess adherence to the clinical investigation plan, MEC review of trial progress, maintenance of records and reports, and selected review of source documents for accuracy, completeness, legibility, and omissions. The monitors will acquire information to assess the progress of the trial (toward meeting trial objective) and identify any concerns that stem from observation of device performance and/or review of the investigator's patient records, trial management documents, and patient informed consent documents. Monitoring reports will be generated along with communications to the investigator, which document the result of the monitoring visit and any recommended actions. Resolution of concerns and completion of assigned tasks will be documented.

13.7 Audits

An on-site audit may be completed periodically throughout the trial at each clinical site by an independent group. The purpose of the audit will be to ensure compliance to the investigational plan and regulatory requirements, e.g., written informed consent was documented, information recorded on the case report forms is complete and accurate as compared to source documentation, protocol deviations are noted, and device accountability is accurate and complete. A randomly selected number of patient records and other supporting documents will be compared to the case report forms. A record of the findings and recommended actions to correct deficiencies will be documented on the audit report.

13.8 Final Monitoring Review

Depending upon the status of the trial at each center, a close-out or final visit may be conducted. Any ongoing responsibilities will be discussed with the investigator and the trial center coordinator. A final monitoring report, which includes, at a minimum, disposition of any unused devices, will be completed.

14 DATA MANAGEMENT PROCEDURES

ZOLL will oversee all data management functions. ZOLL will be responsible for database development, system maintenance, user training, data queries, and report generation.

14.1 Case Report Forms

ZOLL will use an electronic data capture (EDC) system to collect patient data. The electronic case report forms (eCRFs) are the primary component of EDC and are based on the sample forms that

will be provided in a separate document. Training on use of the system will be provided to the trial site personnel. Instructions for completion of the eCRFs also will be provided.

The eCRFs must be completed, saved, and locked via electronic signature by the Investigator using a unique ID and password. This ID and password are for the use of the investigator only and may not be used by any other person. Because of the potential for errors or inaccuracies in transcribing data into eCRFs, source documentation must be maintained in each subject's hospital chart and/or electronic medical record. The eCRFs and source documentation must be available at all times for inspection by the trial monitors or regulatory inspectors.

Changes made to eCRFs will be electronically recorded in a complete audit trail that cannot be changed, but can be accessed by authorized personnel at any time. All data are transmitted via the Internet in an encrypted fashion. When received at the server site, the data are decrypted and stored. Data can be extracted for ZOLL review and analysis at any time.

14.2 Source Documentation

Regulations require that an investigator maintain information in the trial subject's medical records to corroborate data collected on the eCRF. To comply with these regulatory requirements, the following information will be maintained and made available as required by ZOLL and/or its designees and/or regulatory inspectors. Shadow charts are not appropriate or adequate source documentation. Complete medical (clinical and hospital) records include the following documentation.

- Medical history/physical condition of the patient before involvement in the trial sufficient to verify clinical protocol eligibility criteria.
- Description of cooling procedure (material used, drugs administered during the procedure, device identification information and disposition, date, time, angiographic and clinical findings, etc.).
- Electronic data downloaded from the ZOLL Proteus IVTM System.
- Signed notes in the subject's medical record on the enrollment day that identify and include: the subject's date of enrollment, procedure date, the trial sponsor (ZOLL), clinical site name, the subject-assigned identification number, the subject- assigned enrollment number, and documentation and confirmation that the appropriate informed consent was obtained.
- Dated and signed notes for each subject's trial visit.
- Lab results.
- Baseline ECG, angiogram, and MRI reports, etc.
- Dated printouts or reports of special assessments (ECG baseline report, imaging report, etc.).

- Adverse event reporting and follow-up of the adverse events. Information in the medical chart should include at a minimum the following: event description, severity, seriousness, onset date, date site became aware of event, duration, relation to trial device, treatment, and outcome of the adverse event.
- Trial subject's condition upon completion of or withdrawal from the trial.
- Trial subject's medical status, including all SAEs out to 1 year following trial enrollment.
- All notes related to trial subject's KCCQ and the New York Heart Association Functional Class questionnaires.

14.3 Transmission of Data

Required data will be recorded on the appropriate eCRF at the time of or as soon as possible after the patient visit. The eCRFs and any requested supporting source documents must be sent to ZOLL and/or retrieved from the investigator during monitoring visits. Questions about completion of the eCRFs may be directed to the ZOLL COOL AMI clinical team at Clin-safety@zoll.com

14.4 Data Queries

During monitoring visits, the Monitor will perform a 100% review of all variables, i.e., demography, inclusion/exclusion criteria, safety, effectiveness, on the eCRFs with each subject's source documents. Any discrepancies will be queried by ZOLL or its designee and must be resolved by the investigational site staff and investigator in a timely manner. Queries also will be generated by ZOLL data management personnel during routine review of the data on the electronic data capture system.

15 STATISTICAL ANALYSIS PLAN

The objective of this trial is to evaluate the safety and effectiveness of therapeutic hypothermia, using the ZOLL Proteus IVTM System, as an adjunctive therapy for patients presenting with acute anterior myocardial infarction (AMI) and undergoing percutaneous coronary intervention (PCI). An analysis summarizing outcomes for the Primary Effectiveness Endpoint and the Primary Safety Endpoint will be created after the last randomized subject has completed the 30 day follow-up interval. The results of the primary endpoints will be summarized in the final clinical study report.

Two interim analyses are planned to be performed at approximately 50% and 75% of randomization, once subjects have completed 4-6 day cMR follow-up. At the interim stage, the trial will be stopped to reject the null hypothesis of no difference or continue enrolling. Another report will be issued summarizing all endpoints after all subjects have completed 12 month follow-up.

15.1 Data Analysis

Analysis Data Sets

The Intention-to-Treat (ITT) analysis set will be used for primary statistical analyses and summaries. The ITT population includes subjects who have signed an informed consent and have been randomized to the Test Arm or the Control Arm of the trial. ITT subjects will be evaluated according to the group to which they were randomized.

The Per-Protocol (PP) analysis set will also be evaluated. The PP population includes those subjects who met inclusion and exclusion criteria, were randomized to either the Test or Control arm, received the treatment to which they were randomized, and complied substantially with the treatment timeline and steps of this protocol without major protocol violations.

The Safety Analysis Set will be used to evaluate safety endpoints. These will be all of the subjects included in the study as defined by the ITT analysis set and will include Roll-In subjects. For the safety analysis, subjects will be followed for all adverse events for 30 days post procedure. Additionally, all subjects will be followed for 12 months for the incidence of Serious Adverse Events (SAEs), Death and Heart Failure (as assessed by NYHA and Kansas City Cardiomyopathy Questionnaire (KCCQ).

Infarction Size (IS) is defined as % Left Ventricular Mass as measured by Cardiac Magnetic Resonance (cMR) imaging. Infarct Size (IS) will be assessed by Cardiac Magnetic Resonance (cMR) at 4 – 6 days following the index procedure. Infarct Size will be assessed in subjects in the ITT analysis set and also in the Per-Protocol analysis set.

The Safety Analysis Set will be used to evaluate safety endpoints. These will be all of the subjects included in the study as defined by the ITT analysis set and will include the following clinical components evaluated at 30 day follow-up visit (30 day ± 7 days):

Secondary Endpoint Analysis:

The following clinical components of MACE will be evaluated at 30 day follow-up visit (30 day ± 7 days):

- Death (Cardiac, Vascular, Non-Cardiovascular)
- Myocardial Infarction (MI)
  - Attributable to target vessel (TV-MI)
  - Not attributable to target vessel (NTV-MI)
- Target Lesion Revascularization (TLR)

        - Clinically-indicated TLR (CI-TLR)
        - Not clinically-indicated TLR (NCI-TLR)
    - Target Vessel Revascularization (TVR non TLR,)
        - Clinically-indicated TVR non TLR
        - Not clinically-indicated TVR non TLR
    - Non-Target Vessel Revascularization (NTVR,)
        - Clinically-indicated NTVR
        - Not clinically-indicated NTVR
    - All coronary revascularization

In addition, Stent Thrombosis will be evaluated at 30 day follow-up visit (30 day ± 7 days):

- Evidence (Definite and Probable)
    - Timing (Acute, Sub-acute)

Additional Observational and Descriptive Analysis:

In addition to the secondary endpoint, safety of the trial is also analysed by the following observational and descriptive analysis. These events are not endpoints for the study:

- the following serious adverse events will be evaluated at 30 day follow-up visit (30 day ± 7 days):
    - Stroke
    - Cardiogenic shock
    - Pulmonary embolism
    - Pulmonary edema
    - Atrial fibrillation
    - Ventricular fibrillation
    - Vascular complications requiring intervention
    - Bleeding requiring transfusion of 2 units or greater
    - Cooling catheter access site infection
    - Systemic infection
    - Deep Venous Thrombosis (DVT)
    - Bradycardia
    - Hypotension
- The following serious adverse events will be evaluated at 12 month follow-up visit (12 month ± 14 days):
    - Death (Cardiac, Vascular, Non-Cardiovascular)
    - Stent Thrombosis
        - Timing (Acute, Sub-acute)
        - Evidence (Definite and Probable)

- Hospitalizations due to Heart Failure

15.2 Statistical Methods

Baseline demographic and clinical characteristics will be summarized for each arm using descriptive statistics. Continuous variables will be reported with mean, standard deviation, median, and range. Discrete variables will be reported as frequency and proportion. A $\chi 2$ test or Fisher exact test (for small frequencies) will be used to compare discrete variables; t-test or Wilcoxon test (for non-normal data) will be used to compare the 2 arms with continuous variables for randomized subjects in the trial.

The primary effectiveness endpoint is to detect a 20% reduction of mean infarct size in the Test Arm compared to Control Arm where infarct size (%LV Mass) is measured by cMR at 4-6 days. The mean, median, standard deviation, and range will be presented for infarct size. A two sample t-test will be used to test the null-hypothesis of no difference in average infarct size test and control arm P-value will be reported with $p<0.05$ considered statistically significant. Infarct size will further be evaluated in subgroups and with ANOVA models.

For the primary safety endpoint of MACE (as defined by CD, All MI, and CI-TLR) at 30 days, all events will be tabulated and reported. Per-patient rate of composite MACE will be compared between the two arms with 1-sided Fisher's exact test.

Two interim analyses are planned to be performed at approximately 50% and 75% of randomization, once subjects have completed 4-6 day cMR follow-up. At the interim stage, the trial will be stopped to reject the null hypothesis of no difference or will continue enrolling. Based on the Lan-DeMets method for group sequential trials using O'Brien-Fleming boundaries, the levels of significance for the interim analyses are alpha=0.00305 (50% information fraction), alpha=0.01832 (75% information fraction), and alpha=0.044 (final analysis).

All analyses for effectiveness will be conducted in intent-to-treat and per-protocol analyses set. All analyses for safety will be conducted in the safety dataset. Imputation will be made for missing infarct size (LV%) in intent-to-treat analyses set per Intention-to-Treat principle; details are described in the Statistical Analysis Plan.

15.3 Sample Size Justification

The primary effectiveness analyses is designed to detect a relative reduction of 20% in mean anterior myocardial infarct size (IS), as determined by Cardiac Magnetic Resonance (cMR) imaging at 4-6 days post infarct in the Test Arm (cooling + PCI) compared to the Control Arm (PCI only). The absolute magnitude of a relative reduction of 20% depends on the mean IS in the

control arm, which is assumed to be approximately 17 %LV. Therefore, the treatment effect of interest is an absolute difference of 3.5 %LV.

The hypothesis for the primary effectiveness endpoint is the following for patients randomized 1:1 in Treatment Arm vs Control Arm:

Null hypothesis:

The null hypothesis is that the mean infarct size in the Test Arm is equal to the mean IS in the Control Arm.

Alternative hypothesis:

The mean infarct size in the control arm is not equal to mean infarct size of control arm.

This 20% relative reduction is defined as absolute value 3.5 %LV and accounted for in our sample size calculation as minimally detectable effect. This assumption is based on previous studies with anterior infarct size measured with cMR reporting between 17-20% absolute %LV in anterior infarct (***Tables 17 & 18***). Therefore, a relative reduction of 20% can vary depending on the mean infarct size of the control arm. Assuming a representative mean infarct size of ~17% in controls, we assume absolute difference of 3.5 %LV is equivalent to 20% mean anterior infarct size would be an adequate detection limit for effect.

Based on these assumptions-- standard deviation of 12.0 %LV, two-tailed t-test of difference between means, a normal distribution, 80% power (beta=0.2) with the final analysis to be conducted using a two-sided test at the alpha=0.044 level of significance (adjusted for the two interim analyses)-- the required total sample to detect a mean difference of 3.5 %LV with 80% power is 384 subjects (192 subjects per group). Further, assuming 24% loss to follow-up, the trial plans for an enrolment up to 500 randomized subjects (250 in each arm) for 4-6 days cMR imaging follow-up.

Table 17: Clinical trials reporting anterior mean infarct size measured by cMR 4-6 days in PCI trials (Control Group Only) and calculated 20% relative reduction

Study name	Anterior n	Mean infarct size	Standard Deviation	20% relative reduction
APEX-AMI[41]	**60**	**16.6**	**10.7**	**3.3**
LIPSIAABCIXIMAB[42]	**63**	**25.3**	**16.1**	**5.1**
LIPSIA-STEMI[43]	**38**	**18**	**16.0**	**3.6**
CRISP-AMI [44]*	**142**	**37.5**	**20.1**	**7.5**
INFUSE-AMI[45]	**172**	**17.3**	**10.2**	**3.5**
RAPID-MI ICE[1]	**7**	**19.7**	**8.5**	**3.9**
CHILL-MI[37]	**21**	**26.5**	**10.9**	**5.3**
AMI EU PILOT	**21**	**23.3**	**12.0**	**4**

*>60% are large proximal infarcts

A range of standard deviation in the table expected is represented by anterior infarct data measured with cMR from separate and pooled analyses of previous hypothermia trials with AMI patients cooled below 35°C: RAPID-MI ICE (2009), CHILL-MI (2013), AMI EU Pilot (ongoing) as described below in **Table 18.**

Table 18: Hypothermia trials using cMR measured infarct size as primary outcome

	RAPID-MI ICE (2009)	CHILL-MI (2013)	AMI EU Pilot (2017)	Pooled AMI EU Pilot, RAPID-MI-ICE, CHILL-MI
n (Control vs Cooled)	7 vs 5	21 vs 15	21 vs 19	49 vs 39
Control Mean LV%	19.7	26.5	23.3	24.5

	RAPID-MI ICE (2009)	CHILL-MI (2013)	AMI EU Pilot (2017)	Pooled AMI EU Pilot, RAPID-MI-ICE, CHILL-MI
20% reduction in infarct	3.94	5.3	4.7	4.9
Std Dev (control)	8.5	10.9	12.0	10.5
Std Dev (cooled)	6.5	9.3	10.3	11.0

The potential impact of variations in control infarct size and variability is presented in ***Table 19.***

Table 19: Sample size estimates with alternative standard deviation and detection limit

Mean Difference in infarct size for detection (%)	Standard Deviation	Estimated Sample Size	Total Enrollment (with 24% drop-out)
3.0	**9**	**288**	380
3.0	**10**	**356**	468
3.0	**11**	**430**	566
3.0	**12**	**506**	666
3.5	**9**	**212**	280
3.5	**10**	**260**	342
3.5	**11**	**314**	414
3.5	**12**	**374**	500
4.0	**9**	**162**	214
4.0	**10**	**200**	264
4.0	**11**	**240**	316
4.0	**12**	**286**	376

The primary safety endpoint is a composite endpoint. For the sample size calculation, expected incidence is based on a literature review of acute MI hypothermia trials that combined six studies: Dixon et al, COOL MI, ICE-IT, RAPID MI-ICE, CHILL-MI, VELOCITY[46] which resulted in a 30-day MACE rate of 6.6% in the Control patients and 7.5% in treatment patients. Previously, AMIHOT II trial defined 30-day MACE rate comprised of death, reinfarction, target vessel revascularization, and stroke used a non-inferiority hypothesis with a 6% equivalence delta and 7% in the Control patients[47].

The hypothesis for the primary safety endpoint is the following:

$\mathbf{H_0}: \pi_T \geq \pi_C + 6\%$

$\mathbf{H_A}: \pi_T < \pi_C + 6\%$

π_T and π_C are the underlying proportion of patients having a MACE event.

An enrollment of 500 patients would be able to demonstrate 91% power and 95% 1-sided significance. The safety endpoint will be considered to have been met if there is a high posterior probability of non-inferiority [i.e. P ($\pi t < \pi c + 6\% > 95\%$)]. With a drop-out rate of 20%, the power is calculated to be 86%.

16 PUBLICATION

At the conclusion of the trial, a multi-center manuscript will be prepared for publication. Publications will be managed by the Sponsor, its designee and the Advisory board. Additional publications from any single site will be considered but only after the multi-center publication.

17 INTELLECTUAL PROPERTY

In all documents the company name of ZOLL Circulation® will be referred to in short hand as ZOLL. ZOLL® is a registered trademark of ZOLL Medical Corporation. The Proteus IVTM System is a trademark of ZOLL Circulation, Inc. Proteus Catheters, Cassettes and Temperature Probes (X-Probe) are registered trademarks of ZOLL Circulation, Inc.

18 STATEMENT OF COMPLIANCE

1. Sponsor and Investigator will conduct the clinical investigation in accordance with the ethical principles that have their origin in the Declaration of Helsinki.
2. Sponsor and Investigator will comply with ISO 14155:2011 and any regional or national regulations, as appropriate.
3. Investigator will not begin the clinical investigation until Investigator obtains the required written approval or favorable opinion from the MEC or regulatory authority, if appropriate.
4. Investigator will follow any additional requirements imposed by the MEC or regulatory authority, if appropriate.

ATTACHMENT I – REFERENCES

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ATTACHMENT II – ANTI-SHIVERING PROTOCOL

Shivering Suppression Guidelines

Turn on IVTM System console to initiate system and begin cooling of coldwell

↓

Obtain Informed Consent

↓

Administer Buspirone 60 mg PO/NG x 1 immediately

↓

Place Bair Hugger on upper body; set to "high"; forced-air cover should be adjacent to skin. Put one blanket on top.

↓

Closer to the time of device deployment, **Pethidine 1 mg/kg IV (up to 100 mg)**

***Morphine and/or other sedatives are often administered in the setting of an acute MI Morphine and Pethidine (Demerol) are both opiate narcotics and if possible, morphine should be held as the combination may cause over-sedation. Consider 0.5 mg/kg Pethidine IV, if Morphine has been administered.

↓

At 15 minutes, Pethidine 0.5mg/kg IV should be administered.

Then a 25 mg/hr IV infusion of Pethidine (up to 80 kg patient) or 35mg/hr (> 80 kg patient) should be initiated and maintained for the duration of device deployment.

***Make sure the patient has a respiratory rate ≥ 10 breaths/minute.

What to do if shivering occurs:

First, try **repositioning the Bair Hugger** or changing its settings to increase the heat delivered to the patient's surface.

Second, consider **increasing dose of Pethidine**. Prior to giving additional Pethidine, look for signs of respiratory depression (i.e. decreased Respiratory Rate, decreased O2 Saturation by Pulse Ox.) If it is decided that the patient can tolerate additional Pethidine the following may be tried:

1. An IV dose of 25 mg x 1 may be given
2. If Infusion rate is 25mg/hr, the rate may be increased to a maximum of 35 mg/hr

If the shivering persists following the above measures, **consider raising the target temperature on the Proteus Console by 0.5°C** (i.e. from 32.0°C to 32.5°C). If this does not work after 5-10 minutes at the new target temperature, then the process can be repeated until a temperature where no shivering is obtained.

ATTACHMENT III – BEDSIDE SHIVERING ASSESSMENT SCALE (BSAS)

SCORE	SEVERITY	DEFINITION
0	None	No shivering noted on palpation of the masseter, neck or chest wall
1	Mild	Shivering localized to the neck and/or thorax only
2	Moderate	Shivering involves gross movement of the upper extremities in addition to neck and thorax
3	Severe	Shivering involves gross movements of the trunk, upper and lower extremities

ATTACHMENT IV – SPECIFIC NEW-ONSET ADVERSE EVENT DEFINITIONS

SPECIFIC NEW-ONSET ADVERSE EVENT	DEFINITION
1. All-Cause Mortality	Deaths will be classified as cardiac, vascular or noncardiovascular as defined by the Academic Research Consortium.[27] All deaths are considered cardiac unless an unequivocal non-cardiac cause can be established. Specifically, any unexpected death even in patients with coexisting potentially fatal non-cardiac disease (e.g. cancer, infection) should be classified as cardiac. <u>Cardiac death (CD):</u> Any death due to proximate cardiac cause (e.g. MI, low-output failure, fatal arrhythmia), unwitnessed death and death of unknown cause, all procedure related deaths including those related to concomitant treatment. <u>Vascular death:</u> Death due to non-coronary vascular causes such as cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular cause. <u>Non-cardiovascular death</u>: Any death not covered by the above definitions such as death caused by infection, malignancy, sepsis, pulmonary causes, accident, suicide or trauma.
2. Recurrent MI [27,31]	Recurrent MI or re-infarction may be diagnosed when cardiac biomarker levels are stable on 2 samples that are >6 hours apart or are in decline if a subsequent value 3 to 6 hours after the procedure is increased by $\geq$ 20% from the baseline sample. If the baseline value is not stable, then insufficient data exists to recommend biomarker criteria for diagnosis, and the Academic Research Consortium[27,31] recommends that the event be considered as pre-procedure MI. Periprocedural MI is that which occurs within the first 48 hrs after PCI or within the first 72 hrs after coronary artery bypass grafting (CABG). <u>Q wave MI:</u>

	Development of new, pathological Q wave on the baseline ECG (≥ 0.04 seconds in duration and ≥ 1 mm in depth) in ≥ 2 contiguous precordial leads or ≥ 2 adjacent limb leads) Non-Q wave MI: Those MIs which are not Q-wave MI.
3. Need for revascularization of the target vessel (TVR)[27]	TVR is defined as any repeat percutaneous intervention or surgical bypass of any segment of the target vessel. The target vessel is defined as the entire major coronary vessel proximal and distal to the target lesion, which includes upstream and downstream branches and the target lesion itself.
4. Stroke	Development of a new neurological deficit that persists > 24 hours, or worsening of previous neurological symptoms that persist > 24 hours.
5. Cardiogenic shock	Systolic blood pressure of less than 90 mmHg for at least 30 minutes which is secondary to myocardial dysfunction, leading to decreased cardiac output and evidence of tissue hypoxia in the presence of adequate intravascular volume.
6. Pulmonary embolism	Sudden onset of pleuritic chest pain, cough, hemoptysis, hypoxia, tachycardia, and a positive ventilation/perfusion scan or a CT scan.
7. Ventricular Fibrillation (V-Fib)	Rapid uncoordinated fluttering contractions of the heart ventricles recognized by the occurrence on the electrocardiogram of coarse and irregular oscillations without discernible QRS complexes or T waves
8. Vascular complications requiring intervention	Complications arising from the use of the Proteus Catheter including the development of a vessel tear, hematoma, pseudoaneurysm, arteriovenous (AV) fistula, or retroperitoneal bleeding which require an additional surgical intervention for treatment.
9. Bleeding requiring transfusion of 2 units or greater	Any periprocedural bleeding which occurs as a result of the PCI and/ or cooling procedure which requires transfusing > 2 units.
10. Systemic Infection	Sepsis with confirmed positive blood cultures.
11. Cooling Catheter Access Site Wound infection	Infection and inflammation of the incision or puncture site requiring drainage and/or debridement in addition to antibiotic therapy, e.g., cellulitis.
12. Pulmonary Edema	Abnormal accumulation of fluid in the lungs
13. Deep Venous Thrombosis (DVT)[32]	Formation of one or more blood clots in one of the body's large veins, most commonly in the lower limbs. The clot(s) can cause partial or complete blocking of circulation in the vein, which in some patients leads to pain, swelling,

	tenderness, discoloration, or redness of the affected area, and skin that is warm to the touch. As many patients enrolled in the trial will have pre-existing DVT, for the purposes of this trial DVT is defined as the de novo onset of DVT following enrollment which required treatment or worsening of pre-existing DVT.

ATTACHMENT V – ADVERSE EVENT DEFINITIONS

Adverse Event Definitions

In addition to the definitions provided in **Attachment IV– Specific New Onset Serious Adverse Event Definitions**, the following definitions apply to expected adverse events that may occur and must be reported throughout this clinical trial. Events reported should represent a new onset or increase in the severity of the condition from the time of enrollment.

A. CARDIAC COMPLICATIONS	DEFINITION
Recurrent Myocardial ischemia [31]	Recurrent Myocardial Ischemia : is evidenced through baseline ECG changes identified during continuous multilead baseline ECG–ischemia monitoring (or Holter monitoring) which may be accompanied by the development of new clinical symptoms suggesting an ischemic cardiac episode.
Arrhythmias	The development of a new atrial and/or ventricular arrhythmia, significant increase in the severity of a preexisting arrhythmia, or any episode of cardiac arrest.
Congestive Heart Failure[34]	Defined as patients with defined or presumed cardiac disease and one of the following: Class I: without limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea. Class II: slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, or dyspnea. Class III: marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea. Class IV: inability to carry on any physical activity without discomfort. Symptoms are present even at rest or minimal exertion.

B. PULMONARY COMPLICATIONS	DEFINITION
Pneumonia	Clinical evidence as determined by physical, radiographic, and laboratory findings requiring treatment with antibiotics, inhalation therapy, intubation, or suctioning.
Atelectasis	Clinical evidence as determined by physical, radiographic, and laboratory findings requiring treatment with antibiotics, inhalation therapy, intubation, or suctioning.

Respiratory Failure	Need for mechanical ventilation for > 24 hours postoperatively, or reintubation for any reason.

C. RENAL COMPLICATIONS	DEFINITION
Acute Kidney injury (AKI)[35]	AKI is defined as any of the following: Increase in SCr by ≥.3 mg/dl (≥26.5 µmol/l) within 48 hours; or Increase in SCr to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or Urine volume < 0.5 ml/kg/h for 6 hours.

D. VASCULAR COMPLICATIONS	DEFINITION
Arteriovenous Fistula	Formation of an abnormal connection between the lumens of an artery and a vein as documented by CT, ultrasound, angiography, or direct observation.
Embolism	The obstruction of a blood vessel by a blood clot or foreign substance, e.g., air, fat, bacteria.
Vessel perforation	Defined as perforation of the access vessel wall or vena cava confirmed by extravasation of contrast under fluoroscopy, angiography, CT scan, and/ or direct observation at surgery or autopsy.
Hematoma	An abnormal localized collection of blood (clotted or partially clotted) and situated within an organ or a soft tissue space, such as within a muscle. Development of an incisional or retroperitoneal hematoma requiring surgical intervention, evacuation, transfusion or prolonged hospitalization.
Hemorrhage	Post-procedural bleeding requiring transfusion of ≥ 2 units.
Hypotension	Abnormally low systolic blood pressure that is < 80 mm Hg

D. VASCULAR COMPLICATIONS	DEFINITION
Peripheral vascular insufficiency (PVI)	Inadequate peripheral blood flow resulting from the occlusion of vessels by atherosclerotic plaques, thrombi, or emboli; damaged, diseased, or intrinsically weak vascular walls; arteriovenous fistulas; hematologic hypercoagulability; and heavy smoking. Signs of vascular insufficiency include pale, cyanotic, or mottled skin over the affected area; swelling of an extremity; absent or reduced tactile sensation; tingling; diminished sense of temperature; muscle pain, such as intermittent claudication in the calf; and, in advanced disease, ulcers and atrophy of muscles in the involved extremity. As many patients enrolled in the trial will have pre-existing Peripheral Vascular Insufficiency (PVI), for the purposes of this trial PVI is defined as the de novo onset of PVI following enrollment which requires treatment or worsening of pre-existing PVI.
Pseudoaneurysm	Enlargement of the aorta, iliac, or femoral arteries, which contain some or all of the medial layer, the adventitia, and periaortic tissue most commonly associated with previous aortic operative procedures, trauma, and/or infection. Pseudoaneurysms typically present as a well-defined collection of blood outside the vessel wall from contained rupture.
Stenosis	A reduction in the diameter of the vessel lumen when compared to the reference diameter, as documented by angiography, which requires intervention and is related to the procedure, e.g., access vessel.
Thrombosis	Clotting within a blood vessel which may cause infarction of tissues supplied by the vessel; it may be occlusive or attached to the vessel or heart wall without obstructing the lumen.
Transient Ischemic Attack (TIA)	A brief episode of neurological dysfunction caused by focal brain or retinal ischemia with clinical symptoms typically lasting 1 - 24 hours and without evidence of acute infarction.

