Supplementary Online Content


Supplement 1. Trial protocol and statistical analysis plan

This supplementary material has been provided by the authors to give readers additional information about their work.
This supplement contains the following items:

1. Original protocol, final protocol, summary of changes.
2. Original statistical analysis plan, final statistical analysis plan, summary of changes
Prehospital Resuscitation Intranasal Cooling Effectiveness Survival Study
(PRINCESS)

PROTOCOL
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Protocol Synopsis

Purpose: To assess the impact on neurological intact survival on cardiac arrest victims when trans-nasal cooling is initiated as early as possible in the resuscitation process.

Background: The RhinoChill Device is a non-invasive cooling device through which rapid cooling is achieved via the trans-nasal delivery of an evaporative coolant into the nasopharynx. Due to its non-invasive and portable nature, the RhinoChill can be used to begin cooling earlier than other cooling devices.

A 200-patient safety and feasibility study showed a solid trend to improved neurologically-intact survival rates in those patients receiving early intra-nasal cooling prior to achieving ROSC. This study aims at assessing outcome when cooling is begun early in the resuscitation process compared to systemic cooling at hospital only. The primary endpoint is total survival at 90 days.

Design: Prospective, randomized, two-arm study conducted by the pre-hospital emergency system.

Study Population: Up to 900 victims of witnessed cardiac arrest who qualify for advanced cardiac life support with ambulance response time within 15 minutes.

Performance Endpoints: Primary endpoints:

- Neurologic intact survival at 90 days.
- Total survival at 90 days

Secondary endpoints:

- Proportion of patients who achieve ROSC
- Proportion of patients admitted alive
- Proportion of patients reaching target temperature ($\leq 34^\circ$ Celsius) within 4 hours

Safety Endpoint:

- Composite general adverse event rate within the first 24 hours of initiating ALS
- Composite serious adverse event rate within the first 7 days of hospitalization

Safety Follow-Up: Death, hospital discharge, or 1 week post hospital admission
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1. **INTRODUCTION**

1.1. **Background & Study Rationale**

Sudden Cardiac Death is one of the major health issues of the industrialized world [1]. Despite decades of efforts to promote CPR science and education and the introduction of automated external defibrillators, less than 50% of cardiac arrest victims ever achieve a return of spontaneous circulation (ROSC) and this percentage drops to 20% or less for those patients that live in rural areas or do not have an initial rhythm that can be defibrillated (e.g., pulse-less electrical activity (PEA) and asystole) [2-8]. Even fewer of these patients live to hospital admission.

Two randomized studies published in the NEJM in 2002 demonstrated the benefit of therapeutic hypothermia on neurologically intact survival in patients who were cooled to 33-34°C within eight hours of ROSC following an out-of-hospital ventricular fibrillation (VF) cardiac arrest [9,10]. Based on these study results, the International Liaison Committee on Resuscitation published special guidelines recommending the use of mild hypothermia in routine treatment of cardiac arrest patients during post ROSC care [11]. Specifically the guidelines state that patients that achieve ROSC following a VF out of hospital cardiac arrest (OHCA) should be cooled as soon as possible, and that those patients achieving ROSC following a non-shockable OHCA might also benefit from cooling. The American Heart Association [12] and European Resuscitation Council [13] endorsed these recommendations shortly thereafter.

Of these randomized clinical studies, one protocol initiated cooling in the ambulance with ice packs by paramedical personnel [10], while the other study initiated cooling in the hospital [9]. The former study achieved target temperature shortly after ICU admission, whereas the latter study took an average of 8 hours following ROSC to achieve target temperature. The former study suggests a benefit to faster cooling, as it showed a better relative percentage of patients having a good outcome (CPC score 1 or 2) when compared to normothermic controls, with an odds ratio of 5.25.

Two additional studies, however, recently assessed the relative impact of cooling via iced-saline infusion shortly after OHCA patients were resuscitated in the field. The first of these was a feasibility study performed in Seattle USA that [8] showed a trend in improved survival to hospital discharge for the VF group that received early cooling. Ninety percent of subjects that received early cooling in the field survived to hospital admission, and 73% of those survived until hospital discharge (66% of the total achieving ROSC). In contrast, of the 86% of non-cooled patients that survived until hospital admission, only 52% survived (45% of the total achieving ROSC). Even with a relative improvement of 21%, the difference was not statistically significant. For those patients that had a non-VF rhythm and achieved ROSC the trend was reversed: only 6% of the cooled patients versus 20% of the non-cooled patients survived to hospital discharge.

The second study, performed in Melbourne Australia, [14] was powered to detect a 15% increase in neurologically good outcomes at hospital discharge in those patients receiving cooling in the field shortly after achieving ROSC. Interim analysis performed after enrolling 50% of the target population demonstrated no difference in outcomes between the group that was cooled in the field (46% good outcome) compared to those that received cooling later after hospital admission (53% good outcome). This latter study also showed the reverse trend from the Seattle study in that those patients that received
in-field cooling after achieving ROSC from a non-shockable rhythm demonstrated a trend for better outcomes than those that received cooling later.

Moderate hypothermia before cardiac arrest has been used successfully since the 1950s to protect the brain against the global ischemia that occurs during open heart surgery. Animal studies suggest that hypothermia induced during a cardiac arrest and prior to ROSC improve neurological outcomes when compared to animals that are cooled following ROSC [15-19]. These studies support the concept that post-resuscitation injury processes begin immediately after ROSC is achieved, and that intra-arrest cooling may serve as a useful therapeutic approach to improve survival.

The RhinoChill was designed to rapidly induce therapeutic hypothermia intra-arrest or post-resuscitation in emergency settings. The RhinoChill takes advantage of the nose as a natural orifice into the head to overcome the obstacle of cooling through the skull. The upper nasal pathways are composed of conchal folds and turbinates that converge in the pharyngeal zone, and thus provide a large diffuse area and vascularity that is in close proximity to the cerebral circulation. Cooling in the nasopharynx therefore offers the ability to cool via both direct conductive mechanisms that do not rely on spontaneous circulation as well as indirect hematogenous mechanisms that do [20].

Animal studies and preliminary clinical studies support the use of the RhinoChill in the emergency setting of resuscitation from cardiac arrest.

1.2. Device Description

The RhinoChill is intended for temperature reduction in patients where clinically indicated. The RhinoChill is contraindicated for patients with known contraindications to hypothermia (Raynaud’s disease, Cryoglobulinemia, Sickle Cell disease), have specific temperature-sensitive pathologies (e.g., serum cold agglutinins, Buerger’s disease), are pregnant, are medically unstable, have bleeding disorders, require oxygen supplied at > 50% FiO2 to maintain normal saturation (> 98%), intranasal obstruction, or known skull base fracture.

The RhinoChill works by spraying a liquid coolant onto the upper surface of the nasal cavity, where it evaporates and absorbs heat from the tissue, thereby cooling the tissue and the innate vasculature that supplies blood to the brain (refer to schematic). The coolant has a density of 1.68 g/ml and a heat of evaporation of 21cal/g. Therefore 35 calories of heat are absorbed for every ml of coolant that evaporates. Local temperatures within the nasal cavity are expected to cool to around 2°C. The coolant is an inert liquid at one atmosphere of pressure and can carry 20 times more oxygen than saline. It has a surface tension that is lower than water so it will spread uniformly and quickly throughout the space in which it is sprayed. Oxygen or air is delivered with the liquid coolant to maximize its evaporation.

Medical grade oxygen or breathing air with a supply pressure of 60 psi and sufficient quantity to provide a 40 L/min flow rate over the treatment period is required in order to operate the RhinoChill.

The coolant vapor, along with the gasescapes the nasal cavity through the nostrils or the mouth. In the event that all the coolant is not evaporated, it is possible that it will either trickle out of the nostrils or trickle down the pharynx into the mouth or stomach. Because the coolant is immiscible in water, it is not absorbed in any significant quantity.
into the body [21, 22]. The minute quantities that may be absorbed into the blood or inhaled into the lungs are expired through the lungs in a relatively short period.

**RhinoChill Schematic**

The RhinoChill consists of three components: the tubing set, the control unit, and the coolant bottle. The tubing set is a single-use device that delivers the pressurized gas and coolant mixture to the patient. The proximal end attaches to the control unit to which a hospital gassource is connected. Distal to the control unit is the interface for the coolant bottle; this consists of a dip tube connected to a bottle interface collar into which is incorporated a liquid flow indicator. Liquid coolant is driven out of the bottle by the pressurized gas, through a 0.22 micron filter, and then the gas and coolant are delivered to the nasal catheters. The transnasal catheters are joined together with a hub at the proximal ends; the catheters are mated to the gas and liquid delivery lines via an integral manifold. The length of each individual catheter is 10cm, and the outer diameter is 4.0mm. The catheters are designed to be conformable with the anatomy, and have rounded atraumatic tips. The length of the catheter enables deep access into the nasopharynx, and the diameter of the catheter is consistent with the size of epistaxis catheters, and enables venting through the nostrils. The catheters have separate gas and liquid capillaries that converge at each of 12 spray ports along the dorsal surface of the catheter. Close contact of the liquid PFH with the pressurized gas at each of the spray ports results in efficient nebulization of the PFH from each of these ports. Each catheter also has three pressure sensing ports along the ventral surface of the catheter that transmit the local pressure in the nasal cavity to the control unit.
The control unit is a durable component used to both control the flow of the coolant-oxygen mixture as well as to act as an over-pressure shut-off valve. The control unit is composed of a commercially available mechanical oxygen flowmeter that is used to control the flow rate of oxygen as well as electronic circuitry to monitor oxygen supply pressure and intranasal pressure in each nostril. The control unit also has a mechanical over-pressure safety valve which is designed to vent excess oxygen to prevent a pressure greater than 60 psi (7 10%) from entering the device. This limiting pressure is set approximately 10% above the 50 psi 10% standard used for medical grade oxygen in the hospital setting. The patient pressure safety circuitry switches the device to a Stopped/Alarm mode if the pressure in either nasal cavity exceeds 60 cm H₂O (7 10%). During the Stopped/Alarm mode, all gas flow is stopped, and all pressure is vented from the components downstream of the control unit, including the coolant bottle. The device will remain in the Stopped/Alarm condition until the device is manually reset by the operator.

The control unit circuitry is low voltage, and low power (i.e., it is designed to run for at least 10 hours on a set of two nine-volt batteries).

The control unit has user controls to initiate and stop flow as well as user-feedback indicator lights to indicate the operational mode and to alert the user when the circuit needs to be reset as well as when the battery power is becoming low and the batteries need to be replaced.

The coolant bottle is Polyethylene teraphalate (PET) bottle. It holds 1-2 liters of the evaporative coolant, perfluorohexane (PFH). A 1-liter bottle of coolant will last 30 minutes when the oxygen flow rate is set to 40L/min.

The RhinoChill is configured to be used in a stable hospital setting (e.g., hanging from an I.V. pole mount) or packaged in a backpack that integrates a 3L (900 liters gas) oxygen bottle, and weighs approximately 12 kg for use in the ambulance and field setting.
1.3. Non-clinical Studies

Forty-one sheep were studied in the development of the RhinoChill System: five sheep were studied as controls and 36 were studied using a variety of flow conditions and relative proportions of PFH to oxygen to effect evaporative cooling within the nasopharynx [23]. An additional 109 pigs were studied in 9 additional studies of a cardiac arrest model in which 68 pigs were cooled with the RhinoChill device and 41 were used as controls. Table 1 summarizes these studies.

Cardiac arrest studies demonstrated the safety and feasibility of intra-arrest cooling and the ability to 1) facilitate resuscitation [24, 25], 2) increase cardiac recovery time [24], 3) increase survival [24-26], and 4) increase neurological recovery time [26]. In contrast, chilled intravenous saline administered intra-arrest had no positive effect on resuscitation [27].
Table 1. Animal studies performed with the RhinoChill

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Model</th>
<th>Qty</th>
<th>Protocol</th>
<th>Results</th>
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</table>
| Feasibility          | Ovine       | 5   | Surface blanket vs. Single nozzle jet catheter prototype                 | Trans-nasal cooling more effective than surface blanket cooling  
Rectal cooling equivalent in both groups, but brain and core cooling rate higher with trans-nasal cooling  
Higher O₂ and higher PFC flow produce the greatest cooling  
PFC flow must be matched to O₂ flow to produce optimal cooling  
High flow rates caused minimal nasal bleeding associated with shear damage observed in histomicrographs |
| Flow Optimization     |             | 16  | Single nozzle jet catheter prototype – different flow                    | Directed spray design provided consistently better cooling  
No bleeding or other adverse effects seen with dispersed spray  
Brain cooling during spontaneous flow is characterized by initial rapid hematagenic cooling followed by slower conductive cooling;  
Cooling in VF is slower conductive cooling to brain, but total cooling over 60 minutes is the same as in spontaneous flow.  
Cooling during CPR in VF results in a cooling curve between the other 2 extremes |
| Catheter Development |             | 14  | Circumferential vs Directed spray catheter designs                       | PFC wash-out from blood at 1 hour was almost complete  
Organ levels after 1-hr wash-out period nearly undetectable  
Highest levels in liver (83/57 ng/ml); lowest in brain (<9ng/ml)  
Diastolic function (IVCT) significantly improved in early cooling vs no cooling at all time points, and vs blanket cooling thru 4H  
Cooling during CPR increased the power in the VF frequency spectra – a prognostic indicator of defibrillation success |
| PFH Safety            |             | 2   | Directed spray catheter, final design - Dose with 2.5x PFH:O₂ x 60min to force uptake | Brain cooling during spontaneous flow is characterized by initial rapid hematagenic cooling followed by slower conductive cooling;  
Cooling in VF is slower conductive cooling to brain, but total cooling over 60 minutes is the same as in spontaneous flow.  
Cooling during CPR in VF results in a cooling curve between the other 2 extremes |
| Cooling Dynamics      | Porcine     | 10  | Compartmental cooling rate as a function of circulatory state:  
3 Spontaneous flow vs.  
3 Untreated VF vs.  
4 VF treated with Mechanical CPR device (LUCAS)                         | Brain cooling during spontaneous flow is characterized by initial rapid hematagenic cooling followed by slower conductive cooling;  
Cooling in VF is slower conductive cooling to brain, but total cooling over 60 minutes is the same as in spontaneous flow.  
Cooling during CPR in VF results in a cooling curve between the other 2 extremes |
| Cardiac Arrest        | RhinoChill  | 25  | RhinoChill vs. No Cooling vs. Delayed (2H) blanket cooling  
O₂ flow = 1L/min/kg  
10 min VF; CPR/RhinoChill x 5 min; Defibrillation  
RhinoChill cooling x 4H  
Blanket cooling x 8H | ROSC= 100 vs. 87.5 vs. 87.5%  
24H survival = 100 vs. 25 vs. 75%  
Systolic function (EF) significantly improved in early cooling vs no cooling and delayed at all time points (1-4H and 96H)  
Diastolic function (IVCT) significantly improved in early cooling vs no cooling at all time points, and vs blanket cooling thru 4H  
Diastolic function (IVCT) significantly improved in early cooling vs no cooling at all time points, and vs blanket cooling thru 4H  
Cooling during CPR increased the power in the VF frequency spectra – a prognostic indicator of defibrillation success |
| Outcome (WICCM)      | RhinoChill  | 16  | RhinoChill vs. No Cooling  
O₂ flow = 1L/min/kg  
15 min VF; CPR/RhinoChill x 5 min; Defibrillation | RhinoChill = 87.5% ROSC vs  
No Cooling = 25% ROSC  
CPP @ 1st shock significantly higher with RhinoChill  
1st shock success significantly higher with RhinoChill |

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<table>
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<th>Results</th>
</tr>
</thead>
</table>
| Flow Rate vs ROSC Rate           | Porcine ≈40kg | 10  | 50% rate (O2 = 0.5L/min/kg) vs. 25% rate (O2 = 0.25L/min/kg) vs. No Cooling (0 rate) 15min VF; CPR/RhinoChill x 5 min; DF | 50% rate = 100% ROSC  
25% rate = 33% ROSC  
0 rate = 33% ROSC |
| Duration vs 96H Outcome          |               | 10  | Cooling for 1H vs. 4H post ROSC 10min VF; CPR + RhinoChill x 5 min; DF; survival to 96H | ROSC & Survival 100%, both groups  
24H neurological tests indicate moderate improvement in pigs cooled 4H over those cooled 1H  
96H: all equivalent |
| Oxygen vs Air                    |               | 6   | O2 vs. Air @ 0.75L/min/kg 15min VF; CPR+RhinoChill x 5 min; DF | Air: 100% ROSC  
O2: 67% ROSC |
| PEA (Pulseless Electrical Activity) |             | 16  | RhinoChill vs. No Cooling O2 flow = 1L/min/kg 12min VF; PEA conversion; CPR/RhinoChill x 5 min; DF | ROSC = 75 vs 12.5% for RhinoChill vs No Cooling  
CPP significantly higher @ 1st shock for RhinoChill group |
| No airway                        |               | 2   | 15min VF; CPR/RhinoChill x 5 min; DF No airway during VF/resuscitation ETT placed immediately post-ROSC | ROSC successful with un-protected airway  
Post-ROSC PaO2 elevated over baseline values (normally decreased)  
CXR post-ROSC showed pulmonary opacification from inhaled PFC  
Appropriate ventilation strategy (PEEP, bpm) enabled lung clearance ≤ 60min |
| RhinoChill vs cold saline        |               | 14  | RhinoChill vs. IV cold saline (30ml/kg over 30 min) 15min VF; CPR+cooling x 5 min; DF Cooling with blankets x 3H @ 1H post ROSC | Pa temperature significantly lower at 1st shock in saline group  
Jv temperature significantly lower at 1st shock in RhinoChill group  
CPP significantly higher at 1st shock in RhinoChill group  
ROSC = 100% RhinoChill vs. 29% cold IV saline  
Mean survival = 27 vs. 67H for saline vs. trans-nasal cooling |
1.4. Clinical Studies

1.4.1. Cooling after Resuscitation from Cardiac Arrest

The RhinoChill has been used in the emergency room/ICU in 84 cardiac arrest patients following ROSC, in a completed feasibility study in Europe [28]. Cooling was initiated within 35 minutes (median) of patients arriving at the hospital, and therapeutic temperature of 34°C was reached in 27 minutes and 52 minutes by the brain (measured at the tympanon) and body, respectively. Mean temperature reduction was 2.4°C, 1.6°C, and 0.9°C for the tympanon, central compartment (blood, esophagus), and peripheral compartment (bladder/rectum), respectively, within the first 60 minutes of cooling with the RhinoChill.

There was one device-related serious adverse event. A patient cooled with the RhinoChill device developed discoloration around the nose and upper lip approximately 3 hours after RhinoChill use was discontinued. The patient also exhibited skin discoloration of her fingertips and earlobes consistent with a circulatory disorder such as Raynaud’s syndrome. The patient had very high peripheral vascular resistance for the six hours prior to study enrollment and throughout therapeutic cooling. The patient died approximately 36 hours after discontinuing RhinoChill use due to persistent cardiogenic shock, with no resolution of the skin discoloration. Tissue samples were not taken for pathological examination after death, so the reversibility of the condition could not be determined.

