



**Karolinska
Institutet**

Prehospital Resuscitation Intranasal Cooling Effectiveness Survival Study II (PRINCESS II)

PROTOCOL
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PRINCESS II

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Protocol Synopsis PRINCESS II

- Purpose:** To assess the impact on survival with favorable and complete neurologic outcome in out-of-hospital cardiac arrest (OHCA) patients of early transnasal evaporative cooling initiated at the scene of the arrest.
- Background:** Despite recent findings the important knowledge gap remains whether very early initiation of hypothermia started at the scene of the arrest improve survival with good neurologic outcome in patients with initial shockable rhythms.
- Transnasal evaporative cooling is a non-invasive cooling method through which rapid cooling is achieved via the trans-nasal delivery of an evaporative coolant into the nasopharynx.
- Previous randomized studies (PRINCE and PRINCESS) with a total of 877 OHCA patients have shown the method safe and feasible for prehospital use initiation of intra-arrest cooling and effective to shorten time to target temperature. In both individual studies (and pooled data) there was a strong signal towards improved neurologic outcome in patients with initial shockable rhythms. The study aims to assess outcome when cooling is begun at the scene of the arrest by the EMS followed by systemic cooling at the ICU compared to standard ACLS and normothermia at the ICU.
- Design:** Investigator initiated, prospective, randomized, controlled study conducted by the pre-hospital emergency system with a standardized protocol for post resuscitation care and withdrawal of life support for patients admitted at the ICU.
- Study Population:** OHCA patients (18 to 80 years) with initial shockable rhythms who qualify for advanced cardiac life support.
- Intervention:** Early transnasal evaporative cooling initiated during ACLS at the scene of the arrest within 20 minutes from EMS arrival and subsequent hypothermia at 33°C for 24 hours and fever control for 72 hours at the ICU,
- Control:** Standard ACLS, subsequent fever control (Normothermia) for 72 hours at ICU.
- Performance Endpoints:**
- Primary endpoint:
- Survival with complete neurologic recovery at 90 days defined as modified Rankin scale of 0-1.
- Main secondary endpoint:
- Sustained ROSC and admitted alive
 - Survival at hospital discharge
 - Modified Rankin scale 0-3 at hospital discharge
 - Survival at 90 days
 - Modified Rankin scale 0-3 at 90 days
- Safety Endpoint:**
- Device related adverse event rate within the first 24 hours.
 - Composite serious adverse event rate within the first 7 days.
 - New cardiac arrest prior to hospital admission

TABLE OF CONTENTS

1. INTRODUCTION	7
BACKGROUND & STUDY RATIONALE	7
DEVICE DESCRIPTION	8
NON-CLINICAL STUDIES.....	12
CLINICAL STUDIES.....	14
2. STUDY OBJECTIVES AND OUTCOMES.....	17
PERFORMANCE ENDPOINTS.....	17
SAFETY ENDPOINT	18
3. INVESTIGATIONAL PLAN	18
STUDY DESIGN	18
OVERVIEW.....	18
ETHICAL CONSIDERATIONS	2018
STUDY PROCEDURES.....	20
3.4.1. Patient Screening & Point of Enrollment.....	20
3.4.2. Resuscitation Attempt.....	21
3.4.3. ROSC- definitions and actions.....	20
3.4.4. Hospital Admission.....	20
3.4.5. ICU admission	21
3.4.6. Post resuscitation care protocol	25
3.4.6. Study criteria for likely poor neurologic outcome.....	25
3.4.6. Withdrawal of life supporting therapies	25
3.4.7. Follow-Up and blinding.....	26
3.4.8. Concomitant Therapies.....	27
3.4.9. Patient Withdrawal.....	27
4. PATIENT POPULATION	28
PATIENT INCLUSION CRITERIA.....	28
PATIENT EXCLUSION CRITERIA.....	28
5. STUDY MATERIAL & METHODS	29
STUDY DEVICE	29
STORAGE & LABELING	29
PREPARATION & APPLICATION	29
PRODUCT ACCOUNTABILITY	29
6. EVALUATION OF SAFETY	29
ADVERSE EVENT DEFINITIONS.....	29
ADVERSE EVENT ASSESSMENTS	30