E. WOUND COMPLICATIONS	DEFINITION
Hematoma	An abnormal localized collection of blood (clotted or partially clotted) and situated within an organ or a soft tissue space, such as within a muscle. Development of an

	incisional or retroperitoneal hematoma requiring surgical intervention, evacuation, transfusion or prolonged hospitalization.
Arteriovenous Fistula	Formation of an abnormal connection between the lumens of an artery and a vein as documented by CT, ultrasound, angiography, or direct observation.
Nerve Injury/Peripheral Neuropathy	Direct damage to nerves surrounding the access site, operative field, or catheter deployment site, and the resultant signs and/or symptoms of such damage which may include pain and numbness in the affected area associated with muscle weakness and decreased patellar reflex lasting > 1 month after treatment.

F. SYSTEMIC COMPLICATIONS	DEFINITION
Coagulopathy	The development of an abnormal bleeding disorder, e.g., disseminated intravascular coagulopathy or thrombocytopenia, documented by appropriate laboratory studies and requiring therapy with medication or transfusion.
Anesthetic Complications	Reaction or complication caused by administration of an anesthetic.
Liver failure[33]	Acute liver failure is defined as the rapid development of hepatocellular dysfunction, specifically coagulopathy and mental status changes (encephalopathy) in a patient without known prior liver disease.

F. SYSTEMIC COMPLICATIONS	DEFINITION
Pancreatitis[33]	Evidenced on two of the following three conditions: 1) abdominal pain suggestive strongly of acute pancreatitis (epigastric pain often radiating to the back), 2) serum amylase and/or lipase activity at least 3 times greater than the upper limit of normal, (imaging is to be used if the elevated values are <3 times normal); and 3) characteristic findings of acute pancreatitis on transabdominal ultrasound or on Contrast Enhanced Computed Tomography (CECT) [32]

ATTACHMENT VI – INVESTIGATOR LIST

ATTACHMENT VII – LIST OF ABBREVIATIONS

AAR	Area at Risk
ACC	American College of Cardiology
ADE	Adverse Device Effect
AE	Adverse Event
AHA	American Heart Assocation
AKI	Acute Kidney Injury
AMI	Acute Myocardial Infarction
ASADE	Anticipated Serious Adverse Device Effect
AV	Arteriovenous
BSAS	Bedside *Shivering* Assessment *Scale*
CABG	Coronary Artery Bypass Grafting
CD	Cardiac Death
CEC	Clinical Events Committee
CHF	Congestive Heart Failure
CIP	Clinical Investigation Plan
CI-TLR	Clinically-Indicated Target Lesion Revascularization
CMP	Clinical Monitoring Plan
cMR	Cardiac Magnetic Resonance
CNS	Central Nervous System
CRO	Clinincal Research Organization
CRF	Case Report Form
CRMI	Clinically Relevant Myocardial Infarction
CVA	Cerebral Vascular Accident
CVP	Central Venous Pressure
DAPT	Dual Antiplatelet Therapy
DD	Device Deficiency
DES	Drug Eluting Stent
DMC	Data Monitoring Committee
DP	Dorsalis Pedis
DSMB	Data Safety Monitoring Board
DTB	Door-to-Balloon
DVT	Deep Vein Thrombosis
EC	Ethics Committee
ECG	Electrocardiography
EDC	Electronic Data Capture
ED	Emergency Department

ER	Emergency Room
ESC	European Society of Cardiology
EU	European Union
Fr	French
FMECA	Failure Mode, Effects and Criticality Analysis
FEP	Fluorinated Ethylene Propylene
GLP	Good Laboratory Practice
HDPE	High-density Polyethylene
HIPPA	Heath Insurance Portability and Accountability Act
HTN	Hypertension
ICF	Informed Consent Form
IEC	International Electrotechnical Commission
IFU	Instructions for Use
IQR	Interquartile Range
IRB	Institutional Review Board
IRI	Ischemia Reperfusion Injury
IS	Infarct Size
ISO	International Organization for Standardization
ITT	Intention-to-Treat
IVC	Inferior Vena Cava
IVTM	Intravascular Temperature Management
KCCQ	Kansas City Cardiomyopathy Questionnaire
LAL	Limulus Amebocyte Lysate
LED	Light-emitting Diode
LV	Left Ventricular
LVEF	Left Ventricular Ejection Fraction
MACE	Major Adverse Cardiac Events
MAO	*Monoamine Oxidase*
MaR	Myocardium at Risk
MEC	Medical Ethics Committee
MEM	Minimum Essential Medium
MI	Myocardial Infarction
MRI	Magnetic Resonance Imaging
NCA	National Competent Authority

NYHA	New York Health Association
OD	Outer Diameter
PCI	Percutaneous Coronary Intervention
PETG	Polyethylene Terephthalate - Glycol modified
PP	Per-protocol
PVI	Peripheral Vascular Insufficiency
PVP	Polyvinylpyrrolidone
RCN	Radio-Contrast Nephropathy
RF	Radiofrequency
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Events
SBP	Systolic Blood Pressure
SOP	Standard Operating Procedure
SPECT	Single-photon Emission Computed Tomography
STEMI	ST-segment Elevation Myocardial Infarction
SVT	Supraventricular Tachycardia
TIA	Transient Ischemic Attack
TIMI	Thrombolysis In Myocardial Infarction
TH	Therapeutic Hypothermia
TVR	Target Vessel Revascularization
UADE	Unanticipated Adverse Device Effect
UFH	Unfractioned Heparin
USADE	Unanticipated Serious Adverse Device Effect
USP	United States Pharmacopeia
UTI	Urinary Tract Infection

APPENDIX D

COOL-AMI EU Pivotal Trial Clinical Investigational Plan

France Protocol (Rev. 3)

(127 pages)

Clinical Investigation Plan

COOL-AMI EU PIVOTAL TRIAL: A MULTICENTER, PROSPECTIVE, RANDOMIZED-CONTROLLED TRIAL TO ASSESS THE SAFETY AND EFFECTIVENESS OF COOLING AS AN ADJUNCTIVE THERAPY TO PERCUTANEOUS INTERVENTION IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

PROTOCOL NO.: EDC 3135

Revision: 3

EFFECTIVE DATE: JUNE 19, 2018

CONFIDENTIAL & PROPRIETARY

CLINICAL INVESTIGATION PLAN APPROVAL PAGE

CLINICAL INVESTIGATION PLAN:	COOL-AMI EU Pivotal Trial: A multicenter, prospective, randomized controlled Trial to assess the safety and effectiveness of cooling as an adjunctive therapy to percutaneous intervention in patients with acute myocardial infarction
PROTOCOL NO.:	EDC-3135
SPONSOR:	ZOLL Circulation, Inc. 2000 Ringwood Avenue San Jose, CA 95131
SPONSOR REPRESENTATIVE:	ZOLL Medical Deutschland GmbH Emil-Hoffmann - Straße 13 50996 Köln, Germany
CLINICAL TRIAL SPONSOR's CONTACT:	Philippa Hill
REVISION NUMBER :	3

Approval of Clinical Investigation Plan by Sponsor:

Philippa Hill — June 19th 2018

Philippa Hill
Senior Director, Clinical Affairs

Date

Signature Page

Clinical Investigation Plan

COOL-AMI EU PIVOTAL TRIAL: A MULTICENTER, PROSPECTIVE, RANDOMIZED-CONTROLLED TRIAL TO ASSESS THE SAFETY AND EFFECTIVENESS OF COOLING AS AN ADJUNCTIVE THERAPY TO PERCUTANEOUS INTERVENTION IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

PROTOCOL NO.: EDC-3135

Revision: 3

Effective Date: JUNE 19, 2018

Signatures of Investigator below constitute their approval of this clinical investigation plan (CIP) and provide necessary assurances that they have read the CIP, understand it, and will work according to all stipulations of it, and to the ethical principles stated in the latest version of the Declaration of Helsinki and the ISO 14155:2011 (Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice).

Investigator Name (Please Print)	
Investigator Signature	**Date**
Institution Name	
Institution Address	
ZOLL Circulation, Inc. **Sponsor Name**	
2000 Ringwood Avenue, San Jose CA 95131 **Sponsor Address**	
ZOLL Medical Deutschland GmbH **Sponsor Representative**	

Table of Contents

1. SYNOPSIS

Clinical Trial Title	**COOL-AMI EU PIVOTAL TRIAL: A MULTICENTER, PROSPECTIVE, RANDOMIZED-CONTROLLED TRIAL TO ASSESS THE SAFETY AND EFFECTIVENESS OF COOLING AS AN ADJUNCTIVE THERAPY TO PERCUTANEOUS INTERVENTION IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION**
Clinical Trial Sponsor	ZOLL® Circulation, Inc.
Clinical Trial Sponsor's Contact	Philippa Hill Senior Director, Clinical Affairs ZOLL Circulation, Inc. 2000 Ringwood Ave. San Jose, CA 95131 Main: +1 (408) 541-2140 Fax: +1 (408) 541-1030 PHill@zoll.com@zoll.com
Trial Number	EDC-3135
Investigational Device	**Proteus™ Intravascular Temperature Management (IVTM) System**
Trial Objective	The objective of this trial is to evaluate the safety and effectiveness of therapeutic hypothermia, using the ZOLL Proteus IVTM System, as an adjunctive therapy for patients presenting with acute anterior myocardial infarction (AMI) and undergoing percutaneous coronary intervention (PCI) in comparison with patients with acute anterior myocardial infarction and undergoing PCI only.
Trial Design	A multicenter, prospective, interventional, randomized-controlled trial. Randomization will be in a 1:1 ratio, Test Arm (PCI + Cooling) or Control Arm (PCI alone) in up to 500 randomized subjects (250 subjects in each arm). **Roll-In Subjects**: To enhance each site's ability to successfully integrate steps of the protocol and for training purposes prior to randomizing subjects in the trial, each site may enroll up to 4 Roll-In subjects in a non-randomized fashion. Roll-In subjects will be treated

	and followed in the same manner as subjects in the Test Arm of the protocol (PCI + Cooling). Up to a total of 280 Roll-In subjects (up to 4 per site) may be enrolled. Due to limited cMR data available in patients with inferior MI who received an adequate dose of cooling prior to revascularization, Inferior MI subjects will be allowed to be included as Roll-Ins to further evaluate inferior MI infarct size by cMR imaging. Evaluation of infarct size will be performed by cMR imaging at 4-6 days.
Primary Effectiveness Endpoint	Relative reduction of 20% in mean anterior myocardial infarct size as determined by Cardiac Magnetic Resonance (cMR) imaging at 4-6 days post infarct in the Test Arm (cooling + PCI) relative to the Control Arm (PCI only).
Primary Safety Endpoint	Per-patient rate of composite Major Adverse Cardiac Events (MACE) in randomized subjects, defined as Cardiac Death (CD), All Myocardial Infarction (All MI) and Clinically-Indicated Target Lesion Revascularization (CI-TLR) at 30 day follow-up; non-inferiority to the control.
Investigational Sites	Up to 70 clinical sites in Europe
Inclusion & Exclusion Criteria	Patients shall be screened to the following inclusion and exclusion criteria. Subjects are qualified for participation only if all Inclusion Criteria have been met and all Exclusion Criteria have been confirmed not present. **Inclusion Criteria** All Inclusion Criteria must be answered YES for subject to satisfy Inclusion Criteria: 1. The patient is ≥ 18 years of age. 2. The patient must have symptoms consistent with AMI (i.e. chest pain, arm pain, etc.) and unresponsive to nitroglycerin, with symptoms beginning greater than 30 minutes but less than 4.5 hours prior to consent. 3. Qualifying Infarct location: a. **Roll-In subjects**: Evidence of Acute Anterior or Inferior MI with ST-segment elevation of ≥ 0.2 mV in two or more anterior or inferior contiguous precordial leads.(V1-V4)

	b. **Randomized subjects**: Evidence of Acute Anterior MI only with ST-segment elevation of ≥ 0.2 mV in two or more anterior contiguous precordial leads. (V1-V4) 4. The patient is eligible for PCI. 5. The patient is willing to provide written informed consent to participate in this clinical trial. **Exclusion Criteria** All Exclusion Criteria must be answered NO for subject to satisfy Exclusion Criteria: 1. The patient has had a previous Myocardial Infarction. 2. The patient is experiencing cardiogenic shock, systolic blood pressure [SBP] <100 mmHg, HR>100 bpm and arterial oxygen saturation (pulse oximetry) ≤92% without additional oxygen. 3. The patient is presenting with resuscitated cardiac arrest, atrial fibrillation, or Killip risk stratification class II through IV. 4. The patient has an aortic dissection or requires an immediate surgical or procedural intervention other than PCI. 5. The patient has known history of Congestive Heart Failure (CHF), hepatic failure, end-stage kidney disease or severe renal failure (clearance < 30ml/min/1.73m²). 6. The patient is febrile (temperature > 37.5 °C) or has experienced an infection with fever in the last 5 days. 7. The patient has a known previous CABG. 8. The patient has a known recent stroke within 90 days of admission. 9. Cardio-pulmonary decompensation that has occurred prior to consent or, in the opinion of the physician, that is imminent or likely to occur following presentation to the clinical site. 10. Contraindications to hypothermia, such as patients with known hematologic dyscrasias which affect thrombosis (e.g., cryoglobulinemia, sickle cell disease, serum cold agglutinins) or vasospastic disorders (such as Raynaud's or thromboangitis obliterans). 11. Any contraindication to cardiac MRI, or any implant in the upper body which may cause artifacts on cardiac MRI imaging. 12. The patient has a known hypersensitivity or contraindication to aspirin, heparin, or sensitivity to contrast media, which cannot be adequately pre-medicated.

	13. The patient has a known history of bleeding diathesis, coagulopathy, cryoglobulinemia, sickle cell anemia, or will refuse blood transfusions. 14. The patient has a height of <1.5 meters (4 feet 11 inches). 15. The patient has a known hypersensitivity or contraindication to buspirone hydrochloride or Pethidine (Meperidine) and/or has been treated with a monoamine oxidase inhibitor in the past 14 days. 16. Patient has a known history of severe hepatic or renal impairment, untreated hypothyroidism, Addison's disease, benign prostatic hypertrophy, or urethral stricture that in the opinion of the physician would be incompatible with Pethidine administration. 17. The patient has an Inferior Vena Cava filter in place (IVC). 18. The patient has a pre-MI life expectancy of <1 year due to underlying medical conditions or pre-existing co-morbidities. 19. The patient has a known, unresolved history of drug use or alcohol dependency, or lacks the ability to comprehend or follow instructions. 20. The patient is currently enrolled in another investigational drug or device trial. 21. The patient is apprehensive about or unwilling to undergo the required MRI imaging at follow-up, has a documented or suspected diagnosis of claustrophobia, or has Gadolinium allergy, or is in permanent Atrial Fibrillation. 22. The patient has received thrombolytic therapy prior to consent. 23. The patient shows clinical evidence of spontaneous reperfusion as observed symptomatically and/ or from baseline ECG findings (partial or complete ST resolution in baseline ECG prior to informed consent and randomization). 24. The patient is a vulnerable subject, for instance, a person in detention (i.e., prisoner or ward of the state). 25. The patient is a female who is known to be pregnant.
Clinical Trial Population	Adult male and female patients presenting with an acute myocardial infarction. To qualify, patients must have symptoms consistent with AMI (i.e. chest pain, arm pain, etc.) unresponsive to nitroglycerin, with symptom onset greater than 30 minutes <u>but less than 4.5 hours</u> prior to arrival of the Emergency Medical Services or upon arrival to hospital and be eligible for PCI.

	Randomized subjects must have evidence of Acute Anterior MI only with ST-segment elevation of ≥ 0.2 mV in two or more anterior contiguous precordial leads (V1-V4) will be included. **Roll-In subjects** with evidence of Acute Anterior or Inferior MI with ST-segment elevation of ≥ 0.2 mV in two or more anterior or inferior contiguous precordial leads(V1-V4) will be included.
Intervention	Intravascular permissive hypothermia as an adjunct to PCI. Cooling will be initiated prior to PCI with infusion of up to 1 L of cold saline (4°C) (according to the guideline) and with the Proteus Console set at 32.0 degrees Celsius. Total cooling time will be 3 hours (± 15 minutes) and will be followed with active rewarming with the Proteus IVTM System to attain normothermia [36 °C (96.8°F)].
Length of Follow Up	12 months
Enrollment	Initiation of enrollment: December 2017 Completion of Enrollment: June 2019 Follow up completed: June 2020
Summary of Statistical Analysis	Primary efficacy endpoint of infarct size measured as percentage of total LV mass by cMR, the null hypothesis of equal infarct size between two arms will be tested with t-test for the study population. For the safety endpoint, comparison of per patient MACE rate for non-inferiority will be made with Fisher's exact Test.
Planned Interim Analyses	Two interim analyses are planned to be performed at approximately 50% and 75% of randomization, once subjects have completed 4-6 day cMR follow-up. At the interim stage, the trial will be stopped to reject the null hypothesis of no difference or continue enrollment.
Analysis Sets	The **Intention-to-Treat (ITT)** population will be used for primary statistical analyses and summaries for all analyses except for Safety endpoints. The ITT population includes subjects who have signed an informed consent and have been randomized to the Test Arm or the Control Arm of the trial. ITT subjects will be evaluated according to the group to which they were randomized. The **Per-Protocol (PP) population** includes those subjects who met inclusion and exclusion criteria, were randomized to either the Test Arm or Control Arm, received the treatment to which they were

	randomized, and complied substantially with the treatment timeline and steps of this protocol without major protocol violations. The **Safety Analysis Set** will be used to evaluate safety endpoints. These will be all subjects included in the study as defined by the ITT analysis set and Roll-In subjects. For the safety analysis subjects will be followed for all Adverse Events 30 days post procedure. Additionally, all subjects will be followed through 12 months post procedure for the incidence of Serious Adverse Events (SAEs), Death and Heart Failure (as assessed by NYHA and Kansas City Cardiomyopathy Questionnaire (KCCQ)).
Trial Oversight	Each participating site will dedicate one Principal Investigator to oversee the execution of the clinical trial in accordance with the protocol.

2 INTRODUCTION

Clinical investigations have shown that induction of hypothermia before reperfusion of acute coronary occlusion reduces infarct size. A pilot study from Lund University demonstrated that the induction of mild hypothermia (<35°C) in ST Elevation Myocardial Infarction (STEMI) patients prior to performing Percutaneous Coronary Intervention (PCI) can save (preserve) 38% more cardiac tissue compared with the PCI alone.[1]

Hypothermia has proven to be one of the most potent and consistent adjunctive therapies for infarct size reduction in numerous preclinical studies, when administered prior to reperfusion. This is unlike the well accepted approach for therapeutic hypothermia for cardiac arrest, where cooling is applied after reperfusion. The mechanisms leading to protection are multifactorial. However, unlike the consistent findings in preclinical studies, clinical trials (COOL -MI, ICE-IT, CHILL-MI) have failed to show a decrease in infarct size. The major reason is likely due to the difficulty in achieving adequate cooling prior to reperfusion. As shown in **Table 1** below, none of the clinical trials to date has reached target temperature prior to reperfusion, as has been done in all of the animal studies.

Table 1: Major Cooling Trials in STEMI.

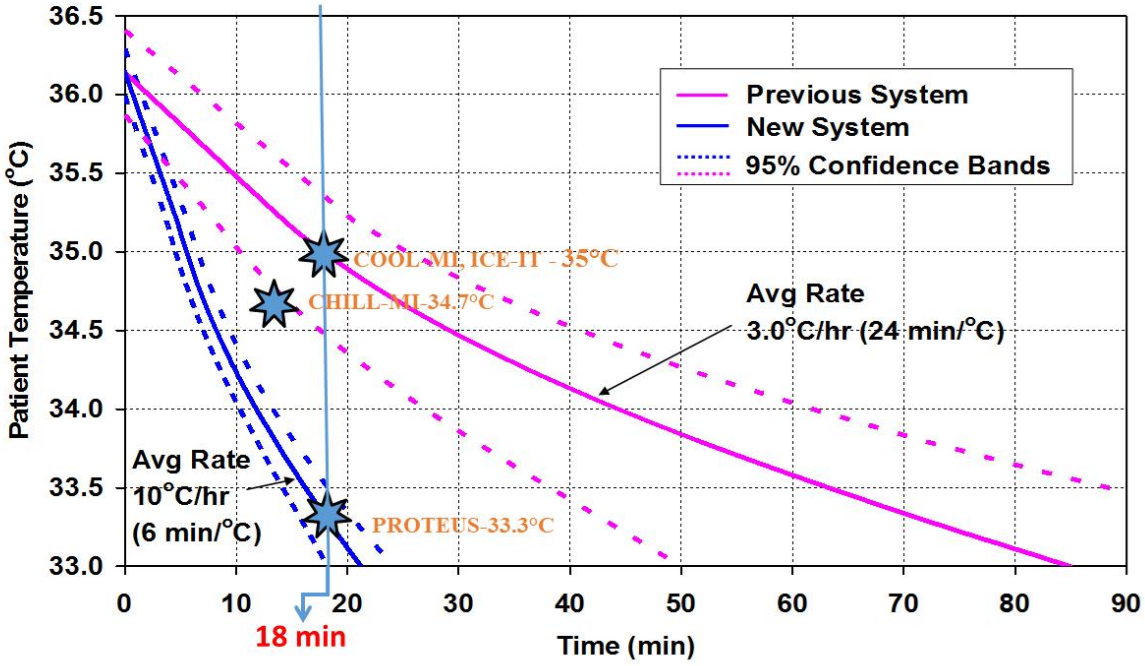
Major Cooling Trials in STEMI					
Trial	**Sample Size**	**Target Temp (°C)**	**Actual Temp at Reperfusion (°C)**	**Temp Miss (°C)**	**Cooling Time before Reperfusion (min)**
COOL -MI	168 – Hyp 157 – Control	33.0	35.0	2.0	18
ICE-IT	105 – Hyp 99 – Control	33.0	35	2.0	16

CHILL-MI	61 – Hyp 59 – Control	33.0	34.7	1.7	13

The target temperature for each trial was 33.0 °C. The actual temperature at the time of reperfusion was 1.7-2.0 °C higher than target. This is a miss in temperature "dose" of around 50% [normal temperature is 37.0 °C, target temperature was 33.0 °C, (37.0 – 35.0) / (37.0 – 33.0) = 50%].

Post hoc analysis of these trials showed that patients with anterior MI that were cooled to less than 35°C at the time of PCI showed a significant reduction in infarct size, supporting the idea of a dose response (**See Figure 1**). Recent preclinical results (Stanford-ZOLL data) have shown that temperature at reperfusion of 32 °C is superior to 35 °C for reducing infarct size, confirming a dose response. Future clinical trials will require more powerful cooling devices, and more consistency in implementing 18 minutes of cooling before reperfusion across all study sites in order to evaluate the actual effectiveness of therapeutic hypothermia as a protection strategy.

Figure 1: Temperature at reperfusion for the Major Therapeutic Hypothermia in AMI Clinical trials.



The Proteus device has a confirmed faster cooling rate. With a duration of cooling of 18 minutes prior to reperfusion, as occurred in the COOL -MI trial, the expected temperature at reperfusion is 33.3°C with the Proteus device. This is significantly better than the 35°C achieved in COOL -MI and ICE-IT, and 34.7°C achieved in CHILL-MI. The relative effectiveness of the Proteus device for cooling, compared to the performance of the prior studies is shown in Figure 1 above. The addition of a bolus infusion of 4°C cold saline is expected to further enhance the temperature achieved at reperfusion with the Proteus System.

This Investigational Plan was developed in accordance with the requirements set forth in the Good Clinical Practices (E6)[2], ISO 14155:2011 Clinical investigation of medical devices for human subjects[3] - Good clinical practice, the Declaration of Helsinki, and the local regulatory requirements an adjunctive therapy to PCI.

3 BACKGROUND

Coronary heart disease complicated by acute myocardial infarction (AMI) remains a leading cause of death and disability worldwide. AMI most commonly occurs when a coronary artery becomes occluded by thrombus following the rupture of an atherosclerotic plaque. Factors that may affect the size of the subsequent infarction include duration of ischemia, size of ischemic territory, collateral blood flow, and myocardial metabolic rate. Long-term sequelae of AMI include ventricular remodeling, loss of ventricular function, congestive heart failure, dysrhythmias, and sudden death.

Although major gains have been made in improving the outcome of patients suffering AMI, and early myocardial reperfusion with the use of thrombolytic therapy or primary percutaneous coronary intervention (PCI) are effective, morbidity and mortality remain substantial. This may be because restoration of blood flow to the ischemic myocardium can itself induce injury through myocardial "ischemia reperfusion injury" (IRI), which can be defined as that portion of the ischemia-reperfusion continuum which is preventable by treatment initiated after restoration of blood flow.[4] It has been proposed that 50% of the final infarct size may be a function of IRI. [4]

Ischemia reperfusion injury is protean in its components, likely including free radical and reactive oxygen species, disordered vasculature, inflammatory injury, programmed cell death, and pathologic remodeling among others.[5] Unfortunately, the cascading nature of these events challenge and, in the end, may defeat the single molecular target pharmacologic model. The long list of failed IRI pharmacologic agents includes antioxidants, calcium channel blockers, anti-inflammatory drugs, sodium hydrogen exchange inhibitors, among others, has led some to question the importance of reperfusion injury in the myocardium.[6] Large infarctions still occur despite timely reperfusion, due to reperfusion injury. Numerous treatments have been studied to reduce reperfusion injury, with little success to date. [7-9]

Therapeutic hypothermia (TH) has been studied for many years as a potential therapy for ischemia and reperfusion.[10 -16] The past few years have seen development of a broad literature reporting both laboratory and clinical trials of mild post-reperfusion TH in the treatment of disease entities as diverse as acute cardiac arrest, stroke, and myocardial infarction, among others. Unlike single pharmacologic agents, TH has the potential to modify and ameliorate multiple pathways of injury.

4 INTENDED USE, SYSTEM OVERVIEW, & DEVICE DESCRIPTION

4.1 Intended Use / Indication for Use

The ZOLL® Proteus™ Intravascular Temperature Management (IVTM) System is indicated for use in adult subjects with acute myocardial infarction to induce and maintain hypothermia prior to percutaneous coronary intervention as an adjunctive therapy to reduce anterior infarct size. The Proteus IVTM System is to be used only as part of the clinical investigation.

4.2 System Overview

The Proteus Intravascular Temperature Management (IVTM) System consists of four primary components: a single-use heat exchange catheter; heat exchange cassette; a temperature probe and a reusable microprocessor-driven console. The system is designed

to achieve and maintain patient temperatures within the range of 32 - 37°C. Its performance profile includes:

1. Rapid patient cooling and warming

2. Precise achievement and maintenance of a desired patient target temperature

3. Quick and simple deployment: See the catheterization lab, critical care unit, emergency department, and other hospital settings

Reference the Investigator Brochure for additional information on the Proteus IVTM System.

The Proteus IVTM System couples a heat exchange catheter with a dual microprocessor-driven controller to manage patient temperature. The Proteus IVTM System is designed to rapidly cool and warm patients, achieve and precisely maintain a target patient temperature and to be quickly and easily deployed.

Cool or warm sterile saline is continuously circulated through the catheter, thereby cooling or warming the blood as it flows over the catheter without perfusion of fluids into the body. The saline is transported from the catheter to the cassette (mounted in the console) via extension lines. The cassette has an integral heat exchange element and a pump that couples with the console to cool or warm the saline being pumped through the closed circuit comprised of the cassette and catheter. The Proteus IVTM Console continuously monitors the patient temperature and controls the catheter temperature to cool, warm or maintain the target temperature.

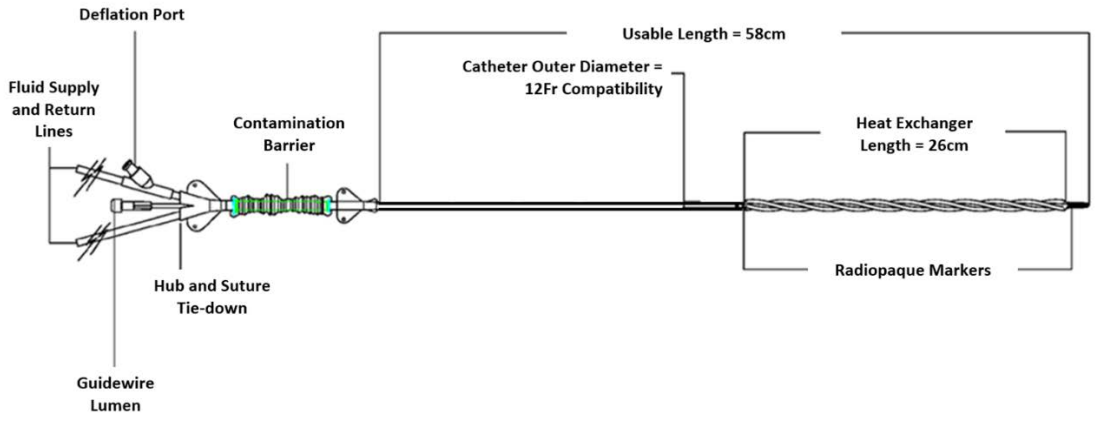
4.3 Device Description

4.3.1 Proteus Catheter

The Proteus Catheter (**Figure 2**) is a single-use, heparin coated, endovascular heat exchange catheter consisting of a triple lobed, helically wound balloon mounted on the distal portion of a multi-lumen shaft. The catheter is designed for placement in the Inferior Vena Cava via the femoral vein using a 12Fr or a 14Fr hemostatic introducer sheath. The catheter has a fluid supply lumen, a fluid return lumen, a guidewire port at the proximal end of the catheter connecting to a guidewire lumen that accommodates guidewires with diameters up to 0.038". The expanded balloon portion of the catheter has an expanded diameter of 17 mm and a length of 26 cm during system operation. The catheter has a radiopaque marker mounted at the distal and proximal end of the balloon portion of the catheter. The distal end of the catheter has a non-traumatic soft tip. The fluid supply and fluid return lumens of the catheter are connected to the cassette via extension lines approximately 2 meters in length, which provide the closed heat transfer fluid circuit. The

0.038", 145-cm. stainless steel guidewire included in the package has a soft atraumatic tip.