1.4.2. Cooling during Resuscitation from Cardiac Arrest

The RhinoChill Device was used in 96 patients randomized to intra-arrest cooling in the pre-hospital setting as part of a 200-patient randomized study [29]. Cooling was begun after the physician team had arrived and had placed an advanced airway, but before ROSC. Thus cooling was not begun until a median of 23 minutes after patient collapse.

There were no significant differences in the proportion of patients achieving return of spontaneous circulation (ROSC) (p=0.8). Among patients admitted alive to the hospital there was a trend towards increased survival in treated patients (43.8 % vs 31.0%, p=0.26, Relative Risk (RR) 1.4). In patients admitted alive in whom cardiopulmonary resuscitation (CPR) was initiated within 10 minutes (76 % of patients) survival to discharge was significantly higher in cooled patients (56.5% vs 29.4%, p=0.04, RR 1.9). In the subgroup with ventricular fibrillation (VF) as presenting rhythm no significant difference was seen in survival rates (62.5% vs 47.6%, p=0.37, RR 1.3).

More patients were neurologically intact at discharge in the treatment group (34.4% vs. 21.4%, p=0.21, RR 1.6) than in controls. Neurologically intact survival to discharge was significantly higher in cooled patients in whom CPR was initiated within 10 minutes of collapse as compared to no-cool controls (43.5% vs 17.6%, p=0.03, RR 2.5). A trend towards good neurologic outcome seen in patients with VF as the presenting rhythm (50% vs 28.6%, p=0.11, RR 1.8).

Neurologically intact survival to discharge was directly related to time to CPR initiation. The benefit of intra-arrest cooling on survival, and especially on neurologically intact survival, was most marked when CPR was initiated by
EMS within 10 minutes (refer to Figure).

**Outcome data on neurologically intact survival** (defined as having a cerebral performance category (CPC) of 1 or 2) for the two groups in all patients and the subgroups with early CPR and VF.

Nasal whitening occurred in 13 of 93 (14%) patients during nasal cooling and resolved spontaneously in all 5 resuscitated patients. There was no relationship between longer duration of treatment and nasal discoloration. Nine of the 13 occurred prior to ROSC. Epistaxis occurred in 3 (3.2%) treated patients and was serious in one patient with an underlying coagulopathy secondary to hepatic failure. This was the only device-related serious adverse event. Periorbital emphysema occurred 75 minutes into treatment in one patient and resolved spontaneously within 24 hours. The total number of serious adverse events was 7 in the treatment group, 1 of which was device-related (epistaxis) and 14 in the control group (p=0.23). There were no unanticipated adverse events in any patient.

This randomized study demonstrated the safety, feasibility and brain cooling efficacy of intra-arrest nasal cooling in the pre-hospital setting. While the study wasn’t powered to detect improvement in neurologically intact survival, such an improvement was apparent for all patients, irrespective of rhythm, and significant for those in whom CPR was initiated within 10 minutes of collapse. Early nasal cooling and early CPR, combined, favorably affected outcome, irrespective of rhythm. In practice, these findings argue in favor of trying to initiate both CPR and nasal cooling as early as possible during the resuscitation process.
1.5. References


2. **STUDY OBJECTIVE**

The objective of this study is to assess the impact on neurological intact survival (CPC-score) rates at 90 days when cooling is initiated as early as possible in the resuscitation process.

2.1. **Performance Endpoints**

The aim of the study is to determine whether the resuscitation process is facilitated by early cooling, and whether this translates into improved neurological intact survival and overall survival in those successfully resuscitated. Specific performance endpoints include the following:

**Primary Endpoint:**
- Neurological intact survival (CPC score 1-2) at 90 days
- Total survival at 90 days

**Secondary Endpoints:**
- ROSC rate
- Survival to hospital admission
- Proportion of patients reaching target temperature ($\leq 34^\circ$ Celsius) within 4 hours of call to dispatcher

2.2. **Safety Endpoint**

The safety endpoints are:
1. All general adverse events occurring within 24 hours of beginning advanced cardiac life support procedures
2. The composite serious adverse event (SAE) rate from the time of patient randomization through the first seven days of hospitalization.

3. **INVESTIGATIONAL PLAN**

3.1. **Study Design**

This will be a prospective, randomized study conducted by the emergency responders in multiple emergency medical systems. It is expected to last approximately 2 years.

Up to 900 cardiac arrest patients that are eligible for cardiac life support procedures will be enrolled in the study if they meet all inclusion and exclusion criteria. This study is powered to detect statistically significant improvement in patients that are cooled early during resuscitation.

3.2. **Overview**

Medical personnel (e.g., nurses or physicians) responding to a cardiac arrest will assess each patient for study inclusion. During resuscitation, patients will be randomized to receive standard ACLS according to ERC guidelines with or without cooling with the RhinoChill upon determining that the patient is in cardiac arrest.
RhinoChill catheters should be placed and cooling initiated immediately after airway management (i.e. laryngeal mask or intubation) for those subjects randomized to early cooling. The aim is that cooling should be started within 15 minutes from the call to the dispatch centre. No other experimental procedures or devices will be used during the resuscitation attempt or after ROSC is achieved in those subjects that do achieve ROSC. Specifically, cooling with chilled saline or cold packs in the field or ambulance will not be permitted in subjects randomized to either group.

Resuscitation attempts should be continued for at least 30 minutes after advanced emergency medical personnel arrive on the scene in all patients before deciding that further interventions are futile. Patients that regain consciousness following ROSC and prior to hospital transport will be analyzed separately from those that remain comatose. Cooling will be halted in the early-cooling group for those that wake up.

Automated external defibrillator (AEDs) with the capability to record chest compression data will be used in each resuscitation attempt so that these data can be used to analyze the CPR record. Specifically, the hands-off time will be assessed to ensure the patients in the early cooling group do not receive poorer quality CPR due to the cooling procedures. The impact of the hands-off time will also be used to assess outcome differences between the two groups.

RhinoChill cooling will be continued in those subjects randomized to early cooling that achieve ROSC and remain comatose. Bolus doses of sedation and analgesia will be administered for their transport to the hospital according to local protocol. RhinoChill cooling will be continued at the hospital until the subject can be successfully transitioned to the standard institutional cooling protocol. All subjects randomized to either group will otherwise be treated according to ERC resuscitation guidelines.

Clinical assessments and clinically relevant adverse events will be documented from the time the patient is randomized into the study until the first of the following three events occur: death, hospital discharge, or one week following enrollment. Subjects that survive will undergo a neurological assessment at the time of hospital discharge and during a short telephone interview 90-135 days months after the cardiac arrest. Acute data concerning the cardiac arrest itself will be gathered Utstein Style [19] by the personnel that enroll the subject. It is understood that the time of collapse, and hence the exact duration of cardiac arrest is an estimate and cannot be quantified accurately. However, a single person will be responsible for collecting an individual patient’s charts and personally interviewing the witnesses, therefore imprecision surrounding the exact time of recognition of collapse and the accurate time of the emergency medical activation will be minimized. In the analysis the time of the call to the dispatch centre to start of CPR will be used to get a more exact event times.

The RhinoChill device has received CE marking, however, this study is considered to be emergency research, in as much as the eligible patients will be unable to provide consent prior to their treatment as they will necessarily be comatose. Ethical consideration for treating subjects without their express consent will be in accordance with the World Medical Association Helsinki Declaration of 1964, as revised at the 59th General Assembly in Seoul in 2008, and the responsible ethic committee for clinical research.

Subjects of this study face a life-threatening condition and treatment by cooling with the RhinoChill device prior to ROSC has shown improved rates of neurologically-intact survival in patients treated in a previous study. If cooling is begun early enough,
it may also improve the rate of resuscitation, as shown in a porcine model of cardiac arrest in which cooling was begun within 15 minutes of arrest. It is therefore expected that the potential benefit of using the RhinoChill in this population outweighs the risks.

The subject’s legal representative will be informed of the subject’s study participation as soon as practical. If the subject regains normal neurological function, they too will be informed of their study participation and be asked to provide their consent to use their data.

### 3.3. Study Procedures

*See Appendix 1 for the study flow diagram and Appendix 2 for table of clinical events and assessments.*

#### 3.3.1. Patient Screening & Point of Enrollment

All supposed victims of cardiac arrest will be screened for study eligibility upon arrival of the first responding team. If the patient is found to be eligible for the study, the patient will be randomized to receive cooling along with standard ACLS or standard ACLS alone. Data collection concerning the arrest will include:

**Arrest Characteristics**

- Time of collapse
- Location of collapse
- Time of emergency call

**Patient Characteristics**

- Gender
- Age/Date of Birth
- Height (approximate)
- Bystander CPR & time initiated
- Time of arrival of basic and advanced life support teams arrival
- Time of first EMS initiated CPR
- Weight (approximate)
- Basic health status (comorbidities)

#### 3.3.2. Resuscitation Attempt

The resuscitation attempt should follow ERC guidelines to the greatest extent possible. After airway management (i.e. laryngeal mask or intubation), patients are randomized to early cooling or standard care. In patients randomized to early cooling, the RhinoChill catheters should be placed and cooling initiated immediately after airway management. To place the nasal catheters and start cooling takes approximately 1 minute. Cooling should be performed with the oxygen flow set to 40L/min. There should be no changes to the care received by patients randomized to the control arm.

ACLS will be continued per local protocol once the advanced medical team (ALS) has arrived.

Data collection concerning the resuscitation effort will include:

- Time CPR initiated by 1st EMS responder
- CPR mechanism (if not manual)
- First rhythm
- Time cooling initiated (if cooled)
- Time IV access obtained
- Total adrenaline/epinephrine dose
Shock time, strength, and success  
Time airway is secured  
Time randomized  
Number of chest compressions/min  
Additional medication(s)/dose(s)  
Recurrent VF or re-arrest  
Time ROSC or death declared  
CPR hand’s off time

3.3.3. **ROSC**

ROSC will be defined as obtaining an organized rhythm and palpable pulse sustained for 20 minutes. Once an organized rhythm and palpable pulse is achieved, subjects will have their temperature taken via the tympanic route, stabilized and then be transported to the hospital.

If a patient wakes up after ROSC is achieved, they will be analyzed separately from patients that remain comatose. Cooling will be discontinued in those patients in the early cooling group if they wake up.

Subjects randomized to early cooling will be intravenously administered bolus doses of sedation and analgesia for transport to the hospital. Doses of sedation and analgesia will be dictated by the institutional standard cooling protocol. The oxygen supply in the transport vehicle should be used to continue RhinoChill cooling during transport to the hospital. Normal transport procedures will be used for patients randomized to the control arm.

Subjects in both the early cooling and the control arm will otherwise undergo standard post-resuscitation care. Infusions of chilled saline or cooling with cold packs will not be permitted in the pre-hospital setting for either group.

3.3.4. **Hospital Admission**

Upon hospital arrival, the following measures will be recorded:

- Tympanic temperature
- Heart rate
- Peripheral oxygen saturation (SpO2)
- Mean arterial pressure
- End-tidal carbon dioxide (EtCO2)
- ST-segment elevation
- Glasgow Coma Scale

A systemic temperature probe will be placed (e.g., bladder, arterial) and core temperature will be recorded. A blood draw will be made to obtain baseline serum glucose and arterial blood gases:

- PaO2
- SaO2
- PaCO2
- Arterial pH
- pH
- Lactate
- Base excess

3.3.5. **Post Resuscitation Care**

All subjects will undergo standard post resuscitation treatment upon hospital arrival. The systemic hypothermia treatment at ICU for both patient groups (treatment and control) will be according to international guidelines. Regular ICU measures such as glycaemia control that are considered as standard monitoring/care will not be recorded specifically in the study. The conditions below have to be fulfilled for each participating study centre.
- Hypothermia treatment for at least 24 hours.
- Target temperature 33°C ± 1°C.
- To record core- and tympanic temperature every 15 minute during the induction period (i.e., until the target therapeutic temperature is initially reached).
- Rewarming rate at 0.2-0.5°C / hour.
- Control of post-cooling hyperthermia

Subjects randomized to the early cooling group with the RhinoChill shall continue being cooled with the RhinoChill until systemic cooling procedures can be started. Intravenous sedation, analgesia and neuromuscular blockade (if used) should be initiated upon hospital arrival according to institutional cooling protocols. Doses should be adjusted as necessary over the course of cooling/re-warming.

After the subject has been prepared with the standard hypothermia device, the RhinoChill should be turned off, but the intranasal catheters should be left in place while transitioning the subject to the standard hypothermia protocol. Intermittent activation of the RhinoChill may be considered if the core temperature does not continue to drop via the systemic cooling method. Cooling via the RhinoChill system will be halted immediately if any adverse event related to the use of the RhinoChill develops.

For those patients in the control group, the standard cooling procedure will be started as soon as practical. Intravenous sedation, analgesia and neuromuscular blockade (if used) should be initiated upon hospital arrival according to institutional cooling protocols. Doses should be adjusted as necessary over the course of cooling/re-warming.

The systemic cooling procedures, including system used, core temperature location, duration at target temperature and the hypothermia reversal algorithm will be recorded.

Cardiac function will be followed. If feasible, echocardiographic examinations should be performed acutely (within 24 hours) and after 72 hours to measure left ventricular ejection fraction (LVEF). If possible, record the investigations (CD/DVD) so that independent physicians can analyse them later.

For those patients in which a full 24-hour therapeutic hypothermia treatment is deemed futile or unnecessary, the time in which cooling is halted in the patients randomized to the early cooling group will be recorded.

Temperatures (tympanic and core, with core being defined by hospital protocol) will be monitored periodically over the first 48 hours after hospital arrival for all patients regardless of whether cooling is performed in the hospital setting.

In the cases where ICU care is withdrawn due to poor prognosis, the reasons (prognostic measures besides clinical examination) for this should be clearly stated in the Case Report Form (CRF) (e.g. MRI, neuro markers, EEG, SSEP).
3.3.6. General Patient Monitoring

ECG, peripheral oxygen saturation, heart rate and blood pressure monitoring will continue throughout the acute care period. Ventilation settings should be adjusted to maintain arterial oxygen saturation > 95% (e.g., PaO₂ 100-150 mmHg). Increased ventilation should be used to excrete CO₂ and maintain normocapnia (e.g., PaCO₂ 40-45mmHg). PEEP should be adjusted to reduce FiO₂ with a target of 5mmHg. Arterial pH should be kept between 7.3 and 7.5. Electrolytes will be substituted as necessary to maintain normal ranges.

Blood pressure will be monitored and the mean blood pressure should be kept above 60 mmHg. Drops in pressure should be treated primarily with crystalloid fluids or hydroxyl ethyl starch. If sufficient pressure control cannot be achieved with fluids alone, vasopressors such as epinephrine (adrenaline) norepinephrine (noradrenaline), dobutamine, and dopamine should be used.

Fluid balance will be controlled. No dextrose, glucose and free water should be administered. Serum blood glucose should be kept between 80 and 150mg/dl. Parenteral nutrition or enteral feeding should be initiated as soon as practical (>24 hours after cardiac arrest).

3.3.7. Follow-Up

Subjects treated with the RhinoChill will undergo rhinoscopic examination of the nasal cavity if it is warranted based on clinical signs of intra-nasal trauma (e.g., bleeding from the nostrils, whitening of the nose or other treatment-related observations).

All patients still alive will undergo an exam 72 hours after hospital admission. If indicated at this time, a follow-up anterior-posterior chest x-ray will be made, a rhinoscopic exam will be performed with an otoscope, and core and tympanic temperatures will be recorded. Additionally, the subject’s general disposition, Cerebral Performance Category (CPC), and modified Rankin Score (mRS) will be recorded.

Cerebral Performance Categories

<table>
<thead>
<tr>
<th></th>
<th>Good recovery - little to no deficit</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Moderate disability</td>
</tr>
<tr>
<td>2</td>
<td>Severe disability</td>
</tr>
<tr>
<td>3</td>
<td>Vegetative state</td>
</tr>
<tr>
<td>4</td>
<td>Dead</td>
</tr>
</tbody>
</table>

Modified Rankin Score

<table>
<thead>
<tr>
<th></th>
<th>No symptoms at all</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No significant disability despite symptoms; able to carry out all usual duties and activities</td>
</tr>
<tr>
<td>1</td>
<td>Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance</td>
</tr>
<tr>
<td>2</td>
<td>Moderate disability; requiring some help, but able to walk without assistance</td>
</tr>
<tr>
<td>3</td>
<td>Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance</td>
</tr>
</tbody>
</table>
assistance
Severe disability; bedridden, incontinent and requiring constant nursing care and attention

6 Dead

Subjects will be followed until death or hospital discharge, and the following data will be recorded concerning their hospital course:
- Date/time subject wakes
- Date/time subject is taken off ventilator
- Date/time subject is discharged from ICU
- Date/time subject dies (if in hospital)
- Date/time subject is discharged from hospital
- Discharge disposition
- CPC and mRS at hospital discharge
- CPC and mRS at 90 days (if still in hospital)

Clinically significant serious adverse events will be recorded from the time ROSC is achieved through the earliest of the following three events: death, hospital discharge, or one week following admission. The nature and severity of the adverse event, the relationship to the RhinoChill Device, management and outcome will be recorded on the case report form.

A telephone follow-up will be made 90-135 days after the arrest to assess the subject’s 90-day survival, neurological function and quality of life by using two acknowledged methods, the Glasgow Outcome Scale (GOS) and the 15D instrument (see appendix 3). This telephone interview will take approximately five minutes to assess the subject’s variable health status.

3.3.8. Concomitant Therapies

Concomitant interventions (e.g., PCI, aortic balloon pump, bypass surgery, ICD placement) will also be recorded.

Medications and/or treatments that are considered to be experimental in nature and are intended to improve outcomes after cardiac arrest are prohibited from use.

3.3.9. Patient Withdrawal

Subjects will be enrolled in the study by rescue personnel if they meet all of the study’s inclusion criteria, but none of the exclusion criteria. Subjects will necessarily be comatose and unable to provide consent prior to their being enrolled in the study. The subject’s legal representative will be informed of the study as soon as it is practical to do so. Subjects that recover will be informed of their study participation and be asked to provide their consent for the use of their study data.

The Principal Investigator, Steering Committee and the individual site investigators and site Ethic Committees (ECs) also have the right to discontinue a patient or terminate the trial for the following reasons:
- A Site Investigator may withdraw a subject from the study for safety reasons (i.e. a device-related serious adverse event). In these cases, data
surrounding the event leading to subject withdrawal will be retained for safety analyses.