ADVERSE EVENTS REPORTING.....	32
SERIOUS ADVERSE EVENT REPORTING.....	32
7. RISK EVALUATION.....	32
POTENTIAL RISKS TO STUDY SUBJECTS.....	32
7.1.1. Device Use.....	32
7.1.2. Mild Hypothermia.....	334
METHODS TO MINIMIZE RISKS.....	34
POTENTIAL BENEFITS OF THE PROCEDURE.....	35
8. STATISTICAL CONSIDERATIONS.....	35
POWER CALCULATION.....	FEL! BOKMÄRKET ÄR INTE DEFINIERAT.
DATA COLLECTION.....	FEL! BOKMÄRKET ÄR INTE DEFINIERAT.
STATISTICAL ANALYSIS.....	35
9. STUDY MONITORING.....	37
10. DATA AND QUALITY MANAGEMENT.....	37
11. ADHERENCE TO PROTOCOL.....	38
12. PROTOCOL AMENDMENT.....	38
13. DATA AND SAFETY MONITORING COMMITTEE.....	38
14. PUBLICATION POLICY.....	39
15. REFERENCES.....	38

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1. INTRODUCTION

Background & Study Rationale

Severe brain injury is the primary cause of death in resuscitated cardiac arrest patients and the evidence-based strategies currently available to improve neurologic outcome are limited.¹ Therapeutic hypothermia reduces ischemic and reperfusion brain injury in experimental models and may have the potential to limit the brain injuries in patients resuscitated from a cardiac arrest.² Animal and recent clinical data suggest a benefit of early cooling initiated during CPR (i.e. intra-arrest) compared to cooling started at a later stage after return of spontaneous circulation (ROSC) at the intensive care unit (ICU).^{3,4 5}

Pragmatic study designs lead to late or delayed cooling

Despite these experimental findings of the importance of early cooling, the vast majority of all major clinical studies have assessed the effect of ‘delayed’ or ‘late’ therapeutic hypothermia, initiated after hospital arrival often 3-4 hours after the arrest with long time delay until the target temperature level has been reached.^{6,7} The reasons for this delayed approach is not fully understood, but most likely it is due to pragmatic reasons. IN addition, in the clinical practice, more diagnostics and inhospital interventions occur prior to admission to the ICU, such as transport to Xray department for CT scan and coronary angiography lab as well as transfer between hospital to so called cardiac arrest centers. Thus, as there is a very limited number of cooling methods that can be used in the settings above and during transport, these measures will further delay or down prioritize the initiation of cooling. Applying this delayed cooling strategy could imply that these trials may not have adequately addressed the underlying pathophysiology of ischemia and reperfusion. Thus, there is an obvious risk that the optimal time window for the greatest effectiveness of hypothermia will be missed.

In the recently published TTM2 trial target, patients were randomized late, up to 3 hours after ROSC and cooling was started sometimes after an even longer duration.⁷ The target temperature of 33°C in the intervention/hypothermia arm was achieved as late as after 7-8 hours after randomization, thus in some cases more than 10 hours after the arrest. Furthermore, Cooling in TTM2 was not implemented pre-hospital or even early after hospital arrival at the Emergency department. Thus, no trials; TTM2, HACA or Bernard trials have really answer the question whether early cooling (define as intra-arrest or very early <20 minutes post-ROSC) cooling initiated at the scene of the arrest is beneficial

Early hypothermia treatment with transnasal evaporative cooling

To induce early therapeutic hypothermia, especially already during CPR or post-ROSC at the scene of the arrest is challenging in real world clinical practice. Therefore, there is a need for a portable and bedside cooling device to be able to start cooling at the scene of the arrest.

Transnasal evaporative cooling (RhinoChill) is a cooling method that can be used to induce intra-arrest cooling at the scene of the arrest and the method has been tested

safe and feasible to use prehospital in two randomized trial with a total of 877 out-of-hospital cardiac arrest patients (OHCA).^{8,9}

The effect of early cooling seems to be most beneficial in shockable rhythm patients

In the PRINCESS trial, there was a potentially important clinical difference in improved neurologic outcome in the subgroup of patients with initial shockable rhythm (i.e. ventricular fibrillation or ventricular tachycardia) with an 8.9% absolute difference in CPC 1-2 at 90 days (34.8% (48/138) in the intervention group and 25.9% (35/135) in controls (difference 8.9%; 95% CI -2.0 to 19.7%; RR 1.28 [0.90–1.72], p= .11) in favor of intra-arrest cooling. In patients with shockable rhythms, the differences in complete neurologic recovery (CPC 1 at 90 days) were statistically significant (32.6% vs 20%, RR 12.6 [2.3-22.9]).