Figure 2 Diagram of Proteus Catheter



4.3.2 Proteus Temperature Probe

The Proteus System measures a patient's core body temperature using a heparin-coated endovascular dual output probe (X-Probe) advanced through the guidewire lumen of the Proteus Catheter after the catheter is placed.

4.3.3 Proteus Cassette

The single-use Proteus Cassette consists of a heat exchange element, a pump, a pump coupling to interface with the motor drive in the console and fluid lines to interface with the heat transfer fluid circulated by the console. The cassette is designed to be removed from the portable control console allowing the catheter to remain in the patient to facilitate moving the patient to another location where temperature management can continue using the same or another control console.

4.3.4 Proteus Console

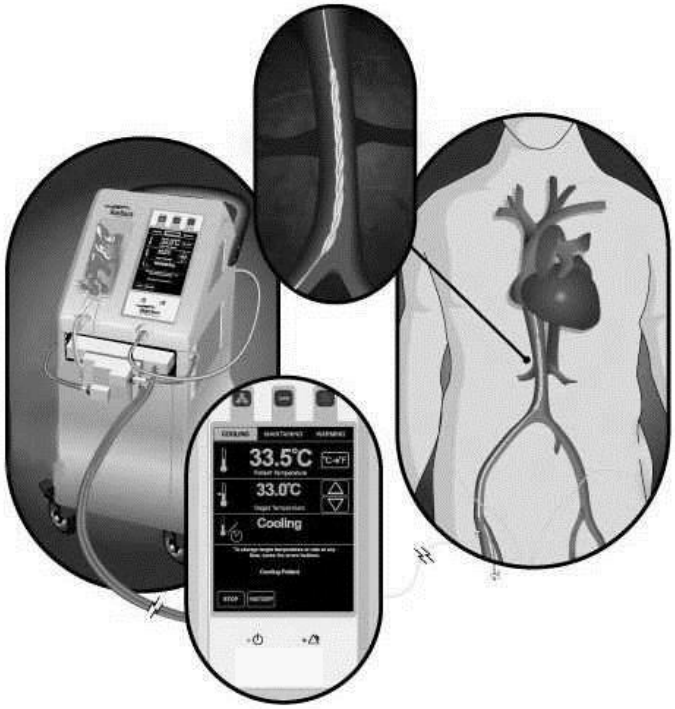
The Proteus Console **(Figure 3)** consists of solid-state thermoelectric modules, a motor drive, dual fluid level detection systems and dual microprocessors. A dilute polypropylene glycol/water mixture (process fluid) circulates within the console to provide heat exchange with the saline heat transfer fluid loop in the cassette. This technology along with microprocessor proportional control of both the saline and the patient temperature enable the following features:

- Designated patient temperature between 32-37°C is maintained within ± 0.3°C continuous calculation and display, in all ambient lighting conditions, of patient actual temperature, target temperature, and rate of cooling/warming

- Redundant safety system to shut down and warn user of patient overheat or overcool, saline leakage, sensor failure, and electrical or mechanical malfunction
- Control console automatically performs a hardware and software diagnostic check of all functional and safety systems upon startup
- Maximum cooling and heating rates vary from patient to patient depending on the patient's cardiac output, size and weight, room temperature and humidity, and the successful implementation of the anti-shivering medication regimen, type and amount anesthesia, combined use with blankets or active heating/cooling apparatus, body cavity exposure to the environment during surgery and other factors.

Figure 3: Proteus Console

Figure 4: Proteus Catheter and Interconnection between Catheter, Temperature Probe (X-Probe), Cassette and Console.



4.3.5 Device Labeling

Written *Instructions for Use*, *Operation Manual, Quick Reference Guide, and Service Manual* for the Proteus IVTM System will be packaged with product shipped to the investigational sites. The Proteus IVTM System is to be used only as part of the clinical investigation. (See Proteus IVTM System Labeling)

5 PRIOR INVESTIGATIONS

5.1 Pre-Clinical Studies

Hypothermia has been shown to reduce metabolic demand and provide ischemic protection. Recent studies across numerous different animal models have demonstrated a strong direct relationship between myocardial temperature and infarct size.[11,12,14-18] Mild to moderate degrees of hypothermia (32-35°C) have resulted in significant reductions in infarct size when applied either before or after the onset of coronary occlusion in animal studies.

In other studies, in 1996, Duncker et al, and in 1998 Miki et al, both demonstrated a dose response relationship between myocardial temperature and infarct size using a laboratory model of AMI.[11,12] Subsequently, Dae et al in collaboration with Radiant Inc. demonstrated that therapeutic hypothermia can be induced safely and rapidly in animal

models using intravascular cooling.[13] They then showed that hypothermic therapy initiated late during ischemia and continuing for several hours after reperfusion significantly improved reflow and reduced macroscopic zones of no-reflow and necrosis in this model.[15] The study showed:

- A striking reduction of myocardial infarct size. The cooled group had an infarct of 9 ± 6% of the area at risk vs. 45 ± 8% of the area at risk for controls
- Preservation of myocardial perfusion and viability in the cooled group as demonstrated by radionuclide imaging
- No evidence of apoptosis in salvaged myocardium in the cooling arm. Well-preserved cardiac output during the cooling process.

Of particular relevance, Gotberg et al reported in 2008 that hypothermia achieved before reperfusion decreased infarct size, while hypothermia initiated at the time of reperfusion prevented microvascular obstruction, but did not decrease myocardial infarct size. [16]

5.2 Human Clinical Studies

5.2.1 COOL MI Trial

The COOL MI Trial[19] was conducted from September 2001 through April 2003. A total of 421 patients were enrolled (199 Control, 193 Intervention, 29 Roll-In) at 27 investigational sites in the US, Germany and Australia. The primary analysis population included 357 patients (180 Control, 177 Intervention) who received the assigned treatment. The COOL MI Trial evaluated the safety and effectiveness of cooling as an adjunctive therapy to percutaneous coronary intervention (PCI) in patients with acute myocardial infarction. **Table 2** below displays enrollment characteristics.

Table 2: COOL MI Trial Enrollment Characteristics

	Control (N=180)	**Intervention (N=177)**	**p-value**
Anterior Myocardial Infarction	77 (44%)	74 (42%)	0.77
Inferior Myocardial Infarction	99 (56%)	103 (58%)	0.77
Failed thrombolytic therapy prior to enrollment	23 (12.8%)	18 (10.3%)	0.67
Time in minutes – median (interquartile range)			
From symptom onset to hospital presentation	123 (69 – 201)	114 (60 – 190)	0.08
From hospital presentation to PCI	88 (61 – 114)	104 (80 – 134)	<0.0001

5.2.1.1 Procedural and Angiographic Results COOL MI Trial

The Trial demonstrated that endovascular cooling using the Radiant Medical's (now ZOLL's) Reprieve System ™ in the setting of myocardial infarction was safe, well tolerated, and readily integrated into the existing treatment pathway. While the primary effectiveness endpoint of the study was not achieved, the data provided a strong signal indicating that when patients were sufficiently cooled prior to reperfusion, myocardial damage was reduced.[19]

The Control and Intervention groups were well matched in terms of culprit vessels, percutaneous coronary intervention (PCI) procedures and treatment success. As expected, cooling did not affect the angiographic success of PCI procedures. Of the 357 patients who underwent primary PCI, the majority were treated with stent implantation and a platelet glycoprotein receptor inhibitor. Approximately 20% of study subjects were determined to have Thrombolysis in Myocardial Infarction (TIMI 3) flow prior to PCI. TIMI Grade Flow is a scoring system from 0-3 referring to levels of coronary blood flow assessed during percutaneous coronary angioplasty:

- TIMI 0 flow (no perfusion) refers to the absence of any antegrade flow beyond a coronary occlusion.
- TIMI 1 flow (penetration without perfusion) is faint antegrade coronary flow beyond the occlusion, with incomplete filling of the distal coronary bed.
- TIMI 2 flow (partial reperfusion) is delayed or sluggish antegrade flow with complete filling of the distal territory.
- TIMI 3 flow (complete perfusion) is normal flow which fills the distal coronary bed completely

After PCI, TIMI 3 flow was achieved in approximately 92% of patients. Only about 30% of patients had TIMI myocardial perfusion grade 3; however the percentage was similar in both treatment groups and is consistent with literature reports of myocardial perfusion. Procedural and angiographic data are presented in **Table 3** below.

Table 3: COOL MI Trial - Procedural and Angiographic Data

	Control (N=180)	Intervention (N=177)	p-value
Infarct related artery, Stent implantation, Glycoprotein & Stenosis Diameter			
Left anterior descending coronary artery	70 (39%)	69 (39%)	0.91
Circumflex artery	13 (7%)	14 (8%)	0.87
Right coronary artery	77 (43%)	74 (42%)	0.93

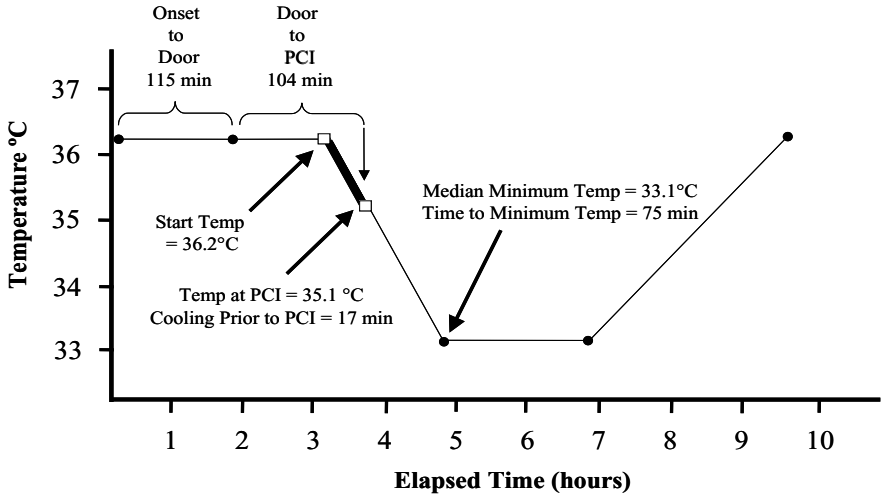
Stent implanted	153 (92%)	157 (94%)	0.59
Glycoprotein IIb/IIIa receptor inhibitor	140 (78%)	142 (80%)	0.74
Initial diameter stenosis (mean ± std dev)	92 ± 14%	92 ± 12%	0.93
Initial TIMI flow			
Grade 0/1	126 (71%)	122 (69%)	0.77
Grade 2	14 (8%)	21 (12%)	0.28
Grade 3	38 (21%)	34 (19%)	0.74
Final diameter stenosis	7 ± 9%	8 ± 10%	1.00
Final TIMI* flow			
Grade 0/1	2 (1%)	5 (3%)	0.33
Grade 2	7 (4%)	12 (7%)	0.31
Grade 3	170 (95%)	160 (90%)	0.11
Final myocardial perfusion grade			
Grade 0/1	63 (43%)	76 (53%)	0.11
Grade 2	35 (24%)	26 (18%)	0.27
Grade 3	49 (33%)	41 (29%)	0.54

*Thrombolysis in Myocardial Infarction

5.2.1.2 COOL MI Trial Results

Of the 177 Intervention patients, 11 (6.2%) patients had the Reprieve Catheter placed in the emergency room (ER), one (0.6%) patient had the catheter placed in the cath lab holding area, and 165 (93.2%) patients had the catheter placed in the cath lab. Overall, patients in the Intervention group received a median of 17 minutes (interquartile range (IQR): 10-27) of cooling prior to PCI. During that time, patient temperature was decreased from a median of 36.2°C (IQR: 35.8-36.5) at the initiation of cooling to 35.1°C (IQR: 34.5-35.6) at the time of PCI (**Figure 1**). The median of the minimum temperature reached by each patient was 33.1°C (IQR: 33.0-33.4), which was achieved in 75 minutes (IQR: 50-108). Target patient temperature was set at a 33°C for 3 hours post-PCI. Patients were then re-warmed at 1°C/hr until Investigator-determined normothermia was reached [median=36.5 (IQR: 36.2-36.8]). **Figure 5** below shows patient temperature over time with cooling and time to PCI. The goal to reach target temperature of 33°C at PCI was not achieved in the trial, due to the inadequate cooling power of the Reprieve System. As noted above, target temperature of 33°C was reached after 75 minutes of cooling, long after PCI had occurred.

Figure 5: Median Temperature and Elapsed Times for Intervention Patients



5.2.1.3 COOL MI Trial Tolerability of Cooling

Shivering was managed according to the shivering suppression guidelines recommended for this study by Dr. Daniel Sessler, Chairman of the Department of Anesthesiology at the University of Louisville. The recommended baseline combination of Pethidine, buspirone and skin warming using a forced-air blanket could be supplemented incrementally in the event of shivering or patient discomfort, by additional Pethidine, or by slightly increasing the target temperature. If these steps were unsuccessful, patients could be actively rewarmed to normothermia.

This protocol proved to be quite effective at maintaining patient comfort. Intervention patients received an average of 56 mg of oral buspirone and an average of 267 mg of intravenous Pethidine over the course of the cooling procedure. Of 177 patients in the treatment group, only one patient (0.6%) required premature warming due to intolerability of cooling. Nine patients (5.1%) required a slight increase in target temperature (0.2°C – 0.5°C) to maintain patient comfort. Ninety-eight patients (55.7%) required supplementary dosing of Pethidine, but 60 of these 98 patients (61.2%) had not received the recommended loading dose of the anti-shivering drugs.

COOL MI Trial Safety Results: The primary safety endpoint of the COOL MI study was the incidence, through 30 days, of Major Adverse Cardiac Events (MACE), defined as the composite of death, recurrent myocardial infarction of the target vessel and the need for urgent revascularization of the target vessel. As shown in **Table 4** below, there was no statistical difference in the incidence of MACE in the Intervention group as compared to the Control group. All MACE were adjudicated by an independent Clinical Events Committee and none were attributed to cooling or use of the Reprieve System. **Table 4**

below demonstrates the results of the study with regard to the incidence of Major Adverse Cardiac Events.

Table 4: COOL MI Trial Incidence of MACE

Events through 30 days	Control (N=180)	Intervention (N=177)	p-value
MACE	**7 (3.9%)**	**11 (6.2%)**	**0.45**
Death	4 (2.2%)	6 (3.4%)	0.71
Recurrent MI	3 (1.7%)	1 (0.6%)	0.63
Urgent Revascularization	0 (0%)	4 (2.3%)	0.12

These MACE rates observed in COOL MI compare favorably with those reported for similar patients in recent AMI trials, such as ADMIRAL, CADILLAC, DANAMI and RAPID MI-ICE (**Table 5**).

Table 5 Incidence of MACE for Comparable Patients in Recent AMI Trials

Trial	Death	Reinfarction	Revascularization
COOL MI (Treatment Group) (n=177)	3.4%	0.6%	2.3%
ADMIRAL (n=149)[17]	3.4%	1.3%	4.7%
CADILLAC (n=524)[18]	2.7%	0.8%	1.6%
DANAMI-2 (n=790)[19]	6.6%	1.6%	NA
RAPID MI-ICE (n=20)[1]	0%	0%	0%

5.2.1.4 COOL MI Trial Adverse Events Related to Cooling

Potential adverse events related to cooling (e.g., arrhythmia or hemodynamic complications) and to placement and/or use of the Reprieve Catheter (e.g., vascular or thrombogenic complications) were also evaluated as a secondary endpoint. The incidence of these types of events is presented. It is important to note that these complications are also risks of myocardial infarction and coronary intervention themselves. **Table 6** below reports the incidence of non-MACE complications.

Table 6: Incidence of Other Complications

Events through 30 days	Control (N=180)	Intervention (N=177)	p-value
Bradyarrhythmia	41 (22.8%)	46 (26.0%)	0.56
Ventricular Tachycardia/Fibrillation	36 (20.0%)	31 (17.5%)	0.64
Cardiogenic Shock	11 (6.1%)	22 (12.4%)	0.06
Pulmonary Edema	3 (1.7%)	6 (3.4%)	0.49
Vascular Complications	15 (8.3%)	15 (8.5%)	0.90
Retroperitoneal bleed	2 (1.1%)	1 (0.6%)	0.95
Hematoma >6cm	12 (6.7%)	13 (7.3%)	0.99
Pseudoaneurysm	1 (0.6%)	3 (1.7%)	0.63
AV fistula	1 (0.6%)	0 (0%)	0.95
Bleeding Requiring Transfusion	14 (7.8%)	20 (11.3%)	0.34
Deep Venous Thrombosis	0	3 (1.7%)	0.24
Pulmonary Embolism	3 (1.7%)	0	0.24
Stroke	1 (0.6%)	0	0.95

Arrhythmias are a known risk of moderate to severe hypothermia. In the COOL MI trial, with its mild hypothermia target temperature, arrhythmias were not more common and appeared to be primarily related to ischemia and/or the coronary intervention. Cardiogenic shock requiring treatment with an intra-aortic balloon pump trended toward a higher incidence in the hypothermic group. However, the majority of shock cases appeared to be more related to complicated MIs and/or complex interventions than to cooling. Other potential contributory factors (e.g., age, weight, Pethidine dose) were compared between shock and stable patients; however, no causal relationships were apparent. The majority of the vascular complications reported in the Intervention group were related to the arterial access site for the PCI procedure rather than the venous access site for the cooling catheter. Three cases of deep venous thrombosis (DVT) were reported in the Intervention group.

5.2.1.5 COOL MI Trial Effectiveness Results

The primary effectiveness endpoint in the COOL MI study was infarct size, measured using SPECT imaging at 30 days. Overall, there was no observed difference in infarct size (%LV) between study groups (**Table 7**). The secondary effectiveness endpoints of LV ejection fraction, CK-MB release, and ST-segment resolution, likewise did not demonstrate a difference between the Intervention and Control groups.

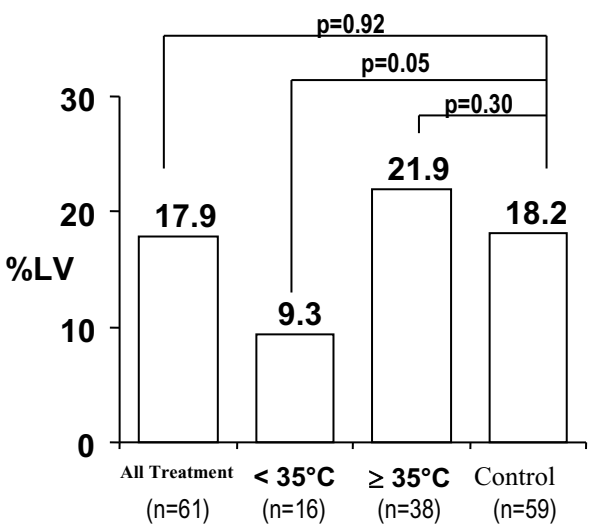
Table 7: COOL MI Results

	Control	Intervention	p-value
% LV Infarct Size (N) mean ± std dev median	157 13.8 ± 15.1 10	168 14.1 ± 14.3 10	 0.83
LV Ejection Fraction (N) mean ± std dev median	104 55.2 ± 11.4 54	115 53.0 ± 12.0 53	 0.17
Peak CK-MB (N) mean ± std dev median	167 42.8 ± 48.1 33.9	168 49.1 ± 50.7 33.6	 0.25
ST-segment resolution - 90 min. post-PCI (N) < 30% 30 - 69% ≥ 70%	90 11.1% 27.8% 53.3%	82 20.7% 35.4% 39.0%	 0.13 0.36 0.09
ST-segment resolution - 180 min. post-PCI (N) < 30% 30 - 69% ≥ 70%	79 10.1% 20.3% 60.8%	80 16.3% 27.5% 51.3%	 0.36 0.38 0.30

In addition, no statistically significant differences were demonstrated when the Intervention and Control patients were compared based on the following stratifications: infarct location, time from onset of symptoms to PCI, prior MI, or TIMI flow prior to PCI. However, subsequent analysis revealed a strong relationship between final infarct size and patient temperature at the time of reperfusion.

The mean temperature at the time of reperfusion, or more specifically, at the time of first balloon inflation, was 35.1°C. As shown in **Figure 6**, in the population of patients with anterior myocardial infarction, those patients who had a temperature <35°C at the time of reperfusion had a statistically significant reduction in final infarct size as compared to both the control group (9.3% vs. 18.2%, p=0.05) and those with a temperature ≥35°C (9.3% vs. 21.9%, p=0.01).

Figure 6: Mean Infarct Sizes (%LV) of Patients with Anterior Infarction



Subject groups:

i) All Intervention patients regardless of temperature at PCI

ii) Intervention patients cooled to < 35°C at PCI

iii) Intervention patients ≥ 35°C at PCI

iv) Control patients

This effect has a strong basis in physiology and was consistent across other clinical measures, i.e., there was a trend toward decreased CK-MB release and increased LV Ejection Fraction in the cooled patients. This effect is not attributable to differences in baseline clinical or angiographic variables. In fact, those patients with a temperature <35°C were more likely to have occlusion of the proximal versus mid left anterior descending coronary artery and a longer time to reperfusion. These factors would be expected to increase infarct size in this group, but the observed reduction in infarct size appears to be the result of cooling.

5.2.2 COOL MI II Trial

Because of the encouraging results in patients with anterior AMI's in whom hypothermia had been achieved at the time of PCI, COOL MI II was initiated. Additionally, COOL MI II Trial was intended to verify the feasibility of initiating cooling earlier in the treatment pathway (e.g., in the emergency department). Only a fraction of the anticipated sample size were enrolled before the trial was ended early because the sponsor became financially insolvent after only 41 patients were enrolled. The study data were submitted by the sites to a Data Management CRO. As a result, the final report is not currently available because the data was not released to ZOLL by the Data Management CRO upon ZOLL acquisition of Radiant Medical.

In COOL MI II, all cooling was initiated in the Cath Lab even though the focus was on earlier cooling. Since earlier initiation of cooling was not accomplished, reaching the goal of a core temperature of 35° C before PCI was dependent on the more powerful GTO System. This was accomplished in 26 of the 27 patients without the intentional delay of PCI. Pivotal data for 23 patients were available and the mean time to reach 35°C was 6.1

minutes (± 3.0), 34°C was 14.5 minutes (± 7.9) and 33°C was 31.3 minutes (± 29.9). Data showed 15 of the patients were cooled to 32°C; the mean time was 36.1 minutes (± 14.0).

Efforts to initiate cooling as early as possible resulted in a median of 39 minutes of cooling time prior to PCI, a significant improvement over the median of 18 minutes of cooling time achieved in the previous study. In addition, the median door-to-balloon time was 106 minutes for these COOL MI II patients, compared to a median of 104 minutes for Test patients in the previous study, indicating that PCI was not delayed by the introduction of cooling. By focusing on cooling earlier in the treatment pathway, additional cooling time can be achieved without significant adverse impact on time to reperfusion.

5.2.2.1 COOL MI II Trial Adverse Events

As with COOL MI, the primary safety endpoint of the COOL MI II study was the incidence, through 30 days, of MACE. Shown below are the adverse events in the COOL MI II trial in the intent to treat (ITT) population. **Table 8** combines the Feasibility and Pilot hypothermia groups for a total of 41 patients (12 Feasibility and 29 Pivotal).

Table 8*:* Incidence of MACE and Other Complications

Events through 30 Days	**Normothermia**	**Hypothermia**
Enrollment	*10*	*41*
UADE	0	0
Cardiac		
Death	0	1 (2.4%)
Repeat MI	0	1 (2.4%)
Repeat PCI	1 (10%)	3 (7.3%)
CABG	0	2 (4.9%)
Hypotension / Shock	1 (10%)	6 (14.6%)
CHF	0	2 (4.9%)
Pericardial Effusion	0	1 (2.4%)
Pericarditis	0	1 (2.4%)
HTN	0	1 (2.4%)
Arrhythmias		
Ventricular Fibrillation	0	4 (9.8%)
Vent. Tachycardia	1 (10%)	7 (17.1%)
Frequent PACs	1 (10%)	0
SVT	0	1 (2.4%)
Atrial Fibrillation	0	11 (26.8%)
Vascular Events		
Bleeding requiring transfusion	0	3 (7.3%)
Thrombocytopenia	0	2 (4.9%)
Anemia	0	2 (4.9%)
Hematoma > 6cm	0	2 (4.9%)
DVT	0	1 (2.4%)
Local Tissue Trauma	0	1 (2.4%)
Epistaxis	1 (10%)	0
Hemoptysis	0	1 (2.4%)
Stroke	0	0
Respiratory Events		
Pulmonary Edema	0	8 (19.5%)
Pulmonary Embolism	0	0
Hypoxia	0	1 (2.4%)
Respiratory Failure	0	1 (2.4%)
Plural Effusion	0	3 (7.3%)
Increased Pulmonary HTN	1 (10%)	0
Pneumonia	1 (10%)	0

Renal		
Renal requiring Treatment	1 (10%)	2 (4.9%)
Hemodialysis	0	0
UTI	0	2 (4.9%)
Hematuria	1 (10%)	0
Other		
Nausea / Vomiting	1 (10%)	15 (36.6%)
Systemic Infection	0	3 (7.3%)
Fever	0	3 (7.3%)
Muscular Pain	1 (10%)	3 (7.3%)
Rhabdomyolysis	1 (10%)	0
Mental Status Changes	0	2 (4.9%)
Hypokalemia	0	1 (2.4%)
Vaginal Infection	0	1 (2.4%)

5.2.3 COOL RCN Trial

The COOL RCN (Radio-Contrast nephropathy) trial was undertaken to evaluate whether endovascular cooling provides more effective protection for patients at high risk of experiencing RCN. The trial was designed as an international, multicenter, 1:1 randomized controlled trial of up to 400 subjects at up to 35 investigational sites. Subjects with a calculated Creatinine clearance of 20 – 50 mL/min and scheduled for a diagnostic or interventional catheterization procedure were enrolled. The trial utilized Radiant Medical's Reprieve System. The study was commenced in March 2006 and was terminated after enrolling only 136 subjects due to the financial insolvency of Radiant Medical.