• The EC at any participating site may decide to withdraw the site from the study for safety reasons.
• The EC at the principal investigator site and Principal Investigator may terminate the study for safety reasons.
• A decision on the part of the Principal Investigator to suspend or discontinue testing, evaluation, or development of the product for any reason.
• The Principal Investigator may decide to close a study site when one of the following occurs:
  ▪ The Site Investigator at an individual site fails to enroll patients into the study at an acceptable rate.
  ▪ A Site Investigator at an individual site fails to comply with pertinent regulations of appropriate regulatory authorities.
  ▪ A Site Investigator fails to adhere sufficiently to protocol requirements
  ▪ A Site Investigator knowingly submits false information from the research facility to the Principal Investigator, Steering Committee or appropriate regulatory authority.

If the study is terminated early, all specified follow-up data on subjects enrolled prior to termination will be collected and reported.

4. PATIENT POPULATION
Subjects will be recruited by rescue personnel from presumed victims of cardiac arrest of non-traumatic origin. It is expected that patients will be enrolled that are later found to not meet all of the exclusion criteria (e.g., Do Not Resuscitate orders are found). Data should be collected on all patients, and the decision to exclude them from analysis will be made by the Principal Investigator.

4.1. Patient Inclusion Criteria
Patients are eligible if they meet all of the following criteria:
1. Age $\geq 18$ years
2. Collapse was witnessed (heard or seen)
3. Do not have a pulse
4. Are unresponsive to external stimuli

4.2. Patient Exclusion Criteria
Patients are not eligible if they meet one or more of the following criteria:
1. Age $\geq 80$ years
2. Have an etiology of cardiac arrest due to trauma, head trauma, severe bleeding, drug overdose, cerebrovascular accident, drowning, smoke inhalation, electrocution, hanging
3. Already hypothermic (e.g., avalanche victim; found in the snow)
4. Have an obvious barrier to placing intra nasal catheters (e.g., intranasal obstruction)
5. Do Not Attempt to Resuscitate (DNAR) orders
6. Have a terminal disease
7. Known or clinically apparent pregnancy
8. Have a known coagulopathy (except therapeutically induced)
9. Are known to have a need for supplemental oxygen
10. Achieve ROSC prior to randomization
11. Response time (call to first EMS CPR) > 15 minutes

If a patient is unaccompanied or accompanied by a person or persons unfamiliar with their history, determination of these exclusion criteria will be left to the best estimation of the emergency personnel. At no time should an attempt to determine these criteria be allowed to delay the administration of life-saving treatment.

5. STUDY MATERIAL & METHODS

5.1. Study Device

The investigational site will use the RhinoChill control units and tubing sets and bottles of liquid coolant at the standard. It is expected that at least one tubing set and 1 bottle of coolant will be needed for each subject enrolled in the early cooling arm. Patients that are resuscitated after RhinoChill cooling is initiated will likely require 1-2 additional bottles of coolant before in-hospital cooling can be initiated. Participating institutions have been provided RhinoChill units to use to continue cooling patients randomized to early cooling until systemic cooling can be initiated in the hospital. No specific surgical skills are necessary to use the device, but basic knowledge of cardiac life support, therapeutic hypothermia and the associated effects are required.

Participating sites are required to supply the pressurized gas source (oxygen or breathing air) that will be used in the field, ambulance, and hospital settings.

5.2. Storage & Labeling

Components are designed to withstand standard transportation, storage and operating temperatures for both ambulance and hospital use. Product provided for the study will carry the CE Mark.

5.3. Preparation & Application

The RhinoChill system will be packaged in a portable pack. A medical grade supply of oxygen will be integrated into the pack by site personnel prior to placing it on the emergency response vehicle. A brief functionality test of the tubing set and control unit pressure relief valve should be performed prior to placing the nasal catheters in the subject.

The individual nasal catheters will be advanced through each nostril so that the distal end is well within the nasal cavity. Care should be taken not to force the individual catheters into the nostrils, but to advance them gently. Once the catheters are placed, cooling will be initiated by turning on the RhinoChill gas supply and adjusting it to 40L/min. The nostrils are to be kept unobstructed to allow venting of the PFH vapor.

5.4. Product Accountability
Product is labeled by lot and serial number where appropriate.

6. **EVALUATION OF SAFETY**

6.1. **Adverse Event Definitions**

An **Adverse Event** (AE) is any untoward medical occurrence in a subject.

A **Serious Adverse Event** (SAE) is any adverse event that:

- a) leads to death
- b) leads to a serious deterioration in the health of the patient that
  1. results in a life-threatening illness or injury
  2. results in a permanent impairment of a body structure or a body function
  3. requires in-patient hospitalization or prolongation of existing hospitalization
  4. results in medical or surgical intervention to prevent permanent impairment to a body structure or a body function
- c) leads to fetal distress, fetal death, congenital abnormality or birth defect

**Adverse Device Effects** and **Serious Adverse Device Effects** are those AEs and SAEs that occur as an untoward or unintended response to a medical device. These events include those which result from insufficiencies or inadequacies in the Instructions for Use or deployment of the device as well as user error.

An **Unanticipated Adverse Device Effect** (UADE) is defined as any *serious* adverse effect on health or safety or any life-threatening problem or death caused by – or associated with – the device, if that effect, problem or death was not previously identified in nature, severity, or degree of incidence in the investigational plan (including documents such as the protocol, Investigator’s Brochure, informed consent form or other study-related documents), or any other unanticipated serious problem associated with the device that relates to the rights, safety or welfare of subjects.

A **Technical Device Failure** is defined as a failure of the device to perform its intended function when used in accordance with the Instructions for Use. Technical device failures will be recorded and evaluated for possible untoward effects on the subject. If a device failure results in an adverse experience in the subject, this adverse experience should be considered an adverse device effect and recorded on the Adverse Event pages of the CRF. Device failures that do not result in a clinically significant adverse effect on the patient will be noted on the CRF pages regarding device performance but will not be considered an adverse device effect.

6.2. **Adverse Event Assessments**

The relation of the event to the investigational device will be categorized by the Investigator as follows:

- **Not related** – AE is due to the underlying disease state or concomitant medication or therapy, and was not caused by the investigational device.
- **Probably not related** – AE had minimal or no temporal relationship to the use of the investigational device and/or a more likely alternative etiology exists.
Probably related – AE had a strong temporal relationship to the use of the investigational device and an alternative etiology is less likely compared to the potential relationship to the investigational device.

Definitely related – AE had a strong temporal relationship to the use of the investigational device and another etiology is highly unlikely.

For the purposes of reporting, an event will be considered associated with the use of the device if it is believed to be due either directly to the mechanical aspects of the device itself (e.g., nosebleed) or the ensuing device-related cooling.

Events believed to be due to study procedures other than the device/cooling (such as events believed to be side effects of the standard hypothermia maintenance) will be recorded but will not be categorized as device-related.

Subjects enrolled in the study will have a high morbidity and mortality rate associated with their cardiac arrest and the ensuing global ischemia. Therefore, careful attention shall be made to assessing the causality of any serious adverse events.

6.3. Adverse Events Reporting

All clinically significant AEs or those that appear to be related to the use of the RhinoChill (e.g., whitening of the nose) as well as those that could potentially harm the patient (e.g., pleural effusion) will be recorded on the CRF from ROSC through the end of the cooling period. Abnormal laboratory values are expected in these patients, and these are not to be recorded as AEs. The date of occurrence, severity, duration, management, outcome and relationship to cooling with the RhinoChill Device will be recorded.

6.4. Serious Adverse Event Reporting

All SAEs that occur within seven days after enrollment must be followed until resolution; this includes those patients that were terminated early or withdrew. These must be reported to Leif Svensson, MD, PhD and Maaret Castrén, MD, PhD The Karolinska Institutet (see contact information on the first page) within 24 hours of their occurrence as well as following their resolution.

SAEs that should be reported generally include any new events that occur after ROSC has been achieved. Examples include the following: re-arrest, a clinically significant arrhythmia that results in symptoms of vital organ hypoperfusion, major bleeding, any new event causing emergency surgery, new neurological dysfunction not attributed to the cardiac arrest (e.g., stroke, seizure), infection, sepsis, pneumonia, hepatic dysfunction, renal dysfunction, respiratory failure, pulmonary edema, arterial desaturation.

The Department of Clinical Science and education, Karolinska Institutet, will immediately review all SAE reports with regard to their causal relationship to use of the RhinoChill. The Steering Committee will determine whether the study should be terminated early or suspended based on review of the composite rate of serious adverse device-related events. The criteria for early termination of the study is a serious adverse device-related event rate > 10%.

Reporting to the regulatory authorities will be performed per European vigilance requirements and other local requirements,
7. **RISK EVALUATION**

7.1. **Potential Risks to Study Subjects**

For purposes of this study, adverse events that may be anticipated and are associated with the use of the device include those associated with the RhinoChill Device or from the device-induced mild hypothermia.

7.1.1. **Device Use**

Potential risks associated with the use of the RhinoChill Device include those associated with the mechanical aspects of an intranasal catheter as well as those associated with the delivery of the PFH-oxygen mixture.

The following events are those *most likely, non-serious events* to occur with the use of the RhinoChill Device:

- **Peri-nasal tissue discoloration** due to local evaporation of the coolant on the external facial structures that is expected to resolve after normal circulation is restored.

- **Mucosal irritation/dryness** caused by high oxygen flows during cooling that would resolve with over the counter medications or on its own;

- **Epistaxis, minor**: bleeding arising from the nasal cavity or paranasal sinuses that would resolve on its own or would be easily controlled with cauterization or simple nasal packing.

- **Para-sinus emphysema**: gas entrapment in the sinus region that will resolve on its own; associated with chronic sinusitis.

The following events are those *least likely, non-serious events* to occur with the use of the RhinoChill Device:

- **Gastrointestinal discomfort** caused by accidental ingestion of PFH that would resolve without intervention;

- **Frostbite/necrosis** to the nasal tissues caused by excessive local cooling that might require intervention;

- **Diminished sense of smell** caused by PFH evaporation in the nasal cavity.

The following *serious events* are anticipated to *very rarely* occur with the use of the RhinoChill Device:

- **Hypoxia**: depletion of oxygen supply due to saturation with PFH requiring prolonged mechanical ventilation with 100% oxygen;

- **Epistaxis, major**: bleeding arising from the nasal cavity or paranasal sinuses that would be characterized by brisk bleeding with no accessible source. A major nosebleed of this type would require posterior nasal packing or balloon packs, or even an arteriogram with embolization of the internal maxillary artery. A transfusion would be required in those cases in which hemoglobin/hematocrit falls significantly due to the bleed;

- **Infection**: presenting as a wound infection in the nasal cavity, or alternately as bacteremia with sepsis, that requires medical or surgical intervention, such as antibiotic therapy and prolonged hospitalization;
**Barotrauma**: Trauma caused by rapid or extreme changes in gas pressure, especially affecting enclosed cavities within the body such as the nasal cavity and lungs. This could cause tearing of mucosal tissue in the nasal cavity and possibly the displacement of the nasal septum that would require endoscopic evaluation and surgical repair. Lung barotrauma could cause tearing of lung tissue and rupture of alveoli/small bronchi or entry of gas into the blood vessels that would require surgical intervention and prolonged hospital stay;

**Air embolus**: air circulating in the blood that results in clinical sequelae that are life threatening and may be amenable to surgical intervention;

**Pulmonary interstitial emphysema**: air circulating through the pulmonary interstitium and lymphatics that results in clinical sequelae that is life threatening and may be amenable to surgical intervention;

**Pulmonary aspiration**: soiling of the respiratory tract by foreign, non-gaseous substances (e.g., PFH or food particles) that could result in aspiration pneumonitis or aspiration pneumonia where the former represents inflammation of the lung tissue without infection, whereas the latter also has superimposed infection. Systemic medication with prolonged hospital stay would be required in the event of either developing;

**Burns**: due to oxygen-enhanced fire/explosion that could be life threatening, requiring prolonged hospital stay and potential surgical intervention;

**Intracranial pressure** increases due to uncontrolled re-warming of the brain during the transition to systemic cooling after it has been cooled with the RhinoChill Device. Uncontrolled re-warming of the brain from a cooled state can lead to severe levels of intracranial pressure that could herniate the brainstem and lead to death.

### 7.1.2. Mild Hypothermia

Hypothermia results in various physiological effects on the body which are generally managed with medical care. These effects include the following:

- The oxyhemoglobin-dissociation curve shifts to the left.
- Metabolic acidosis results from lactate generation from shivering and decreased tissue perfusion; this is exacerbated by hypothermia-induced impairment of hepatic metabolism and impaired acid excretion.
- Hematocrit increases 2% per 1°C decline in temperature, resulting in increased blood viscosity.
- Hypokalemia may occur due to inhibition of the sodium-potassium ATP pump.
- Hyperglycemia may occur due to decreased insulin release and increased peripheral insulin resistance.
- Coagulopathies may arise due to hypothermia induced impairment of the enzymatic reactions of the coagulation cascade (despite normal clotting factor levels).
- Platelet activity is impaired because platelet production of thromboxane B₂ is temperature-dependent; in addition, bone marrow production can be suppressed and hepatosplenic platelet sequestration can be increased;
• Direct impairment of immune function (especially via oxidative killing by neutrophils) can increase susceptibility to infection.

The magnitude and clinical significance of the effects of hypothermia are generally dependent upon the degree and duration of systemic hypothermia. The depth and duration of hypothermia used in this study is mild hypothermia (33°C). The use of a mild level of hypothermia will therefore minimize the risk of hypothermia-associated effects.

Anticipated events associated with mild hypothermia include the following:

• **CNS**: linear depression of cerebral metabolism; amnesia; apathy; dysarthria; impaired judgment; maladaptive behavior;

• **Cardiovascular**: tachycardia, then progressive bradycardia; cardiac-cycle prolongation; vasoconstriction; increase in cardiac output and blood pressure;

• **Respiratory**: tachypnea, then progressive decrease in respiratory minute volume; declining oxygen consumption; bronchorrhea; bronchospasm;

• **Renal, Endocrine, Metabolic**: hyperglycemia, hypokalemia, lactic acidosis; cold diuresis; increase in catecholamine, adrenal steroids, triiodothyronine, thyroxine; increase in metabolism with shivering;

• **Neuromuscular**: increased pre-shivering muscle tone, then fatiguing; shivering induced thermogenesis; ataxia;

• **Infectious**: pneumonia, sepsis;

• **Coagulopathy**: hemorrhagic conversion of an ischemic infarct.

### 7.2. Methods to Minimize Risks

The target patient population is comatose and will die with no intervention. Even with advanced cardiac life support interventions, mortality is high following cardiac arrest.

All serious adverse events related to the use of the RhinoChill have been analyzed with respect to their likelihood and severity, and have been minimized through both the design and manufacture of the device and the design of the study. The Investigator Brochure contains a detailed analysis of the risks associated with each of the individual adverse events described above and the manner in which each is minimized.

### 7.3. Potential Benefits of the Procedure

Hypothermia has a putative benefit in out-of-hospital cardiac arrest of cardiac origin. Two seminal studies published in 2002 [9,10] demonstrated that cooling following out-of-hospital cardiac arrest could significantly improve neurologically intact survival. It has been suggested that hypothermia may provide an even greater protective effect if initiated sooner than it was in these studies.

The RhinoChill has been demonstrated as feasible to use in the pre-hospital environment, and significantly reduces patient temperature by hospital arrival. Cooling was begun approximately 24 minutes after arrest, but patients admitted to the hospital following intra-arrest intranasal cooling were more likely to survive neurologically intact and suffer less serious adverse events. Use of the RhinoChill in a porcine model of cardiac arrest demonstrated improved resuscitation and increased
ROSC rates when cooling was begun within 15 minutes of arrest. It is therefore believed that cooling with the RhinoChill earlier during the resuscitation efforts may also improve ROSC rates in humans.

8. STATISTICAL CONSIDERATIONS
This study is powered to detect clinically significant changes in total survival at 90 days after cardiac arrest. An interim analysis for safety and futility will be performed by an external committee after the first 200 patients have provided endpoint data. Conditional power for meeting the primary endpoint will if needed, be computed at that time, and if the interim results do not correspond to the primary endpoints, termination of the study for futility will be considered. Early stopping for efficacy reasons will only be considered if major outcome differences are seen between the groups according to the Haybittle rule with a p-value ≤0.001.

8.1. Randomization
Once the patient has been confirmed to meet all inclusion criteria and none of the exclusion criteria they will be randomized to receive ACLS with or without cooling.

Randomization will be carried out in blocks of four and each site will be given sets of sequentially numbered envelopes with randomization assignments provided in a 1:1 manner to distribute to the participating pre-hospital vehicles.

Each institute will be assigned a certain number of envelopes based on projected enrollment. Individual envelopes will be placed in each RhinoChill pack at the time of site initiation, and replaced as patients are enrolled. The RhinoChill pack will be carried to every potential subject, and the envelope will be opened once the subject has been qualified as meeting all inclusion and exclusion criteria.

8.2. Blinding
Neither EMS or hospital personnel will be blinded to treatment, since the control patients are easily distinguishable from patients undergoing device placement and nasal cooling. However, medical personnel making the final neurological assessment of the patient prior to discharge will be blinded as to the patient’s group assignment.

8.3. Performance Endpoints
Performance endpoints include ROSC rate, resuscitation parameters, early cardiac performance, and outcome measures (total survival and neurological intact survival at 90 days). These parameters will be compared between those patients that receive nasal cooling during ACLS and those that do not.

Resuscitation parameters will be calculated for those patients that achieve ROSC:

• Time to ROSC
• Success of 1st shock
• Number of shocks
• Catecholamine dose

Early post-resuscitation cardiac performance parameters along with core and tympanic temperatures will be calculated for those patients that survive to hospital admission:

• Heart rate
• Blood pressure
• ST-segment elevation
• EtCO₂
• Arterial blood gases

Outcome parameters will be:
• Survival to 24 hours
• Survival to ICU discharge
• Survival to hospital discharge
• CPC at hospital discharge
• mRS at hospital discharge
• Survival at 90 days (Primary)
• Neurological outcome at 90 days, CPC-score 1-2 (Primary)
• Glasgow Outcome Score at 90 Days
• 15D Instrument Quality of Life at 90-135 days

8.4. Safety Endpoints

The safety profile associated with the RhinoChill Device will be assessed via the composite adverse event rate at the earlier of death or 24-hours post ROSC and the composite serious adverse event rate within the first 7 days of hospitalization.

8.5. Statistical Analysis

Summary, descriptive statistics will be calculated for all performance, safety, demographic, and baseline variables. Means, standard deviations, and ranges will be used to describe continuous measurements. Counts and percentages will be used to describe categorical parameters. Differences between variables associated at different time points will be evaluated using an appropriate comparative statistic. Data from the two treatment groups will be analyzed for treatment effect. A 2-sided p-value less than 0.05 will be considered to be statistically significant.

Analysis of variance will be performed to assess the impact of baseline characteristics or subject-related characteristics if there appears to be trend or outlier data that suggest a biased effect.

The quality of CPR will be evaluated by computing the compressions/minute and hands-off time for each case where the record is available. These data will be compared across groups to determine if the cooling procedure had a negative impact on CPR quality as well as if CPR quality impacted any of the outcome variables.

Intention to treat and per protocol analyses will be performed for all randomized patients. No imputed values will be used for patients for whom data is not available.