In a sub-analysis of the Princess trial in relation to time to initiation of intra-arrest cooling, early cooling, started within 20 minutes from the cardiac arrest was associated with improved favorable outcome and complete recovery in the subgroup with shockable rhythms.⁵ Furthermore, a recent pooled analysis of the PRINCE and PRINCESS trials show a significant difference in neurologic outcome at discharge in the group with initial shockable rhythms. In the subgroup with non-shockable rhythms there is no differences between groups.¹⁰

PRINCESS II

In the present PRINCESS II trial, therefore only patients with shockable rhythm will be included. This subgroup, i.e. initial shockable rhythms, witnessed arrest, limited in age, short EMS times, is similar to the patient populations studied in the HACA and Bernard studies.^{6,11} Besides the findings in PRINCE and PRINCESS, the rationale behind this is that a first rhythm of ventricular fibrillation or pulseless ventricular tachycardia is a very strong factor for cardiac etiologies and therefore improved outcome. This strategy, to separate patients with shockable and non-shockable rhythms, is in accordance with the clinical management in regards acute myocardial infarction patients with STEMI and NSTEMI (intervention strategy vs medical).

In summary, despite recent findings the important knowledge gap still remains whether very, early initiation of hypothermia started at the scene of the arrest improve survival with good neurologic outcome in patients with initial shockable rhythms.

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.

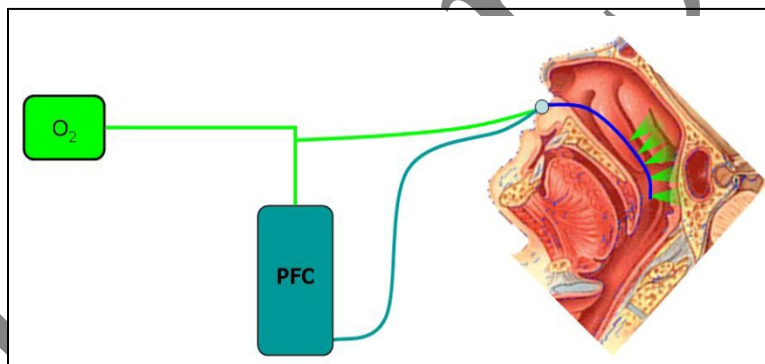
The RhinoChill works by spraying a liquid coolant onto the upper surface of the nasal cavity, where it evaporates and absorbs heat from the tissue, thereby cooling the tissue and the innate vasculature that supplies blood to the brain (refer to schematic). The coolant has a density of 1.68 g/ml and a 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 gas escapes 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.^{12,13} 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

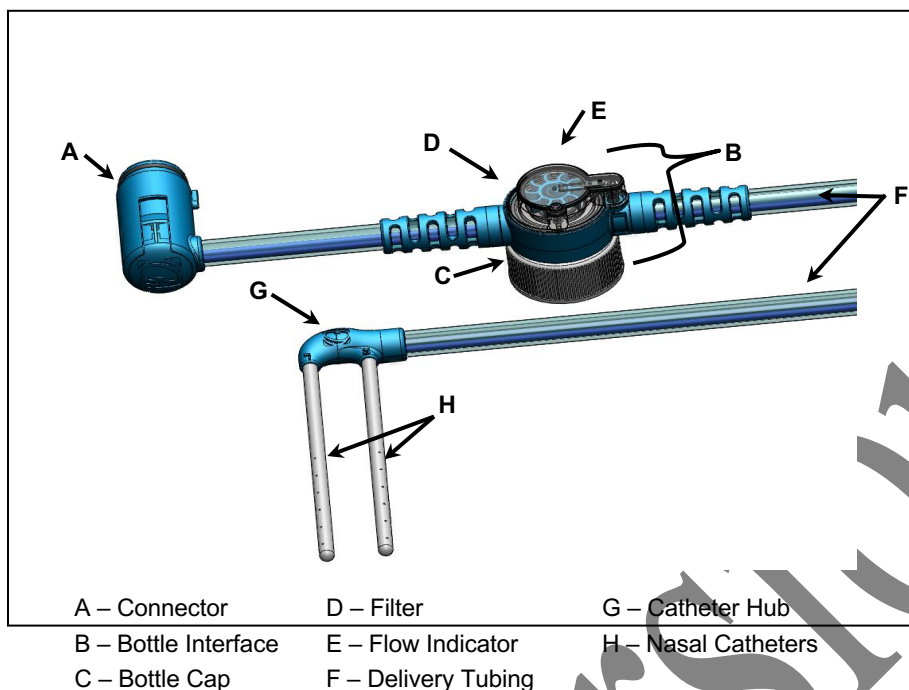


The RhinoChill consists of three components: the tubing set, the control unit, and the coolant bottle. The tubing set is a single-use device that delivers the pressurized gas and coolant mixture to the patient. The proximal end attaches to the control unit to which a hospital gassource is connected. 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.