Table 9: COOL RCN Trial*:* Adverse Events Incidence of Complications In-Hospital

	Normothermia	**Hypothermia**	**P Value**
Enrollment	*70*	*58*	
Nausea/Vomiting	6 / 70 (8.6%)	26 / 58 (44.8%)	<0.01
Bradycardia	2 / 70 (2.9%)	7 / 58 (12.1%)	0.04
Bleeding Requiring Transfusion	7 / 70 (10.0%)	1 / 58 (1.7%)	0.05
Atrial Fibrillation	2 / 70 (2.9%)	3 / 58 (5.2%)	0.5
CABG	4 / 70 (5.7%)	1 / 58 (1.7%)	0.25
Pulmonary Edema	4 / 70 (5.7%)	1 / 58 (1.7%)	0.25
Renal Complication	2 / 70 (2.9%)	3 / 58 (5.2%)	0.5

	Normothermia	Hypothermia	P Value
Acute Renal Failure	2 / 70 (2.9%)	2 / 58 (3.4%)	0.85
Elevated Serum Creatinine	0 / 70 (0%)	1 / 58 (1.7%)	--
Hemodialysis	2 / 70 (2.9%)	0 / 58 (0%)	--
Urinary Tract Infection	3 / 70 (0.4%)	1 / 58 (1.7%)	0.41
Hypotension/Shock	1 / 70 (1.4%)	3 / 58 (5.2%)	0.22
Hematoma >6cm	0 / 70 (0%)	3 / 58 (5.2%)	--
SVT	0 / 70 (0%)	2 / 58 (3.4%)	--
MI	0 / 70 (0%)	1 / 58 (1.7%)	--
Ventricular Tachycardia	1 / 70 (1.4%)	1 / 58 (1.7%)	0.89
Death	0 / 70 (0%)	1 / 58 (1.7%)	--
Repeat PCI	1 / 70 (1.4%)	1 / 58 (1.7%)	0.89
Stroke	0 / 70 (0%)	1 / 58 (1.7%)	--

Table 10: COOL RCN Trial: Incidence of Complications to 30 Days

	Normothermia	Hypothermia	P Value
Enrollment	*70*	*58*	
Renal	7	2	0.15
Acute Renal Failure	5	1	0.15
Renal Stent	2	0	--
Kidney Infection	0	1	--
Cardiac	8	14	0.1
MI	1	1	0.89
CABG	2	3	0.5
PCI	1	3	0.22

	Normothermia	Hypothermia	P Value
PCI or CABG	3	6	0.18
Death - Cardiac	1	2	0.45
Shock	0	3	--
CHF	2	1	0.67
Angina	1	0	--
Hypertension	0	1	--
Arrhythmia	3	3	0.81
Atrial Fibrillation	2	1	0.67
Bradycardia	0	2	--
SVT	1	0	--
Ventricular Fibrillation	0	0	--
Non-Cardiac	3	3	0.81
Stroke	1	0	--
Bleed/Transfusion	2	3	0.5
Dialysis	0	0	--
Vascular Complications Requiring Surgery	0	0	--
Rehospitalization	13	13	0.59
Other	9	12	0.23
Anasarca	1		--
Fatigue	1		--
Ischemic Bowel	1	1	0.89
Hypoglycemia	1		--
Lesion Excision	1		--
Anemia	1		--
Hiatal Hernia	1	1	0.89
Pulmonary Edema	1		--
Knee Injury	1		--
Rash		1	--
Debridement of Sternal Wound		1	--
Leg Weakness		1	--
Nausea/Vomiting		2	--
Dehydration		1	--
Acute Respiratory Failure		1	--
Metabolic Acidosis		1	--
Back Pain		1	--
Systemic Infection		1	--

5.2.3.1 Unanticipated Adverse Events

COOL MI Trial – Unanticipated Adverse Events

There was one Unanticipated Adverse Device Effect (UADE) in the COOL MI Trial; A patient experienced nasopharyngeal trauma and bleeding potentially caused by the nasoesophageal temperature probe used as part of the Reprieve System. This resulted in a modification to the Informed Consent Form to explain the risk of nasal trauma and/or bleeding due to the nasoesophageal probe.

COOL MI II Trial – Unanticipated Adverse Events

There were no UADE's in the COOL MI II Trial.

COOL RCN Trial – Unanticipated Adverse Events

There was one UADE in the COOL-RCN Trial. A 73 year old male with chronic renal insufficiency and a history of aortobifemoral bypass scheduled for cardiac catheterization. The patient was randomized to the Hypothermia arm. The Reprieve catheter was placed via the left femoral vein. The angiogram and stenting procedures were performed via right radial arterial access. After approximately 1 hour of cooling, the patient complained that his feet were itching and it was noted that the patient's left foot and leg were cyanotic up to mid-thigh, with no left DP pulse, and the right foot was slightly discolored. He was subsequently rewarmed at the maximum rate for approximately 40 minutes. It was observed that the cyanosis lightened as the patient rewarmed and was apparently resolved with no further sequelae after discontinuation of treatment with the Reprieve catheter, indicating that cooling with the device contributed to the reduced peripheral circulation. The already compromised peripheral vascular circulation is suspected to have been exacerbated by hypothermia induced vasoconstriction. It is known that hypothermia induces superficial vasoconstriction, but this degree of cyanosis had not been observed with previous use of the device. Additionally, after the patient had received Pethidine and versed as part of the anti-shivering protocol, his respiration became depressed, requiring assisted ventilation, Romazicon and Narcan. It is possible that this transient hypoxic event may have also contributed to the cyanosis.

Lower extremity cyanosis in the presence of peripheral vascular insufficiency had not been identified in the protocol or informed consent document as a potential risk of mild hypothermia or use of the Reprieve catheter. The resolution of the cyanosis upon rewarming and removal of the catheter indicated that these may have contributed to the event. The risk section of the protocol and informed consent were subsequently revised.

5.2.4 ICE- IT Trial

The Intravascular Cooling Adjunctive to Percutaneous Coronary Intervention for Acute Myocardial Infarction Trial (ICE-IT) [23] randomized 228 patients presenting with an acute

MI within 6 hours of symptom onset to endovascular cooling concomitant with PCI versus routine PCI. The primary endpoint of infarct size at 30 days as measured by SPECT imaging was similar between the 2 groups (10% for the hypothermia group versus 13% for the control group, p = 0.14). Like the COOL MI trial, ICE-IT was also an overall negative trial. But while TH did not demonstrate any significant decrease in infarct size overall, a trend towards benefit was again observed on post-hoc analysis of the subgroup with anterior infarction who were sufficiently cooled to a temperature of < 35°C at the time of revascularization (infarct size of 12.9% of the left ventricle in the TH population compared to 22.7% in the control group, p = 0.09).[23]

5.2.5 RAPID-MI ICE Trial

Recently, Lund University presented a preliminary report of their RAPID-MI ICE Trial.[1] This trial enrolled 20 patients presenting with acute myocardial infarction, and 10 patients each were randomized to TH by intravascular cooling or a control group. Cooling was accomplished with a combination of 2L of cold saline infusion and the Phillips InnerCool catheter-based cooling system. The endpoint was infarct size normalized to myocardium at risk assessed by cardiac magnetic resonance using T2 weighted imaging and late gadolinium enhancement. Although the sample size is relatively small, the trial produced a number of potentially important results:

- Core body temperature less than for 35°C was achievable before reperfusion without significant delay in the door to balloon time.
- Infarct size normalized to myocardium at risk was reduced by a remarkable 38% in patients receiving hypothermia.
- There were also significant decreases in peak and cumulative Troponin I or T in the hypothermia group.

5.2.6 CHILL-MI Trial

Lund University recently reported the results of the CHILL-MI trial[37], which was a multi-center study of 120 patients with STEMI (< 6 hours) planned to undergo PCI who were randomized to hypothermia induced by rapid infusion of 600 – 2000 ml of cold saline and endovascular cooling, or standard of care. Hypothermia was initiated before PCI and continued for 1 hour after reperfusion. The primary endpoint was infarct size as a percentage of the myocardium at risk (IS/MaR), assessed by cardiac MRI at 4±2 days. The goal to reach target temperature of 33°C at reperfusion was also not achieved in the CHILL-MI trial, due to the inadequate cooling power of the cooling device. Patients randomized to cooling achieved a core body temperature at reperfusion of 34.7°C with a 9 minute longer door-to-balloon time. Hypothermia induced by cold saline infusion and endovascular cooling was feasible and safe, however, there was no significant difference in IS/MaR between the groups. Exploratory analysis of early anterior infarctions (0-4 hrs) showed a significant reduction in IS/AAR of 33% ($p<0.05$). Further, the incidence of

heart failure was lower with hypothermia at 45 days (3% vs 14%, p<0.05). This trial, as the others cited above, shows potential efficacy of cooling in patients with anterior STEMI, supporting further research for confirmation.

5.2.7 Induction of Mild Systemic Hypothermia With Endovascular Cooling During Primary Percutaneous Coronary Intervention for Acute Myocardial Infarction

This multi-center study included 42 patients with acute myocardial infarction (AMI) (onset less than 6hrs) and evaluated the safety and feasibility of endovascular cooling during primary PCI for AMI.[39] Subjects were randomized to PCI with or without endovascular cooling (target core temperature 33°C). Cooling was maintained for 3 h after reperfusion. Skin warming, oral buspirone, and intravenous meperidine were used to reduce the shivering threshold. The primary end point was major adverse cardiac events at 30 days. Infarct size at 30 days was measured using SPECT imaging. All patients successfully cooled did achieved a core temperature below 34°C (mean target temp 33.2 ± 0.9°C). MACE events occurred in 0% vs. 10% (p = NS) of treated versus control patients. The median infarct size was not significantly smaller in patients who received cooling compared with the control group (2% vs. 8% of the left ventricle, p = 0.80).

5.2.8 VELOCITY Trial

The VELOCITY trial[38] randomized 54 STEMI patients at 7 centers in the United States and Canada to emergent PCI with (n = 28) or without (n = 26) hypothermia induced by the Velomedix Automated Peritoneal Lavage System (Velomedix; Menlo Park, CA) between January 2013 and January 2014. Baseline characteristics were similar between the 2 groups, and 46.3% of all infarcts were anterior.

Hypothermia (core temperature at or below 34.9°C) was achieved in 96.3% of patients and PCI was performed in all but 1 patient in each treatment group. Median door-to-balloon time was shorter in the control vs hypothermia group (47 vs 62 minutes; *P* = .007). Among the 46 PCI patients who underwent MRI 3 to 5 days post procedure, the median myocardial infarct size was similar in the control vs hypothermia group (16.1% vs 17.2% of LV mass; *P* = .54).

VELOCITY Investigators observed that prolonged door-to-balloon time in the hypothermia group may have attenuated the effect of hypothermia on infarct size though it is unlikely to have been totally responsible for absence of effect as DTB times were short in both groups and within the range wherein further reductions in mortality may not be realized.

At 30-day follow-up, no patients in the control group had a primary composite safety endpoint event, compared with 6 (21.4%) of the patients who underwent hypothermia (P = .01). Further details in Section 5.2.8.1.

In conclusion, the VELOCITY study found that controlled systemic hypothermia through automated peritoneal lavage may be safely and rapidly established in patients with evolving STEMI undergoing primary PCI at the expense of a modest increase in door-to-balloon time. In the VELOCITY randomized trial, peritoneal hypothermia was associated with an increased rate of adverse events (including stent thrombosis) without reducing infarct size. Adequately powered randomized trials (likely limited to patients with anterior MI) are needed to assess the effect of rapidly induced hypothermia on myocardial salvage and clinical outcomes after primary PCI.

5.2.8.1 VELOCITY Trial Adverse Events at 30 Days

At 30-day follow-up, no patients in the control group had a primary composite safety endpoint event (death, reinfarction, ischemia-driven TLR, major bleeding, sepsis, pneumonia, peritonitis, severe arrhythmias, or renal failure), compared with 6 (21.4%) of the patients who underwent hypothermia (P = .01). Four patients (14.3%) experienced MACE (cardiac death, reinfarction, or ischemia-driven TVR), and 3 (11.0%)—all in the hypothermia arm—developed definite stent thrombosis.

Table 11: VELOCITY Trial Clinical Event Rates Within 30 Days

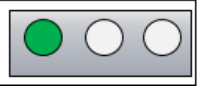
	Control (N=26)	Hypothermia (N=28)	*P* Value
Primary composite safety end point	0% (0)	21.4% (6)	0.01
Cardiac death	0% (0)	3.6% (1)	0.34
Noncardiac death	0% (0)	0% (0)	…
Reinfarction	0% (0)	3.6% (1)	0.34
Ischemia-driven target vessel revascularization	0% (0)	11.0% (3)	0.09
Major bleeding	0% (0)	3.6% (1)	0.34
Ventricular tachycardia or fibrillation	0% (0)	3.6% (1)	0.34
Sepsis	0% (0)	3.6% (1)	0.34
Pneumonia	0% (0)	0% (0)	…
Renal failure	0% (0)	0% (0)	…
Peritonitis	0% (0)	0% (0)	…
Major adverse cardiac events	0% (0)	14.3% (4)	0.047
Stent thrombosis	0% (0)	11.0% (3)	0.09
Acute (≤24 h)	0% (0)	7.1% (2)	0.17
Subacute (1–30 days)	0% (0)	3.6% (1)	0.34
Definite	0% (0)	11.0% (3)	0.09
Probable	0% (0)	0% (0)	…

Data are expressed as Kaplan–Meier estimates, % (n). *P* values are from the log-rank test.

5.2.9 EU AMI Case Series

ZOLL is currently enrolling patients in the COOL-AMI EU Case Series Trials to assess the ability to integrate hypothermia into the current pathway for patients receiving PCI for ST elevation MI. To date, 308 patients have been enrolled at 36 sites in the EU. Both anterior and non-anterior STEMI patients have been enrolled, and cooling is performed using the ZOLL Thermogard XP (TGXP) System or Proteus IVTM system. A series of six standards has been developed and monitored to enable consistency in the execution of the protocol. The standards include delivery of the antishivering regimen correctly, delivery of 1 L of iced saline before PCI, and at least 18 minutes of cooling delivered prior to wire crossing the lesion. Feedback in the form of a report card (**Figure 7**) is provided to the site after each case as indicated in the following diagram:

Figure 7: Report Card Standards

Standards	Measured	Expected	
1. Anti-shivering Regimen Delivered prior to Iced Saline Delivery	C-B-P-S	Per-protocol C-B-P-S	
2. 1 Liter Iced Saline delivered with pressure bag prior to PCI	1 Liter	1 Liter	
3. At least 18 minutes of cooling delivered prior to PCI	18 min	18 min	
4. Door-to-Balloon Time	59 min	< 90min	
5. Ischemic Time	3 hrs. 9 min	< 6 hrs.	
6. DAPT Agent Administered	Yes	Pre-PCI	

These six standards are consistently achieved at all sites. The 18 minute duration of cooling matches the average duration of cooling in the previous EU COOL AMI trial. The ability to deliver 18 minutes of cooling prior to PCI is consistently achieved in the recent EU Case Series, where the door to balloon (DTB) times, at all sites, were less than 60 minutes (ranging from 38 minutes to 58 minutes). This is far less than the maximum door to balloon time of 90 minutes recommended by the current guidelines for PCI, 2011 ACCF/AHA/SCAI PCI Guideline[24,50]). The experience of one of the sites has been published[26], and notes that the average DTB time for the first 11 patients enrolled in the trial was 38 minutes, compared to a mean DTB time of 37 minutes for all patients presenting with STEMI without cooling. In view of the validation that implementation of hypothermia in the treatment pathway for PCI of STEMI patients is feasible, ZOLL has also conducted the COOL-AMI EU PILOT Trial, following the same standards of implementation, with cooling done by the more powerful Proteus device. The goal is to maximize the dose of cooling prior to PCI.

5.2.10 COOL-AMI EU PILOT Trial

ZOLL has completed enrollment in the COOL-AMI EU PILOT Trial that evaluated the retention of subjects after integrating therapeutic hypothermia using the ZOLL Proteus IVTM System into existing STEMI treatment protocols for subjects who presented with acute anterior myocardial infarction. 50 subjects were randomized at 16 sites in the EU. 22 patients (88%; 95% confidence interval [CI]: 69-97%) in the hypothermia group and 23 patients (92%; 95% CI: 74-99) in the control group completed cardiac magnetic resonance imaging at four to six days and 30-day follow-up. A series of three standards were monitored to enable consistency in the execution of the protocol. The standards included delivery of the antishivering regimen correctly, delivery of up to 1 L of iced saline, and 18 minutes of cooling delivered prior to wire crossing the lesion. Patients with

anterior STEMI were rapidly and safely cooled. Intravascular temperature at coronary guidewire crossing after 20.5 minutes of endovascular cooling decreased to 33.6° C (range 31.9-35.5° C), which is ≥1.1° C lower than in previous cooling studies. There was a 17-minute (95% CI: 4.6-29.8 min) cooling-related delay to reperfusion. In the "per protocol" analysis, median infarct size/left ventricular mass was 16.7% in the hypothermia group versus 23.8% in the control group (absolute reduction 7.1%, relative reduction 30%; p=0.31) and median left ventricular ejection fraction (LVEF) was 42% in the hypothermia group and 40% in the control group (absolute reduction 2.4%, relative reduction 6%; p=0.36). There were no statistically significant differences between the groups, in adverse events or serious adverse events.[49]

5.3 Summary and Clinical Trial Rationale

Previous clinical trials in patients experiencing acute myocardial infarction (AMI) have demonstrated that therapeutic hypothermia is safe, well tolerated and showed reductions in infarct size.[19] Additionally, recent preclinical results (Stanford-ZOLL data) have shown that temperature at reperfusion of 32 °C is superior to 35 °C for reducing infarct size, confirming a dose response. Future clinical trials will require more powerful cooling devices, and more consistency in implementing 18 minutes of cooling before reperfusion across all study sites in order anterior infarctions. It is therefore the objective of the COOL-AMI EU PIVOTAL Trial to evaluate the actual effectiveness of therapeutic hypothermia as a protection strategy.

Further clinical trials are needed to evaluate more powerful cooling devices, along with a refined therapeutic hypothermia protocol (target temperature of 32°C + 18 minutes of cooling prior to PCI). It will also be important to understand whether adequate cooling to 32°C + 18 minutes of cooling prior to PCI can be implemented into existing STEMI treatment protocols with no significant delay in door-to-balloon times. This trial aims to address the need for a powered clinical evaluation assessing the safety and effectiveness of the Proteus IVTM for this refined therapeutic hypothermia protocol as an adjunct therapy for AMI patients undergoing PCI. Among these refinements are: 1) A larger dose of cooling was achieved with the Proteus System (temp at PCI was 33.6°C as opposed to 35°C for COOL MI), 2) Delivery of at least 18 minutes of cooling prior to PCI was possible (mean 20 minutes in the EU Pilot Study), 3) the anti-shivering protocol was refined and worked successfully, and 4) the use of report cards for every case to track : a) anti-shivering protocol impementation, b) infusion of 1 liter of cold saline prior to PCI, c) 18 minutes of cooling prior to PCI, d) door to balloon time less than 90 minutes, e) total ischemic time less than 6 hours, and f) proper administration of dual antiplatelet therapy (DAPT) are all refinements ready to be implemented.

6 CLINICAL TRIAL PLAN

6.1 Trial Objective

The objective of this randomized clinical trial is to evaluate the safety and effectiveness of therapeutic hypothermia, using the ZOLL Proteus IVTM System, as an adjunctive therapy for patients presenting with acute anterior myocardial infarction and undergoing PCI, in comparison with patients with acute anterior myocardial infarction and undergoing PCI only. Therapeutic Hypothermia may be initiated prior to arrival at the treating hospital.

6.2 Trial Endpoints

6.2.1 Primary Effectiveness Endpoint

Relative reduction of 20% in mean anterior myocardial infarct size (IS), as determined by Cardiac Magnetic Resonance (cMR) imaging at 4-6 days post-infarct in the Test Arm (cooling + PCI) compared to the Control Arm (PCI only). Infarction Size (IS) is defined as % Left Ventricular Mass as measured by Cardiac Magnetic Resonance (cMR) imaging. Infarct Size (IS) will be assessed by Cardiac Magnetic Resonance (cMR) at 4 – 6 days following the index procedure. The trial is considered to have met the primary efficacy endpoint if the Test Arm demonstrates a 20% relative reduction in infarct size compared to the Control Arm.

The ITT analysis set will be used for primary statistical analyses and summaries. The ITT population includes those subjects who have signed an informed consent and have been randomized to the Test Arm or the Control Arm of the trial. ITT subjects will be evaluated according to the group to which they were randomized.

The PP analysis set will also be evaluated. The PP population includes those subjects who met inclusion and exclusion criteria, were randomized to either the Test or Control arm, received the treatment to which they were randomized, and complied substantially with the treatment timeline and steps of this protocol without major protocol violations.

6.2.2 Primary Safety Endpoint

Per-patient rate of composite Major Adverse Cardiac Events (MACE) subjects, defined as Cardiac Death (CD), All Myocardial Infarction (All MI) and Clinically-Indicated Target Lesion Revascularization (CI-TLR) at 30 day follow-up; non-inferiority to the control.

6.2.3 Additional Assessments: Demographics and Other Parameters

Subject demographics and various baseline characteristics will also be collected. Additional clinical data collected and evaluated will include the number of patients who can successfully be enrolled and randomized, the timing of subject presentation to hospital, the timing of therapeutic and adjunctive interventions, the timing of reaching the

target temperature zone, temperature at PCI, subsequent maintenance of hypothermia and temperature data from the IVTM System. Observations will be evaluated relating to the use of the ZOLL Proteus IVTM System and how it performs in relation to the induction of therapeutic cooling and follow-up cMR imaging. New York Health Association[24] (NYHA) Functional Class and Kansas City Cardiomyopathy Questionnaire[25] (KCCQ) will be evaluated at 12 month follow-up.

6.3 Trial Design

This clinical trial is a multicenter, prospective, interventional, randomized-controlled trial. Randomization will be in a 1:1 ratio, Test Arm (PCI + Cooling) or Control Arm (PCI alone) in up to a total of 500 patients (250 subjects in each arm), at up to 70 clinical sites.

To enhance each site's ability to successfully integrate steps of the protocol and for training purposes prior to randomization, each site may enroll up to 4 Roll-In subjects in a non-randomized fashion. Roll-In subjects will be treated and followed as subjects in the Test Arm of the protocol (PCI + Cooling). Up to a total of 280 Roll-In subjects (up to 4 per site) may be enrolled. Due to limited cMR data in patients with inferior MI who received an adequate dose of cooling prior to revascularization, Inferior MI subjects will be allowed to be included as Roll-Ins to further evaluate inferior MI infarct size by cMR imaging. Evaluation will be done of cMR imaging at 4-6 days following the index procedure.

6.4 Patient Population

Subjects will include those who meet the trial eligibility requirements and who can provide informed consent for cooling treatment. Subjects considered for enrollment in this trial will include adult patients presenting with an acute anterior myocardial infarction. To qualify, patients must have symptoms consistent with AMI (i.e., chest pain, arm pain, etc.) unresponsive to nitroglycerin, qualifying ST-segment elevation of ≥ 0.2 mV in two or more anterior contiguous precordial leads (V1-V4), with symptom onset greater than 30 minutes, but less than 4.5 hours prior to arrival of the Emergency Medical Services or upon arrival to hospital, and be eligible for PCI. This ensures that the overall ischemic time from symptom onset to time of wire crossing is less than 6 hours.

Subjects randomized to the Test Arm, as well as all Roll-In subjects, will receive intravascular cooling with the Proteus IVTM device. While undergoing temperature management, the Anti-shivering Protocol must be followed (see **Attachment II**).

6.5 Selection Criteria

Patients shall be screened to the following inclusion and exclusion criteria. Patients are qualified for participation only if all Inclusion Criteria have been met and all Exclusion Criteria have been confirmed not present.

6.6 Inclusion Criteria

All Inclusion Criteria must be answered YES for subject to satisfy Inclusion Criteria:

1. The patient is ≥ 18 years of age.
2. The patient has symptoms consistent with AMI (i.e. chest pain, arm pain, etc.) and unresponsive to nitroglycerin, with symptoms beginning greater than 30 minutes but less than 4.5 hours prior to consent..
3. Qualifying Infarct Location:
    a. **Roll-In subjects**: Evidence of Acute Anterior or Inferior MI with ST-segment elevation of ≥ 0.2 mV in two or more anterior or inferior contiguous precordial leads (V1-V4).
    b. **Randomized subjects**: Evidence of Acute Anterior MI only with ST-segment elevation of ≥ 0.2 mV in two or more anterior contiguous precordial leads (V1-V4).
4. The patient is eligible for PCI.
5. The patient is willing to provide written informed consent to participate in this clinical trial.

6.7 Exclusion Criteria

All Exclusion Criteria must be answered NO for subject to satisfy Exclusion Criteria:

1. The patient has had a previous Myocardial Infarction.
2. The patient is experiencing cardiogenic shock, systolic blood pressure [SBP] <100 mmHg, HR>100 bpm and arterial oxygen saturation (pulse oximetry) ≤92% without additional oxygen.
3. The patient is presenting with resuscitated Cardiac Arrest, Atrial Fibrillation, or Killip risk stratification class II through IV.
4. The patient has an aortic dissection or requires an immediate surgical or procedural intervention other than PCI.
5. The patient has known history of Congestive Heart Failure (CHF), Hepatic Failure, end-stage kidney disease or severe Renal Failure (clearance < 30ml/min/1.73m²).
6. The patient is febrile (temperature > 37.5 °C) or has experienced an Infection with Fever in the last 5 days.
7. The patient has a known previous CABG.
8. The patient has a known recent Stroke within 90 days of admission.
9. Cardio-Pulmonary Decompensation that has occurred prior to consent or, in the opinion of the physician, that is imminent or likely to occur following presentation to the clinical site.

10. Contraindications to hypothermia, such as patients with known Hematologic Dyscrasias which affect thrombosis (e.g., cryoglobulinemia, sickle cell disease, serum cold agglutinins) or Vasospastic Disorders (such as Raynaud's or thromboangitis obliterans).
11. Any contraindication to cardiac MRI, or any implants in the upper body which may cause artifacts on cardiac MRI imaging.
12. The patient has a known hypersensitivity or contraindication to aspirin, heparin, or sensitivity to contrast media, which cannot be adequately pre-medicated.
13. The patient has a known history of Bleeding Diathesis, Coagulopathy, Cryoglobulinemia, Sickle Cell Anemia, or will refuse blood transfusions.
14. The patient has a height of <1.5 meters (4 feet 11 inches).
15. The patient has a known hypersensitivity or contraindication to buspirone hydrochloride or Pethidine (Meperidine) and/or has been treated with a monoamine oxidase inhibitor in the past 14 days.
16. Patient has a known history of severe hepatic or renal impairment, untreated hypothyroidism, Addison's disease, benign prostatic hypertrophy, or urethral stricture that in the opinion of the physician would be incompatible with Pethidine administration.
17. The patient has an Inferior Vena Cava filter in place (IVC).
18. The patient has a pre-MI life expectancy of <1 year due to underlying medical conditions or pre-existing co-morbidities.
19. The patient has a known, unresolved history of drug use or alcohol dependency, or lacks the ability to comprehend or follow instructions.
20. The patient is currently enrolled in another investigational drug or device trial.
21. The patient is apprehensive about or unwilling to undergo the required MRI imaging at follow-up, has a documented or suspected diagnosis of claustrophobia, or has Gadolinium allergy, or is in permanent Atrial Fibrillation.
22. The patient has received thrombolytic therapy prior to consent
23. The patient shows clinical evidence of spontaneous reperfusion as observed symptomatically and/or from baseline ECG findings (partial or complete ST resolution in ECG prior to informed consent and randomization).
24. The patient is a vulnerable subject, for instance, a person in detention (i.e., prisoner or ward of the state).
25. The patient is a female who is known to be pregnant.

6.8 Clinical Trial Procedures

6.8.1 Patient Screening

Patients presenting with clinical signs and symptoms of AMI will be expeditiously triaged and offered the opportunity to participate in this clinical trial without regard to age, gender or ethnicity. To ensure that patients are approached for potential trial participation without

bias, patient screening information will be maintained on a patient screening log at each site. This log will track patients that were enrolled in the trial as well as patients who were excluded from participation and the reason(s) for their exclusion. The use of a patient screening log assures that all eligible subjects are given an opportunity to participate or decline participation in the trial.

The subject's eligibility for treatment with the Proteus IVTM System will be evaluated based on the medical and anatomical criteria outlined above in the inclusion/exclusion criteria section. The Investigator will explain the elements of this clinical trial, including the risks, potential benefits and required interventional and follow-up procedures, to each subject prior to obtaining informed consent.

If a subject is found to be ineligible during baseline screening and routine diagnostic tests, the subject shall be considered a screen failure and will be documented on the patient screening log. Roll-In subjects are considered enrolled in the trial when all inclusion and exclusion criteria have been satisfied, and informed consent has been signed. Randomized subjects are considered enrolled in the trial when all inclusion and exclusion criteria have been satisfied, informed consent has been signed, and the patient is randomized to either Test or Control Arm of the trial.

6.8.2 Informed Consent

The reviewing Medical Ethics Committee (MEC) must review and approve an Informed Consent Form (ICF) specific to this study. The Sponsor will provide each study center with an example ICF. The study center, to meet specific requirements, may modify this example ICF; however, the ICF to be used for subject consent under this protocol must contain all of the elements required by the study Sponsor and the governing regulatory requirements for informed consent (21 CFR Part 50). Therefore, each investigational site will provide the Sponsor with a copy of the MEC approved ICF - as well as any amendments - for the duration of the study.

Informed consent will be required from each subject. The (MEC) approved Informed Consent document must be signed by the patient or by the legal authorized representative (LAR) prior to any related procedures (or according to the MEC's approved guidelines), including the collection of data on case report forms (CRFs). Only subjects that have the appropriate informed consent form will be included in the trial. Consent may be obtained either at upon EMS arrival or at hospital admission.

The informed consent process (including time and date of discussion), should be documented in the subject's medical record and signed/dated by the individual (investigator or designee) who recorded it. The original signed consent form must be filed in the subject's medical record and a copy of the signed informed consent documentation given to the subject.

All subjects must sign, date and note the time on the Institutional Medical Ethics Committee (MEC) approved informed consent prior to any clinical trial/investigation-specific procedures. Obtaining the consent with the documented date and time, and the provision of a copy to the subject will be documented in the subject's medical record.

Due to the emergent nature of treating acute myocardial infarction, patients who have been enrolled in the study may receive a subsequent consent which provides more detailed information about their participation in the trial (based on MEC requirements), which may be reviewed and signed after the acute phase of their treatment has been completed. If the patient decides they no longer want to be included in the study, they will be withdrawn and their data will be included in the analysis up until the time of withdrawal.