Stratified analyses will be performed for patients whose first recorded rhythm is VF/VT versus those in whom the first recorded rhythm is PEA or asystole. Stratification analyses will be performed for subjects where CPR was initiated within 10 minutes by a first responder. Stratified analyses will also be performed for subjects in the treatment group where cooling was started within 15 minutes.
9. **STUDY MONITORING**

The Steering Committee (see contact information on page 2) has the responsibility to perform periodic and spot checks visits to monitor the progress of the clinical study. Completed Case Report Forms (CRFs) will be reviewed for completeness, compliance with the investigation plan, and appropriate device use and accountability.

10. **DATA AND QUALITY MANAGEMENT**

Case Report Forms (CRFs) will be provided to each site for each subject enrolled in the study. Required data concerning patient treatment and test results will be recorded on the CRFs at the time of the procedure or as soon as possible thereafter. Information recorded in the CRFs will be corroborated by data in the subject’s medical records. Completed and monitored CRFs will be sent to Karolinska Institutet, Stockholm who will be overseeing data entry and data quality management in accordance with SOPs for clinical data entry, clarification and verification. Data on safety will be provided to the Steering Committee with regular time intervals.

The Steering Committee will review study integrity, safety and risk/benefit issues at periodic intervals throughout the study. The frequency of these reviews will be dependent upon the rate of patient enrollment and relevant safety issues. Independent analyses of serious adverse events will be performed and adjudicated if the frequency or nature of serious adverse events warrants it. A first interim analysis for safety and futility will be performed by an external committee after the first 200 patients have provided endpoint data. If needed, conditional power for meeting the primary endpoint will be computed at that time.

Individual Site Investigators shall maintain all study-related correspondence, CRFs, device disposition records, and information on Ethics Committee approvals for a minimum of five years. Individual Site Investigators shall maintain all patient records, plus the investigator’s copy of the CRFs, device disposition records, and signed informed consent forms for a minimum of five years.

11. **ADHERENCE TO PROTOCOL**

A deviation from the protocol will be allowed without a protocol amendment if generally accepted standards of clinical research and medical practice relating to the safety of research subjects require such deviation from the protocol. In those cases in which the deviation was made emergently to protect the life or physical well-being of a subject. The Karolinska Institutet will be notified within 48 hours of any deviations required due to device-related adverse events. Deviations that represent major, serious, or significant departures from the investigational plan shall be recorded on the CRF along with an explanation for the deviation. The site investigator will analyze and assess the significance of deviations as they occur, and the Steering Committee will assess site-specific deviations. Significant Deviations will be reported to the EC as required.

12. **PROTOCOL AMENDMENT**

Changes to the protocol that may be made during the clinical study will be made by the Principal Investigator. An amendment will be effective when: a) signed by the Principal Investigator, b) the individual site investigators, and c) the amendment has been approved by the EC, if required by the Institution’s policies.
13. REPORTING

Sites will report all SAEs that occur within 7 days of enrollment directly to The Karolinska Institutet (see contact information on the first page). Individual site investigators are responsible for preparing and submitting complete and timely reports over the course of the study. Types of reports to be submitted include reports pertaining to serious adverse device effects, withdrawal of Ethics Committee approval, and deviations from the investigational plan. These reports are to be submitted to the Chairman of the Steering Committee. Upon study completion, a final report synopsis shall be prepared by the Steering committee. The final report synopsis should be forwarded to all of the participating site investigators and their respective Ethic Committee.

Central Ethics Committee (EC) approval for the protocol and consent materials must be obtained in each country prior to initiating the study in that country. Site Investigators will comply with local reporting requirements to the local EC.

14. PUBLICATION POLICY

At the conclusion of the study, a multi-center abstract reporting the primary results will be prepared and presented at key Cardiology/Resuscitation Symposia. A multi-center publication will also be prepared by the Steering committee for publication in a reputable scientific journal.

Publication of the principal results from any single center experience within the study is not allowed until both the preparation and publication of the multi-center results. Thus, no publication or presentation of the data or results of the study may be presented until The Principal Investigator determines that the database for the study is clean and locked and that the primary and secondary endpoint analyses are consistent with the Protocol.
Algorithm for Randomization

1. Determine Patient Is Eligible
2. Place Airway
3. Randomize
4. RhinoChill → Control
5. Place nasal catheters
   Begin cooling
6. Continue Standard Resuscitation Protocol
7. ROSC?
8. Take Tympanic Temperature
Algorithm for Post-ROSC Care

Randomization

RhinoChill
- Infuse bolus dose: Sedation, analgesia, neuromuscular blockade
- Attach RhinoChill to vehicle O₂ for continued cooling
- Transport pt to hospital

Control

Hospital Arrival

Get vitals, ABGs & CXR

Attach pt to hospital O₂ for continued cooling

Continue sedation, analgesia, neuromuscular blockade

Initiate Systemic Cooling
- Cool to 33°
- Maintain for 24 hrs
- Rewarm over 8-12 hours

72-Hour Follow-Up
- Take vitals, CXR
- Perform rhinoscopy
- Assess pt disposition
- Determine CPC & mRS scores

Hospital Course
- Date/Time of death
- Date/Time taken off ventilator
- Date/Time of ICU D/C
- Date/Time wakens

Hospital Discharge
- Assess pt disposition
- Determine CPC & mRS scores
# APPENDIX 2: CLINICAL EVENT TABLES

<table>
<thead>
<tr>
<th>Early Cooling Arm</th>
<th>Screening</th>
<th>Reanimation</th>
<th>ROSC</th>
<th>Hospital Admission</th>
<th>ICU</th>
<th>72-Hours</th>
<th>1-Week</th>
<th>Hospital Discharge</th>
<th>3-Month Follow-Up</th>
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APPENDIX 3 Quality of Life assessment – Glasgow Outcome Scale (GOS) and the 15D Instrument

Neurological assessment will be assessed during a telephone interview with the method Glasgow Outcome Scale (GOS) and the 15D instrument at 90-135 days after arrest. For the GOS only two questions need to be asked: (1) Do you require help from another person for everyday activities? and (2) Do you feel that you have made a complete recovery from your heart arrest? The assessment of 15D can be made either by telephone or be sent home to the patient.

The following assessment will be asked about the patient regarding their status (as best as can be recalled) at 90 Days following their cardiac arrest.

<table>
<thead>
<tr>
<th>Glasgow Outcome Scale</th>
<th>CPC</th>
<th>mRS</th>
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<tr>
<td>Dead</td>
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<td>5</td>
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<tr>
<td>Comatose or Vegetative</td>
<td>2</td>
<td>4</td>
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<tr>
<td>Severe disability (conscious but disabled)</td>
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<td>3</td>
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<td>Moderate disability (disabled but independent)</td>
<td>4</td>
<td>2</td>
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<tr>
<td>Good recovery</td>
<td>5</td>
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QUALITY OF LIFE QUESTIONNAIRE (15D©)

Please read through all the alternative responses to each question before placing a cross (X) against the alternative which best describes your present health status. Continue through all 15 questions in this manner, giving only one answer to each.

QUESTION 1. MOBILITY
1 ( ) I am able to walk normally (without difficulty) indoors, outdoors and on stairs.
2 ( ) I am able to walk without difficulty indoors, but outdoors and/or on stairs I have slight difficulties.
3 ( ) I am able to walk without help indoors (with or without an appliance), but outdoors and/or on stairs only with considerable difficulty or with help from others.
4 ( ) I am able to walk indoors only with help from others.
5 ( ) I am completely bed-ridden and unable to move about.

QUESTION 2. VISION
1 ( ) I can see normally, i.e. I can read newspapers and TV text without difficulty (with or without glasses).
2 ( ) I can read papers and/or TV text with slight difficulty (with or without glasses).
3 ( ) I can read papers and/or TV text with considerable difficulty (with or without glasses).
4 ( ) I cannot read papers or TV text either with glasses or without, but I can see enough to walk about without guidance.
5 ( ) I cannot see enough to walk about without a guide, i.e. I am almost or completely blind.

QUESTION 3. HEARING
1 ( ) I can hear normally, i.e. normal speech (with or without a hearing aid).
2 ( ) I hear normal speech with a little difficulty.
3 ( ) I hear normal speech with considerable difficulty, in conversation I need voices to be louder than normal.
4 ( ) I hear even loud voices poorly, I am almost deaf.
5 ( ) I am completely deaf.

QUESTION 4. BREATHING
1 ( ) I am able to breathe normally, i.e. with no shortness of breath or other breathing difficulty.
2 ( ) I have shortness of breath during heavy work or sports, or when walking briskly on flat ground or slightly uphill.
3 ( ) I have shortness of breath when walking on flat ground at the same speed as others my age.
4 ( ) I get shortness of breath even after light activity, e.g. washing or dressing myself.
5 ( ) I have breathing difficulties almost all the time, even when resting.

QUESTION 5. SLEEPING
1 ( ) I am able to sleep normally, i.e. I have no problems with sleeping.
2 ( ) I have slight problems with sleeping, e.g. difficulty in falling asleep, or sometimes waking at night.
3 ( ) I have moderate problems with sleeping, e.g. disturbed sleep, or feeling I have not slept enough.
4 ( ) I have great problems with sleeping, e.g. having to use sleeping pills often or routinely, or usually waking at night and/or too early in the morning.
5 ( ) I suffer severe sleeplessness, e.g. sleep is almost impossible even with full use of sleeping pills, or staying awake most of the night.

QUESTION 6. EATING
1 ( ) I am able to eat normally, i.e. with no help from others.
2 ( ) I am able to eat by myself with minor difficulty (e.g. slowly, clumsily, shake or with special appliances).
3 ( ) I need some help from another person in eating.
4 ( ) I am unable to eat by myself at all, so I must be fed by another person.
5 ( ) I am unable to eat at all, so I am fed either by tube or intravenously.

QUESTION 7. SPEECH
1 ( ) I am able to speak normally, i.e. clearly, audibly and fluently.
2 ( ) I have slight speech difficulties, e.g. occasional fumbling for words, mumbling, or changes of pitch.
3 ( ) I can make myself understood, but my speech is e.g. disjointed, stammering, slurred or stammering.
4 ( ) Most people have great difficulty understanding my speech.
5 ( ) I can only make myself understood by gestures.

15D© Harri Sainio
QUESTION 8. ELIMINATION
1 ( ) My bladder and bowel work normally and without problems.
2 ( ) I have slight problems with my bladder and/or bowel function, e.g., difficulties with urination, or loose or hard bowels.
3 ( ) I have marked problems with my bladder and/or bowel function, e.g., occasional "accidents", or severe constipation or diarrhoea.
4 ( ) I have serious problems with my bladder and/or bowel function, e.g., routine "accidents", or need of catheterization or enemas.
5 ( ) I have no control over my bladder and/or bowel function.

QUESTION 9. USUAL ACTIVITIES
1 ( ) I am able to perform my usual activities (e.g., employment, studying, housework, free time activities) without difficulty.
2 ( ) I am able to perform my usual activities slightly less effectively or with minor difficulty.
3 ( ) I am able to perform my usual activities much less effectively, with considerable difficulty, or not completely.
4 ( ) I can only manage a small proportion of my previously usual activities.
5 ( ) I am unable to manage any of my previously usual activities.

QUESTION 10. MENTAL FUNCTION
1 ( ) I am able to think clearly and logically, and my memory functions well.
2 ( ) I have slight difficulties in thinking clearly and logically, or my memory sometimes fails me.
3 ( ) I have marked difficulties in thinking clearly and logically, or my memory is somewhat impaired.
4 ( ) I have great difficulties in thinking clearly and logically, or my memory is seriously impaired.
5 ( ) I am permanently confused and disoriented in space and time.

QUESTION 11. DISCOMFORT AND_SYMPTOMS
1 ( ) I have no physical discomfort or symptoms, e.g., pain, ache, nausea, itching etc.
2 ( ) I have mild physical discomfort or symptoms, e.g., pain, ache, nausea, itching etc.
3 ( ) I have marked physical discomfort or symptoms, e.g., pain, ache, nausea, itching etc.
4 ( ) I have severe physical discomfort or symptoms, e.g., pain, ache, nausea, itching etc.
5 ( ) I have unbearable physical discomfort or symptoms, e.g., pain, ache, nausea, itching etc.

QUESTION 12. DEPRESSION
1 ( ) I do not feel at all sad, melancholic or depressed.
2 ( ) I feel slightly sad, melancholic or depressed.
3 ( ) I feel moderately sad, melancholic or depressed.
4 ( ) I feel very sad, melancholic or depressed.
5 ( ) I feel extremely sad, melancholic or depressed.

QUESTION 13. DISTRESS
1 ( ) I do not feel at all anxious, stressed or nervous.
2 ( ) I feel slightly anxious, stressed or nervous.
3 ( ) I feel moderately anxious, stressed or nervous.
4 ( ) I feel very anxious, stressed or nervous.
5 ( ) I feel extremely anxious, stressed or nervous.

QUESTION 14. VITALITY
1 ( ) I feel healthy and energetic.
2 ( ) I feel slightly weary, tired or feeble.
3 ( ) I feel moderately weary, tired or feeble.
4 ( ) I feel very weary, tired or feeble, almost exhausted.
5 ( ) I feel extremely weary, tired or feeble, totally exhausted.

QUESTION 15. SEXUAL ACTIVITY
1 ( ) My state of health has no adverse effect on my sexual activity.
2 ( ) My state of health has a slight effect on my sexual activity.
3 ( ) My state of health has a considerable effect on my sexual activity.
4 ( ) My state of health makes sexual activity almost impossible.
5 ( ) My state of health makes sexual activity impossible.
Prehospital Resuscitation Intranasal Cooling Effectiveness Survival Study
(PRINCESS)

PROTOCOL
Version 15.01.2017

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Protocol Synopsis

**Purpose:** To assess the impact on neurological intact survival on cardiac arrest victims when trans-nasal cooling is initiated as early as possible in the resuscitation process.

**Background:** The RhinoChill Device is a non-invasive cooling device through which rapid cooling is achieved via the trans-nasal delivery of an evaporative coolant into the nasopharynx. Due to its non-invasive and portable nature, the RhinoChill can be used to begin cooling earlier than other cooling devices.

A 200-patient safety and feasibility study showed a solid trend to improved neurologically-intact survival rates in those patients receiving early intra-nasal cooling prior to achieving ROSC. This study aims at assessing outcome when cooling is begun early in the resuscitation process compared to systemic cooling at hospital only. The primary endpoint is total survival at 90 days.

**Design:** Prospective, randomized, two-arm study conducted by the pre-hospital emergency system.

**Study Population:** Up to 900 victims of witnessed cardiac arrest who qualify for advanced cardiac life support with ambulance response time within 15 minutes.

**Performance Endpoints:**

- **Primary endpoint:** Neurologic intact survival at 90 days.

- **Secondary endpoint:**
  - Total survival at 90 days
  - Proportion of patients who achieve ROSC
  - Proportion of patients admitted alive
  - Proportion of patients reaching target temperature (≤34°C Celsius) within 4 hours

**Safety Endpoint:**

- Composite general adverse event rate within the first 24 hours of initiating ALS
- Composite serious adverse event rate within the first 7 days of hospitalization

**Safety Follow-Up:** Death, hospital discharge, or 1 week post hospital admission
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1. INTRODUCTION

1.1. Background & Study Rationale

Sudden Cardiac Death is one of the major health issues of the industrialized world [1]. Despite decades of efforts to promote CPR science and education and the introduction of automated external defibrillators, less than 50% of cardiac arrest victims ever achieve a return of spontaneous circulation (ROSC) and this percentage drops to 20% or less for those patients that live in rural areas or do not have an initial rhythm that can be defibrillated (e.g., pulse-less electrical activity (PEA) and asystole) [2-8]. Even fewer of these patients live to hospital admission.

Two randomized studies published in the NEJM in 2002 demonstrated the benefit of therapeutic hypothermia on neurologically intact survival in patients who were cooled to 33-34°C within eight hours of ROSC following an out-of-hospital ventricular fibrillation (VF) cardiac arrest [9,10]. Based on these study results, the International Liaison Committee on Resuscitation published special guidelines recommending the use of mild hypothermia in routine treatment of cardiac arrest patients during post ROSC care [11]. Specifically the guidelines state that patients that achieve ROSC following a VF out of hospital cardiac arrest (OHCA) should be cooled as soon as possible, and that those patients achieving ROSC following a non-shockable OHCA might also benefit from cooling. The American Heart Association [12] and European Resuscitation Council [13] endorsed these recommendations shortly thereafter.

Of these randomized clinical studies, one protocol initiated cooling in the ambulance with ice packs by paramedical personnel [10], while the other study initiated cooling in the hospital [9]. The former study achieved target temperature shortly after ICU admission, whereas the latter study took an average of 8 hours following ROSC to achieve target temperature. The former study suggests a benefit to faster cooling, as it showed a better relative percentage of patients having a good outcome (CPC score 1 or 2) when compared to normothermic controls, with an odds ratio of 5.25.

Two additional studies, however, recently assessed the relative impact of cooling via iced-saline infusion shortly after OHCA patients were resuscitated in the field. The first of these was a feasibility study performed in Seattle USA that [8] showed a trend in improved survival to hospital discharge for the VF group that received early cooling. Ninety percent of subjects that received early cooling in the field survived to hospital admission, and 73% of those survived until hospital discharge (66% of the total achieving ROSC). In contrast, of the 86% of non-cooled patients that survived until hospital admission, only 52% survived (45% of the total achieving ROSC). Even with a relative improvement of 21%, the difference was not statistically significant. For those patients that had a non-VF rhythm and achieved ROSC the trend was reversed: only 6% of the cooled patients versus 20% of the non-cooled patients survived to hospital discharge.

The second study, performed in Melbourne Australia, [14] was powered to detect a 15% increase in neurologically good outcomes at hospital discharge in those patients receiving cooling in the field shortly after achieving ROSC. Interim analysis performed after enrolling 50% of the target population demonstrated no difference in outcomes between the group that was cooled in the field (46% good outcome) compared to those that received cooling later after hospital admission (53% good outcome). This latter study also showed the reverse trend from the Seattle study in that those patients that received
in-field cooling after achieving ROSC from a non-shockable rhythm demonstrated a trend for better outcomes than those that received cooling later.

Moderate hypothermia before cardiac arrest has been used successfully since the 1950s to protect the brain against the global ischemia that occurs during open heart surgery. Animal studies suggest that hypothermia induced during a cardiac arrest and prior to ROSC improve neurological outcomes when compared to animals that are cooled following ROSC [15-19]. These studies support the concept that post-resuscitation injury processes begin immediately after ROSC is achieved, and that intra-arrest cooling may serve as a useful therapeutic approach to improve survival.

The RhinoChill was designed to rapidly induce therapeutic hypothermia intra-arrest or post-resuscitation in emergency settings. The RhinoChill takes advantage of the nose as a natural orifice into the head to overcome the obstacle of cooling through the skull. The upper nasal pathways are composed of conchal folds and turbinates that converge in the pharyngeal zone, and thus provide a large diffuse surface area and vascularity that is in close proximity to the cerebral circulation. Cooling in the nasopharynx therefore offers the ability to cool via both direct conductive mechanisms that do not rely on spontaneous circulation as well as indirect hematogenous mechanisms that do [20].