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RhinoChill Tubing Set



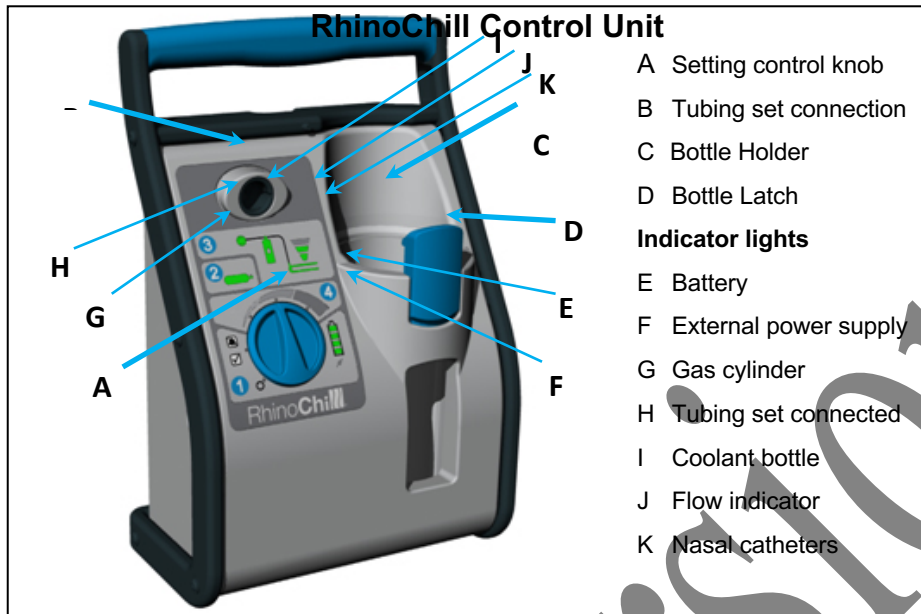
The control unit is a durable component used to both control the flow of the coolant-oxygen mixture as well as to act as an over-pressure shut-off valve. The control unit is composed of a commercially available mechanical oxygen flowmeter that is used to control the flow rate of oxygen as well as electronic 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 ($\approx 10\%$) from entering the device. This limiting pressure is set approximately 10% above the 50 psi $\approx 10\%$ 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 ($\approx 10\%$). 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 terephthalate (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.



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.¹² 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,^{14,15} 2) increase cardiac recovery time,¹⁴ 3) increase survival,¹⁴⁻¹⁶ and 4) increase neurological recovery time.¹⁶ In contrast, chilled intravenous saline administered intra-arrest had no positive effect on resuscitation.¹⁷

Table 1. Animal studies performed with the RhinoChill

Study Name	Model	Qty	Protocol	Results
Feasibility	Ovine 20-25kg	5	Surface blanket vs.	Trans-nasal cooling more effective than surface blanket cooling
		4	Single nozzle jet catheter prototype	Rectal cooling equivalent in both groups, but brain and core cooling rate higher with trans-nasal cooling
Flow Optimization		16	Single nozzle jet catheter prototype – different flow	Higher O ₂ and higher PFC flow produce the greatest cooling PFC flow must be matched to O ₂ flow to produce optimal cooling High flow rates caused minimal nasal bleeding associated with shear damage observed in histomicrographs
Catheter Development		14	Circumferential vs Directed spray catheter designs	Directed spray design provided consistently better cooling No bleeding or other adverse effects seen with dispersed spray
PFH Safety		2	Directed spray catheter, final design Dose with 2.5x PFH:O ₂ x 60min to force uptake	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 (83757 ng/ml); lowest in brain (<9ng/ml)
Cooling Dynamics	Porcine ≈40kg	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 Outcome (WICCM)		25	RhinoChill vs. No Cooling vs. Delayed (2H) blanket cooling O ₂ 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 Cooling during CPR increased the power in the VF frequency spectra – a prognostic indicator of defibrillation success
ROSC Rate (WICCM)		16	RhinoChill vs. No Cooling O ₂ flow = 1L/min/kg 15min VF; CPR/RhinoChill x 5 min; Defibrillation	RhinoChill = 87.5% ROSC vs No Cooling = 25% ROSC CPP @ 1 st shock significantly higher with RhinoChill 1 st shock success significantly higher with RhinoChill