If in the course of the pre-study evaluations prior to consent, the patient is found not to be eligible for inclusion in the study, the patient should be notified and the reason for ineligibility documented on the appropriate Screening Log.

All information pertinent to this clinical investigation (including at a minimum the description and purpose of the study, potential benefits, potential risks and inconveniences, active procedures, confidentiality, compensation, circumstances for termination and site contact persons) will be provided to the subjects in writing and in their native, non-technical, language by Investigator or designee, who has been trained on the protocol.

If new information becomes available that can significantly affect a subject's future health and medical care, this information shall be provided to the affected subject(s) in written form. If relevant, all affected subjects shall be asked to confirm their continuing informed consent in writing.

6.8.3 Roll-In Enrollment

Prior to randomizing patients, each participating center may enroll up to 4 patients Roll-In subjects in a non-randomized fashion. Roll-In subjects are treated and followed as patients in the Test Arm (PCI + Cooling) for training purposes. The justification for the number Roll-In patients in this study is based on ZOLL's previous clinical trial experience in relationship to a site's ability to successfully incorporate the cooling protocol including consent, anti-shivering regimen and an adequate dose of cooling without significantly delaying door-to-balloon time. Successful implementation takes teamwork and often several cases to assure the cooling protocol is adhered to with consistent accuracy.

In light of the fact that previous clinical trials (e.g., COOL-MI[19], ICE-IT[23] and CHILL-MI[37]) have failed to provide an adequate dose of cooling prior to reperfusion, ZOLL has implemented a tool called a "Report Card". This Report Card notes the site's success in achieving critical aspects of the protocol, called "Standards", and is provided to the site after every patient is enrolled into the trial. The objective of the Report Card is to report

back to the site their success in implementing a set of standards according to the protocol, and to encourage continuous improvement following each enrollment. The Standards, as noted on the Report Card, include but are not limited to accuracy of antishivering regimen administration and 18 minutes of cooling delivered prior to the wire crossing the lesion. The Standard of 18 minutes of cooling has been demonstrated in previous ZOLL trials to be the amount of time required to deliver an optimal dose of cooling so the patient's core body temperature is as close to target temperature as possible prior to reperfusion without significantly delaying door-to-balloon time.

Consistent achievement of each standard allows sites to move from Roll-In to randomization and enables consistency in execution of the protocol. Feedback will be provided to the site after each enrollment to assure the standards have been met and an adequate dose of cooling has been achieved. Use of the Report Card and Standards is intended to assist sites in ascending their learning curve as rapidly as possible. All centers will transition from Roll-In to Randomization as soon as possible once they have demonstrated their ability to enroll patients while consistently meeting the standards, thereby minimizing the number of Roll-In patients but ensuring accurate, precise adherence to the investigational protocol. Based on the site's performance with the Roll-In patients, as determined by the Sponsor, the site will be notified of authorization to randomize patients in the trial.

Additionally, Roll-In patients will undergo cMR as part of the cMR training process at each site. This will allow the site to train and qualify acquisition of cMR images per cMR protocol and ensure high quality and consistent imaging throughout the study across sites. Roll-In patients will not be included in the primary endpoint analysis; however, they will be included in the safety endpoint analysis. All performed activities on Roll-In subjects will be recorded as if performed in the Test Arm of the trial and hence documented in the Case Report Forms (CRF) for training and evaluation.

Roll-In subjects will be considered to be enrolled when all inclusion and exclusion criteria have been met and the informed consent form has been signed.

6.8.4 Approval to Randomize in the Trial

It will be at the discretion of the sponsor to advance a site to Randomization. Based on the site's performance with the Roll-In patients, as determined by the Sponsor, the site will be notified of authorization to randomize patients in the trial.

6.8.5 Randomization

In the randomization phase, patients who meet eligibility criteria for participation will be randomly assigned to either the Test Arm (PCI + Cooling) or Control Arm (PCI alone) in a 1:1 ratio.

Randomization will be applied using an internet based Interactive Web Response Systems (IWRS). In the trial, randomization will be done using random permuted blocks (based on procedure outlined in Pocock SJ. Clinical Trials: A Practical Approach. Wiley, Chichester, 1983), stratified by site, with 1:1 allocation ratio using a randomization list. At randomization, inclusion and exclusion criteria will be verified, and confirmation of informed consent signature will be done.

Subjects will be considered to be enrolled in the Test Arm and Control Arms of the trial when all inclusion and exclusion criteria have been met, the informed consent form has been signed, and randomization assignment has been completed.

6.8.6 Acute Care and Emergency Room Triage

Prior to the initiation of this trial at each participating institution, training will be conducted by the Sponsor targeted toward the integrated care of each trial subject and emphasizing the shared responsibility between the Departments of Emergency Medicine and Interventional Cardiology, where applicable at each center, with the goal of rapid screening, enrollment and treatment of appropriate patients.

Each center will clearly delineate departmental responsibilities for the following:

- Assessment of patient clinical features, signs and symptoms
- Administration of Informed Consent
- Review of Inclusion/Exclusion Criteria
- Assurance that diagnostic procedures mandated by the protocol are completed prior to randomization into this trial and are appropriately documented
- Patient Randomization
- Administration of pre-treatment medication(s)
- Administration of Anti-shivering medications to subjects randomized to the Test Arm of the trial
- Consensus on location in EMS ambulance and/or hospital where cooling using the Proteus IVTM System will be initiated
- Set-up of Proteus IVTM System, including insertion of the Proteus Catheter into the femoral vein induction of cooling, initiation of re-warming, Proteus IVTM System shutdown and catheter extraction for Test Subjects.

6.8.7 Standardized Care Prior to the Cooling Procedure

It is anticipated that subjects may receive one or more of the following therapies as part of current clinical practice in the treatment of acute myocardial infarction:

- Intravenous fluids and electrolytes
- Oxygen
- Antiplatelets and/or antithrombotics
- Vasoactive agents and diuretics

Clinicians will be encouraged to manage the subject in a standardized manner with respect to oxygenation, anti-coagulation and/or anti-platelet medications.

6.8.8 Documentation Procedures

Trial procedures and treatment data will be documented on standardized Case Report Forms (CRFs) which may be on paper or via an electronic data capture system (EDC). The completion of the CRFs may be delegated to a member of the study team (e.g., the study coordinator) as long as that person is listed on the Delegation of Authority Log. However, the Principal Investigator retains responsibility for the accuracy and integrity of the data entered on the CRF. The CRF will be monitored for accuracy and completeness per the source documents (medical records, charts, interventional systems, worksheets as applicable, etc.) at each clinical center. Temperature data from the Proteus IVTM System will be downloaded and sent to Sponsor. A flow diagram for the Test Arm is represented in **Figure 10**.

It is anticipated that technology and/or techniques such as edit checks and double entry of data may be utilized to minimize the rate of error. Additionally, ZOLL or its assignees may ask for data clarification or re-check of data for accuracy. Monitoring visits and CRF completion logs will be used to track data entry in accordance with trial logistics and expectations.

Any source documentation (procedure reports, imaging studies, lab reports, death certificates, etc.) that is sent to the Sponsor should have all patient identifiers removed and replaced with the subject's trial ID, and processes ensuring patient privacy and clinical data confidentiality will be followed in accordance with local regulations and applicable laws.

6.8.9 Study Flow and Procedures

Figure 8 Screening and Enrollment Flow

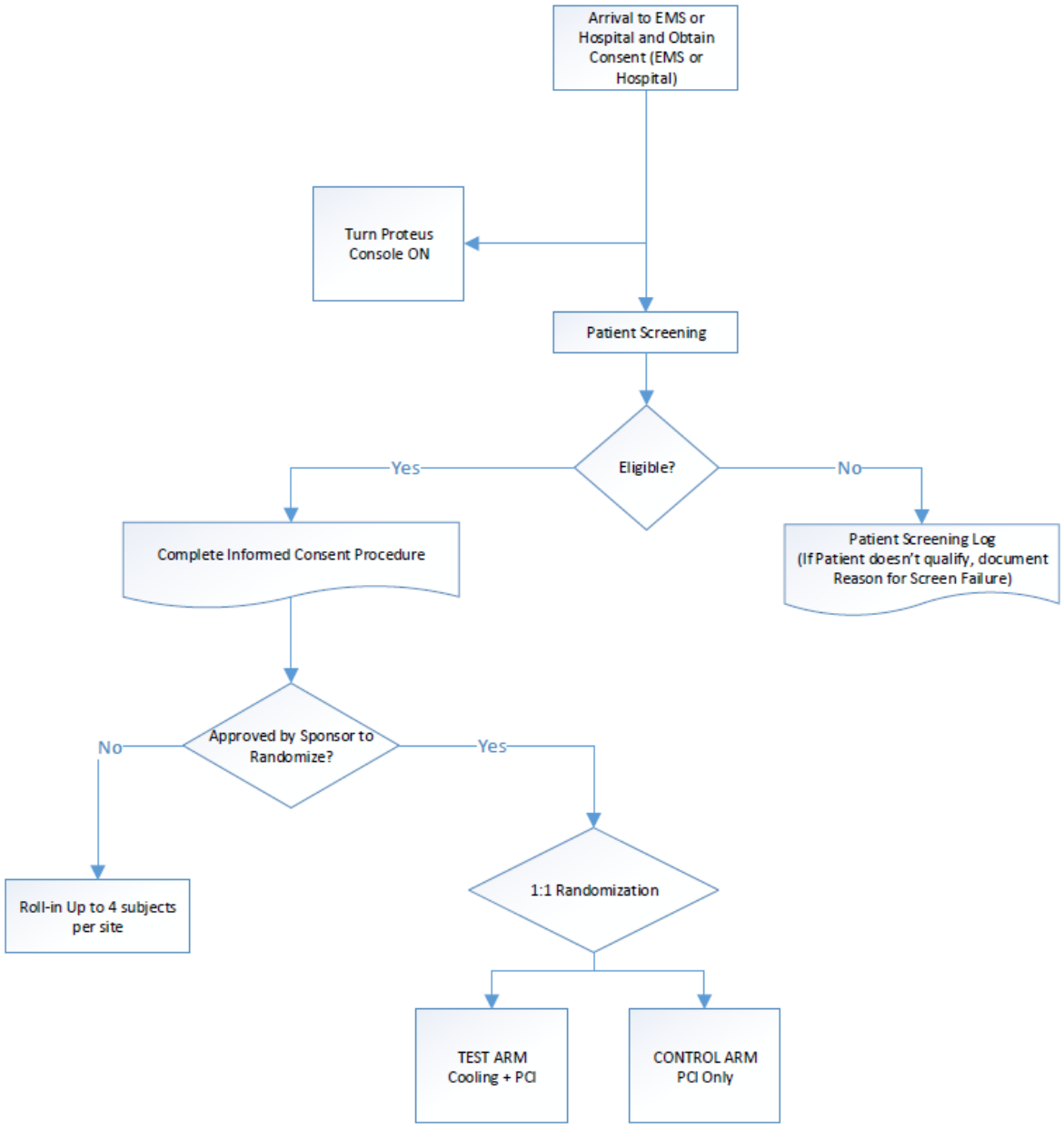


Figure 9 Control Arm Flow

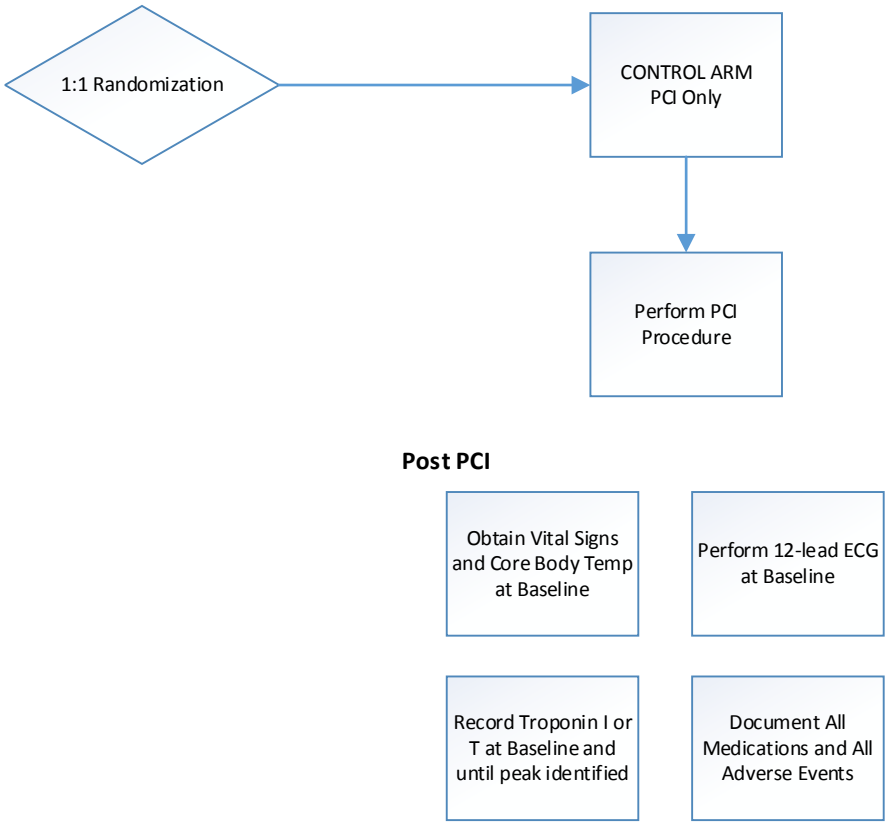


Figure 10 Test Arm Flow

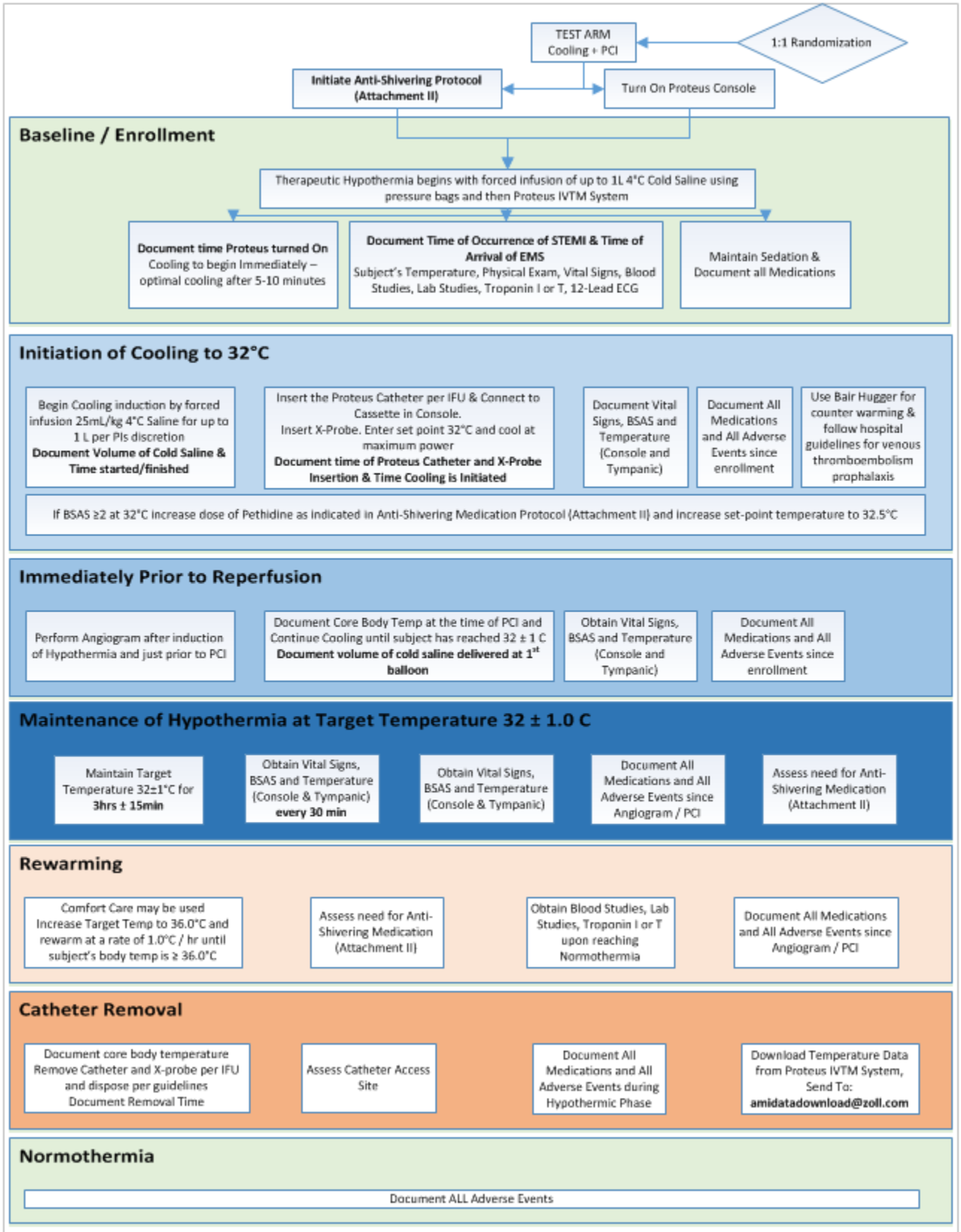


Figure 11 All Patient Procedures

6.8.10 Pre-Cooling Assessment Procedures

All required procedures and data collection from the time of subject screening (as from arrival of the Emergency Medical Services or hospital)) through the pre-cooling assessment period are given below in **Table 11.**

Table 11: Baseline / Screening and Enrollment Procedures/Evaluations and Data Collection for the Test & Control Arms of the Trial

Procedures/ Evaluations	Data
Trial Eligibility	At arrival of Emergency Medical Services or upon arrival to hospital
Informed Consent	Obtain Consent from patient before any trial-related procedure is initiated (upon arrival of EMS or to the hospital).
Trial Enrollment	- Follow randomization process to assign patient to Roll-In, Test or Control Arms of the trial - Complete Enrollment Form, document randomization, and FAX or email to ZOLL at +1 800.243.0360 or ami-eu@zoll.com to enter in the eCRF
Temperature	Document subject's temperature using a tympanic thermometer
Vital Signs	Blood Pressure, Heart Rate, Respiratory Rate, BSAS measurement
Physical Exam	Complete Physical Examination
Blood Studies	RBC's, WBC's, Hct, Hgb, Platelets,
Lab Studies	BUN, Creatinine, sodium, potassium, calcium, phosphate, magnesium, chloride, lactic acid, glucose, amylase, lipase
Cardiac Markers	Baseline and peak Troponin I or Troponin T including upper limit of normal
ECG	12-lead baseline
Medications	Document as indicated on Case Report Form since STEMI onset
Adverse Events	Collect all adverse events as soon as patients are enrolled in the trial

6.8.11 Initiation, Maintenance, and Reversal of Cooling with Proteus IVTM System Procedures / Evaluations and Data Collection for Subjects Enrolled in the Test Arm

6.8.12 Test Arm: Temperature Management Protocol and Data Collection Time Points

Treatment with therapeutic hypothermia will begin with a forced infusion of up to 1 L of cold saline (4°C) (according to the guideline) using pressure bags, and at the time of administration of the anti-shivering medication according to the anti-shivering guidelines, then will continue with the Proteus IVTM System as soon as possible. Cooling will be initiated with the Proteus IVTM System set at a temperature of 32.0 °C, and the subject's temperature will be measured with the Proteus IVTM System immediately before PCI has occurred (measured as time the wire crosses the target lesion). Cooling will be maintained for 3 hours and will be followed with active rewarming to attain normothermia 36.0 °C (96.8°F).

Cooling induction, maintenance of hypothermia, and rewarming are described in the following **Table 12.** The data collection schedule for Test Arm subjects is summarized in **Section 6.8.13**.

Table 12: Initiation, Maintenance, and Reversal of Cooling with Proteus IVTM System Procedures / Evaluations and Data Collection for Subjects Enrolled in the Test Arm

Phase	Task
Immediately Upon Arrival of Emergency Medical Services or at Hospital	1. **Turn the Proteus Console on** (in preparation for cooling with the device) 2. **Document time of occurrence of STEMI and ECG** 3. **Document time of arrival of Emergency Medical Service EMS (Paramedics)**

Phase	Task
Baseline / Enrollment	4. Immediately after informed consent is obtained and patient is randomized to the Test Arm of the trial, **initiate anti-shivering medication protocol using Guidelines outlined in Attachment II**. 5. Begin cooling induction by forced infusion with 25mL/kg of 4°C cold saline using pressure bags up to 1 L of cold saline (4°C) (according to the guideline) at the physician's discretion. Use Bair Hugger™ (CE marked device) for patient comfort. 6. **Document the time the Proteus console is turned on.** The device will begin cooling the patient immediately; however, optimal cooling is achieved in 5-10 minutes after it is turned on. 7. Perform Physical Examination and obtain Vital Signs. 8. Obtain Blood and Lab studies. 9. Obtain Troponin I or Troponin T . 10. Obtain 12-lead baseline ECG. 11. Document all medication use since STEMI onset. 12. Measure body temperature using an independent tympanic thermometer. The independent measurement is to be used in addition to the core body temperature collected by the Proteus Temperature Probe (X-Probe). 13. Document all Adverse Events.

Phase	Task
Initiation of Cooling	14. Document the volume of cold saline, the time the cold saline infusion is started and the time the cold saline infusion is finished. 15. Following the ZOLL Proteus IVTM System Instructions for Use (IFU), insert the Proteus Catheter into the Inferior Vena Cava via either femoral vein. The Proteus Catheter is then connected to the Cassette that has been inserted into the Proteus Console. 16. Following insertion of the Proteus Catheter, insert the Proteus Temperature Probe (X-Probe). Access site selection may vary by both operator preference and anatomical considerations; however, the function of the system is not dependent on which femoral vein is chosen. 17. Once the Proteus System Catheter & Proteus Temperature Probe (X-Probe) have been inserted, enter set point temperature to 32.0°C on the Proteus Console and perform cooling at maximum power as soon as the console is ready to cool. **18. Document the time of Proteus Catheter & X-Probe (temperature probe) insertion.** **19. Document the time cooling is initiated with the Proteus IVTM System.** **20. Document vital signs (BP, HR, RR), and temperature measurements (Tympanic and Proteus Console measurements).** 21. Document all medication use. 22. Document all adverse events since the time of enrollment. 23. Use Bair Hugger™ warming blankets for counter-warming. If choosing to use low dose anticoagulation during the cooling phase, follow hospital's guidelines for venous thromboembolism prophylaxis.

Phase	Task
Hospital arrival and transfer to catheterization lab	24. Please refer to 6.8.19 Transferring Subject during Cooling. 25. Please take all necessary steps to minimize the transfer time

Phase	Task
Immediately Prior to Reperfusion	26. If clinically relevant shivering (Bedside Shivering Assessment Scale (BSAS) of 2 or greater) occurs at 32° (see **Anti-Shivering Guidelines, Attachment II, and BSAS Attachment III),** increase the dose of Pethidine (Meperdine) as indicated in shivering protocol and increase set point temperature on the Proteus IVTM System to 32.5°C. If clinically relevant shivering continues (BSAS ≥2), once again increase dose of Pethidine as indicated in Anti-Shivering Protocol and increase set point temperature on the Proteus IVTM System to 33°C. Continue this process until a temperature is reached where there is no shivering. Follow sedation procedures using **Anti-Shivering Guidelines, Attachment II, and the BSAS Attachment III.** 27. Perform *angiogram after the induction of hypothermia has been initiated and just prior to PCI. **28. Obtain vital signs (BP, HR, RR), BSAS and temperature measurements (Tympanic and Proteus Console measurements) just prior to PCI.** 29. Document all medication use since the initiation of cooling. 30. Document all adverse events since the initiation of cooling. **CAUTION: Anticipate changes in electrolytes and laboratories values secondary to hypothermia.** 31. Document core body temperature at the time of PCI. 32. If subject has not reached 32.0 ± 1.0°C (or temperature where shivering does not occur, as indicated above) at the time of PCI, continue cooling induction until target temperature has been reached. **33. Document the time wire crossed the target lesion.**

Phase	Task
Maintenance of Hypothermia Target Temperature 32 ±1°C	34. Maintain the patient at the set target temperature of 32.0 (or temperature where shivering does not occur, as indicated above) for 3 hours ± 15 minutes from the initiation of cooling with the Proteus System. **35. Obtain vital signs (BP, HR, RR), BSAS and temperature measurements (Tympanic and Proteus Console measurements) every 30 minutes during the 3 hours of cooling.** 36. Document all medication use since the angiogram/ PCI procedure. 37. Document all adverse events since the angiogram/ PCI procedure. 38. If clinically relevant shivering [Bedside Shivering Assessment Scale (BSAS) of 2 or greater] occurs at 32.0°C (See **Anti-Shivering Guidelines, Attachment II, and BSAS, Attachment III),** increase dose of Pethidine (Meperidine) as indicated in shivering protocol and increase temperature on the Proteus IVTM System console to 32.5°C. 39. If clinically relevant shivering continues (BSAS ≥ 2), once again increase dose of Pethidine as indicated in shivering protocol and increase temperature on the Proteus IVTM System to 33°C. Continue this process until a temperature is reached where there is no shivering. Follow sedation procedures using Anti-Shivering Guidelines outlined in **Attachment II** and BSAS assessment in **Attachment III.**

Phase	Task
Rewarming	40. After 3 hours of cooling with the Proteus IVTM System, begin active rewarming to normothermia. Palliative care such as blankets, Bair Hugger patient warming systems, and warm liquids may be used. 41. Using the Proteus System Console, press **STOP** and Increase target temperature to 36.0°C using the arrow touch buttons and then press **Continue**. 42. Set rewarming rate to 1.0°C/hr using the arrow touch buttons and press **Continue** to start rewarming. 43. Maintain the Pethidine infusion during rewarming using the Anti-Shivering Protocol outlined in Attachment II. 44. Obtain blood studies, lab studies and record peak Troponin I or Troponin T including upper limit of normal for site. 45. Document all medication use during the rewarming phase. 46. Document all adverse events during the rewarming phase. **CAUTION: Anticipate changes in electrolytes and laboratories secondary to re-warming**

Phase	Task
Catheter Removal	47. Document core body temperature at time of Proteus Catheter removal. 48. Remove Proteus Catheter and X-Probe per IFU and document time of removal. 49. Dispose of the Proteus Catheter, X-Probe and Proteus Cassette per institution's guidelines (single-use). 50. Assess catheter access site for signs of bleeding, access vessel trauma, or hematoma formation. **51. Download temperature data from the Proteus Console after the cooling phase has been completed. Send downloaded data to amidatadownload@zoll.com immediately upon downloading. Device data must be saved according to Section 16.1, Investigator Records.** 52. Document all medication use during the hypothermic phase. 53. Document all adverse events during the hypothermic phase. **DO NOT DISCARD SPLITTER CABLE (MULTI–USE TEMPERATURE CABLE)**
Normothermia	54. Document all adverse events until patient is discharged from the hospital.
Post-Procedure	55. If required, provide additional Informed Consent document to patients who were consented with the short consent form (if required by MEC or country-specific regulations).

NOTE: All post-PCI times will be measured from the start of PCI, defined as time the wire crosses the target lesion. In the event that PCI is not performed, the time of the first cineangiogram of the infarct related artery will be referenced. If PCI is staged for the non-culprit lesion, then the PCI will be performed after the 4-6 day cMR

***Angiograms are to be uploaded for all adjudicable events.**

6.8.13 Trial Schedule for Test Arm Subjects

Procedure/ Interval	Baseline / Enrollment	Initiation of Cooling	Immediately prior to reperfusion (PCI)	Maintenance of Target Temp 32 ±1°C	Rewarming to 36°C	Catheter Removal	Discharge	Follow-Up @ 4-6 Days	Follow-Up @ 30 Days (±7 days)	Follow-Up @ 12 months (±14 days)	Unscheduled Visit
Trial Eligibility & Informed Consent	**X**										
Physical Exam	**X**						**X**				
Anti-Shivering Protocol	**X**			**X**[a]							
Cold Saline Infusion		**X**									
Catheter Insertion Time		**X**									
Catheter Removal Time						**X**					
Temperature Documented	**X**	**X**	**X**	**every 30 min during 3 hr cooling**	**every 60 min during rewarming**						
Temperature Data Download						**X**					
Vital Signs	**X**	**X**	**X**	**every 30 min**	**every 60 min**						
Blood Studies (upon arrival at hospital) RBC's, WBC's, Hct, Hgb, Platelets,	**X**				**X upon reaching normothermia**						
NT-pro **BNP**										X	
Lab Studies (upon arrival at hospital) BUN, Creatinine, Na, K, Ca, Mg, Cl, P, lactic acid, glucose, amylase, lipase	**X**				**upon reaching normothermia**						
Any Medication Use since AMI onset	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Troponin I or T(including ULN) during hospitalization	**X**	**Perform Troponin until peak value identified**									
12 lead ECG	**X**										
Adverse Events		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**SAE only**	**X****
Catheter Access Site Assessment						**X**	**X**	**X**			
Cardiac Magnetic Resonance (cMR) imaging								**X**			
NYHA Assessment										**X**	
KCCQ										**X**	

[a] **For persistent clinically relevant shivering (BSAS ≥ 2), increase dose of Pethidine as indicated in shivering protocol and increase temperature on Proteus IVTM System console by 0.5°C. Continue this process until a temperature is reached where there is no shivering. Follow sedation procedure using Anti-Shivering Guidelines outlined in Attachment II and BSAS assessment in Attachment III Include BSAS measurement and temperatures from independent method.**

If unscheduled visit occurred within 30 days follow-up, report all AEs. However, if unscheduled visit occurred after 30 days follow-up within 12 months, report only SAEs.