Animal studies and preliminary clinical studies support the use of the RhinoChill in the emergency setting of resuscitation from cardiac arrest.

1.2. Device Description

The RhinoChill is intended for temperature reduction in patients where clinically indicated. The RhinoChill is contraindicated for patients with known contraindications to hypothermia (Raynaud’s disease, Cryoglobulinemia, Sickle Cell disease), have specific temperature-sensitive pathologies (e.g., serum cold agglutinins, Buerger’s disease), are pregnant, are medically unstable, have bleeding disorders, require oxygen supplied at > 50% FiO2 to maintain normal saturation (> 98%), intranasal obstruction, or known skull base fracture.

The RhinoChill works by spraying a liquid coolant onto the upper surface of the nasal cavity, where it evaporates and absorbs heat from the tissue, thereby cooling the tissue and the innate vasculature that supplies blood to the brain (refer to schematic). The coolant has a density of 1.68 g/ml and a heat of evaporation of 21cal/g. Therefore 35 calories of heat are absorbed for every ml of coolant that evaporates. Local temperatures within the nasal cavity are expected to cool to around 2°C.

The coolant is an inert liquid at one atmosphere of pressure and can carry 20 times more oxygen than saline. It has a surface tension that is lower than water so it will spread uniformly and quickly throughout the space in which it is sprayed. Oxygen or air is delivered with the liquid coolant to maximize its evaporation.

Medical grade oxygen or breathing air with a supply pressure of 60 psi and sufficient quantity to provide a 40 L/min flow rate over the treatment period is required in order to operate the RhinoChill.

The coolant vapor, along with the gasescapes the nasal cavity through the nostrils or the mouth. In the event that all the coolant is not evaporated, it is possible that it will either trickle out of the nostrils or trickle down the pharynx into the mouth or stomach. Because the coolant is immiscible in water, it is not absorbed in any significant quantity.
into the body [21, 22]. The minute quantities that may be absorbed into the blood or inhaled into the lungs are expired through the lungs in a relatively short period.

**RhinoChill Schematic**

The RhinoChill consists of three components: the tubing set, the control unit, and the coolant bottle. The tubing set is a single-use device that delivers the pressurized gas and coolant mixture to the patient. The proximal end attaches to the control unit to which a hospital gassource is connected. Distal to the control unit is the interface for the coolant bottle; this consists of a dip tube connected to a bottle interface collar into which is incorporated a liquid flow indicator. Liquid coolant is driven out of the bottle by the pressurized gas, through a 0.22 micron filter, and then the gas and coolant are delivered to the nasal catheters. The transnasal catheters are joined together with a hub at the proximal ends; the catheters are mated to the gas and liquid delivery lines via an integral manifold. The length of each individual catheter is 10cm, and the outer diameter is 4.0mm. The catheters are designed to be conformable with the anatomy, and have rounded atraumatic tips. The length of the catheter enables deep access into the nasopharynx, and the diameter of the catheter is consistent with the size of epistaxis catheters, and enables venting through the nostrils. The catheters have separate gas and liquid capillaries that converge at each of 12 spray ports along the dorsal surface of the catheter. Close contact of the liquid PFH with the pressurized gas at each of the spray ports results in efficient nebulization of the PFH from each of these ports. Each catheter also has three pressure sensing ports along the ventral surface of the catheter that transmit the local pressure in the nasal cavity to the control unit.
The control unit is a durable component used to both control the flow of the coolant-oxygen mixture as well as to act as an over-pressure shut-off valve. The control unit is composed of a commercially available mechanical oxygen flowmeter that is used to control the flow rate of oxygen as well as electronic circuitry to monitor oxygen supply pressure and intranasal pressure in each nostril. The control unit also has a mechanical over-pressure safety valve which is designed to vent excess oxygen to prevent a pressure greater than 60 psi (7 10%) from entering the device. This limiting pressure is set approximately 10% above the 50 psi 10% standard used for medical grade oxygen in the hospital setting. The patient pressure safety circuitry switches the device to a Stopped/Alarm mode if the pressure in either nasal cavity exceeds 60 cm H2O (7 10%). During the Stopped/Alarm mode, all gas flow is stopped, and all pressure is vented from the components downstream of the control unit, including the coolant bottle. The device will remain in the Stopped/Alarm condition until the device is manually reset by the operator.

The control unit circuitry is low voltage, and low power (i.e., it is designed to run for at least 10 hours on a set of two nine-volt batteries).

The control unit has user controls to initiate and stop flow as well as user-feedback indicator lights to indicate the operational mode and to alert the user when the circuit needs to be reset as well as when the battery power is becoming low and the batteries need to be replaced.

The coolant bottle is Polyethylene teraphalate (PET) bottle. It holds 1-2 liters of the evaporative coolant, perfluorohexane (PFH). A 1-liter bottle of coolant will last 30 minutes when the oxygen flow rate is set to 40L/min.

The RhinoChill is configured to be used in a stable hospital setting (e.g., hanging from an I.V. pole mount) or packaged in a backpack that integrates a 3L (900 liters gas) oxygen bottle, and weighs approximately 12 kg for use in the ambulance and field setting.
1.3. Non-clinical Studies

Forty-one sheep were studied in the development of the RhinoChill System: five sheep were studied as controls and 36 were studied using a variety of flow conditions and relative proportions of PFH to oxygen to effect evaporative cooling within the nasopharynx [23]. An additional 109 pigs were studied in 9 additional studies of a cardiac arrest model in which 68 pigs were cooled with the RhinoChill device and 41 were used as controls. **Table 1** summarizes these studies.

Cardiac arrest studies demonstrated the safety and feasibility of intra-arrest cooling and the ability to 1) facilitate resuscitation [24, 25], 2) increase cardiac recovery time [24], 3) increase survival [24-26], and 4) increase neurological recovery time [26]. In contrast, chilled intravenous saline administered intra-arrest had no positive effect on resuscitation [27].
Table 1. Animal studies performed with the RhinoChill

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Model</th>
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<th>Protocol</th>
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<tr>
<td>Study Name</td>
<td>Model</td>
<td>Qty</td>
<td>Protocol</td>
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<tr>
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<td></td>
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</tr>
<tr>
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<td>No airway</td>
<td></td>
<td>2</td>
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</tr>
<tr>
<td></td>
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<td></td>
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</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

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1.4. Clinical Studies

1.4.1. Cooling after Resuscitation from Cardiac Arrest

The RhinoChill has been used in the emergency room/ICU in 84 cardiac arrest patients following ROSC, in a completed feasibility study in Europe [28]. Cooling was initiated within 35 minutes (median) of patients arriving at the hospital, and therapeutic temperature of 34°C was reached in 27 minutes and 52 minutes by the brain (measured at the tympanon) and body, respectively. Mean temperature reduction was 2.4°C, 1.6°C, and 0.9°C for the tympanon, central compartment (blood, esophagus), and peripheral compartment (bladder/rectum), respectively, within the first 60 minutes of cooling with the RhinoChill.

There was one device-related serious adverse event. A patient cooled with the RhinoChill device developed discoloration around the nose and upper lip approximately 3 hours after RhinoChill use was discontinued. The patient also exhibited skin discoloration of her fingertips and earlobes consistent with a circulatory disorder such as Raynaud’s syndrome. The patient had very high peripheral vascular resistance for the six hours prior to study enrollment and throughout therapeutic cooling. The patient died approximately 36 hours after discontinuing RhinoChill use due to persistent cardiogenic shock, with no resolution of the skin discoloration. Tissue samples were not taken for pathological examination after death, so the reversibility of the condition could not be determined.

1.4.2. Cooling during Resuscitation from Cardiac Arrest

The RhinoChill Device was used in 96 patients randomized to intra-arrest cooling in the pre-hospital setting as part of a 200-patient randomized study [29]. Cooling was begun after the physician team had arrived and had placed an advanced airway, but before ROSC. Thus cooling was not begun until a median of 23 minutes after patient collapse.

There were no significant differences in the proportion of patients achieving return of spontaneous circulation (ROSC) (p=0.8). Among patients admitted alive to the hospital there was a trend towards increased survival in treated patients (43.8% vs 31.0%, p=0.26, Relative Risk (RR) 1.4). In patients admitted alive in whom cardiopulmonary resuscitation (CPR) was initiated within 10 minutes (76% of patients) survival to discharge was significantly higher in cooled patients (56.5% vs 29.4%, p=0.04, RR 1.9). In the subgroup with ventricular fibrillation (VF) as presenting rhythm no significant difference was seen in survival rates (62.5% vs 47.6%, p=0.37, RR 1.3).

More patients were neurologically intact at discharge in the treatment group (34.4% vs. 21.4%, p=0.21, RR 1.6) than in controls. Neurologically intact survival to discharge was significantly higher in cooled patients in whom CPR was initiated within 10 minutes of collapse as compared to no-cool controls (43.5% vs 17.6%, p=0.03, RR 2.5). A trend towards good neurologic outcome seen in patients with VF as the presenting rhythm (50% vs 28.6%, p=0.11, RR 1.8).

Neurologically intact survival to discharge was directly related to time to CPR initiation. The benefit of intra-arrest cooling on survival, and especially on neurologically intact survival, was most marked when CPR was initiated by
EMS within 10 minutes (refer to Figure).

Outcome data on neurologically intact survival (defined as having a cerebral performance category (CPC) of 1 or 2) for the two groups in all patients and the subgroups with early CPR and VF.

Nasal whitening occurred in 13 of 93 (14%) patients during nasal cooling and resolved spontaneously in all 5 resuscitated patients. There was no relationship between longer duration of treatment and nasal discoloration. Nine of the 13 occurred prior to ROSC. Epistaxis occurred in 3 (3.2%) treated patients and was serious in one patient with an underlying coagulopathy secondary to hepatic failure. This was the only device-related serious adverse event. Periorbital emphysema occurred 75 minutes into treatment in one patient and resolved spontaneously within 24 hours. The total number of serious adverse events was 7 in the treatment group, 1 of which was device-related (epistaxis) and 14 in the control group (p=0.23). There were no unanticipated adverse events in any patient.

This randomized study demonstrated the safety, feasibility and brain cooling efficacy of intra-arrest nasal cooling in the pre-hospital setting. While the study wasn’t powered to detect improvement in neurologically intact survival, such an improvement was apparent for all patients, irrespective of rhythm, and significant for those in whom CPR was initiated within 10 minutes of collapse. Early nasal cooling and early CPR, combined, favorably affected outcome, irrespective of rhythm. In practice, these findings argue in favor of trying to initiate both CPR and nasal cooling as early as possible during the resuscitation process.
1.5. References


2. **STUDY OBJECTIVE**

The objective of this study is to assess the impact on neurological intact survival (CPC-score) rates at 90 days when cooling is initiated as early as possible in the resuscitation process.

2.1. **Performance Endpoints**

The aim of the study is to determine whether the resuscitation process is facilitated by early cooling, and whether this translates into improved neurological intact survival in those successfully resuscitated. Specific performance endpoints include the following:

- **Primary Endpoint:**
  - Neurological intact survival (CPC score 1-2) at 90 days

- **Secondary Endpoints:**
  - Total survival at 90 days
  - ROSC (Sustained) rate
  - Survival to hospital admission
  - Proportion of patients reaching target temperature (≤34°C Celsius) within 4 hours of call to dispatcher

2.2. **Safety Endpoint**

The safety endpoints are:
1. All general adverse events occurring within 24 hours of beginning advanced cardiac life support procedures
2. The composite serious adverse event (SAE) rate from the time of patient randomization through the first seven days of hospitalization.

3. **INVESTIGATIONAL PLAN**

3.1. **Study Design**

This will be a prospective, randomized study conducted by the emergency responders in multiple emergency medical systems. It is expected to last approximately 2 years.

Up to 900 cardiac arrest patients that are eligible for cardiac life support procedures will be enrolled in the study if they meet all inclusion and exclusion criteria. This study is powered to detect statistically significant improvement in patients that are cooled early during resuscitation.

3.2. **Overview**

Medical personnel (e.g., nurses or physicians) responding to a cardiac arrest will assess each patient for study inclusion. During resuscitation, patients will be randomized to receive standard ACLS according to ERC guidelines with or without cooling with the RhinoChill upon determining that the patient is in cardiac arrest. The RhinoChill catheters should be placed and cooling initiated immediately after airway management (i.e. laryngeal mask or intubation) for those subjects randomized to early cooling. The aim is that cooling should be started within 15 minutes from the call to
the dispatch centre. No other experimental procedures or devices will be used during the resuscitation attempt or after ROSC is achieved in those subjects that do achieve ROSC. Specifically, cooling with chilled saline or cold packs in the field or ambulance will not be permitted in subjects randomized to either group.

Resuscitation attempts should be continued for at least 30 minutes after advanced emergency medical personnel arrive on the scene in all patients before deciding that further interventions are futile. Patients that regain consciousness following ROSC and prior to hospital transport will be analyzed separately from those that remain comatose. Cooling will be halted in the early-cooling group for those that wake up.

Automated external defibrillator (AEDs) with the capability to record chest compression data will be used in each resuscitation attempt so that these data can be used to analyze the CPR record. Specifically, the hands-off time will be assessed to ensure the patients in the early cooling group do not receive poorer quality CPR due to the cooling procedures. The impact of the hands-off time will also be used to assess outcome differences between the two groups.

RhinoChill cooling will be continued in those subjects randomized to early cooling that achieve ROSC and remain comatose. Bolus doses of sedation and analgesia will be administered for their transport to the hospital according to local protocol. RhinoChill cooling will be continued at the hospital until the subject can be successfully transitioned to the standard institutional cooling protocol. All subjects randomized to either group will otherwise be treated according to ERC resuscitation guidelines.

Clinical assessments and clinically relevant adverse events will be documented from the time the patient is randomized into the study until the first of the following three events occur: death, hospital discharge, or one week following enrollment. Subjects that survive will undergo a neurological assessment at the time of hospital discharge and during a short telephone interview 90-135 days months after the cardiac arrest. Acute data concerning the cardiac arrest itself will be gathered Utstein Style [20] by the personnel that enroll the subject. It is understood that the time of collapse, and hence the exact duration of cardiac arrest is an estimate and cannot be quantified accurately. However, a single person will be responsible for collecting an individual patient’s charts and personally interviewing the witnesses, therefore imprecision surrounding the exact time of recognition of collapse and the accurate time of the emergency medical activation will be minimized. In the analysis the time of the call to the dispatch centre to start of CPR will be used to get a more exact event times.

The RhinoChill device has received CE marking, however, this study is considered to be emergency research, in as much as the eligible patients will be unable to provide consent prior to their treatment as they will necessarily be comatose. Ethical consideration for treating subjects without their express consent will be in accordance with the World Medical Association Helsinki Declaration of 1964, as revised at the 59th General Assembly in Seoul in 2008, and the responsible ethic committee for clinical research.

Subjects of this study face a life-threatening condition and treatment by cooling with the RhinoChill device prior to ROSC has shown improved rates of neurologically-intact survival in patients treated in a previous study. If cooling is begun early enough, it may also improve the rate of resuscitation, as shown in a porcine model of cardiac arrest in which cooling was begun within 15 minutes of arrest. It is therefore expected that the potential benefit of using the RhinoChill in this population outweighs the
risks.
The subject’s legal representative will be informed of the subject’s study participation as soon as practical. If the subject regains normal neurological function, they too will be informed of their study participation and be asked to provide their consent to use their data.

3.3. Study Procedures

See Appendix 1 for the study flow diagram and Appendix 2 for table of clinical events and assessments.

3.3.1. Patient Screening & Point of Enrollment

All supposed victims of cardiac arrest will be screened for study eligibility upon arrival of the first responding team. If the patient is found to be eligible for the study, the patient will be randomized to receive cooling along with standard ACLS or standard ACLS alone. Data collection concerning the arrest will include:

Arrest Characteristics
- Time of collapse
- Location of collapse
- Time of emergency call

Patient Characteristics
- Gender
- Age/Date of Birth
- Height (approximate)

3.3.2. Resuscitation Attempt

The resuscitation attempt should follow ERC guidelines to the greatest extent possible. After airway management (i.e. laryngeal mask or intubation), patients are randomized to early cooling or standard care. In patients randomized to early cooling, the RhinoChill catheters should be placed and cooling initiated immediately after airway management. To place the nasal catheters and start cooling takes approximately 1 minute. Cooling should be performed with the oxygen flow set to 40L/min. There should be no changes to the care received by patients randomized to the control arm.

ACLS will be continued per local protocol once the advanced medical team (ALS) has arrived.

Data collection concerning the resuscitation effort will include:
- Time CPR initiated by 1st EMS responder
- CPR mechanism (if not manual)
- First rhythm
- Shock time, strength, and success
- Time airway is secured
- Time cooling initiated (if cooled)
- Time IV access obtained
- Total adrenaline/epinephrine dose
- Additional medication(s)/dose(s)
- Recurrent VF or re-arrest
- Time randomized
- Number of chest compressions/min
- Time ROSC or death declared
- CPR hand’s off time

### 3.3.3. ROSC

ROSC will be defined as obtaining an organized rhythm and palpable pulse sustained for 20 minutes. Once an organized rhythm and palpable pulse is achieved, subjects will have their temperature taken via the tympanic route, stabilized and then be transported to the hospital.

If a patient wakes up after ROSC is achieved, they will be analyzed separately from patients that remain comatose. Cooling will be discontinued in those patients in the early cooling group if they wake up.

Subjects randomized to early cooling will be intravenous bolus doses of sedation and analgesia for transport to the hospital. Doses of sedation and analgesia will be dictated by the institutional standard cooling protocol. The oxygen supply in the transport vehicle should be used to continue RhinoChill cooling during transport to the hospital. Normal transport procedures will be used for patients randomized to the control arm.

Subjects in both the early cooling and the control arm will otherwise undergo standard post-resuscitation care. Infusions of chilled saline or cooling with cold packs will not be permitted in the pre-hospital setting for either group.

### 3.3.4. Hospital Admission

Upon hospital arrival, the following measures will be recorded:

- Tympanic temperature
- Heart rate
- Peripheral oxygen saturation (SpO₂)
- Mean arterial pressure
- End-tidal carbon dioxide (EtCO₂)
- ST-segment elevation
- Glasgow Coma Scale

A systemic temperature probe will be placed (e.g., bladder, arterial) and core temperature will be recorded. A blood draw will be made to obtain baseline serum glucose and arterial blood gases:

- PaO₂
- SaO₂
- PaCO₂
- Arterial pH
- pH
- Lactate
- Base excess

### 3.3.5. Post Resuscitation Care

All subjects will undergo standard post resuscitation treatment upon hospital arrival. The systemic hypothermia treatment at ICU for both patient groups (treatment and control) will be according to international guidelines. Regular ICU measures such as glycaemia control that are considered as standard monitoring/care will not be recorded specifically in the study. The conditions below have to be fulfilled for each participating study centre:

- Hypothermia treatment for at least 24 hours.
- Target temperature 33°C ± 1°C.
To record core- and tympanic temperature every 15 minute during the induction period (i.e., until the target therapeutic temperature is initially reached).