Study Name	Model	Qty	Protocol	Results
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 @ 1 st 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 1 st shock in saline group Jv temperature significantly lower at 1 st shock in RhinoChill group CPP significantly higher at 1 st shock in RhinoChill group ROSC = 100% RhinoChill vs. 29% cold IV saline Mean survival = 27 vs. 67H for saline vs. trans-nasal cooling

Clinical Studies

1.1.1. Cooling after Resuscitation from Cardiac Arrest

The RhinoChill has been used in the emergency departments or intensive care units in 84 cardiac arrest patients following ROSC, in a completed feasibility study in Europe.¹⁸ 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.

1.1.2. Cooling during CPR in OHCA (PRINCE and PRINCESS)

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.⁸ 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.

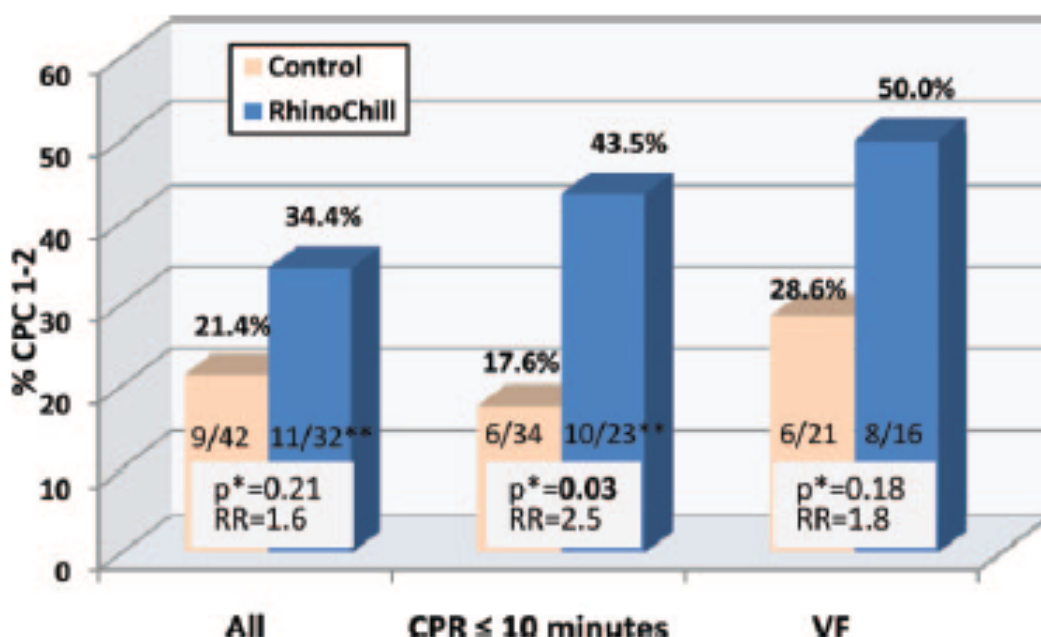
There were no significant differences in the proportion of patients achieving return of spontaneous circulation (ROSC) ($p=0.8$). Among patients admitted alive to the hospital there was a signal towards increased survival in treated patients (43.8 % vs 31.0%, $p=0.26$, Relative Risk (RR) 1.4). In patients 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 and was admitted alive 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.

The PRINCESS trial published in JAMA in May, 2019 had very similar study criteria.⁹ The main differences were an upper age limit of <80 years and that the EMS response time was to be <15 minutes.

The safety and feasibility data were similar to the PRINCE study. The time to initiation of intra-arrest cooling could be shortened to 19 minutes from the cardiac arrest.

The time to target temperature was significantly shortened in the intervention group (105 vs 182 minutes, $p < 0.001$).

The number of patients with CPC 1-2 at 90 days (the primary outcome) was 56 of 337 (16.6%) in the intervention cooling group vs 45 of 334 (13.5%) in the control group (difference, 3.1% [95%CI, -2.3% to 8.5%]; relative risk [RR], 1.23 [95%CI, 0.86-1.72]; $P = .25$).

In the intervention group, 60 of 337 patients (17.8%) were alive at 90 days vs 52 of 334 (15.6%) in the control group (difference, 2.2% [95%CI, -3.4% to 7.9%]; RR, 1.14 [95%CI, 0.81-1.57]; $P = .44$). Minor nosebleed was the most common device-related adverse event, reported in 45 of 337 patients (13%) in the intervention group. The adverse event rate within 7 days was similar between groups.