6.8.14 Trial Schedule for Control Arm Subjects

Procedure/ Interval	Baseline / Enrollment	Immediately prior to reperfusion (PCI)Post-PCI	Discharge*	Follow-Up @ 4-6 Days	Follow-Up @ 30 Days (±7 days)	Follow-Up @ 12 months (±14 days)	Unscheduled Visit
Trial Eligibility & Informed Consent	**X**						
Physical Exam	**X**		**X**				
Catheter Insertion Time	**X**						
Catheter Removal Time							
Temperature Documented	**X**						
Vital Signs	**X**						
Blood Studies RBC's, WBC's, Hct, Hgb, Platelets,	**X**						
NT-pro **BNP**						X	
Lab Studies BUN, Creatinine, Na, K, Ca, Mg, Cl, P, lactic acid, glucose, amylase, lipase	**X**						
Any Medication Use	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Troponin I or T(including ULN)	**X**	**Perform Troponin until peak value identified**					
12 lead ECG	**X**						
Adverse Events		**X**	**X**	**X**	**X**	**SAE only**	**X**
Cardiac Magnetic Resonance (cMR)				**X**			
NYHA Assessment						**X**	
KCCQ						**X**	

If unscheduled visit occurred within 30 days follow-up, report all AEs. However, if unscheduled vist occurred after 30 days follow-up within 12 months, report only SAEs.

6.8.15 Control Arm Protocol and Data Collection Time Points

The data collection schedule for Control Arm subjects is summarized in **Section 6.8.14**. For patients randomized to the Control Arm, i.e., PCI alone, the following procedures will be performed:

i. Document time of occurrence of the STEMI & ECG results

ii. Document time of arrival of Emergency Medical Service EMS (Paramedics) & time of arrival at hospital

iii. Collect all adverse events as soon as patients are enrolled in the trial

iv. Perform Blood Studies, Labs, and record Baseline and peak Troponin I or T

v. Perform PCI. If PCI is staged for the non-culprit lesion, then the PCI will be performed after the 4-6 day cMR

vi. Monitor and record the patient's vital signs, temperature, blood pressure, heart rate and respiratory rate, at baseline

vii. Obtain 12-lead baseline ECG

viii. Monitor and record all pharmacological agents

ix. Measure and record baselineTroponin I or T including upper limit of normal, and when a peak is identified.

x. Monitor and record all adverse events for the duration of 30 days follow-up and serious adverse events for the duration of 12 month follow-up.

xi. Complete physical exam prior to discharge.

6.8.16 Follow-up at 4-6 days and at 30 days following the PCI Procedure

Subjects enrolled in the Test and Control Arms, and Roll-In patients, will undergo Cardiac Magnetic Resonance (cMR) to assess infarct size at 4-6 days In addition, the following procedures are to be performed at 4 - 6 days and at 30 days after the index procedure (PCI) for all patients:

i. Monitor and record all adverse events for the duration of 30 days follow-up.
ii. Review and record all medication changes since index.

6.8.17 Follow-up at 12 months following PCI

Following completion of the 30 day follow-up and, all subjects will be followed through 12 months for the incidence of Serious Adverse Events, Death and Heart Failure (as assessed by NYHA and Kansas City Cardiomyopathy Questionnaire (KCCQ)).

i. Monitor and record all serious adverse events for the duration of 12 month follow-up.
ii. Collect NT-pro BNP value to assess clinical prognosis of Heart Failure.
iii. Review and record all medication changes
iv. Perform blinded NYHA Assessment and administer Kansas City Cardiomyopathy Questionnaire (KCCQ).

6.8.18 Use of other Cooling Methods

For the purposes of this trial, no other cooling methods may be used.

6.8.19 Transferring Subject during Cooling

Although interruption during the induction phase of hypothermia is not recommended, if subject transfer is required during any phase of the cooling, follow relevant instructions in the device Instructions for Use.

For additional detail, refer to the Proteus IVTM System Instructions for Use**.** The console screen also provides prompts for entry of user-defined parameters and system start-up.

6.8.20 Patient Withdrawal and Discontinuation

The term "patient withdrawal" refers to the patient deciding to terminate their participation in the trial. The term "discontinuation" refers to the physician deciding that the patient will not continue trial participation as defined below.

A subject has the right to withdraw from the trial at any time and for any reason without prejudice to his or her future medical care by the physician or the institution. Trial withdrawal by a subject specifically means withdrawal of consent from further participation in the trial. Subjects who withdraw consent after enrollment will be evaluated to the time of withdrawal, and withdrawal of consent precludes any further trial related treatment or data collection. If possible, a complete, final physical examination should be performed on all subjects who withdraw from the trial. At a minimum, every effort should be made to document subject outcome at the time of trial withdrawal.

A subject may withdraw from the clinical investigation for the following reason:

- Subjects may choose to withdraw from the clinical investigation under the terms of the Declaration of Helsinki and their consent documentation without having to give a reason;

A subject may be discontinued from the clinical investigation for the following reasons:

- Any unanticipated adverse reaction which is, in the opinion of the Investigator, related to the treatment and will endanger the well-being of the patient if treatment is continued;
- Development of any illness(es), infection or condition(s) that might interfere with the Clinical Investigational Plan;
- Non-compliance with the clinical investigation procedures deemed by the Investigator to be sufficient to cause discontinuation;
- Any problem deemed by the Investigator to be sufficient to cause discontinuation.

- Investigator will treat all subjects discontinued from the investigation due to an unanticipated adverse reaction, directly related to the investigation, until the reaction resolves.

- Investigator will not replace subjects who have withdrawn from the clinical investigation if they have received the investigational device. If possible, Investigator will perform any procedures or assessments planned for the subject at the time of withdrawal.

All subjects are expected to continue in the trial through the final follow-up assessment or until ZOLL notifies the Investigator in writing that further follow-up is no longer required, except in the event of death or upon the subject's request for early withdrawal from the clinical trial.

6.8.21 Patient Lost to Follow-up

The investigator will attempt to contact a subject at least three times prior to designating them as lost-to-follow-up subjects. The investigator will document the date and type of attempted communication. The investigator will complete and sign the Study Exit Form when a subject is lost to follow-up.

6.8.22 Early Termination of a Clinical Investigation

Both the Sponsor and Investigator reserve the right to terminate the clinical investigation at any time. If necessary, and after review and consultation with the Principal Investigator, the Sponsor will make a final determination on whether to terminate the study.

A clinical investigation or Investigator may be terminated at a clinical center for any of the following reasons, or for reasons not listed that affect patient safety or integrity of the trial:

- Unsatisfactory rate of patient enrollment or compliance to eligibility criteria.
- Repeated noncompliance with the investigational plan.
- Inaccurate, incomplete, and/or untimely submission of data.
- Inadequate accountability of the investigational device.

The sponsor may terminate this trial if there are new, previously unknown adverse events related to device or cooling procedure, deaths, SAEs/AEs exceeding those reported as related to device/cooling procedures in previous trials, and/or if recommended by DMC (Data Monitoring Committee) to stop the trial. The sponsor will make the final determination on whether to terminate the study.

The sponsor may terminate the trial for any other unforeseen circumstances. In case of premature termination/suspension, ZOLL will stop the enrollment, inform all investigators at all sites and all regulatory agencies governing the study. ZOLL will perform complete device accountability of all investigational devices and retrieve them from the clinical sites. All study subjects will be followed through the specified follow-up periods. ZOLL will issue a final report of the clinical study.

6.8.23 Amendments and Protocol Deviations

Investigator will not deviate from the CIP without prior written confirmation by Sponsor, or their designee, except as required in a medical emergency. In medical emergencies, Sponsor does not require prior confirmation for protocol deviations, but Investigator will notify Sponsor within 5 days of the incident and will notify the EC according to local requirements. Investigator, or designee, will record deviations with an explanation for the deviation. Investigator will report to Sponsor who will analyze them and assess their significance. Significant deviations from the CIP will be reported to the Competent Authority.

Examples of protocol deviations may include those relating to:

- Eligibility
- Enrollment and randomization
- Informed consent
- Protocol adherence (e.g., tests and assessments done as required in Trial Schedule, etc.)

Routine monitoring will assess Investigator compliance to the protocol.

Investigator must not modify the CIP without the prior and written permission from Sponsor. All modifications to the clinical protocol must be submitted to the Competent Authority (where required) to allow the Competent Authority review and approval.

The Sponsor is responsible for management, processing and approval of any amendment to the Investigational Plan. Should the site consider an amendment necessary, the Sponsor will work with the site to make the appropriate changes. The Sponsor will manage documentation of such changes through the existing document control system. A history of changes and a redline version of the documentation will be maintained per the applicable quality system procedures. The proposed amendment will be submitted to the reviewing MEC/ IRB and government agency as applicable. Any necessary approvals will be received in writing before the requested change is implemented.

This study will be conducted in compliance with ISO 14155, ICH E6 Consolidated Good Clinical Practice Guidance, 21 CFR 812, 21 CFR Part 50, and any requirements imposed by countries with participating clinical sites. The study will not commence until the necessary government and MEC/IRB approvals have been obtained.

6.8.24 Trial Exit

The Trial Exit Form (CRF) should be completed at the time a subject is exited from the trial. A subject will be considered to have exited from the trial for any of the following reasons.

- Subject completes follow-ups required by the investigational plan.
- Subject dies.
- Subject requests to be withdrawn.
- Physician requests that patient be withdrawn to protect the welfare of the patient.
- Patient is lost to follow-up.
- Other (specify)

6.8.25 Subject Confidentiality

Subject confidentiality will be maintained throughout the clinical trial to the extent permitted by law. That is, every attempt will be made to remove patient identifiers from clinical trial documents. For this purpose, a unique subject identification code (site number, subject number and subject initials) will be assigned and used to allow identification of all data reported for each subject. This will also ensure that the information can be traced back to the source data.

Trial data may be made available to third parties, e.g., in the case of an audit performed by regulatory authorities, provided the data are treated confidentially and that the subject's privacy is guaranteed. The identity of a subject will never be disclosed in the event that trial data are published.

Security and Unique usernames and passwords will be utilized by data entry, data verification and other personnel who have database access to insure confidentiality and protection of data.

Trial sites must comply with Health Insurance Portability and Accountability Act (HIPPA) and/or the subject confidentiality provisions and privacy laws of each participating country, local regulations, and institutional requirements, whichever is stricter.

6.8.26 Device Accountability

ZOLL is responsible for the availability and traceability of all investigational products. Documentation is required at each step of the process via a device accountability log. Investigational product will be reconciled on a regular basis.

The investigator also is required to maintain adequate records of the receipt and disposition of all investigational devices. A device accountability log will be provided for this purpose.

All unused product must be returned to ZOLL prior to the close of the trial.

6.8.27 Return of Materials upon Trial Termination

Sponsor will ship investigational devices only to qualified Investigators participating in this clinical investigation. Sponsor will not ship investigational devices to any site until evidence of EC approval has been provided to Sponsor, or designee.
Investigator will control access to investigational devices, and will only use investigational devices in the clinical investigation and according to the CIP.
Sponsor will keep investigational device records to document the physical location of each device. Record(s) will include information documenting devices shipped, devices at investigation sites, devices disposed of, and devices returned.
Investigator, or designee, will keep records documenting the receipt, use, return and disposal of the investigational devices, which will include:

- Date of receipt,
- Identification of each investigational device (serial number or unique code),
- Expiry date, if applicable,
- Date or dates of use,
- Subject identification,
- Date on which the investigational device was returned, or explanted from subject, if applicable, and
- Date of return of unused, expired or malfunctioning investigational devices, if applicable.

After the trial procedures have been completed, all unused devices must be accounted for and returned to ZOLL. Instructions for device return to ZOLL will be reviewed at the site initiation visit.

6.8.28 Trial Closure

Trial closure can occur under the following circumstances:

a. termination of site participation in the trial (i.e., closure that occurs prior to meeting defined endpoints) of the trial
b. upon completion of the trial (i.e., when all patients enrolled have completed the follow-up visits or previously exited the trial, and the CRFs and queries have been completed)

Under any circumstance for closure of the trial at the site, ZOLL and/or its designees will notify the site of this occurrence in writing. Trial closeout visits will be performed once a determination has been made that the trial is closed. All unused trial devices and any unused trial materials and equipment will be collected and returned to ZOLL and/or its designees. The monitors will ensure that the investigator's regulatory files are current and complete and that any outstanding issues from previous visits have been resolved. Other issues that will be reviewed at this visit include: discussing record retention requirements (refer to **Section 14.1**—Investigator Records), device accountability, possibility of site audits, publication policy, and notifying the Medical Ethics Committee and Competent Authorities of trial closure, etc., as applicable.

6.9 Cardiac Magnetic Resonance (cMR) imaging Core Laboratory

Cardiac Magnetic Resonance (cMR) imaging must be collected per the Manual of Operations provided by the sponsor. Images must be submitted to the core laboratory designated by the sponsor for analysis.

7 ADVERSE EVENTS & DEVICE DEFICIENCIES

7.1 Definitions

7.1.1 Adverse Event (AE)

Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.

NOTE 1- This definition includes events related to the investigational medical device or the comparator.

NOTE 2- This definition includes events related to the procedures involved.

NOTE 3- For users or other persons, this definition is restricted to events related to investigational medical devices.

7.1.2 Serious Adverse Event (SAE)

Adverse event that:

a) led to a death, injury or permanent impairment to a body structure or a body function.

b) led to a serious deterioration in health of the subject, that either resulted in:

- a life-threatening illness or injury, or
- a permanent impairment of a body structure or a body function, or
- in-patient hospitalization or prolongation of existing hospitalization, or
- in medical or surgical intervention to prevent life threatening illness

c) led to foetal distress, foetal death or a congenital abnormality or birth defect.

NOTE 1: Planned hospitalization for pre-existing condition, or a procedure required by the Clinical Investigation Plan, without a serious deterioration in health, is not considered a serious adverse event.

7.1.3 Device Deficiency (DD)

Inadequacy of an investigational medical device related to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, use error, or inadequacy in the information supplied by the manufacturer.

7.1.4 Adverse Device Effect (ADE)

Adverse event related to the use of an investigational medical device.

NOTE 1- This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device.

NOTE 2- This includes any event that is a result of a use error or intentional abnormal use of the investigational medical device.

7.1.5 Serious Adverse Device Effect (SADE)

A adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

7.1.6 Unanticipated Serious Adverse Device Effect (USADE)

Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

NOTE: Anticipated SADE (ASADE): an effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report.

7.2 Adverse Event Reporting

7.2.1 Adverse Event Reporting from Site to Sponsor and MEC

The collection of AEs will begin after the informed consent is signed. All AEs that occur through completion of the final follow-up visit, whether observed by the investigator or by the subject, and whether or not thought to be device related, will be reported in detail on the appropriate CRF and followed to resolution or the end of trial participation.

The description of the AE will include the date and time of onset, seriousness, relationship to the device or procedure, the results of any diagnostic procedures or laboratory tests, any treatment recommended, and the outcome of the event. In the circumstance that an AE has not resolved by the time of the subject's completion of the trial, an explanation will be entered on the appropriate CRF.

ZOLL will implement and maintain a system to ensure that the reporting of the reportable events by the investigator to ZOLL occur immediately, but no later than 3 calendar days after investigational site study personnel awareness of the event.

7.2.2 Serious Adverse Event Reporting to Sponsor and MEC

Serious adverse events (SAEs) and device deficiencies should be reported as soon as possible.

Serious adverse events and device deficiencies must be reported no later than 3 calendar days from the site becoming aware of the event or as per the investigative site's local requirements if the requirement is more stringent than those outlined.

The date the site staff became aware of the SAE must be recorded in the source document. The Investigator will further report the event to the IRB/EC according to the institution's IRB/EC reporting requirements.

Serious adverse events that do not occur in the study subject but occur in the user or other persons need to be reported on the fax notification form titled SAE Notification Form. Serious adverse events that occur in the user or other persons other than the study subject should not be entered into the clinical database.

Serious adverse events should be reported on the SAE Notification Form in the occurrence that the clinical database is not available. This does not replace the electronic clinical database. All information must still be entered in the clinical database once the system is back to normal function.

7.2.3 UADE/USADE Reporting to Sponsor and MEC

ZOLL requires the Investigator to report any USADE to the sponsor within 3 calendar days of the investigator's knowledge of the event and to the EC per EC requirements.

7.2.4 Sponsor Reporting to NCAs (National Competent Authority) when European Sites Participate in the Trial

7.2.4.1 What to Report

The following events are considered reportable events:

- any SAE,
- any Device Deficiency that might have led to a SAE if:
    - suitable action had not been taken or
    - intervention had not been made or
    - if circumstances had been less fortunate
- new findings/updates in relation to already reported events.

7.2.4.2 Report to Whom

Reportable events must be reported at the same time to all NCAs where the clinical investigation has commenced using the summary tabulation featured in the of MEDDEV 2.7/3.

7.2.4.3 Reporting Timelines

ZOLL must report to the NCAs where the clinical investigation has commenced:

- for all reportable events as described in section **7.2.4.1** which indicate an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it: immediately, but not later than 2 calendar days after awareness by ZOLL of a new reportable event or of new information in relation with an already reported event.

- any other reportable events as described in section **7.2.4.1** or a new finding/update to it: immediately, but not later than 7 calendar days following the date of awareness by the ZOLL of the new reportable event or of new information in relation with an already reported event.

7.3 Device Relationship

Determination of whether there is a reasonable possibility that an investigational product or device caused or contributed to an AE is to be determined by the Investigator and recorded on the appropriate CRF form. Determination should be based on assessment of temporal relationships, biologic plausibility, association (or lack of association) with underlying disease and presence (or absence) of a more likely cause.

7.3.1.1 Causality Assessment

The relationship between the use of the medical device (including the medical - surgical procedure) and the occurrence of each adverse event shall be assessed and categorized.

The above considerations apply also to the serious adverse events occurring in the comparison group.

The following definitions are used to assess the relationship of the serious adverse event to the investigational medical device or procedures.

1) Not related: relationship to the device or procedures can be excluded when:

- the event is not a known side effect of the product category the device belongs to or of similar devices and procedures;
- the event has no temporal relationship with the use of the investigational device or the procedures;
- the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
- the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event;
- the event involves a body-site or an organ not expected to be affected by the device or procedure;
- the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);
- the event does not depend on a false result given by the investigational device used for diagnosis, when applicable;
- harms to the subject are not clearly due to use error;
- In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

2) Unlikely: the relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.

3) Possible the relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.

4) Probable the relationship with the use of the investigational device seems relevant and/or the event cannot reasonably explained by another cause, but additional information may be obtained.

5) Causal relationship: the serious event is associated with the investigational device or with procedures beyond reasonable doubt when:

- the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
- the event has a temporal relationship with investigational device use/application or procedures;
- the event involves a body-site or organ that
- the investigational device or procedures are applied to;
- the investigational device or procedures have an effect on;
- the serious event follows a known response pattern to the medical device (if the response pattern is previously known);
- the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible);
- other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
- harm to the subject is due to error in use;
- the event depends on a false result given by the investigational device used for diagnosis 17, when applicable;
- In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

ZOLL and the investigators will distinguish between the serious adverse events related to the investigational device and those related to the procedures (any procedure specific to the clinical investigation). An adverse event can be related both to procedures and the investigational device. Complications of procedures are considered not related if the said procedures would have been applied to the patients also in the absence of investigational device use or application.

In some particular cases the event may be not adequately assessed because information is insufficient or contradictory or the data cannot be verified or supplemented. The ZOLL and the Investigators will make the maximum effort to define and categorize the event and avoid these situations.

Particular attention shall be given to the causality evaluation of unanticipated serious adverse (device) events. The occurrence of unanticipated events related to the use of the device (USADE) could suggest that the clinical investigation places subjects at increased risk of harm than was to be expected beforehand.

8 MONITORING BY DATA MONITORING COMMITTEE

The Data Monitoring Committee (DMC) is used to ensure safety by reviewing cumulative data from the clinical trial at pre-defined intervals for the purpose of safe-guarding the interest of trial participants. The DMC will serve in an advisory role in this trial. The composition, guiding policies, and operating procedures governing the DMC are described in a separate DMC charter. Based on safety data, the DMC may recommend a modification to the protocol or that the sponsor stops the clinical trial/investigation. All final decisions regarding clinical trial/investigation modifications, however, rest with the Sponsor.

9 ADJUDICATION OF EVENTS

The Clinical Events Committee (CEC) is comprised of qualified physicians who are not investigators in the trial. The Clinical Events Committee is responsible for adjudicating specified clinical endpoints based on the specific criteria used for the categorization of clinical events in the trial.

Periprocedural MI will be adjudicated according to the Clinically Relevant Myocardial Infarction After Coronary Revascularization (CRMI) definition.[40] Death, Stent Thrombosis, Spontaneous MI, and Revascularization will be adjudicated per ARC definitions.[27]

Hospitalization due to Heart Failure will be adjudicated per ACC/AHA definition.[48]

The composition, guiding policies, and operating procedures governing the CEC are described in a separate CEC Manual of Operations.

When applicable, sites will provide patients' source documentation per request from the Sponsor and will aploade angiograms into AMBRA website through software service Dicom Grid, Inc., which will de-identify angiograms.

10 RECOMMENDATION FOR DAPT AND STENTS

Control and intervention group patients should receive dual antiplatelet therapy (DAPT) and anticoagulation medication as recommended by the ESC Guideline for the management of acute myocardial infarction in patients presenting with ST-segment elevation.

- This includes aspirin 162 or 325 mg po chewed as soon as feasible.
- This should be followed by loading dose of ticagrelor (preferably crushed or chewed) 180 mg before PCI. If ticagrelor not available, loading dose of prasugrel (60 mg) can be used.
    - Clopidogrel can be used only if the patient cannot take ticagrelor or prasugrel.
- This also includes unfractionated heparin (UFH) given as an intravenous bolus as soon as feasible with subsequent boluses targeted to an activated clotting time of 200 to 250 seconds. If Bivalirudin is used, the infusion should continue for 1-2 hours after PCI is finished.
- Use of an intravenous GP IIb/IIIa inhibitor should be used according to the decision of interventional cardiologist.
- In patients with STEMI in whom clopidogrel was initiated before coronary angiography, it is recommended to switch to either ticagrelor or prasugrel before, or during, or at latest immediately after PCI, if ticagrelor or prasugrel are not contraindicated.
    - Switching from clopidogrel to ticagrelor or prasugrel should include a loading dose of ticagrelor 180 mg (preferably crushed or chewed if before or during PCI) or prasugrel 60 mg if the patient is not at high risk of bleeding, irrespective of the prior dose of clopidogrel.
- Recommended maintenance therapy consists of aspirin 81 mg once daily (or per local practice); ticagrelor 90 mg twice daily for at least 12 months. If ticagrelor not available, prasugrel 5 or 10 mg according to label recommendation can be used.
- If needed, transition to clopidogrel can take place after 30 days post index PCI.
    - The recommended first dose of clopidogrel is 600 mg po 12 h after the last dose of ticagrelor or prasugrel. If maintenance therapy consists of aspirin and clopidogrel, the recommended doses are aspirin 81 mg once daily (or per local practice) and clopidogrel 75 mg once daily.
- Use second or third generation DES. Do not use BMS or BVS or BRS such as Absorb in study patients.

11 RISK ANALYSIS

11.1 Risk Assessment Process

ZOLL has a documented EN ISO 14971:2012 compliant Risk Management process, which includes the identification of risks, risk assessment, identification, implementation and verification of adequate controls (mitigations) to ensure that identified risks have been reduced as low as possible and to ensure the benefits of the intended use as compared to any residual risk is acceptable.

The intent of the Risk Management process is to identify potential hazardous situations related to the design, manufacture, and use of the Proteus IVTM System, evaluate each risk and implement controls to reduce the risks as low as possible.

Risks related to the IVTM System and Sub-Systems (Console, Catheter, Cassette and Temperature Probe) have been evaluated in a number of ways:

- Hazard Analysis – The purpose of the Hazards Analysis is to identify, evaluate and control potential hazards to the patient, user and the environment.
- Software Hazards Analysis - The Software Hazards Analysis is used to investigate potential device Software related hazards and control the potential hazards.
- Design FMECA - The purpose of the Design FMECA is to evaluate failure modes of the device components, or subsystems, to identify potential design failure risk, then evaluate and control potential hazards.
- Process FMECA - The purpose of the Process FMECA is to evaluate failure modes of the device manufacturing process steps to identify process failure risks, then evaluate and control potential hazards.

The results of the Proteus IVTM System Risk Management process was reviewed, and concluded that the risk controls are effective to reduce the risks as low as possible. The ZOLL Proteus IVTM System presents an acceptable risk benefit ratio when used in accordance with its labeling for its proposed intended use: The Proteus IVTM System is intended for use in adult subjects with acute anterior myocardial infarction to induce and maintain hypothermia prior to percutaneous coronary intervention as an adjunctive therapy to reduce anterior infarct size.

Note: See the Investigator Brochure for additional information on the Proteus IVTM System, as applicable.

11.2 Expected Clinical Observations

In subjects who have been treated for myocardial infarction, there are many sequelae of such an event that may be thought to be "normal" effects and not due to the treatment provided. These events may be outside the range of what is considered to be "normal" (e.g., a high lab value such as a shift in potassium), but do not put the patient at risk for harm. These events are therefore expected physiological responses to treatment with therapeutic hypothermia in all patients. Prospectively, these observations may include but are not limited to the following:

- Shift in Potassium levels
- High or low levels of glucose

The expected clinical sequelae of patients treated with hypothermia include, but are not limited to, the following[28]:

- Shivering
- Prolonged ECG intervals
- Bradycardia defined as a heart rate of 40 beats per minute and not requiring treatment (e.g., pacemaker, medications, etc.)
- J wave (also called Osborne wave) can occur at any temperature < 32.3°C
- Blood electrolyte shifts: Calcium, Phosphorus, Magnesium, Chloride
- High or low levels of glucose: Decreased insulin sensitivity and insulin secretion
- Asymptomatic shifts in serum amylase and lipase levels
- Peripheral pulses may be difficult to detect

Cold Diuresis: Increased resistance to ADH or Vasopressin resulting in decreased water or solute reabsorption.

11.3 Potential Clinical Risks

Adverse events that are inherent to a PCI procedure and expected to occur in most subjects for a projected duration according to the opinion of the investigator may be considered unavoidable. Such events include, but are not limited to, those listed in **Table 14**. These adverse events should not be reported during this trial.

Table *14* Expected and unavoidable adverse events related to the PCI procedure

Description of the Event	Time Frame from the Index Procedure (PCI)
Back pain related to laying on Cath lab table	Within 48 hours
Peripheral vasoconstriction	Within 24 hours
Thermal discomfort	Within 24 hours
Incisional pain (pain at access site)	Within 72 hours
Sleep problems or insomnia	Within 72 hours

Mild to moderate bruising or ecchymosis	Within 168 hours

A list of potential (expected) risks that may be associated with use of the Proteus IVTM System is provided below. Since this clinical study utilizes an investigational device, all risks may not be known. However, they are believed to be similar to those associated with the existing intra-vascular temperature management devices in clinical use or commercially available.

The following potential adverse events may occur during the course of the clinical trial.