- Rewarming rate at 0.2-0.5°C / hour.

- Control of post-cooling hyperthermia

Subjects randomized to the early cooling group with the RhinoChill shall continue being cooled with the RhinoChill until systemic cooling procedures can be started. Intravenous sedation, analgesia and neuromuscular blockade (if used) should be initiated upon hospital arrival according to institutional cooling protocols. Doses should be adjusted as necessary over the course of cooling/re-warming.

After the subject has been prepared with the standard hypothermia device, the RhinoChill should be turned off, but the intranasal catheters should be left in place while transitioning the subject to the standard hypothermia protocol. Intermittent activation of the RhinoChill may be considered if the core temperature does not continue to drop via the systemic cooling method. Cooling via the RhinoChill system will be halted immediately if any adverse event related to the use of the RhinoChill develops.

For those patients in the control group, the standard cooling procedure will be started as soon as practical. Intravenous sedation, analgesia and neuromuscular blockade (if used) should be initiated upon hospital arrival according to institutional cooling protocols. Doses should be adjusted as necessary over the course of cooling/re-warming.

The systemic cooling procedures, including system used, core temperature location, duration at target temperature and the hypothermia reversal algorithm will be recorded.

Cardiac function will be followed. If feasible, echocardiographic examinations should be performed acutely (within 24 hours) and after 72 hours to measure left ventricular ejection fraction (LVEF). If possible, record the investigations (CD/DVD) so that independent physicians can analyse them later.

For those patients in which a full 24-hour therapeutic hypothermia treatment is deemed futile or unnecessary, the time in which cooling is halted in the patients randomized to the early cooling group will be recorded.

Temperatures (tympanic and core, with core being defined by hospital protocol) will be monitored periodically over the first 48 hours after hospital arrival for all patients regardless of whether cooling is performed in the hospital setting.

In the cases where ICU care is withdrawn due to poor prognosis, the reasons (prognostic measures besides clinical examination) for this should be clearly stated in the Case Report Form (CRF) (e.g. MRI, neuro markers, EEG, SSEP).

### 3.3.6. General Patient Monitoring

ECG, peripheral oxygen saturation, heart rate and blood pressure monitoring will continue throughout the acute care period. Ventilation settings should be adjusted to maintain arterial oxygen saturation > 95% (e.g., PaO₂ 100-150 mmHg). Increased ventilation should be used to excrete CO₂ and maintain
normocapnia (e.g., PaCO₂ 40-45mmHg). PEEP should be adjusted to reduce FiO₂ with a target of 5mmHg. Arterial pH should be kept between 7.3 and 7.5. Electrolytes will be substituted as necessary to maintain normal ranges.

Blood pressure will be monitored and the mean blood pressure should be kept above 60 mmHg. Drops in pressure should be treated primarily with crystalloids or hydroxyl ethyl starch. If sufficient pressure control cannot be achieved with fluids alone, vasopressors such as epinephrine (adrenaline), norepinephrine (noradrenaline), dobutamine, and dopamine should be used.

Fluid balance will be controlled. No dextrose, glucose and free water should be administered. Serum blood glucose should be kept between 80 and 150mg/dl. Parenteral nutrition or enteral feeding should be initiated as soon as practical (>24 hours after cardiac arrest).

### 3.3.7. Follow-Up

Subjects treated with the RhinoChill will undergo rhinoscopic examination of the nasal cavity if it is warranted based on clinical signs of intra-nasal trauma (e.g., bleeding from the nostrils, whitening of the nose or other treatment-related observations).

All patients still alive will undergo an exam 72 hours after hospital admission. If indicated at this time, a follow-up anterior-posterior chest x-ray will be made, a rhinoscopic exam will be performed with an otoscope, and core and tympanic temperatures will be recorded. Additionally, the subject’s general disposition, Cerebral Performance Category (CPC), and modified Rankin Score (mRS) will be recorded.

### Cerebral Performance Categories

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Good recovery - little to no deficit</td>
</tr>
<tr>
<td>2</td>
<td>Moderate disability</td>
</tr>
<tr>
<td>3</td>
<td>Severe disability</td>
</tr>
<tr>
<td>4</td>
<td>Vegetative state</td>
</tr>
<tr>
<td>5</td>
<td>Dead</td>
</tr>
</tbody>
</table>

### Modified Rankin Score

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No symptoms at all</td>
</tr>
<tr>
<td>1</td>
<td>No significant disability despite symptoms; able to carry out all usual duties and activities</td>
</tr>
<tr>
<td>2</td>
<td>Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance</td>
</tr>
<tr>
<td>3</td>
<td>Moderate disability; requiring some help, but able to walk without assistance</td>
</tr>
<tr>
<td>4</td>
<td>Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance</td>
</tr>
<tr>
<td>5</td>
<td>Severe disability; bedridden, incontinent and requiring constant nursing care and attention</td>
</tr>
<tr>
<td>6</td>
<td>Dead</td>
</tr>
</tbody>
</table>
Subjects will be followed until death or hospital discharge, and the following data will be recorded concerning their hospital course:

- Date/time subject wakes
- Date/time subject is taken off ventilator
- Date/time subject is discharged from ICU
- Date/time subject dies (if in hospital)
- Date/time subject is discharged from hospital
- Discharge disposition
- CPC and mRS at hospital discharge
- CPC and mRS at 90 days (if still in hospital)

Clinically significant serious adverse events will be recorded from the time ROSC is achieved through the earliest of the following three events: death, hospital discharge, or one week following admission. The nature and severity of the adverse event, the relationship to the RhinoChill Device, management and outcome will be recorded on the case report form.

A telephone follow-up will be made 90-135 days after the arrest to assess the subject’s 90-day survival, neurological function and quality of life by using two acknowledged methods, the Glasgow Outcome Scale (GOS) and the 15D instrument (see appendix 3). This telephone interview will take approximately five minutes to assess the subject’s variable health status.

3.3.8. Concomitant Therapies

Concomitant interventions (e.g., PCI, aortic balloon pump, bypass surgery, ICD placement) will also be recorded.

Medications and/or treatments that are considered to be experimental in nature and are intended to improve outcomes after cardiac arrest are prohibited from use.

3.3.9. Patient Withdrawal

Subjects will be enrolled in the study by rescue personnel if they meet all of the study’s inclusion criteria, but none of the exclusion criteria. Subjects will necessarily be comatose and unable to provide consent prior to their being enrolled in the study. The subject’s legal representative will be informed of the study as soon as it is practical to do so. Subjects that recover will be informed of their study participation and be asked to provide their consent for the use of their study data.

The Principal Investigator, Steering Committee and the individual site investigators and site Ethic Committees (ECs) also have the right to discontinue a patient or terminate the trial for the following reasons:

- A Site Investigator may withdraw a subject from the study for safety reasons (i.e. a device-related serious adverse event). In these cases, data surrounding the event leading to subject withdrawal will be retained for safety analyses.
- The EC at any participating site may decide to withdraw the site from the study for safety reasons.
• The EC at the principal investigator site and Principal Investigator may terminate the study for safety reasons.

• A decision on the part of the Principal Investigator to suspend or discontinue testing, evaluation, or development of the product for any reason.

• The Principal Investigator may decide to close a study site when one of the following occurs:
  ▪ The Site Investigator at an individual site fails to enroll patients into the study at an acceptable rate.
  ▪ A Site Investigator at an individual site fails to comply with pertinent regulations of appropriate regulatory authorities.
  ▪ A Site Investigator fails to adhere sufficiently to protocol requirements
  ▪ A Site Investigator knowingly submits false information from the research facility to the Principal Investigator, Steering Committee or appropriate regulatory authority.

If the study is terminated early, all specified follow-up data on subjects enrolled prior to termination will be collected and reported.

4. **PATIENT POPULATION**

Subjects will be recruited by rescue personnel from presumed victims of cardiac arrest of non-traumatic origin. It is expected that patients will be enrolled that are later found to not meet all of the exclusion criteria (e.g., Do Not Resuscitate orders are found). Data should be collected on all patients, and the decision to exclude them from analysis will be made by the Principal Investigator.

4.1. **Patient Inclusion Criteria**

Patients are eligible if they meet all of the following criteria:
1. Age $\geq 18$ years
2. Collapse was witnessed (heard or seen)
3. Do not have a pulse
4. Are unresponsive to external stimuli

4.2. **Patient Exclusion Criteria**

Patients are not eligible if they meet one or more of the following criteria:
1. Age $\geq 80$ years
2. Have an etiology of cardiac arrest due to trauma, head trauma, severe bleeding, drug overdose, cerebrovascular accident, drowning, smoke inhalation, electrocution, hanging
3. Already hypothermic (e.g., avalanche victim; found in the snow)
4. Have an obvious barrier to placing intra nasal catheters (e.g., intranasal obstruction)
5. Do Not Attempt to Resuscitate (DNAR) orders
6. Have a terminal disease
7. Known or clinically apparent pregnancy
8. Have a known coagulopathy (except therapeutically induced)
9. Are known to have a need for supplemental oxygen
10. Achieve ROSC prior to randomization
11. Response time (call to first EMS CPR) > 15 minutes

If a patient is unaccompanied or accompanied by a person or persons unfamiliar with their history, determination of these exclusion criteria will be left to the best estimation of the emergency personnel. At no time should an attempt to determine these criteria be allowed to delay the administration of life-saving treatment.

5. STUDY MATERIAL & METHODS

5.1. Study Device

The investigational site will use the RhinoChill control units and tubing sets and bottles of liquid coolant at the standard. It is expected that at least one tubing set and 1 bottle of coolant will be needed for each subject enrolled in the early cooling arm. Patients that are resuscitated after RhinoChill cooling is initiated will likely require 1-2 additional bottles of coolant before in-hospital cooling can be initiated. Participating institutions have been provided RhinoChill units to use to continue cooling patients randomized to early cooling until systemic cooling can be initiated in the hospital. No specific surgical skills are necessary to use the device, but basic knowledge of cardiac life support, therapeutic hypothermia and the associated effects are required.

Participating sites are required to supply the pressurized gas source (oxygen or breathing air) that will be used in the field, ambulance, and hospital settings.

5.2. Storage & Labeling

Components are designed to withstand standard transportation, storage and operating temperatures for both ambulance and hospital use. Product provided for the study will carry the CE Mark.

5.3. Preparation & Application

The RhinoChill system will be packaged in a portable pack. A medical grade supply of oxygen will be integrated into the pack by site personnel prior to placing it on the emergency response vehicle. A brief functionality test of the tubing set and control unit pressure relief valve should be performed prior to placing the nasal catheters in the subject.

The individual nasal catheters will be advanced through each nostril so that the distal end is well within the nasal cavity. Care should be taken not to force the individual catheters into the nostrils, but to advance them gently. Once the catheters are placed, cooling will be initiated by turning on the RhinoChill gas supply and adjusting it to 40L/min. The nostrils are to be kept unobstructed to allow venting of the PFH vapor.

5.4. Product Accountability

Product is labeled by lot and serial number where appropriate.
6. EVALUATION OF SAFETY

6.1. Adverse Event Definitions

An Adverse Event (AE) is any untoward medical occurrence in a subject.

A Serious Adverse Event (SAE) is any adverse event that:

a) leads to death
b) leads to a serious deterioration in the health of the patient that
   1. results in a life-threatening illness or injury
   2. results in a permanent impairment of a body structure or a body function
   3. requires in-patient hospitalization or prolongation of existing hospitalization
   4. results in medical or surgical intervention to prevent permanent impairment to
      a body structure or a body function
c) leads to fetal distress, fetal death, congenital abnormality or birth defect

Adverse Device Effects and Serious Adverse Device Effects are those AEs and SAEs that occur as an untoward or unintended response to a medical device. These events include those which result from insufficiencies or inadequacies in the Instructions for Use or deployment of the device as well as user error.

An Unanticipated Adverse Device Effect (UADE) is defined as any serious adverse effect on health or safety or any life-threatening problem or death caused by – or associated with – the device, if that effect, problem or death was not previously identified in nature, severity, or degree of incidence in the investigational plan (including documents such as the protocol, Investigator’s Brochure, informed consent form or other study-related documents), or any other unanticipated serious problem associated with the device that relates to the rights, safety or welfare of subjects.

A Technical Device Failure is defined as a failure of the device to perform its intended function when used in accordance with the Instructions for Use. Technical device failures will be recorded and evaluated for possible untoward effects on the subject. If a device failure results in an adverse experience in the subject, this adverse experience should be considered an adverse device effect and recorded on the Adverse Event pages of the CRF. Device failures that do not result in a clinically significant adverse effect on the patient will be noted on the CRF pages regarding device performance but will not be considered an adverse device effect.

6.2. Adverse Event Assessments

The relation of the event to the investigational device will be categorized by the Investigator as follows:

Not related – AE is due to the underlying disease state or concomitant medication or therapy, and was not caused by the investigational device.

Probably not related– AE had minimal or no temporal relationship to the use of the investigational device and/or a more likely alternative etiology exists.

Probably related – AE had a strong temporal relationship to the use of the investigational device and an alternative etiology is less likely compared to the potential relationship to the investigational device.

Definitely related – AE had a strong temporal relationship to the use of the investigational device and another etiology is highly unlikely.
For the purposes of reporting, an event will be considered associated with the use of the device if it is believed to be due either directly to the mechanical aspects of the device itself (e.g., nosebleed) or the ensuing device-related cooling.

Events believed to be due to study procedures other than the device/cooling (such as events believed to be side effects of the standard hypothermia maintenance) will be recorded but will not be categorized as device-related.

Subjects enrolled in the study will have a high morbidity and mortality rate associated with their cardiac arrest and the ensuing global ischemia. Therefore, careful attention shall be made to assessing the causality of any serious adverse events.

### 6.3. Adverse Events Reporting

All clinically significant AEs or those that appear to be related to the use of the RhinoChill (e.g., whitening of the nose) as well as those that could potentially harm the patient (e.g., pleural effusion) will be recorded on the CRF from ROSC through the end of the cooling period. Abnormal laboratory values are expected in these patients, and these are not to be recorded as AEs. The date of occurrence, severity, duration, management, outcome and relationship to cooling with the RhinoChill Device will be recorded.

### 6.4. Serious Adverse Event Reporting

All SAEs that occur within seven days after enrollment must be followed until resolution; this includes those patients that were terminated early or withdrew. These must be reported to Leif Svensson, MD, PhD and Maaret Castrén, MD, PhD The Karolinska Institutet (see contact information on the first page) within 24 hours of their occurrence as well as following their resolution.

SAEs that should be reported generally include any new events that occur after ROSC has been achieved. Examples include the following: re-arrest, a clinically significant arrhythmia that results in symptoms of vital organ hypoperfusion, major bleeding, any new event causing emergency surgery, new neurological dysfunction not attributed to the cardiac arrest (e.g., stroke, seizure), infection, sepsis, pneumonia, hepatic dysfunction, renal dysfunction, respiratory failure, pulmonary edema, arterial desaturation.

The Department of Clinical Science and education, Karolinska Institutet, will immediately review all SAE reports with regard to their causal relationship to use of the RhinoChill. The Steering Committee will determine whether the study should be terminated early or suspended based on review of the composite rate of serious adverse device-related events. The criteria for early termination of the study is a serious adverse device-related event rate > 10%.

Reporting to the regulatory authorities will be performed per European vigilance requirements and other local requirements,

### 7. RISK EVALUATION

#### 7.1. Potential Risks to Study Subjects
For purposes of this study, adverse events that may be anticipated and are associated with the use of the device include those associated with the RhinoChill Device or from the device-induced mild hypothermia.

7.1.1. Device Use

Potential risks associated with the use of the RhinoChill Device include those associated with the mechanical aspects of an intranasal catheter as well as those associated with the delivery of the PFH-oxygen mixture.

The following events are those most likely, non-serious events to occur with the use of the RhinoChill Device:

**Peri-nasal tissue discoloration** due to local evaporation of the coolant on the external facial structures that is expected to resolve after normal circulation is restored.

**Mucosal irritation/dryness** caused by high oxygen flows during cooling that would resolve with over the counter medications or on its own;

**Epistaxis, minor**: bleeding arising from the nasal cavity or paranasal sinuses that would resolve on its own or would be easily controlled with cauterization or simple nasal packing.

**Para-sinus emphysema**: gas entrapment in the sinus region that will resolve on its own; associated with chronic sinusitis.

The following events are those least likely, non-serious events to occur with the use of the RhinoChill Device:

**Gastrointestinal discomfort** caused by accidental ingestion of PFH that would resolve without intervention;

**Frostbite/necrosis** to the nasal tissues caused by excessive local cooling that might require intervention;

**Diminished sense of smell** caused by PFH evaporation in the nasal cavity.

The following serious events are anticipated to very rarely occur with the use of the RhinoChill Device:

**Hypoxia**: depletion of oxygen supply due to saturation with PFH requiring prolonged mechanical ventilation with 100% oxygen;

**Epistaxis, major**: bleeding arising from the nasal cavity or paranasal sinuses that would be characterized by brisk bleeding with no accessible source. A major nosebleed of this type would require posterior nasal packing or balloon packs, or even an arteriogram with embolization of the internal maxillary artery. A transfusion would be required in those cases in which hemoglobin/hematocrit falls significantly due to the bleed;

**Infection**: presenting as a wound infection in the nasal cavity, or alternately as bacteremia with sepsis, that requires medical or surgical intervention, such as antibiotic therapy and prolonged hospitalization;

**Barotrauma**: Trauma caused by rapid or extreme changes in gas pressure, especially affecting enclosed cavities within the body such as the nasal cavity and lungs. This could cause tearing of mucosal tissue in the nasal cavity and possibly the displacement of the nasal septum that would require endoscopic
evaluation and surgical repair. Lung barotrauma could cause tearing of lung tissue and rupture of alveoli/small bronchi or entry of gas into the blood vessels that would require surgical intervention and prolonged hospital stay;

**Air embolus**: air circulating in the blood that results in clinical sequelae that are life threatening and may be amenable to surgical intervention;

**Pulmonary interstitial emphysema**: air circulating through the pulmonary interstitium and lymphatics that results in clinical sequelae that is life threatening and may be amenable to surgical intervention;

**Pulmonary aspiration**: soiling of the respiratory tract by foreign, non-gaseous substances (e.g., PFH or food particles) that could result in aspiration pneumonitis or aspiration pneumonia where the former represents inflammation of the lung tissue without infection, whereas the latter also has superimposed infection. Systemic medication with prolonged hospital stay would be required in the event of either developing;

**Burns**: due to oxygen-enhanced fire/explosion that could be life threatening, requiring prolonged hospital stay and potential surgical intervention;

**Intracranial pressure** increases due to uncontrolled re-warming of the brain during the transition to systemic cooling after it has been cooled with the RhinoChill Device. Uncontrolled re-warming of the brain from a cooled state can lead to severe levels of intracranial pressure that could herniate the brainstem and lead to death.