In the subgroup analysis we could see an 8.9% (34.8 vs 25.9, $p = 0.11$) absolute difference in favor of the intervention group. In the post hoc analysis in regard to complete recovery (CPC 1) at 90 days the difference among patients with initial shockable rhythm was 32.6% vs 20%, $p = 0.02$. These differences in neurologic outcome among patients with shockable rhythms have been strengthened in a pooled analysis of PRINCE and PRINCESS data.¹⁰

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2. STUDY OBJECTIVE AND OUTCOMES

To study the effect on 90 days survival with complete neurologic outcome (mRs 0-1) and good recovery (mRs 0-3) of a strategy with early cooling initiated at the scene of the arrest by the EMS within 20 minutes from the EMS arrival followed by systemic cooling at the ICU compared to a strategy with standard ACLS followed by normothermia applied at the ICU in out of hospital cardiac arrest (OHCA) with initial shockable rhythms. In addition to mRs, CPC-scores will be presented to evaluate neurologic outcomes.

Our study hypothesis is that early initiation of transnasal evaporative cooling initiated intra-arrest or early post-ROSC in OHCA patients with initial shockable rhythms followed by systemic hypothermia to 33°C for 24 hours at that target temperature level at the ICU increase survival with complete (mRs 0-1) and good neurologic outcome (mRs 0-3) at 90 days compared to normothermia at the ICU.

Performance Endpoints

Primary outcome:

- Survival with complete neurologic recovery at 90 days defined as modified Rankin scale (mRs) of 0-1.

Main secondary outcomes:

- Sustained ROSC and admitted alive to hospital
- Survival at hospital discharge
- Modified Rankin scale 0-3 at hospital discharge
- Survival at 90 days
- Modified Rankin scale 0-3 at 90 days

Tertiary outcomes

- Distribution of MRs at 90 days
- Hospital free days alive at 90 days.
- 1-year survival
- Modified Rankin scale 0-1 at 1 year.
- Distribution of CPC scores at 90 days
- Health related outcomes (to be defined)
- Quality of life EQ5D at 90 days

Safety Endpoints

The main safety endpoints are:

1. Adverse events, including device related, occurring within 24 hours of enrolment.
2. The composite serious adverse event (SAE) rate from the time of patient randomization through the first seven days of hospitalization (see specified in section below).
3. New cardiac arrest prior to hospital admission

3. INVESTIGATIONAL PLAN

Study Design

This will be an investigator-initiated, prospective, randomized controlled study conducted by the emergency responders in multiple emergency medical systems. It is expected to last approximately 3 years.

Up to 924 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 complete neurologic recovery in patients that are cooled early during resuscitation compared to normothermia.

Overview

Medical personnel (e.g., nurses or physicians) responding to a cardiac arrest will assess each patient for study inclusion. At the scene of the OHCA, patients with initial shockable rhythm will be randomized to receive standard ACLS according to ERC guidelines with or without transnasal evaporative cooling. Thus, also patients with initial shockable rhythms that has achieved ROSC will be eligible with a time window to inclusion of 20 minutes from EMS arrival at the scene. In general, 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. 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 included in the intention to treat analysis, but will also be analyzed separately from those that remain comatose. Cooling will be halted in the early-cooling group for those that wake up.

Transnasal 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. Transnasal 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 post-

resuscitation care 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 enrolment. Subjects that survive will undergo a neurological assessment at the time of hospital discharge and at 90 days after the cardiac arrest. This assessment will be blinded to the patient treatment group. Acute data concerning the cardiac arrest itself will be gathered Utstein Style [19]. 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 at each site, 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 emergency call from the scene of the arrest to the dispatch centre to start of CPR will be used to get more exact event times.

Ethical considerations

The cooling device (RhinoChill) 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 complete neurologic recovery in a previous study. If cooling is begun at a very early stage (i.e. within 20 minutes from the arrest) this seems to be beneficial for neurologic recovery. In total, 877 OHCA has been studied in randomized trials with RhinoChill without any major safety concerns. It is therefore expected that the potential benefit of using the RhinoChill in this population outweighs the risks.

The study patients's next of kin will be informed of the subject's study participation as soon as practical after enrollment. If the subject regains normal neurological function, they too will be informed of their study participation and be asked to provide their written consent to use their data and to be included into further follow up.