11.3.1 Potential Adverse Events associated with the Proteus Catheter and Cooling System:

Potential risks related to the Proteus Catheter are reasonably believed to be consistent with the common, known risks of central venous catheters and/or venous introducer sheaths. Potential risks related to cooling, re-warming, and/or the Proteus IVTM System include but are not limited to the following:

- Catheter related injury [embolism (air, thrombus, catheter fragment), clinically significant hematoma, vascular perforation or dissection, arteriovenous fistula, nerve injury, excessive bleeding, pseudoaneurysm]
- Deep vein thrombosis (DVT) requiring treatment
- Infection [local or systemic (pneumonia, sepsis, meningitis, visceral organ)]

11.3.2 Potential Adverse Events associated with the cooling procedure include but are not limited to the following:

- Acute renal failure
- Acute renal insufficiency
- Adverse drug reaction
- Angina
- Blood lysis
- Congestive Heart Failure
- Clinically relevant shivering (BSAS $\geq$ 2) that cannot be controlled by the antishivering medication regimen
- Dysrhythmia [ventricular tachycardia, ventricular fibrillation or atrial fibrillation requiring intervention, bradycardia (HR $\leq$ 40 bpm, block)]
- Hyperglycemia / Hypoglycemia
- Hyperkalemia / Hypokalemia

- Hyperphosphatemia / Hypophosphatemia
- Hypotension
- Infection (local, systemic)
- Liver Failure
- Myocardial infarction
- Multi-system organ failure
- Overcooling (temperature <31.0°C for ≥ 20 continuous minutes)
- Overwarming (temperature >38°C for ≥ 20 continuous minutes including dehydration, burns and neurological damage)
- Pancreatitis
- Pulmonary edema
- Peripheral vascular insufficiency
- Thrombocytopenia
- Rebound hyperthermia
- Respiratory failure during cooling or rewarming
- Seizures
- Stroke [Cerebral vascular Accident (CVA)]
- Transient Ischemic Attack (TIA)
- Unstable angina

11.3.3 Risks Associated with Anti-shivering Medications

In order to preserve patient comfort and suppress the shivering response during cooling, a combination of recommended buspirone, where available (or equivalent alternative) and required Pethidine (Meperidine) should be used (see **Attachment II**). As identified in their labeling, the risks associated with the use of these pharmacologic agents in this trial population include the following:

Buspirone (or equivalent alternative)

- Interaction with MAO Inhibitors
- Dizziness
- Nausea
- Headache
- Nervousness
- Lightheadedness
- Excitement

Pethidine (Meperidine)

- CNS Depression
- Hypotension
- Respiratory Depression
- Circulatory Depression
- Respiratory Arrest
- Shock
- Cardiac Arrest

Other reported reactions:

- Lightheadedness
- Dizziness
- Nausea
- Vomiting
- Sweating

11.4 Additional investigations due to the trial

Participation in the clinical trial will involve extra blood sampling for laboratory markers (electrolytes, complete blood count, baseline and peak troponin including upper limit of normal), additional ECGs and the need for cardiac MRI imaging. All of these are standard clinical procedures, and the risks to participants are low. Sites will be carefully monitored for adherence to the protocol. Patients will be screened for appropriateness for MRI prior to enrollment.

11.4.1 Delay in PCI through the use of hypothermia therapy

The probability for potential delay in PCI is considered Occasional. In prior trials of hypothermia for STEMI, the increase in door to balloon time ranged from 9 minutes to 18 minutes. It is noteworthy that this delay was not associated with an increase in infarct size hypothermia patients compared to controls. In fact, patients with anterior STEMI with < 35°C at the time of reperfusion showed smaller infart size. Sites will be trained to incorporate hypothermia into the cath lab workflow while minimizing delay. Feedback will be provided for each case to help maintain efficiency.

11.4.2 Implementation of PCI in patients undergoing hypothermia (patient-related risks).

Potential risks related to the use of hypothermia therapy in patients are outlined in sections 11.2.1 and 11.2.2 above. These risks include: potential adverse events associated with the Proteus Catheter and Cooling System, potential adverse events associated with cooling, and potential risks associated with the anti-shivering medications.

11.4.3 Implementation of PCI with concurrent use of endovascular hypothermia.

The addition of hypothermia as adjunctive treatment of STEMI will potentially lead to more difficult conditions for the Investigator and other users. The ability to integrate hypothermia into the cath lab workflow has been demonstrated successfully in prior clinical trials. Again, thorough training, frequent monitoring, and rapid feedback will help mitigate the challenges of incorporating hypothermia into treatment for STEMI.

11.4.4 The concurrent medication.

Patients who have received medications such as monoamine oxidase inhibitor within a 14 day period will be excluded from the trial to prevent potential interaction with the anti-shivering medications. In patients that receive morphine, the pethidine dose will be lowered to decrease the likelihood of respiratory depression.

11.4.5 The supply of 4°C cooled saline solution

The amount of cooled saline solution is limited to 1,000 ml, an amount shown to be well tolerated in the CHILL-MI trial, where the average amount of cooled saline was 1475 ml. Again, careful training and monitoring will help to avoid unnecessary exposure to larger volumes of saline.

11.4.6 Other procedures within the clinical trial

The risk of adverse interaction or influence of other procedures within the clinical trial are deemed to be low. In prior hypothermia trials in STEMI, there was no interference with the stenting procedure, with resuscitation efforts for arrhythmias or cardiogenic shock. Hypothermia does inhibit the absorption and metabolism of clopidogrel, a anti-platelet inhibitor, given to reduce the risk of stent thrombosis. This risk will be mitigated by calling for adherence to ESC guidelines which recommend either prasugrel or ticagrelor, both of which are less affected by hypothermia.

11.5 Potential Clinical Benefits

Although no assurances or guarantees can be made, there is a reasonable expectation that the use of this investigational device is safe within the context of the trial and may be beneficial. Cooling using the device, for instance, may result in improved temperature control relative to the standard techniques already in use at the sites.

The primary benefits of therapeutic hypothermia have been shown to be:

- Improved patient survival
- Improved heart tissue salvage after the ischemic event

Additional potential benefits of therapeutic hypothermia with the Proteus System may include:

- Faster cooling
- More accurate control of the cooling procedure than with surface cooling
- Further improved survival

There is no guarantee that participation in this trial or use of hypothermia will benefit the trial subject. However, collection of such trial data may provide added benefit for future myocardial infarction subjects.

11.6 Methods to Minimize Risk

All efforts will be made to minimize risks by selecting investigators who are experienced and skilled in using minimally invasive catheter-based cardiovascular interventions and who have been adequately trained. Also, risk minimization activities were performed during development and design verification tests of the device. Activities intended to minimize risks include the following.

- Investigator and trial personnel training will be conducted to share information regarding the design of the Proteus IVTM System, its application, pre-clinical results, and clinical trials on comparable intra-vascular cooling devices.
- Adherence to eligibility criteria and screening procedures will ensure that appropriate patients are enrolled.
- Adherence to the Proteus IVTM System Instructions for Use packaged with the device.
- Corrective and preventative actions will be implemented by ZOLL, as necessary, if deviations from recommendations in the protocol or IFU are observed.
- Clinical support by ZOLL representative will be provided during the enrollment in the study and thereafter if needed. ZOLL representatives will only have advisory role.
- The subjects will be carefully monitored throughout the trial period.
- The investigator will evaluate the subject adverse events during the course of the trial.
- Data submitted from the investigative centers will be monitored during the course of the trial.

- Monitoring visits will be conducted to evaluate protocol compliance and data quality.
- Safety and effectiveness data obtained during the course of the trial will be shared with investigators in periodic reports to increase understanding of the device and potential adverse events.
- An independent Data Safety Monitoring Board (DSMB) will monitor safety throughout the clinical trial. Stopping rules will be discussed with the DSMB and applied for subject safety through enrollment.

Detailed trial procedures are provided in **Section 6.8 - Clinical Trial Procedures**.

11.7 Risk – Benefit Assessment

To date, there have been five clinical trials that have reported on the safety and effectiveness of therapeutic hypothermia in AMI and one in Radio-Contrast nephropathy (COOL-RCN Trial), with a total of more than eleven hundred patients being enrolled in total with at least half of those treated with therapeutic hypothermia. The rate of adverse events are well reported in these populations (see section 5, Prior Investigations), and the risks are clearly categorized for these trials. In summary, the number of trials, patients enrolled, and low numbers of safety events reported indicate that therapeutic hypothermia in this patient population is at an acceptable risk level to engage in this trial.

There is significant morbidity and mortality associated with the numerous clinical conditions outlined in this report, and therapeutic hypothermia has shown promise to greatly improve clinical outcomes in these patients. In particular, patients with anterior STEMI have a higher incidence of congestive heart failure, cardiogenic shock, and cardiac mortality. A significant reduction in infarct size in these patients, with therapeutic hypothermia, has the promise to reduce these adverse clinical outcomes. Risks associated with the use of the Proteus IVTM system have been reduced via the Risk Management Process, and are deemed acceptable, considering the potential benefits. We conclude that the use of the Proteus IVTM system for medical practice is justified and warranted.

Risk assessment of the Proteus IVTM System has been performed in accordance with the ISO 14971:2012.[30] The Proteus IVTM System is safe and presents an acceptable risk benefit ratio to provide cooling or warming of patients when:

- Used by and under the supervision of a qualified medical practitioner
- In patients for whom the risks of a central line are acceptable

- In intensive care environments equipped to handle clinical conditions warranting use of the device under this protocol
- Used according to the Instructions For Use (IFU)

12 RECORDS AND REPORTS

Throughout the course of this clinical trial, ZOLL, the investigators, and reviewing MEC are responsible for the records and reports detailed in the following sections.

12.1 Investigator Records

Investigators must retain all trial records required by ZOLL and by the applicable regulations in a secure and safe facility. The investigator must consult a ZOLL representative before disposal of any trial records and must notify ZOLL of any change in the location, disposition, or custody of the trial files.

Trial records are those that individually and collectively permit evaluation of the conduct of the trial and the quality of the data produced. ZOLL's SOP requires that all clinical trial data be kept for a minimum of 15 years and all data used in submissions be kept for the life of the corporation. It is the site's obligation to inform ZOLL if their own policy does not comply with the sponsor's requirement so necessary arrangements can be negotiated. It is ZOLL's responsibility to inform the investigator/institution as to when these documents no longer need to be retained.

The investigator is responsible for the preparation (review and signature) and retention of the records cited below.

- All correspondence with another investigator, MEC, ZOLL, a monitor, or FDA, including required reports and trial documents which pertain to the investigation.
- Records of receipt, use, and final disposition of a device.
- Records of each subject's case history and exposure to the device. Case histories include the Case Report Forms (CRFs) and supporting source data (signed and dated informed consent forms, medical records, e.g., progress notes of the physician, patient's hospital chart, nursing notes).
- The clinical investigational plan, with documents showing the dates of and reasons for each deviation from the protocol.
- Any other records that are required to be maintained by local regulations or by specific regulatory requirements for a category of investigations or a particular investigation.
- Any other record that the reviewing MEC requires to be maintained for the subject investigation.

12.2 Investigator Responsibilities

The participating investigator is responsible for adhering to this Clinical Investigational Plan (CIP), FDA CFR, ISO 14155 and Declaration of Helsinki (Regulatory requirements of his/her country local law).

Specifically, the Principal Investigator at each site shall:

a) indicate his/her acceptance of the CIP in writing,
b) conduct the clinical investigation in compliance with the CIP,
c) create and maintain source documents throughout the clinical investigation and make them available as requested during monitoring visits or audits,
d) ensure that the investigational device is used solely by authorized users as specified in 6.2, and in accordance with the CIP and instructions for use,
e) propose to the sponsor any appropriate modification(s) of the CIP or investigational device or of the use of the investigational device,
f) refrain from implementing any modifications to the CIP without agreement from the sponsor, EC and regulatory authorities, if required,
g) document and explain any deviation from the approved CIP that occurred during the course of the clinical investigation,
h) ensure that an adequate investigation site team and facilities exist and are maintained and documented during the clinical investigation,
i) ensure that maintenance and calibration of the equipment relevant for the assessment of the clinical investigation is appropriately performed and documented, where applicable,
j) ensure the accuracy, completeness, legibility and timeliness of the data reported to the sponsor in the CRFs and in all required reports,
k) maintain the device accountability records,
l) allow and support the sponsor to perform monitoring and auditing activities,
m) be accessible to the monitor and respond to questions during monitoring visits,
n) allow and support regulatory authorities and the EC when performing auditing activities,
o) ensure that all clinical-investigation-related records are retained as required by the applicable regulatory requirement(s), and
p) sign the clinical investigation report, where applicable.

The investigator is responsible for the preparation and submission of the reports cited in **Table 15**. Reports must be prepared in complete, accurate and timely manner. These reports may be subject to regulatory inspection (and ZOLL) and copying, and the retention requirements described above for Investigator Records. In addition to the reports listed in **Table 15**, the reviewing MEC may request reports pertaining to any aspect of the clinical trial.

Written approval from the Medical Ethics Committee (MEC) with authority for the participating site will be obtained prior to the start of the study. The investigator or if applicable, the Sponsor, is responsible for submitting all required documents to the MEC. At a minimum the following documents will be submitted:

• Clinical Investigational Plan (CIP)

• Patient Informed Consent documents in the local language

• Any other written information to be provided to the subjects in the local language

• Investigator Brochure (IB) (as required)

• Other documents will be submitted as per local requirements

After obtaining MEC approval, the investigator will submit the approval letter indicating the approved version of the CIP, Patient Informed Consent, IB and any other reviewed documentation to ZOLL.

Table 15 Investigator Reporting Responsibilities to Sponsor and MEC

REPORT	SUBMIT TO	DESCRIPTION/CONSTRAINTS
Withdrawal of MEC Approval	Sponsor	The investigator must report a withdrawal of the reviewing authority within **5 working days**.
Case Report Form (CRF)	Sponsor & Monitor	CRFs should be completed as soon as possible after any trial related procedure takes place.
Deviation from Investigation Plan (Emergency)	Sponsor & MEC	Notification must be made within **5 working days** if the deviation was made to protect the life or physical well-being of a subject.
Deviation from Investigation Plan (Other – Non Emergency)	Sponsor & MEC	If the deviation may affect the scientific soundness of the plan or the rights, safety and welfare of the subjects (and is not an emergency), then **the deviation must be approved by ZOLL, the MEC, and the reviewing authority prior to its implementation**. If the deviation does not affect these issues (trial soundness, rights, safety, etc.) then only ZOLL must approve it, (except in cases which are beyond the control of the investigator—see section on Protocol Deviations).
Failure to Obtain Informed Consent	Sponsor & MEC	The Investigator must notify ZOLL and the reviewing authority within **5 working days** after device use. The investigator must submit notification after device use or after the investigator first learns of the absence of informed consent. The report must include a brief description of the circumstances surrounding the failure to obtain informed consent and include written concurrence by a licensed physician not involved in the investigation. Failure to obtain informed consent must be reported to the MEC as required by local regulations.
Final Report	Sponsor & MEC	This report must be submitted within **3 months** after termination or completion of the investigation.

12.3 Sponsor Records

All Sponsor documents and records shall be maintained as indicated by ZOLL's Quality System. ZOLL will maintain the following trial -related records in accordance with ZOLL record retention policies and procedures following the completion of this investigational plan. Clinical data for regulatory submissions and publications will be retained for the life of the corporation.

- All correspondence pertaining to the investigation with the sponsor, a monitor, an investigator, an MEC, regulatory agencies, including required reports.

- Records of shipment and disposition of the investigational device.
- Signed investigator agreements including the financial disclosure information required to be collected and current signed and dated curriculum vitae.
- Records of adverse events and device deficiencies.
- List of participating institutions
- Investigational product accountability reports including record of receipt, use, or disposition of the device(s) that relate to type, quantity, serial numbers of devices, and date of receipt, names of persons who received, used, or disposed of each device and why and how many devices have been returned to ZOLL or otherwise disposed
- All signed and dated case report forms submitted by investigator, samples of patient informed consents, and other information provided to the subjects
- Copies of all MEC approval letters and relevant MEC correspondence
- Names and evidence of the institutions in which the clinical investigation will be conducted
- Insurance certificates
- Forms for reporting adverse events and device deficiencies
- Names/contact addresses of monitors
- Statistical analyses and underlying supporting data
- Final report of the clinical investigation
- The Clinical Investigational Plan, Clinical Monitoring Plan (CMP), Investigator Brochure (as applicable), and study related reports
- Study training records for center personnel and ZOLL personnel participating in the trial
- Any other records that MEC and /or competent authority requires to be maintained by regulation or by specific requirement for a category of investigation or a particular investigation.

12.4 Sponsor Reports

ZOLL Circulation, Inc. is responsible for the classification and reporting of reportable adverse events and device deficiencies and ongoing safety evaluation of the clinical investigation in line with local regulatory requirements.

ZOLL Circulation, Inc. will assure that all Serious Adverse Events and reportable Device Deficiencies are reported to the Competent Authorities in accordance with European Medical Devices directives and all applicable national regulations.

ZOLL Circulation, Inc. is responsible for the reports cited in **Table 16**. These reports are subject to regulatory retention and inspection requirements. Governing Regulatory Agencies or the reviewing MEC may request reports pertaining to any aspect of the clinical trial.

Table 16: ZOLL Reporting Responsibilities

REPORT	SUBMIT TO	DESCRIPTION
Unanticipated Adverse Device Effects; SAEs and Reportable DDs	Relevant authorities and MECs	Reporting timeframe as per local regulatory requirements.
	Investigators	Notification throughout the course of the trial when appropriate (based on perceived risk)
Premature termination or suspension of the Clinical investigation	Investigators, MECs, Relevant Authorities	Provide prompt notification of termination or suspension and reason(s).
Subject enrollment Completed	Investigators, MEC and Relevant regulatory Authorities upon request	ZOLL will notify the investigators within 30 working days of the completion of enrollment. Investigators will, in turn, inform their MECs, when required.
Withdrawal of MEC approval	Investigators, MECs	Notification within five working days.
Final Report	Investigators, MECs, (and other relevant Authorities upon request)	A final report will be submitted to investigators, and MECs within six months after completion or termination of this study. The investigators shall have the opportunity to review and comment on the final report. If a clinical investigator does not agree with the final report, his/her comments shall be communicated to the other investigators. The principal clinical investigator in each center shall sign the report.

13 MONITORING AND AUDITING PROCEDURES

13.1 Clinical Trial Sponsor and Monitors

ZOLL is the Sponsor of the clinical trial. It is the responsibility of the sponsor to ensure that proper monitoring of the investigation is conducted. Clinical trial monitoring and auditing will be done by appropriately trained personnel appointed by the trial sponsor to ensure that the investigation is conducted in accordance with ZOLL's requirements and applicable laws and regulations.

A monitor is an individual designated by a sponsor or contract research organization to oversee the progress of an investigation. The monitor may be an employee of a sponsor or a consultant to the sponsor, or an employee of or consultant to a contract research organization. The monitor will be trained on the device, investigational plan, informed consent, instructions for use, applicable ZOLL procedures, electronic data capture system, and regulatory requirements. The monitor will periodically check and report on the progress of the clinical trial at an investigational site or other data gathering organization or ZOLL facility.

13.2 Monitoring Methods

Monitoring of the clinical trial will be a continuous, interactive process to ensure that high-quality data is obtained in compliance with the clinical investigational plan and regulatory requirements. Monitoring functions will be conducted by ZOLL, and/ or a contract research organization and/or other designees. Specific monitoring requirements are detailed in the Trial Monitoring Plan (maintained in the ZOLL COOL-AMI clinical trial project files). Frequent communication will be maintained with each investigational site to keep both the clinical center and ZOLL up-to-date and aware of the trial progress. Case Report Forms will be reviewed for completeness and accuracy.

ZOLL will monitor sites in accordance with the monitor's tasks set under Section 8.2.4 of Standard DIN EN ISO 14155:2012-01. These include visits to the clinical trial sites before the start of, during and at the end of the clinical trial. On-site monitoring of all trial centers will be frequent enough (at a minimum annually) to assure continued integrity and acceptability of the data. Accuracy of data reported on case report forms will be verified by comparison to source documents. Reports of monitoring visits will be provided to the clinical trial personnel at each site. Corrective action will be taken to resolve any issues of noncompliance. If ZOLL finds that an investigator is not complying with the executed trial agreements, the investigational plan, the applicable national regulations, or the requirements of the reviewing MEC, then prompt action will be taken to secure compliance. In addition, shipment of the device may be stopped or the participation of the investigator may be terminated. Additional information is provided in **Section 6.30** – **Trial Closure**.

13.3 Monitoring Visits

Scheduled visits to the clinical investigational site will occur at the following times: prior to the start of the clinical trial (pre- trial qualification visit), at initiation of the trial (during first index procedure or shortly thereafter), interim visits throughout the clinical trial as required, annually, and upon completion of the clinical trial.

13.4 Pre-trial Qualification Visit

A pre- trial visit will be conducted by ZOLL personnel (or designees) to review the clinical investigational plan and regulatory requirements with the investigator and the trial personnel to assure that they:

- Understand the investigational status of the device and the requirements for its use and accountability.
- Understand the clinical investigational plan.
- Understand the requirements for an adequate and well-controlled clinical trial.
- Understand and accept the obligation to conduct the clinical investigation in accordance with the national regulations.
- Understand and accept the obligation to obtain informed consent in accordance with the national regulations.
- Understand and accept the obligation to obtain MEC approval before the clinical trial is initiated, ensure continuing review of the trial by the MEC, and keep ZOLL informed of MEC approval and actions concerning the clinical trial.
- Have access to an adequate number of eligible patients to participate in the trial (at a minimum: 1 patient/center/month).
- Have adequate facilities and resources to conduct the trial. This includes resources appropriate for use of electronic data capture systems.
- Have sufficient time from other obligations to carry out the responsibilities of the clinical trial.
- Sign the Investigator Agreement and trial contracts (prior to enrollment of patients).

A report of the pre- trial qualification visit will be completed. Resolution of any concerns or completion of any appropriate follow-up activities stemming from the pre- trial visit also will be documented.

13.5 Initiation Visit

ZOLL clinical personnel (or designees) will provide assistance for both technical concerns and trial management issues during the initiation visit. Enrollment of the first patient at each clinical

site may or may not coincide with this visit. Any observations will be documented and issues requiring follow-up will be identified on a monitoring report. Training of trial personnel also will be documented.

13.6 On-Site Interim Monitoring Visits

On-site monitoring visits will be made on an as-required basis (and at least annually) to assess adherence to the clinical investigation plan, MEC review of trial progress, maintenance of records and reports, and selected review of source documents for accuracy, completeness, legibility, and omissions. The monitors will acquire information to assess the progress of the trial (toward meeting trial objective) and identify any concerns that stem from observation of device performance and/or review of the investigator's patient records, trial management documents, and patient informed consent documents. Monitoring reports will be generated along with communications to the investigator, which document the result of the monitoring visit and any recommended actions. Resolution of concerns and completion of assigned tasks will be documented.

13.7 Audits

An on-site audit may be completed periodically throughout the trial at each clinical site by an independent group. The purpose of the audit will be to ensure compliance to the investigational plan and regulatory requirements, e.g., written informed consent was documented, information recorded on the case report forms is complete and accurate as compared to source documentation, protocol deviations are noted, and device accountability is accurate and complete. A randomly selected number of patient records and other supporting documents will be compared to the case report forms. A record of the findings and recommended actions to correct deficiencies will be documented on the audit report.

13.8 Final Monitoring Review

Depending upon the status of the trial at each center, a close-out or final visit may be conducted. Any ongoing responsibilities will be discussed with the investigator and the trial center coordinator. A final monitoring report, which includes, at a minimum, disposition of any unused devices, will be completed.

14 DATA MANAGEMENT PROCEDURES

ZOLL will oversee all data management functions. ZOLL will be responsible for database development, system maintenance, user training, data queries, and report generation.

14.1 Case Report Forms

ZOLL will use an electronic data capture (EDC) system to collect patient data. The electronic case report forms (eCRFs) are the primary component of EDC and are based on the sample forms that will be provided in a separate document. Training on use of the system will be provided to the trial site personnel. Instructions for completion of the eCRFs also will be provided.

The eCRFs must be completed, saved, and locked via electronic signature by the Investigator using a unique ID and password. This ID and password are for the use of the investigator only and may not be used by any other person. Because of the potential for errors or inaccuracies in transcribing data into eCRFs, source documentation must be maintained in each subject's hospital chart and/or electronic medical record. The eCRFs and source documentation must be available at all times for inspection by the trial monitors or regulatory inspectors.

Changes made to eCRFs will be electronically recorded in a complete audit trail that cannot be changed, but can be accessed by authorized personnel at any time. All data are transmitted via the Internet in an encrypted fashion. When received at the server site, the data are decrypted and stored. Data can be extracted for ZOLL review and analysis at any time.

14.2 Source Documentation

Regulations require that an investigator maintain information in the trial subject's medical records to corroborate data collected on the eCRF. To comply with these regulatory requirements, the following information will be maintained and made available as required by ZOLL and/or its designees and/or regulatory inspectors. Shadow charts are not appropriate or adequate source documentation. Complete medical (clinical and hospital) records include the following documentation.

- Medical history/physical condition of the patient before involvement in the trial sufficient to verify clinical protocol eligibility criteria.
- Description of cooling procedure (material used, drugs administered during the procedure, device identification information and disposition, date, time, angiographic and clinical findings, etc.).
- Electronic data downloaded from the ZOLL Proteus IVTM System.
- Signed notes in the subject's medical record on the enrollment day that identify and include: the subject's date of enrollment, procedure date, the trial sponsor (ZOLL), clinical site name, the subject-assigned identification number, the subject- assigned enrollment number, and documentation and confirmation that the appropriate informed consent was obtained.
- Dated and signed notes for each subject's trial visit.

- Lab results.
- Baseline ECG, angiogram, and MRI reports, etc.
- Dated printouts or reports of special assessments (ECG baseline report, imaging report, etc.).
- Adverse event reporting and follow-up of the adverse events. Information in the medical chart should include at a minimum the following: event description, severity, seriousness, onset date, date site became aware of event, duration, relation to trial device, treatment, and outcome of the adverse event.
- Trial subject's condition upon completion of or withdrawal from the trial.
- Trial subject's medical status, including all SAEs out to 1 year following trial enrollment.
- All notes related to trial subject's KCCQ and the New York Heart Association Functional Class questionnaires.

14.3 Transmission of Data

Required data will be recorded on the appropriate eCRF at the time of or as soon as possible after the patient visit. The eCRFs and any requested supporting source documents must be sent to ZOLL and/or retrieved from the investigator during monitoring visits. Questions about completion of the eCRFs may be directed to the ZOLL COOL AMI clinical team at Clin-safety@zoll.com

14.4 Data Queries

During monitoring visits, the Monitor will perform a 100% review of all variables, i.e., demography, inclusion/exclusion criteria, safety, effectiveness, on the eCRFs with each subject's source documents. Any discrepancies will be queried by ZOLL or its designee and must be resolved by the investigational site staff and investigator in a timely manner. Queries also will be generated by ZOLL data management personnel during routine review of the data on the electronic data capture system.

15 STATISTICAL ANALYSIS PLAN

The objective of this trial is to evaluate the safety and effectiveness of therapeutic hypothermia, using the ZOLL Proteus IVTM System, as an adjunctive therapy for patients presenting with acute anterior myocardial infarction (AMI) and undergoing percutaneous coronary intervention (PCI). An analysis summarizing outcomes for the Primary Effectiveness Endpoint and the Primary Safety Endpoint will be created after the last randomized subject has completed the 30 day follow-up interval. The results of the primary endpoints will be summarized in the final clinical study report.

Two interim analyses are planned to be performed at approximately 50% and 75% of randomization, once subjects have completed 4-6 day cMR follow-up. At the interim stage, the

trial will be stopped to reject the null hypothesis of no difference or continue enrolling. Another report will be issued summarizing all endpoints after all subjects have completed 12 month follow-up.

15.1 Data Analysis

Analysis Data Sets

The Intention-to-Treat (ITT) analysis set will be used for primary statistical analyses and summaries. The ITT population includes subjects who have signed an informed consent and have been randomized to the Test Arm or the Control Arm of the trial. ITT subjects will be evaluated according to the group to which they were randomized.

The Per-Protocol (PP) analysis set will also be evaluated. The PP population includes those subjects who met inclusion and exclusion criteria, were randomized to either the Test or Control arm, received the treatment to which they were randomized, and complied substantially with the treatment timeline and steps of this protocol without major protocol violations.

The Safety Analysis Set will be used to evaluate safety endpoints. These will be all of the subjects included in the study as defined by the ITT analysis set and will include Roll-In subjects. For the safety analysis, subjects will be followed for all adverse events for 30 days post procedure. Additionally, all subjects will be followed for 12 months for the incidence of Serious Adverse Events (SAEs), Death and Heart Failure (as assessed by NYHA and Kansas City Cardiomyopathy Questionnaire (KCCQ)).

Infarction Size (IS) is defined as % Left Ventricular Mass as measured by Cardiac Magnetic Resonance (cMR) imaging. Infarct Size (IS) will be assessed by Cardiac Magnetic Resonance (cMR) at 4 – 6 days following the index procedure. Infarct Size will be assessed in subjects in the ITT analysis set and also in the Per-Protocol analysis set.