### 7.1.2. Mild Hypothermia

Hypothermia results in various physiological effects on the body which are generally managed with medical care. These effects include the following:

- The **oxyhemoglobin-dissociation** curve shifts to the left.
- **Metabolic acidosis** results from lactate generation from shivering and decreased tissue perfusion; this is exacerbated by hypothermia-induced impairment of hepatic metabolism and impaired acid excretion.
- **Hematocrit increases** 2% per 1°C decline in temperature, resulting in increased blood viscosity.
- **Hypokalemia** may occur due to inhibition of the sodium-potassium ATP pump.
- **Hyperglycemia** may occur due to decreased insulin release and increased peripheral insulin resistance.
- **Coagulopathies** may arise due to hypothermia induced impairment of the enzymatic reactions of the coagulation cascade (despite normal clotting factor levels).
- **Platelet activity is impaired** because platelet production of thromboxane B₂ is temperature-dependent; in addition, bone marrow production can be suppressed and hepatosplenic platelet sequestration can be increased;
- Direct impairment of immune function (especially via oxidative killing by neutrophils) can **increase susceptibility to infection**.
The magnitude and clinical significance of the effects of hypothermia are generally dependent upon the degree and duration of systemic hypothermia. The depth and duration of hypothermia used in this study is mild hypothermia (33°C). The use of a mild level of hypothermia will therefore minimize the risk of hypothermia-associated effects.

Anticipated events associated with mild hypothermia include the following:

- **CNS**: linear depression of cerebral metabolism; amnesia; apathy; dysarthria; impaired judgment; maladaptive behavior;
- **Cardiovascular**: tachycardia, then progressive bradycardia; cardiac-cycle prolongation; vasoconstriction; increase in cardiac output and blood pressure;
- **Respiratory**: tachypnea, then progressive decrease in respiratory minute volume; declining oxygen consumption; bronchorrhea; bronchospasm;
- **Renal, Endocrine, Metabolic**: hyperglycemia, hypokalemia, lactic acidosis; cold diuresis; increase in catecholamine, adrenal steroids, triiodothyronine, thyroxine; increase in metabolism with shivering;
- **Neuromuscular**: increased pre-shivering muscle tone, then fatiguing; shivering induced thermogenesis; ataxia;
- **Infectious**: pneumonia, sepsis;
- **Coagulopathy**: hemorrhagic conversion of an ischemic infarct.

### 7.2. Methods to Minimize Risks

The target patient population is comatose and will die with no intervention. Even with advanced cardiac life support interventions, mortality is high following cardiac arrest.

All serious adverse events related to the use of the RhinoChill have been analyzed with respect to their likelihood and severity, and have been minimized through both the design and manufacture of the device and the design of the study. The Investigator Brochure contains a detailed analysis of the risks associated with each of the individual adverse events described above and the manner in which each is minimized.

### 7.3. Potential Benefits of the Procedure

Hypothermia has a putative benefit in out-of-hospital cardiac arrest of cardiac origin. Two seminal studies published in 2002 [9,10] demonstrated that cooling following out-of-hospital cardiac arrest could significantly improve neurologically intact survival. It has been suggested that hypothermia may provide an even greater protective effect if initiated sooner than it was in these studies.

The RhinoChill has been demonstrated as feasible to use in the pre-hospital environment, and significantly reduces patient temperature by hospital arrival. Cooling was begun approximately 24 minutes after arrest, but patients admitted to the hospital following intra-arrest intranasal cooling were more likely to survive neurologically intact and suffer less serious adverse events. Use of the RhinoChill in a porcine model of cardiac arrest demonstrated improved resuscitation and increased ROSC rates when cooling was begun within 15 minutes of arrest. It is therefore believed that cooling with the RhinoChill earlier during the resuscitation efforts may also improve ROSC rates in humans.
8. STATISTICAL CONSIDERATIONS

This study is powered to detect clinically significant changes in total survival at 90 days after cardiac arrest. An interim analysis for safety and futility will be performed by an external committee after the first 200 patients have provided endpoint data. Conditional power for meeting the primary endpoint will if needed, be computed at that time, and if the interim results do not correspond to the primary endpoint, termination of the study for futility will be considered. Early stopping for efficacy reasons will only be considered if major outcome differences are seen between the groups according to the Haybittle rule with a p-value ≤0.001.

8.1. Randomization

Once the patient has been confirmed to meet all inclusion criteria and none of the exclusion criteria they will be randomized to receive ACLS with or without cooling.

Randomization will be carried out in blocks of four and each site will be given sets of sequentially numbered envelopes with randomization assignments provided in a 1:1 manner to distribute to the participating pre-hospital vehicles.

Each institute will be assigned a certain number of envelopes based on projected enrollment. Individual envelopes will be placed in each RhinoChill pack at the time of site initiation, and replaced as patients are enrolled. The RhinoChill pack will be carried to every potential subject, and the envelope will be opened once the subject has been qualified as meeting all inclusion and exclusion criteria.

8.2. Blinding

Neither EMS or hospital personnel will be blinded to treatment, since the control patients are easily distinguishable from patients undergoing device placement and nasal cooling. However, medical personnel making the final neurological assessment of the patient prior to discharge will be blinded as to the patient’s group assignment.

8.3. Performance Endpoints

Performance endpoints include ROSC rate, resuscitation parameters, early cardiac performance, and outcome measures (total survival and neurological intact survival at 90 days). These parameters will be compared between those patients that receive nasal cooling during ACLS and those that do not.

Resuscitation parameters will be calculated for those patients that achieve ROSC:

- Time to ROSC
- Success of 1st shock
- Number of shocks
- Catecholamine dose

Early post-resuscitation cardiac performance parameters along with core and tympanic temperatures will be calculated for those patients that survive to hospital admission:

- Heart rate
- Blood pressure
- ST-segment elevation
- EtCO₂
- Arterial blood gases

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Outcome parameters will be:

- Survival to 24 hours
- Survival to ICU discharge
- Survival to hospital discharge
- CPC at hospital discharge
- mRS at hospital discharge
- Survival at 90 days
- **Neurological outcome at 90 days, CPC-score 1-2 (Primary)**
- Glasgow Outcome Score at 90 Days
- 15D Instrument Quality of Life at 90-135 days

### 8.4. Safety Endpoints

The safety profile associated with the RhinoChill Device will be assessed via the composite adverse event rate at the earlier of death or 24-hours post ROSC and the composite serious adverse event rate within the first 7 days of hospitalization.

### 8.5. Statistical Analysis

Summary, descriptive statistics will be calculated for all performance, safety, demographic, and baseline variables. Means, standard deviations, and ranges will be used to describe continuous measurements. Counts and percentages will be used to describe categorical parameters. Differences between variables associated at different time points will be evaluated using an appropriate comparative statistic. Data from the two treatment groups will be analyzed for treatment effect. A 2-sided p-value less than 0.05 will be considered to be statistically significant.

Analysis of variance will be performed to assess the impact of baseline characteristics or subject-related characteristics if there appears to be trend or outlier data that suggest a biased effect.

The quality of CPR will be evaluated by computing the compressions/minute and hands-off time for each case where the record is available. These data will be compared across groups to determine if the cooling procedure had a negative impact on CPR quality as well as if CPR quality impacted any of the outcome variables.

Analyses according to ‘Modified Intention to treat’, ‘Intention to treat’, ‘Per protocol’ and ‘As treated’ will be performed for all randomized patients. No imputed values will be used for patients for whom data is not available.

Stratified analyses will be performed for patients whose first recorded rhythm is VF/VT versus those in whom the first recorded rhythm is PEA or asystole. Stratification analyses will be performed for subjects where CPR was initiated within 10 minutes by a first responder. Stratified analyses will also be performed for subjects in the treatment group where cooling was started within 15 minutes.

### 9. STUDY MONITORING

The Steering Committee (see contact information on page 2) has the responsibility to perform periodic and spot checks visits to monitor the progress of the clinical study. Completed Case Report Forms (CRFs) will be reviewed for completeness, compliance with the investigation plan, and appropriate device use and accountability.
10. DATA AND QUALITY MANAGEMENT

Case Report Forms (CRFs) will be provided to each site for each subject enrolled in the study. Required data concerning patient treatment and test results will be recorded on the CRFs at the time of the procedure or as soon as possible thereafter. Information recorded in the CRFs will be corroborated by data in the subject’s medical records. Completed and monitored CRFs will be sent to Karolinska Institutet, Stockholm who will be overseeing data entry and data quality management in accordance with SOPs for clinical data entry, clarification and verification. Data on safety will be provided to the Steering Committee with regular time intervals.

The Steering Committee will review study integrity, safety and risk/benefit issues at periodic intervals throughout the study. The frequency of these reviews will be dependent upon the rate of patient enrollment and relevant safety issues. Independent analyses of serious adverse events will be performed and adjudicated if the frequency or nature of serious adverse events warrants it. A first interim analysis for safety and futility will be performed by an external committee after the first 200 patients have provided endpoint data. If needed, conditional power for meeting the primary endpoint will be computed at that time.

A second interim analysis for safety and futility will be performed by an external committee after the first 500 patients have provided endpoint data. This is an addition to the original protocol. The main reasons for this are that the study period has been extended. The in-hospital treatment regarding hypothermia has to some extent been changed after the publication of an in-hospital hypothermia trial (Nielsen et al, NEJM 2013). This was also suggested by the external interim committee.

Individual Site Investigators shall maintain all study-related correspondence, CRFs, device disposition records, and information on Ethics Committee approvals for a minimum of five years. Individual Site Investigators shall maintain all patient records, plus the investigator’s copy of the CRFs, device disposition records, and signed informed consent forms for a minimum of five years.

11. ADHERENCE TO PROTOCOL

A deviation from the protocol will be allowed without a protocol amendment if generally accepted standards of clinical research and medical practice relating to the safety of research subjects require such deviation from the protocol. In those cases in which the deviation was made emergently to protect the life or physical well-being of a subject. The Karolinska Institutet will be notified within 48 hours of any deviations required due to device-related adverse events. Deviations that represent major, serious, or significant departures from the investigational plan shall be recorded on the CRF along with an explanation for the deviation. The site investigator will analyze and assess the significance of deviations as they occur, and the Steering Committee will assess site-specific deviations. Significant Deviations will be reported to the EC as required.

12. PROTOCOL AMENDMENT

Changes to the protocol that may be made during the clinical study will be made by the Principal Investigator. An amendment will be effective when: a) signed by the Principal Investigator, b) the individual site investigators, and c) the amendment has been approved by the EC, if required by the Institution’s policies.
13. REPORTING

Sites will report all SAEs that occur within 7 days of enrollment directly to The Karolinska Institutet (see contact information on the first page). Individual site investigators are responsible for preparing and submitting complete and timely reports over the course of the study. Types of reports to be submitted include reports pertaining to serious adverse device effects, withdrawal of Ethics Committee approval, and deviations from the investigational plan. These reports are to be submitted to the Chairman of the Steering Committee. Upon study completion, a final report synopsis shall be prepared by the Steering committee. The final report synopsis should be forwarded to all of the participating site investigators and their respective Ethic Committee.

Central Ethics Committee (EC) approval for the protocol and consent materials must be obtained in each country prior to initiating the study in that country. Site Investigators will comply with local reporting requirements to the local EC.

14. PUBLICATION POLICY

At the conclusion of the study, a multi-center abstract reporting the primary results will be prepared and presented at key Cardiology/Resuscitation Symposia. A multi-center publication will also be prepared by the Steering committee for publication in a reputable scientific journal. The steering committee, via the principal investigators Leif Svensson and Per Nordberg, will finally decide the list of authors and how these will be ordered in the final publication. The principal investigators Per Nordberg and Leif Svensson will be the first author and the last author respectively. Fabio Taccone will be the second author and Anatolij Truhlar the third author. In addition the responsible investigators from each site will be co-author in the final publication. From each study site there will be room for two to three collaborating authors that will be mentioned in a separate appendix to the final publication.

Publication of the principal results from any single center experience within the study is not allowed until both the preparation and publication of the multi-center results. Thus, no publication or presentation of the data or results of the study may be presented until The Principal Investigator determines that the database for the study is clean and locked and that the primary and secondary endpoint analyses are consistent with the Protocol
APPENDIX 1: STUDY FLOW DIAGRAMS

Algorithm for Randomization

1. Determine Patient Is Eligible
2. Place Airway
3. Randomize
   - RhinoChill
   - Control
4. Place nasal catheters
   - Begin cooling
5. Continue Standard Resuscitation Protocol
6. ROSC?
7. Take Tympanic Temperature
Algorithm for Post-ROSC Care

Randomization

RhinoChill
- Infuse bolus dose: Sedation, analgesia, neuromuscular blockade
- Attach RhinoChill to vehicle O₂ for continued cooling
  - Transport pt to hospital

Control
  - Transport pt to hospital

Hospital Arrival

Get vitals, ABGs & CXR

Attach pt to hospital O₂ for continued cooling
- Continue sedation, analgesia, neuromuscular blockade

Initiate Systemic Cooling
- Cool to 33°C
- Maintain for 24 hrs
- Rewarm over 8-12 hours

72-Hour Follow-Up
- Take vitals, CXR
- Perform rhinoscopy
- Assess pt disposition
- Determine CPC & mRS scores

Hospital Course
- Date/Time of death
- Date/Time taken off ventilator
- Date/Time of ICU D/C
- Date/Time of weans

Hospital Discharge
- Assess pt disposition
- Determine CPC & mRS scores
## APPENDIX 2: CLINICAL EVENT TABLES

<table>
<thead>
<tr>
<th>Early Cooling Arm</th>
<th>Screening</th>
<th>Reanimation</th>
<th>ROSC</th>
<th>Hospital Admission</th>
<th>ICU</th>
<th>72-Hours</th>
<th>1-Week</th>
<th>Hospital Discharge</th>
<th>3-Month Follow-Up</th>
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APPENDIX 3 Quality of Life assessment – Glasgow Outcome Scale (GOS) and the 15D Instrument

Neurological assessment will be assessed during a telephone interview with the method Glasgow Outcome Scale (GOS) and the 15D instrument at 90-135 days after arrest. For the GOS only two questions need to be asked: (1) Do you require help from another person for everyday activities? and (2) Do you feel that you have made a complete recovery from your heart arrest? The assessment of 15D can be made either by telephone or be sent home to the patient.

The following assessment will be asked about the patient regarding their status (as best as can be recalled) at 90 Days following their cardiac arrest.

<table>
<thead>
<tr>
<th>Glasgow Outcome Scale</th>
<th>CPC</th>
<th>mRS</th>
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</thead>
<tbody>
<tr>
<td>Dead</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Comatose or Vegetative</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Severe disability (conscious but disabled)</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Moderate disability (disabled but independent)</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Good recovery</td>
<td>5</td>
<td>1</td>
</tr>
</tbody>
</table>
QUALITY OF LIFE QUESTIONNAIRE (15D®)

Please read through all the alternative responses to each question before placing a cross (x) against the alternative which best describes your present health status. Continue through all 13 questions in this manner, giving only one answer to each.

QUESTION 1. MOBILITY
1 ( ) I am able to walk normally (without difficulty) indoors, outdoors and on stairs.
2 ( ) I am able to walk without difficulty indoors, but outdoors and/or on stairs I have slight difficulties.
3 ( ) I am able to walk without help indoors (with or without an appliance), but outdoors and/or on stairs only with considerable difficulty or with help from others.
4 ( ) I am able to walk indoors only with help from others.
5 ( ) I am completely bed-ridden and unable to move about.

QUESTION 2. VISION
1 ( ) I see normally, i.e. I can read newspapers and TV text without difficulty (with or without glasses).
2 ( ) I can read papers and/or TV text with slight difficulty (with or without glasses).
3 ( ) I can read papers and/or TV text with considerable difficulty (with or without glasses).
4 ( ) I cannot read papers or TV text either with glasses or without; but I can see enough to walk about without guidance.
5 ( ) I cannot see enough to walk about without a guide, i.e. I am almost or completely blind.

QUESTION 3. HEARING
1 ( ) I can hear normally, i.e. normal speech (with or without a hearing aid).
2 ( ) I can hear normal speech with a little difficulty.
3 ( ) I can hear normal speech with considerable difficulty, in conversation I need voices to be louder than normal.
4 ( ) I hear even loud voices poorly; I am almost deaf.
5 ( ) I am completely deaf.

QUESTION 4. BREATHING
1 ( ) I am able to breathe normally, i.e. with no shortness of breath or other breathing difficulty.
2 ( ) I have shortness of breath during heavy work or sports, or when walking briskly on flat ground or slightly uphill.
3 ( ) I have shortness of breath when walking on flat ground at the same speed as others my age.
4 ( ) I get shortness of breath even after light activity, e.g. washing or dressing myself.
5 ( ) I have breathing difficulties almost all the time, even when resting.

QUESTION 5. SLEEPING
1 ( ) I am able to sleep normally, i.e. I have no problems with sleeping.
2 ( ) I have slight problems with sleeping, e.g. difficulty in falling asleep, or sometimes waking at night.
3 ( ) I have moderate problems with sleeping, e.g. disturbed sleep, or feeling I have not slept enough.
4 ( ) I have great problems with sleeping, e.g. having to use sleeping pills often or routinely, or usually waking at night and/or too early in the morning.
5 ( ) I suffer severe sleeplessness, e.g. sleep is almost impossible even with full use of sleeping pills, or staying awake most of the night.

QUESTION 6. EATING
1 ( ) I am able to eat normally, i.e. with no help from others.
2 ( ) I am able to eat by myself with minor difficulty (e.g. slowly, clumsily, shakily, or with special appliances).
3 ( ) I need some help from another person in eating.
4 ( ) I am unable to eat by myself at all, so I must be fed by another person.
5 ( ) I am unable to eat at all, so I am fed either by tube or intravenously.

QUESTION 7. SPEECH
1 ( ) I am able to speak normally, i.e. clearly, audibly and fluently.
2 ( ) I have slight speech difficulties, e.g. occasional fumbling for words, mumbling, or changes of pitch.
3 ( ) I can make myself understood, but my speech is e.g. disjointed, slurring, stuttering or stammering.
4 ( ) Most people have great difficulty understanding my speech.
5 ( ) I can only make myself understood by gestures.

15D® Harri Sainio

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QUESTION 8. ELIMINATION
1 ( ) My bladder and bowel work normally and without problems.
2 ( ) I have slight problems with my bladder and/or bowel function, e.g. difficulties with urination, or loose or hard bowels.
3 ( ) I have marked problems with my bladder and/or bowel function, e.g. occasional ‘accidents’, or severe constipation or diarrhea.
4 ( ) I have serious problems with my bladder and/or bowel function, e.g. routine ‘accidents’, or need of catheterization or enemas.
5 ( ) I have no control over my bladder and/or bowel function.