Study Procedures

Screening and randomization

OHCA patients will be screened for study eligibility upon arrival of the first EMS team after the first rhythm analysis. If the patient is found to be eligible for the study, the patient will be randomized to receive transnasal evaporative cooling started at the scene of the arrest along with standard ACLS or standard ACLS alone.

Trial sites will have access to an internet-based randomization application to allow for immediate allocation and to ensure adequate allocation concealment and adequate generation of allocation sequence. Each patient will be assigned a unique trial and randomization number. Randomization will be performed with permuted blocks of concealed size, stratified for trial site.

A screening log will be compiled and include all out-of-hospital cardiac arrest-patients, whether they are eligible for inclusion, or not.

Resuscitation Attempt

The resuscitation attempt in both study groups should follow ERC guidelines. In the patients randomized to early cooling the RhinoChill catheters should be placed and cooling initiated as soon as possible after airway management (i.e. laryngeal mask or intubation). To place the nasal catheters and start cooling takes approximately 1 minute. Cooling should be performed with the oxygen flow set to 40L/min.

Patients randomized to the control arm will receive ACLS according to the ERC guidelines.

After ROSC - definition and actions

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 before transported to the hospital.

Subjects randomized to early cooling will, only if needed, be given intravenously administered bolus doses of sedation for transport to the hospital. Doses of sedation 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.

At hospital Admission

Upon hospital arrival it is very important that the transnasal evaporative cooling is continued to be able to reach target temperature as fast as possible and avoid rewarming before systemic cooling is initiated at the ICU.

A systemic temperature probe will be placed (e.g., esophageal or bladder) and core temperature will be recorded. ECG, vital signs, level of consciousness and other standard diagnostic measures including serum glucose and arterial blood gases will be recorded.

Clinical decisions regarding diagnostics measures, such as coronary angiography or CT scan, prior to ICU admission will be according to local protocols.

If diagnostic measures are performed prior to ICU admission, transnasal evaporative cooling should be continued during intra hospital transports and at the cathlab, X-ray department etc.

At ICU admission

At admission to the ICU the start of systemic cooling in the intervention group should be prioritized and started as soon as possible. After systemic cooling is initiated transnasal cooling could be ended. At admission data in regard to Sequential Organ Failure Assessment score will be collected at time of admission. See attachment of SOFA score and ICU CRF for definitions and specific variables. The data collected at the ICU will consist of a daily ICU CRF for the first 72 hours including SOFA scores, cardiac biomarkers, lactate clearance, adverse events, and a summary of ICU measures and findings of other diagnostic and therapeutic interventions during the ICU stay.

Post Resuscitation Care protocol

All subjects will undergo standard post resuscitation treatment upon hospital arrival according to the ERC guidelines 2021. Selected key variables in the CRF will be monitored from each site to ensure adherence to guidelines.

The specific difference between the study groups is that subjects in the intervention group will receive:

- (1) transnasal evaporative cooling initiated at the scene of the arrest and;
- (2) systemic hypothermia treatment at ICU with the core body target temperature of 33°C with a duration of that target temperature level for at least 24 hours. Thereafter, the patients in the intervention group will be rewarmed at a rate of 0,25°C/hour until they reach normothermia of 36.5°C.

Fever, defined core body temperature >37.7°C should be avoided for the first 72 hours from the cardiac arrest in both study groups. In first-hand use antipyretics according to local treatment guidelines, but use cooling devices if needed.

Cooling protocol at ICU for the intervention group

Treatment with systemic cooling device should be initiated as soon as possible after admission to ICU and should not be delayed by other measures.

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.

Temperature recordings (core and tympanic) should be registered every 20 minutes until the patient has reached core body temperature of 33°C (target).

In the maintenance phase, the patients should be treated at 33°C for at least 24 hours. During that period, core body temperature should be registered once per hour.

The rewarming rate should be 0,25 per hour until the patient has reached core body temperature of 36,5°C.

Fever control (avoid and treat core body temperatures >37,7 with antipyretics or cooling device) should be done for 72 hours.

Shivering should be assessed using the The Bedside Shivering Assessment Scale (BSAS) and treated with buspirone, magnesium, clonidine, meperidine or increased sedation or, if needed, neuromuscular blocking agents.

Specific mandatory measures in the study protocol of post resuscitation management for both study groups

Sedation

Sedation will be mandatory for 40 hours after randomization in both study groups. Sedation strategies will follow international guidelines with short acting drugs and opioids. Avoid using a neuromuscular blocking drug routinely in patients undergoing TTM, but it may be used in case of severe shivering.