The Safety Analysis Set will be used to evaluate safety endpoints. These will be all of the subjects included in the study as defined by the ITT analysis set and will include the following clinical components evaluated at 30 day follow-up visit (30 day ± 7 days):

Secondary Endpoint Analysis:

The following clinical components of MACE will be evaluated at 30 day follow-up visit (30 day ± 7 days):

- Death (Cardiac, Vascular, Non-Cardiovascular)
- Myocardial Infarction (MI)
  - Attributable to target vessel (TV-MI)
  - Not attributable to target vessel (NTV-MI)
- Target Lesion Revascularization (TLR)
  - Clinically-indicated TLR (CI-TLR)
  - Not clinically-indicated TLR (NCI-TLR)
- Target Vessel Revascularization (TVR non TLR,)
  - Clinically-indicated TVR non TLR
  - Not clinically-indicated TVR non TLR
- Non-Target Vessel Revascularization (NTVR,)
  - Clinically-indicated NTVR
  - Not clinically-indicated NTVR
- All coronary revascularization

In addition, Stent Thrombosis will be evaluated at 30 day follow-up visit (30 day ± 7 days):

- Evidence (Definite and Probable)
- Timing (Acute, Sub-acute)

Additional Observational and Descriptive Analysis:

In addition to the secondary endpoint, safety of the trial is also analysed by the following observational and descriptive analysis. These events are not endpoints for the study:

- the following serious adverse events will be evaluated at 30 day follow-up visit (30 day ± 7 days):
  - Stroke
  - Cardiogenic shock
  - Pulmonary embolism
  - Pulmonary edema
  - Atrial fibrillation
  - Ventricular fibrillation
  - Vascular complications requiring intervention
  - Bleeding requiring transfusion of 2 units or greater
  - Cooling catheter access site infection
  - Systemic infection
  - Deep Venous Thrombosis (DVT)
  - Bradycardia
  - Hypotension

- The following serious adverse events will be evaluated at 12 month follow-up visit (12 month ± 14 days):
  - Death (Cardiac, Vascular, Non-Cardiovascular)
  - Stent Thrombosis
    - Timing (Acute, Sub-acute)
    - Evidence (Definite and Probable)
  - Hospitalizations due to Heart Failure

15.2 Statistical Methods

Baseline demographic and clinical characteristics will be summarized for each arm using descriptive statistics. Continuous variables will be reported with mean, standard deviation, median, and range. Discrete variables will be reported as frequency and proportion. A $\chi 2$ test or Fisher exact test (for small frequencies) will be used to compare discrete variables; t-test or Wilcoxon test (for non-normal data) will be used to compare the 2 arms with continuous variables for randomized subjects in the trial.

The primary effectiveness endpoint is to detect a 20% reduction of mean infarct size in the Test Arm compared to Control Arm where infarct size (%LV Mass) is measured by cMR at 4-6 days. The mean, median, standard deviation, and range will be presented for infarct size. A two sample t-test will be used to test the null-hypothesis of no difference in average infarct size test and control arm P-value will be reported with $p<0.05$ considered statistically significant. Infarct size will further be evaluated in subgroups and with ANOVA models.

For the primary safety endpoint of MACE (as defined by CD, All MI, and CI-TLR) at 30 days, all events will be tabulated and reported. Per-patient rate of composite MACE will be compared between the two arms with 1-sided Fisher's exact test.

Two interim analyses are planned to be performed at approximately 50% and 75% of randomization, once subjects have completed 4-6 day cMR follow-up. At the interim stage, the trial will be stopped to reject the null hypothesis of no difference or will continue enrolling. Based on the Lan-DeMets method for group sequential trials using O'Brien-Fleming boundaries, the levels of significance for the interim analyses are alpha=0.00305 (50% information fraction), alpha=0.01832 (75% information fraction), and alpha=0.044 (final analysis).

All analyses for effectiveness will be conducted in intent-to-treat and per-protocol analyses set. All analyses for safety will be conducted in the safety dataset. Imputation will be made for missing infarct size (LV%) in intent-to-treat analyses set per Intention-to-Treat principle; details are described in the Statistical Analysis Plan.

15.3 Sample Size Justification

The primary effectiveness analyses is designed to detect a relative reduction of 20% in mean anterior myocardial infarct size (IS), as determined by Cardiac Magnetic Resonance (cMR) imaging at 4-6 days post infarct in the Test Arm (cooling + PCI) compared to the Control Arm (PCI only). The absolute magnitude of a relative reduction of 20% depends on the mean IS in the control arm, which is assumed to be approximately 17 %LV. Therefore, the treatment effect of interest is an absolute difference of 3.5 %LV.

The hypothesis for the primary effectiveness endpoint is the following for patients randomized 1:1 in Treatment Arm vs Control Arm:

H_0: $\mu_T = \mu_C$
H_A: $\mu_T \neq \mu_C$

Null hypothesis:

The null hypothesis is that the mean infarct size in the Test Arm is equal to the mean IS in the Control Arm.

Alternative hypothesis:

The mean infarct size in the control arm is not equal to mean infarct size of control arm.

This 20% relative reduction is defined as absolute value 3.5 %LV and accounted for in our sample size calculation as minimally detectable effect. This assumption is based on previous studies with anterior infarct size measured with cMR reporting between 17-20% absolute %LV in anterior infarct (***Tables 17 & 18***). Therefore, a relative reduction of 20% can vary depending on the mean infarct size of the control arm. Assuming a representative mean infarct size of ~17% in controls, we assume absolute difference of 3.5 %LV is equivalent to 20% mean anterior infarct size would be an adequate detection limit for effect.

Based on these assumptions--standard deviation of 12.0 %LV, two-tailed t-test of difference between means, a normal distribution, 80% power (beta=0.2), with the final analysis will be conducted using a two-sided test at the alpha=0.044 level of significance (adjusted for the two interim analyses)-- the required total sample to detect a mean difference of 3.5 %LV with 80% power is 384 subjects (192 subjects per group). Assuming 24% loss to follow-up, the trial plans for an enrolment up to 500 randomized subjects (250 in each arm) for 4-6 days cMR imaging follow-up.

Table 17: Clinical trials reporting anterior mean infarct size measured by cMR 4-6 days in PCI trials (Control Group Only) and calculated 20% relative reduction

Study name	Anterior n	Mean infarct size	Standard Deviation	20% relative reduction
APEX-AMI[41]	**60**	**16.6**	**10.7**	**3.3**
LIPSIAABCIXIMAB[42]	**63**	**25.3**	**16.1**	**5.1**
LIPSIA-STEMI[43]	**38**	**18**	**16.0**	**3.6**
CRISP-AMI [44]*	**142**	**37.5**	**20.1**	**7.5**
INFUSE-AMI[45]	**172**	**17.3**	**10.2**	**3.5**
RAPID-MI ICE[1]	**7**	**19.7**	**8.5**	**3.9**
CHILL-MI[37]	**21**	**26.5**	**10.9**	**5.3**
AMI EU PILOT	**21**	**23.3**	**12.0**	**4**

*>60% are large proximal infarcts

A range of standard deviation in the table expected is represented by anterior infarct data measured with cMR from separate and pooled analyses of previous hypothermia trials with AMI patients cooled below 35°C: RAPID-MI ICE (2009), CHILL-MI (2013), AMI EU Pilot (ongoing) as described below in **Table 18.**

Table 18: Hypothermia trials using cMR measured infarct size as primary outcome

	RAPID-MI ICE (2009)	CHILL-MI (2013)	AMI EU Pilot (2017)	Pooled AMI EU Pilot, RAPID-MI-ICE, CHILL-MI
n (Control vs Cooled)	7 vs 5	21 vs 15	21 vs 19	49 vs 39
Control Mean LV%	19.7	26.5	23.3	24.5

	RAPID-MI ICE (2009)	CHILL-MI (2013)	AMI EU Pilot (2017)	Pooled AMI EU Pilot, RAPID-MI-ICE, CHILL-MI
20% reduction in infarct	3.94	5.3	4.7	4.9
Std Dev (control)	8.5	10.9	12.0	10.5
Std Dev (cooled)	6.5	9.3	10.3	11.0

The potential impact of variations in control infarct size and variability is presented in ***Table 19.***

Table 19: Sample size estimates with alternative standard deviation and detection limit

Mean Difference in infarct size for detection (%)	Standard Deviation	Estimated Sample Size	Total Enrollment (with 24% drop-out)
3.0	**9**	**288**	380
3.0	**10**	**355**	468
3.0	**11**	**430**	566
3.0	**12**	**506**	666
3.5	**9**	**212**	280
3.5	**10**	**260**	342
3.5	**11**	**314**	414
3.5	**12**	**374**	500
4.0	**9**	**162**	214
4.0	**10**	**200**	264
4.0	**11**	**240**	316
4.0	**12**	**286**	376

The primary safety endpoint is a composite endpoint. For the sample size calculation, expected incidence is based on a literature review of acute MI hypothermia trials that combined six studies: Dixon et al, COOL MI, ICE-IT, RAPID MI-ICE, CHILL-MI, VELOCITY[46] which resulted in a 30-day MACE rate of 6.6% in the Control patients and 7.5% in treatment patients. Previously, AMIHOT II trial defined 30-day MACE rate comprised of death, reinfarction, target vessel revascularization, and stroke used a non-inferiority hypothesis with a 6% equivalence delta and 7% in the Control patients[47].

The hypothesis for the primary safety endpoint is the following:

$\mathbf{H_0}: \pi_T \geq \pi_C + 6\%$

$\mathbf{H_A}: \pi_T < \pi_C + 6\%$

π_T and π_C are the underlying proportion of patients having a MACE event.

An enrollment of 500 patients would be able to demonstrate 91% power and 95% 1-sided significance. The safety endpoint will be considered to have been met if there is a high posterior probability of non-inferiority [i.e. P ($\pi t < \pi c + 6\% > 95\%$)]. With a drop-out rate of 20%, the power is calculated to be 86%.

16 PUBLICATION

At the conclusion of the trial, a multi-center manuscript will be prepared for publication. Publications will be managed by the Sponsor, its designee and the Advisory board. Additional publications from any single site will be considered but only after the multi-center publication.

17 INTELLECTUAL PROPERTY

In all documents the company name of ZOLL Circulation® will be referred to in short hand as ZOLL. ZOLL® is a registered trademark of ZOLL Medical Corporation. The Proteus IVTM System is a trademark of ZOLL Circulation, Inc. Proteus Catheters, Cassettes and Temperature Probes (X-Probe) are registered trademarks of ZOLL Circulation, Inc.

18 STATEMENT OF COMPLIANCE

1. Sponsor and Investigator will conduct the clinical investigation in accordance with the ethical principles that have their origin in the Declaration of Helsinki.
2. Sponsor and Investigator will comply with ISO 14155:2011 and any regional or national regulations, as appropriate.
3. Investigator will not begin the clinical investigation until Investigator obtains the required written approval or favorable opinion from the MEC or regulatory authority, if appropriate.
4. Investigator will follow any additional requirements imposed by the MEC or regulatory authority, if appropriate.

ATTACHMENT I – REFERENCES

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ATTACHMENT II – ANTI-SHIVERING PROTOCOL

Shivering Suppression Guidelines

Turn on IVTM System console to initiate system and begin cooling of coldwell

↓

Obtain Informed Consent (EMS arrival/at hospital)

↓

Administer Buspirone 60 mg PO/NG x 1 immediately

↓

Place Bair Hugger on upper body; set to "high"; forced-air cover should be adjacent to skin. Put one blanket on top.

↓

Closer to the time of device deployment, **Pethidine 1 mg/kg IV (up to 100 mg)**

***Morphine and/or other sedatives are often administered in the setting of an acute MI Morphine and Pethidine (Demerol) are both opiate narcotics and if possible, morphine should be held as the combination may cause over-sedation. Consider 0.5 mg/kg Pethidine IV, if Morphine has been administered.

↓

At 15 minutes, Pethidine 0.5mg/kg IV should be administered.

Then a 25 mg/hr IV infusion of Pethidine (up to 80 kg patient) or 35mg/hr (> 80 kg patient) should be initiated and maintained for the duration of device deployment.

***Make sure the patient has a respiratory rate ≥ 10 breaths/minute.

What to do if shivering occurs:

First, try **repositioning the Bair Hugger** or changing its settings to increase the heat delivered to the patient's surface.

Second, consider **increasing dose of Pethidine**. Prior to giving additional Pethidine, look for signs of respiratory depression (i.e. decreased Respiratory Rate, decreased O2 Saturation by Pulse Ox.) If it is decided that the patient can tolerate additional Pethidine the following may be tried:

1. An IV dose of 25 mg x 1 may be given
2. If Infusion rate is 25mg/hr, the rate may be increased to a maximum of 35 mg/hr

If the shivering persists following the above measures, **consider raising the target temperature on the Proteus Console by 0.5°C** (i.e. from 32.0°C to 32.5°C). If this does not work after 5-10 minutes at the new target temperature, then the process can be repeated until a temperature where no shivering is obtained.

ATTACHMENT III – BEDSIDE SHIVERING ASSESSMENT SCALE (BSAS)

SCORE	SEVERITY	DEFINITION
0	None	No shivering noted on palpation of the masseter, neck or chest wall
1	Mild	Shivering localized to the neck and/or thorax only
2	Moderate	Shivering involves gross movement of the upper extremities in addition to neck and thorax
3	Severe	Shivering involves gross movements of the trunk, upper and lower extremities

ATTACHMENT IV – SPECIFIC NEW-ONSET ADVERSE EVENT DEFINITIONS

SPECIFIC NEW-ONSET ADVERSE EVENT	DEFINITION
1. All-Cause Mortality	Deaths will be classified as cardiac, vascular or noncardiovascular as defined by the Academic Research Consortium.[27] All deaths are considered cardiac unless an unequivocal non-cardiac cause can be established. Specifically, any unexpected death even in patients with coexisting potentially fatal non-cardiac disease (e.g. cancer, infection) should be classified as cardiac. <u>Cardiac death (CD):</u> Any death due to proximate cardiac cause (e.g. MI, low-output failure, fatal arrhythmia), unwitnessed death and death of unknown cause, all procedure related deaths including those related to concomitant treatment. <u>Vascular death:</u> Death due to non-coronary vascular causes such as cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular cause. <u>Non-cardiovascular death</u>: Any death not covered by the above definitions such as death caused by infection, malignancy, sepsis, pulmonary causes, accident, suicide or trauma.
2. Recurrent MI [27,31]	Recurrent MI or re-infarction may be diagnosed when cardiac biomarker levels are stable on 2 samples that are >6 hours apart or are in decline if a subsequent value 3 to 6 hours after the procedure is increased by $\geq$ 20% from the baseline sample. If the baseline value is not stable, then insufficient data exists to recommend biomarker criteria for diagnosis, and the Academic Research Consortium[27,31] recommends that the event be considered as pre-procedure MI. Periprocedural MI is that which occurs within the first 48 hrs after PCI or within the first 72 hrs after coronary artery bypass grafting (CABG).

	Q wave MI: Development of new, pathological Q wave on the baseline ECG (≥ 0.04 seconds in duration and ≥ 1 mm in depth) in ≥ 2 contiguous precordial leads or ≥ 2 adjacent limb leads) Non-Q wave MI: Those MIs which are not Q-wave MI.
3. Need for revascularization of the target vessel (TVR)[27]	TVR is defined as any repeat percutaneous intervention or surgical bypass of any segment of the target vessel. The target vessel is defined as the entire major coronary vessel proximal and distal to the target lesion, which includes upstream and downstream branches and the target lesion itself.
4. Stroke	Development of a new neurological deficit that persists > 24 hours, or worsening of previous neurological symptoms that persist > 24 hours.
5. Cardiogenic shock	Systolic blood pressure of less than 90 mmHg for at least 30 minutes which is secondary to myocardial dysfunction, leading to decreased cardiac output and evidence of tissue hypoxia in the presence of adequate intravascular volume.
6. Pulmonary embolism	Sudden onset of pleuritic chest pain, cough, hemoptysis, hypoxia, tachycardia, and a positive ventilation/perfusion scan or a CT scan.
7. Ventricular Fibrillation (V-Fib)	Rapid uncoordinated fluttering contractions of the heart ventricles recognized by the occurrence on the electrocardiogram of coarse and irregular oscillations without discernible QRS complexes or T waves
8. Vascular complications requiring intervention	Complications arising from the use of the Proteus Catheter including the development of a vessel tear, hematoma, pseudoaneurysm, arteriovenous (AV) fistula, or retroperitoneal bleeding which require an additional surgical intervention for treatment.
9. Bleeding requiring transfusion of 2 units or greater	Any periprocedural bleeding which occurs as a result of the PCI and/ or cooling procedure which requires transfusing > 2 units.
10. Systemic Infection	Sepsis with confirmed positive blood cultures.
11. Cooling Catheter Access Site Wound infection	Infection and inflammation of the incision or puncture site requiring drainage and/or debridement in addition to antibiotic therapy, e.g., cellulitis.
12. Pulmonary Edema	Abnormal accumulation of fluid in the lungs

13. Deep Venous Thrombosis (DVT)[32]	Formation of one or more blood clots in one of the body's large veins, most commonly in the lower limbs. The clot(s) can cause partial or complete blocking of circulation in the vein, which in some patients leads to pain, swelling, tenderness, discoloration, or redness of the affected area, and skin that is warm to the touch. As many patients enrolled in the trial will have pre-existing DVT, for the purposes of this trial DVT is defined as the de novo onset of DVT following enrollment which required treatment or worsening of pre-existing DVT.

ATTACHMENT V – ADVERSE EVENT DEFINITIONS

Adverse Event Definitions

In addition to the definitions provided in **Attachment IV– Specific New Onset Serious Adverse Event Definitions**, the following definitions apply to expected adverse events that may occur and must be reported throughout this clinical trial. Events reported should represent a new onset or increase in the severity of the condition from the time of enrollment.

A. CARDIAC COMPLICATIONS	DEFINITION
Recurrent Myocardial ischemia [31]	Recurrent Myocardial Ischemia : is evidenced through baseline ECG changes identified during continuous multilead baseline ECG–ischemia monitoring (or Holter monitoring) which may be accompanied by the development of new clinical symptoms suggesting an ischemic cardiac episode.
Arrhythmias	The development of a new atrial and/or ventricular arrhythmia, significant increase in the severity of a preexisting arrhythmia, or any episode of cardiac arrest.
Congestive Heart Failure[34]	Defined as patients with defined or presumed cardiac disease and one of the following: Class I: without limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea. Class II: slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, or dyspnea. Class III: marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea. Class IV: inability to carry on any physical activity without discomfort. Symptoms are present even at rest or minimal exertion.

B. PULMONARY COMPLICATIONS	DEFINITION
Pneumonia	Clinical evidence as determined by physical, radiographic, and laboratory findings requiring treatment with antibiotics, inhalation therapy, intubation, or suctioning.
Atelectasis	Clinical evidence as determined by physical, radiographic, and laboratory findings requiring treatment with antibiotics, inhalation therapy, intubation, or suctioning.

Respiratory Failure	Need for mechanical ventilation for > 24 hours postoperatively, or reintubation for any reason.

C. RENAL COMPLICATIONS	DEFINITION
Acute Kidney injury (AKI)[35]	AKI is defined as any of the following: Increase in SCr by ≥.3 mg/dl (≥26.5 µmol/l) within 48 hours; or Increase in SCr to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or Urine volume < 0.5 ml/kg/h for 6 hours.

D. VASCULAR COMPLICATIONS	DEFINITION
Arteriovenous Fistula	Formation of an abnormal connection between the lumens of an artery and a vein as documented by CT, ultrasound, angiography, or direct observation.
Embolism	The obstruction of a blood vessel by a blood clot or foreign substance, e.g., air, fat, bacteria.
Vessel perforation	Defined as perforation of the access vessel wall or vena cava confirmed by extravasation of contrast under fluoroscopy, angiography, CT scan, and/ or direct observation at surgery or autopsy.
Hematoma	An abnormal localized collection of blood (clotted or partially clotted) and situated within an organ or a soft tissue space, such as within a muscle. Development of an incisional or retroperitoneal hematoma requiring surgical intervention, evacuation, transfusion or prolonged hospitalization.
Hemorrhage	Post-procedural bleeding requiring transfusion of ≥ 2 units.
Hypotension	Abnormally low systolic blood pressure that is < 80 mm Hg

D. VASCULAR COMPLICATIONS	DEFINITION
Peripheral vascular insufficiency (PVI)	Inadequate peripheral blood flow resulting from the occlusion of vessels by atherosclerotic plaques, thrombi, or emboli; damaged, diseased, or intrinsically weak vascular walls; arteriovenous fistulas; hematologic hypercoagulability; and heavy smoking. Signs of vascular insufficiency include pale, cyanotic, or mottled skin over the affected area; swelling of an extremity; absent or reduced tactile sensation; tingling; diminished sense of temperature; muscle pain, such as intermittent claudication in the calf; and, in advanced disease, ulcers and atrophy of muscles in the involved extremity. As many patients enrolled in the trial will have pre-existing Peripheral Vascular Insufficiency (PVI), for the purposes of this trial PVI is defined as the de novo onset of PVI following enrollment which requires treatment or worsening of pre-existing PVI.
Pseudoaneurysm	Enlargement of the aorta, iliac, or femoral arteries, which contain some or all of the medial layer, the adventitia, and periaortic tissue most commonly associated with previous aortic operative procedures, trauma, and/or infection. Pseudoaneurysms typically present as a well-defined collection of blood outside the vessel wall from contained rupture.
Stenosis	A reduction in the diameter of the vessel lumen when compared to the reference diameter, as documented by angiography, which requires intervention and is related to the procedure, e.g., access vessel.
Thrombosis	Clotting within a blood vessel which may cause infarction of tissues supplied by the vessel; it may be occlusive or attached to the vessel or heart wall without obstructing the lumen.
Transient Ischemic Attack (TIA)	A brief episode of neurological dysfunction caused by focal brain or retinal ischemia with clinical symptoms typically lasting 1 - 24 hours and without evidence of acute infarction.

E. WOUND COMPLICATIONS	DEFINITION

Hematoma	An abnormal localized collection of blood (clotted or partially clotted) and situated within an organ or a soft tissue space, such as within a muscle. Development of an incisional or retroperitoneal hematoma requiring surgical intervention, evacuation, transfusion or prolonged hospitalization.
Arteriovenous Fistula	Formation of an abnormal connection between the lumens of an artery and a vein as documented by CT, ultrasound, angiography, or direct observation.
Nerve Injury/Peripheral Neuropathy	Direct damage to nerves surrounding the access site, operative field, or catheter deployment site, and the resultant signs and/or symptoms of such damage which may include pain and numbness in the affected area associated with muscle weakness and decreased patellar reflex lasting > 1 month after treatment.

F. SYSTEMIC COMPLICATIONS	DEFINITION
Coagulopathy	The development of an abnormal bleeding disorder, e.g., disseminated intravascular coagulopathy or thrombocytopenia, documented by appropriate laboratory studies and requiring therapy with medication or transfusion.
Anesthetic Complications	Reaction or complication caused by administration of an anesthetic.
Liver failure[33]	Acute liver failure is defined as the rapid development of hepatocellular dysfunction, specifically coagulopathy and mental status changes (encephalopathy) in a patient without known prior liver disease.

F. SYSTEMIC COMPLICATIONS	DEFINITION
Pancreatitis[36]	Evidenced on two of the following three conditions: 1) abdominal pain suggestive strongly of acute pancreatitis (epigastric pain often radiating to the back), 2) serum amylase and/or lipase activity at least 3 times greater than the upper limit of normal, (imaging is to be used if the elevated values are <3 times normal); and 3) characteristic findings of acute pancreatitis on transabdominal ultrasound or on Contrast Enhanced Computed Tomography (CECT) [32]

ATTACHMENT VI – INVESTIGATOR LIST

ATTACHMENT VII – LIST OF ABBREVIATIONS

AAR	Area at Risk
ACC	American College of Cardiology
ADE	Adverse Device Effect
AE	Adverse Event
AHA	American Heart Assocation
AKI	Acute Kidney Injury
AMI	Acute Myocardial Infarction
ASADE	Anticipated Serious Adverse Device Effect
AV	Arteriovenous
BSAS	Bedside *Shivering* Assessment *Scale*
CABG	Coronary Artery Bypass Grafting
CD	Cardiac Death
CEC	Clinical Events Committee
CHF	Congestive Heart Failure
CIP	Clinical Investigation Plan
CI-TLR	Clinically-Indicated Target Lesion Revascularization
CMP	Clinical Monitoring Plan
cMR	Cardiac Magnetic Resonance
CNS	Central Nervous System
CRO	Clinincal Research Organization
CRF	Case Report Form
CRMI	Clinically Relevant Myocardial Infarction
CVA	Cerebral Vascular Accident
CVP	Central Venous Pressure
DAPT	Dual Antiplatelet Therapy
DD	Device Deficiency
DES	Drug Eluting Stent
DMC	Data Monitoring Committee
DP	Dorsalis Pedis
DSMB	Data Safety Monitoring Board
DTB	Door-to-Balloon
DVT	Deep Vein Thrombosis
EC	Ethics Committee

ECG	Electrocardiography
EDC	Electronic Data Capture
ED	Emergency Department
ER	Emergency Room
ESC	European Society of Cardiology
EU	European Union
Fr	French
FMECA	Failure Mode, Effects and Criticality Analysis
FEP	Fluorinated Ethylene Propylene
GLP	Good Laboratory Practice
HDPE	High-density Polyethylene
HIPPA	Heath Insurance Portability and Accountability Act
HTN	Hypertension
ICF	Informed Consent Form
IEC	International Electrotechnical Commission
IFU	Instructions for Use
IQR	Interquartile Range
IRB	Institutional Review Board
IRI	Ischemia Reperfusion Injury
IS	Infarct Size
ISO	International Organization for Standardization
ITT	Intention-to-Treat
IVC	Inferior Vena Cava
IVTM	Intravascular Temperature Management
KCCQ	Kansas City Cardiomyopathy Questionnaire
LAL	Limulus Amebocyte Lysate
LED	Light-emitting Diode
LV	Left Ventricular
LVEF	Left Ventricular Ejection Fraction
MACE	Major Adverse Cardiac Events
MAO	*Monoamine Oxidase*
MaR	Myocardium at Risk
MEC	Medical Ethics Committee

MEM	Minimum Essential Medium
MI	Myocardial Infarction
MRI	Magnetic Resonance Imaging
NCA	National Competent Authority
NYHA	New York Health Association
OD	Outer Diameter
PCI	Percutaneous Coronary Intervention
PETG	Polyethylene Terephthalate - Glycol modified
PP	Per-protocol
PVI	Peripheral Vascular Insufficiency
PVP	Polyvinylpyrrolidone
RCN	Radio-Contrast Nephropathy
RF	Radiofrequency
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Events
SBP	Systolic Blood Pressure
SOP	Standard Operating Procedure
SPECT	Single-photon Emission Computed Tomography
STEMI	ST-segment Elevation Myocardial Infarction
SVT	Supraventricular Tachycardia
TIA	Transient Ischemic Attack
TIMI	Thrombolysis In Myocardial Infarction
TH	Therapeutic Hypothermia
TVR	Target Vessel Revascularization
UADE	Unanticipated Adverse Device Effect
UFH	Unfractioned Heparin
USADE	Unanticipated Serious Adverse Device Effect
USP	United States Pharmacopeia
UTI	Urinary Tract Infection

APPENDIX E

Change Log (2 pages)

COOL AMI EU PIVOTAL PROTOCOL (EDC-3135)
SUMMARY OF CHANGES*

Section	Summary of Changes	Rationale
Cover Page	*Deleted text:* ~~Appendix A~~	Deleted text for clarification
Footer	*Revised text In the Footer:* ~~Appendix A,~~ ~~Rev 5,~~ ~~12 Feb 2018~~	Revised text for clarification
Sponsor Approval Signature page	*Added page #2* CLINICAL INVESTIGATION PLAN APPROVAL PAGE	Added clarification per advisory board recommendation in response to questions regarding qualifying Infarct location.
Synopsis	*Updated Clinical Trial Sponsor's Contact:* ~~Renee Kochevar, PhD, AL M~~ Philippa Hill ~~Vice President~~ Senior Director, Clinical Affairs ZOLL Circulation, Inc. 2000 Ringwood Ave. San Jose, CA 95131 Main: +1 (408) 541-2140 Fax: +1 (408) 541-1030 PHill@zoll.com ~~rkochevar@zoll.com~~	Updated with current Sponsor Contact Information
6.8.9	*Revised text in Figure 11. All Patient Procedures:* Collect NT-pro BNP	Added text for clarification
6.8.13 6.8.14	*Revised text in Trial schedule for Test and Control Arm:* NT-pro BNP	Added text for clarification
6.8.17	*Revised text:* ii. Collect NT-pro BNP value to assess clinical prognosis of Heart Failure iv. Perform blinded NYHA Assessment and administer ~~blinded~~ Kansas City Cardiomyopathy Questionnaire (KCCQ).	Revised for clarification.

16	*Added a new section 16:* **16 PUBLICATION** At the conclusion of the trial, a multi-center manuscript will be prepared for publication. Publications will be managed by the Sponsor, its designee and the Advisory board. Additional publications from any single site will be considered but only after the multi-center publication.	Added a publication section for ISO 14551 compliance

*The Summary of changes applies to COOL AMI EU Pivotal Protocol (EDC-3135) revisions listed below:

1. Pivotal Protocol (EDC-3135) from Rev 5. to Rev 6. - For sites that don't require specific Dual Anti-Platelet Therapy details
2. Pivotal Protocol (EDC-3135) from Rev 5. to Rev 6. – For Germany Only
3. Pivotal Protocol (EDC-3135) from Rev 5. to Rev 6. - For sites that require specific Dual Anti-Platelet Therapy details
4. Pivotal Protocol (EDC-3135) from Rev 2. to Rev 3. – For France Only