QUESTION 9. USUAL ACTIVITIES
1 ( ) I am able to perform my usual activities (e.g., employment, studying, housework, free-time activities) without difficulty.
2 ( ) I am able to perform my usual activities slightly less effectively or with minor difficulty.
3 ( ) I am able to perform my usual activities much less effectively, with considerable difficulty, or not completely.
4 ( ) I can only manage a small proportion of my previously usual activities.
5 ( ) I am unable to manage any of my previously usual activities.

QUESTION 10. MENTAL FUNCTION
1 ( ) I am able to think clearly and logically, and my memory functions well.
2 ( ) I have slight difficulties in thinking clearly and logically, or my memory sometimes fails me.
3 ( ) I have marked difficulties in thinking clearly and logically, or my memory is somewhat impaired.
4 ( ) I have great difficulties in thinking clearly and logically, or my memory is seriously impaired.
5 ( ) I am permanently confused and disoriented in place and time.

QUESTION 11. DISCOMFORT AND SYMPTOMS
1 ( ) I have no physical discomfort or symptoms, e.g. pain, ache, nausea, itching etc.
2 ( ) I have mild physical discomfort or symptoms, e.g. pain, ache, nausea, itching etc.
3 ( ) I have marked physical discomfort or symptoms, e.g. pain, ache, nausea, itching etc.
4 ( ) I have severe physical discomfort or symptoms, e.g. pain, ache, nausea, itching etc.
5 ( ) I have unbearable physical discomfort or symptoms, e.g. pain, ache, nausea, itching etc.

QUESTION 12. DEPRESSION
1 ( ) I do not feel at all sad, melancholic or depressed.
2 ( ) I feel slightly sad, melancholic or depressed.
3 ( ) I feel moderately sad, melancholic or depressed.
4 ( ) I feel very sad, melancholic or depressed.
5 ( ) I feel extremely sad, melancholic or depressed.

QUESTION 13. DISTRESS
1 ( ) I do not feel at all anxious, stressed or nervous.
2 ( ) I feel slightly anxious, stressed or nervous.
3 ( ) I feel moderately anxious, stressed or nervous.
4 ( ) I feel very anxious, stressed or nervous.
5 ( ) I feel extremely anxious, stressed or nervous.

QUESTION 14. VITALITY
1 ( ) I feel healthy and energetic.
2 ( ) I feel slightly weary, tired or feeble.
3 ( ) I feel moderately weary, tired or feeble.
4 ( ) I feel very weary, tired or feeble, almost exhausted.
5 ( ) I feel extremely weary, tired or feeble, totally exhausted.

QUESTION 15. SEXUAL ACTIVITY
1 ( ) My state of health has no adverse effect on my sexual activity.
2 ( ) My state of health has a slight effect on my sexual activity.
3 ( ) My state of health has a considerable effect on my sexual activity.
4 ( ) My state of health makes sexual activity almost impossible.
5 ( ) My state of health makes sexual activity impossible.
The number of participating study sites has been changed during the study period.

In the original protocol (version 20100601) we had two primary outcome measures. Survival with good neurologic outcome at 90 days (Cerebral performance category scale 1-2) and overall survival at 90 days. This was changed in 2011 to only one primary outcome measure, survival with good neurologic outcome.

One additional interim analysis was performed in 2016 after 500 enrolled patients. This was not planned for in the original protocol.

After the interim analysis in 2016 and after having reviewed the TTM trial in NEJM 2013 we decided to use ‘Modified intention to treat’ as the primary analysis. This was based on that we had a number of cases where patients in the treatment group could not receive the intervention due to technical problems.

In association with the interim analysis in 2016, The Steering committee decided to stop enrollment at the site using helicopter emergency medical system due to prolonged response times and enrollment after the intended 15 minutes after the cardiac arrest. This was considered as a safety measure and to ensure adherence to protocol.
Statistical analysis plan

PRINCESS-study

2010-06-01

SAP version: 1.0
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1. Introduction

The purpose of this SAP is to describe the planned statistical analyses and data presentation for the primary follow-up period for the PRINCESS study.

2. Objectives and outcome variables

2.1. Objectives

2.1.1. Primary Objective

- To compare neurological intact survival and overall survival 3 months after inclusion between patients treated with trans-nasal evaporative intra-arrest cooling compared to standard treatment with hypothermia at the intensive care unit (ICU) in patients with out-of-hospital cardiac arrest (OHCA).
- To compare 3-month survival between intervention and control group.

2.1.2. Secondary Objective(s)

- To compare sustained return of spontaneous circulation (ROSC) and admitted alive to hospital.
- To compare cooling efficiency defined as time to <34º C between the groups.

2.2. Outcome variables

2.2.1. Primary outcome variables

- Neurological intact survival at 3 months defined as Cerebral Performance Category (CPC) 1-2 in the ITT population.
- 3-month survival between intervention and control group.

2.2.2. Secondary outcome variables

Pre-defined in the trial protocol

- Sustained ROSC rate
- Proportion admitted alive to hospital.
- Time to target temperature (<34ºC)

3. Study design

3.1. Design

Randomization will be carried out in blocks of four and each site will be given sets of sequentially numbered envelopes with randomization assignments provided in a 1:1 manner to distribute to the participating pre-hospital vehicles.

Each institute will be assigned a certain number of envelopes based on projected enrollment. Individual envelopes will be placed in each RhinoChill pack at the time of site initiation, and replaced as patients
are enrolled. The RhinoChill pack will be carried to every potential subject, and the envelope will be opened once the subject has been qualified as meeting all inclusion and exclusion criteria.

3.2. Population
Witnessed out-of-hospital cardiac arrest in the age-group 18-79.

Inclusion criteria
1. Age $\geq$18 years
2. Collapse was witnessed (heard or seen)
3. Do not have a pulse
4. Are unresponsive to external stimuli

Exclusion criteria
1. Age $\geq$80 years
2. Have an etiology of cardiac arrest due to trauma, head trauma, severe bleeding, drug overdose, cerebrovascular accident, drowning, smoke inhalation, electrocution, hanging
3. Already hypothermic (e.g., avalanche victim; found in the snow)
4. Have an obvious barrier to placing intra nasal catheters (e.g., intranasal obstruction)
5. Do Not Attempt to Resuscitate (DNAR) orders
6. Have a terminal disease
7. Known or clinically apparent pregnancy
8. Have a known coagulopathy (except therapeutically induced)
9. Are known to have a need for supplemental oxygen
10. Achieve ROSC prior to randomization
11. Response time (call to first EMS CPR) $>$ 15 minutes

3.3. Interventions
- Prehospital intra-arrest transnasal cooling
- Standard care (hypothermia at ICU)

3.4. Follow-up
Neurological assessment at 3-month will be made by medical personnel 3 months after the cardiac arrest.

3.5. Blinding
Neither EMS or hospital personnel will be blinded to treatment, since the control patients are easily distinguishable from patients undergoing device placement and nasal cooling. However, medical personnel making the final neurological assessment of the patient prior to discharge will be blinded as to the patient’s group assignment.

4. Definition of Analysis Populations
4.1. **ITT (Intention-to-treat population)**

The primary analysis will be on patients admitted alive to hospital. All randomized patients possible to identify for follow-up will be included.

4.2. **VF (Ventricular fibrillation population)**

All ITT patients with VF/VT as initial rhythm, assessed by the EMS personnel.

4.3. **PP (Per-protocol population)**

All ITT patients, excluding patients with reported treatment not completed. Including no hypothermia treatment at ICU.

4.4. **EMS response time <10 min**

All ITT patients where the EMS arrived at scene within 10 minutes and started CPR. This predefined time is recorded by the EMS personnel in the CRF.

4.5. **Cooling within 15 minutes**

ITT patients where prehospital cooling were started within 15 minutes from OHCA. Time will be calculated from time of cardiac arrest.
5. Description of statistical analysis

5.1. Baseline Characteristics and Treatment Group Comparability
Baseline characteristics will be described between treatment and control group. Categorical data will be described as total number and percentage. Numerical data will be described using median, quartiles, arithmetic mean and standard deviation. Balance between the groups will be assessed using p-values.

5.2. Efficacy analyses

5.2.1. General analytical considerations
All efficacy analyses will compare treatment and control group, and the results will be presented as treatment contrasts with 95% confidence interval and two-sided p-value. No formal adjustment for multiplicity above designating a primary outcome and analysis model will be used.

5.2.2. General considerations for descriptive statistics
Tables will present outcome data by randomized treatment group and in total for the ITT, PP, VF, response time <10 minutes, cooling <15 minutes groups. Categorical data will be presented as the number and percentage of patients in each category.
Tables for events will present the number of patients with event, during the 90-day follow. Events will be presented graphically by randomized treatment as Kaplan-Meier curves up to 90 days, for the ITT, PP, VF, Response time <10 minutes, cooling <15 minutes groups.

5.2.3. Cerebral Performance Category 1-2 (CPC), primary end point
Primary analysis
The proportion with neurological intact survival, defined, as CPC 1-2 at 3 months will be tested using a Pearson X^2-test. A two-sided p-value <0.05 will be regarded as statistically significant. The primary analysis will be performed using intention to treat selection.
Per-protocol population
All analyses will be repeated in the PP population
Subgroup analyses
The primary outcome analysis will be performed on the following subgroups of patients
- VF/VT as primary rhythm.
- Response time less than 10 minutes
- Cooling within 15 minutes

5.2.4. Survival at 90-days
The ITT population will be analyzed with 90-day survival as outcome measure (regardless of CPC score).

5.3. Secondary efficacy analyses

5.3.1. Cooling efficiency
The effect of the cooling device will be analyzed by comparing the time to <34° C. Results will be presented as box plots.

5.3.2. **Sustained return of spontaneous circulation (ROSC)**
The rate of patients with sustained ROSC (>20 minutes) will be compared between the intervention and control group.

5.4. **Handling of Missing Data**
Any loss to follow-up will be handled as censoring. No imputation methods will be used.

6. **Analysis data base definitions**

6.1. **Data sources and terminology**
Data will be collected from using the PRINCESS case report form (CRF). Data will be stored in a database at Karolinska Institutet, Stockholm, Sweden.

6.2. **Analysis populations**

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<thead>
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<th>Name</th>
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<tr>
<td>&lt;10</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Cool &lt; 10</td>
<td></td>
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</tbody>
</table>

7. **Determination of sample size**
Assuming a neurological intact survival rate among admitted patients of 21% in the control group and 37% in the intervention group we estimated that the sample would need to be 150 admitted patients in each study arm to detect a statistically significant difference using 80% power and a 2 sided alpha of 0.05. This would result in approximately 840 patients included in the study, assuming a ROSC rate of 40% and 10% lost to follow-up.
8. Interim Analysis Plan

An interim analysis for safety and futility will be performed after 200 included patients. Early stopping for efficacy reasons will only be considered if major outcome differences are seen between the groups according to the Haybittle rule with a p-value ≤0.001.
Statistical software

Statistical analyses will be performed using SPSS version 18 or later.
Statistical analysis plan

PRINCESS-study

2017-01-15
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1. Introduction

The purpose of this SAP is to describe the planned statistical analyses and data presentation for the primary follow-up period for the PRINCESS study.

2. Objectives and outcome variables

2.1. Objectives

2.1.1. Primary Objective

• To compare neurological intact survival and overall survival 3 months after inclusion between patients treated with trans-nasal evaporative in-arrest cooling compared to standard treatment with hypothermia at the intensive care unit (ICU) in patients with out-of-hospital cardiac arrest (OHCA).

2.1.2. Secondary Objective(s)

• To compare 3-month survival between intervention and control group.
• To compare sustained return of spontaneous circulation (ROSC) and admitted alive to hospital.
• To compare cooling efficiency defined as time to <34° C between the groups.

2.2. Outcome variables

2.2.1. Primary outcome variable

• Neurological intact survival at 3 months defined as Cerebral Performance Category (CPC) 1-2 in the modified ITT population.

2.2.2. Main secondary outcome variables

Pre-defined in the trial protocol

• Survival at 3-months.
• Sustained ROSC rate
• Proportion admitted alive to hospital.
• Time to target temperature (<34°C)

3. Study design

3.1. Design

Randomization will be carried out in blocks of four and each site will be given sets of sequentially numbered envelopes with randomization assignments provided in a 1:1 manner to distribute to the participating pre-hospital vehicles.

Each institute will be assigned a certain number of envelopes based on projected enrollment. Individual envelopes will be placed in each RhinoChill pack at the time of site initiation, and replaced as patients
are enrolled. The RhinoChill pack will be carried to every potential subject, and the envelope will be opened once the subject has been qualified as meeting all inclusion and exclusion criteria.

### 3.2. Population

Witnessed out-of-hospital cardiac arrest in the age-group 18-79.

**Inclusion criteria**

1. Age ≥18 years
2. Collapse was witnessed (heard or seen)
3. Do not have a pulse
4. Are unresponsive to external stimuli

**Exclusion criteria**

1. Age ≥80 years
2. Have an etiology of cardiac arrest due to trauma, head trauma, severe bleeding, drug overdose, cerebrovascular accident, drowning, smoke inhalation, electrocution, hanging
3. Already hypothermic (e.g., avalanche victim; found in the snow)
4. Have an obvious barrier to placing intra nasal catheters (e.g., intranasal obstruction)
5. Do Not Attempt to Resuscitate (DNAR) orders
6. Have a terminal disease
7. Known or clinically apparent pregnancy
8. Have a known coagulopathy (except therapeutically induced)
9. Are known to have a need for supplemental oxygen
10. Achieve ROSC prior to randomization
11. Response time (call to first EMS CPR) > 15 minutes

### 3.3. Interventions

- Prehospital intra-arrest transnasal cooling
- Standard care (hypothermia at ICU)

### 3.4. Follow-up

Neurological assessment at 3-month will be made by medical personnel 3 months after the cardiac arrest.

### 3.5. Blinding

Neither EMS or hospital personnel will be blinded to treatment, since the control patients are easily distinguishable from patients undergoing device placement and nasal cooling. However, medical personnel making the final neurological assessment of the patient prior to discharge will be blinded as to the patient’s group assignment.

### 4. Definition of Analysis Populations
4.1. **mITT (Modified Intention-to-treat population)**
The primary analysis will be on patients admitted alive to hospital. All randomized patients possible to identify for follow-up will be included. Patients that were randomized but later discovered to fulfill exclusion criteria will be excluded. Patients randomized to prehospital cooling but who did not receive treatment will also be excluded in the primary analysis.

4.2. **ITT (Intention-to-treat population)**
The ITT population will be defined as all randomized patients with non-missing values on the primary outcome variable (CPC 1-2).

4.3. **VF (Ventricular fibrillation population)**
All mITT patients with VF/VT as initial rhythm, assessed by the EMS personnel.

4.4. **PP (Per-protocol population)**
All mITT patients, excluding patients with reported treatment not completed. Including no hypothermia treatment at ICU.

4.5. **EMS response time <10 min**
All mITT patients where the EMS arrived at scene within 10 minutes and started CPR. This predefined time is recorded by the EMS personnel in the CRF.

4.6. **Cooling within 15 minutes**
mITT patients where prehospital cooling were started within 15 minutes from OHCA. Time will be calculated from time of cardiac arrest. Data will be matched using propensity score.
5. Description of statistical analysis

5.1. Baseline Characteristics and Treatment Group Comparability
Baseline characteristics will be described between treatment and control group. Categorical data will be described as total number and percentage. Numerical data will be described using median, quartiles, arithmetic mean and standard deviation. Balance between the groups will be assessed using standardized mean differences (SMD).

5.2. Efficacy analyses

5.2.1. General analytical considerations
All efficacy analyses will compare treatment and control group, and the results will be presented as treatment contrasts with 95% confidence interval and two-sided p-value. No formal adjustment for multiplicity above designating a primary outcome and analysis model will be used.

5.2.2. General considerations for descriptive statistics
Tables will present outcome data by randomised treatment group and in total for the mITT, ITT, PP, VF, response time <10 minutes, cooling <15 minutes groups. Categorical data will be presented as the number and percentage of patients in each category. Survival will be presented graphically by randomised treatment as Kaplan-Meier curves up to 90 days, for the mITT, ITT, PP, VF, Response time <10 minutes, cooling <15 minutes groups.

5.2.3. Cerebral Performance Category 1-2 (CPC), primary end point
Primary analysis
The proportion with neurological intact survival, defined, as CPC 1-2 at 3 months will be tested using a Pearson X²-test. A two-sided p-value <0.05 will be regarded as statistically significant. The primary analysis will be performed using modified intention to treat selection.

Per-protocol population
All analyses will be repeated in the PP population

Subgroup analyses
The primary outcome analysis will be performed on the following subgroups of patients
- VF/VT as primary rhythm.
- Response time less than 10 minutes
- Cooling within 15 minutes

5.3. Secondary efficacy analyses

5.3.1. Survival at 90-days
The modified ITT population will be analyzed with 90-day survival as outcome measure (regardless of CPC score).
5.3.2. Cooling efficiency
The effect of the cooling device will be analyzed by comparing the time to <34° C. Results will be presented as box plots.

5.3.3. Sustained return of spontaneous circulation (ROSC)
The rate of patients with sustained ROSC (>20 minutes) will be compared between the intervention and control group.

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Any loss to follow-up will be handled as censoring. No imputation methods will be used.

6. Analysis data base definitions

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7. Determination of sample size
Assuming a neurological intact survival rate among admitted patients of 21% in the control group and 37% in the intervention group we estimated that the sample would need to be 150 admitted patients in
each study arm to detect a statistically significant difference using 80% power and a 2-sided alpha of 0.05. This would result in approximately 700 patients included in the study.
8. Interim Analysis Plan

An interim analysis for safety and futility will be performed after 200 included patients. Early stopping for efficacy reasons will only be considered if major outcome differences are seen between the groups according to the Haybittle rule with a p-value $\leq 0.001$.

Another interim analysis was conducted after 500 included patients. The ROSC rate were higher than expected so the total number of patients included is now estimated to 700.

9. Changes in the Planned Analysis

The primary population to be analyzed for the primary outcome has changed from ITT to modified ITT in the new version of the protocol. Partly due to the TTM-trial publication (nejm, 2013)

The primary outcome is changed to only neurological intact survival. 3-months survival is moved to secondary outcomes.

After the interim analysis the interim board raised concerns about only analyze patients admitted alive to the hospital. After the interim analysis a decision were made to analyze both patients admitted to the hospital and “all” patients fulfilling the modified intention to treat criteria.

The statistical software has changed from SPSS to R.
10. Statistical software

Statistical analyses will be performed using R version 3.0.1 or later.
Statistical analysis plan – Major changes

PRINCESS-study

- The primary outcome is changed to only neurological intact survival. 3-months survival was in 2011 moved to secondary outcomes.

- The primary population to be analyzed for the primary outcome has changed from ITT to modified ITT in the new version of the protocol. Partly due to the TTM-trial publication (NEJM, 2013)

- After the interim analysis the interim board raised concerns about only analyze patients admitted alive to the hospital. After the interim analysis a decision were made to analyze both patients admitted to the hospital (as stated in the original protocol) and “all” patients fulfilling the modified intention to treat criteria.

- The statistical software has changed from SPSS to R.