The drugs used will be recorded for each patient and we will perform stratified analyses according to different sedation strategies (e.g. propofol vs no propofol).

The sedative should be titrated to achieve deep sedation, a Richmond Agitation-Sedation Scale (RASS) of minus 4 should be targeted (No response to voice, but any movement to physical stimulation).

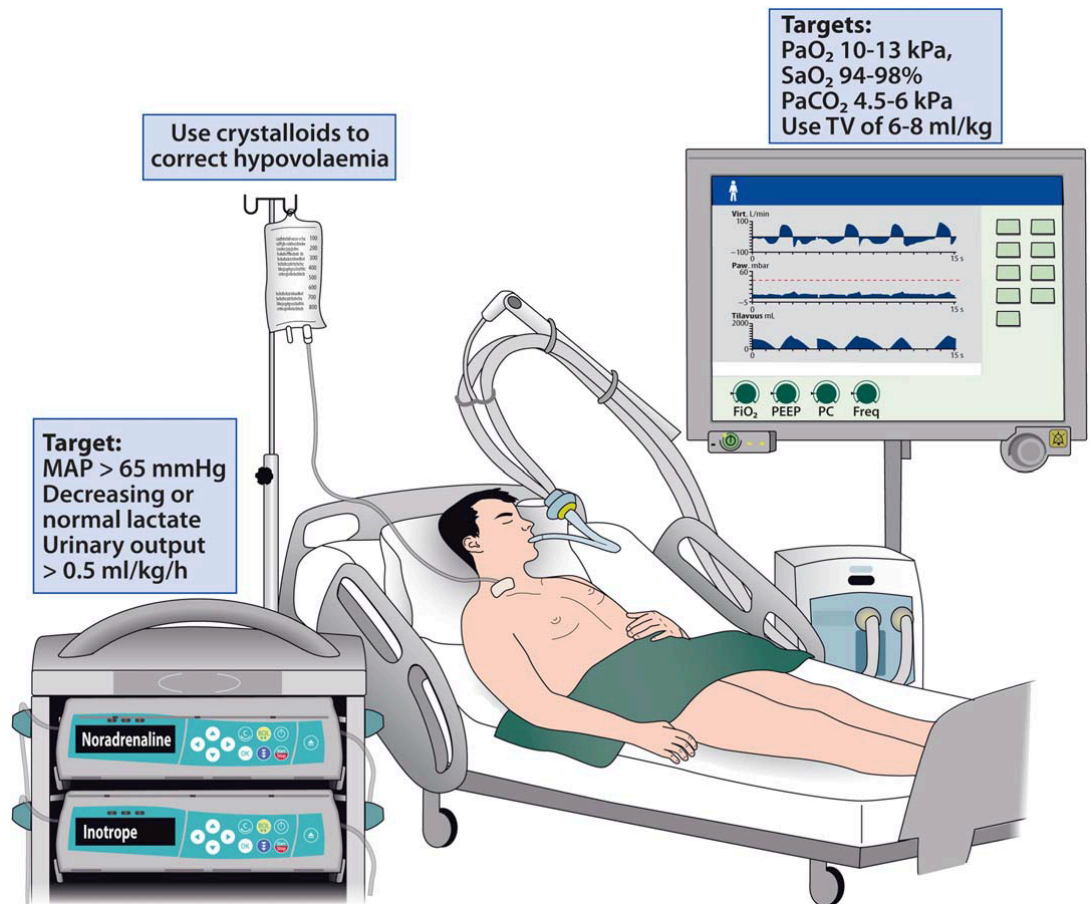
This approach with a minimal time for sedation is to facilitate a true comparison of two study groups.

Haemodynamic and respiration

Regarding coronary reperfusion, emergent cardiac catheterisation laboratory evaluation (and immediate PCI if required) should be performed in adult patients with ST-elevation on the ECG. In patients without ST-elevation on the ECG, emergent cardiac catheterization laboratory evaluation may be considered if there is an estimated high probability of acute coronary occlusion.

In study sites with the capacity, cardiac function will be followed. If feasible, echocardiographic examinations should be performed and recorded at 24 hours and after 72 hours to measure left ventricular ejection fraction (LVEF). Biomarkers such as Troponin and NTproBNP will also be registered at specific time points (see section on data collection).

Targets for circulation and respiration follow the ERC guidelines. Please see summary from Figure below (adapted from guidelines document).



Control of seizures

Electroencephalography (EEG) is recommended to be used to diagnose electrographic seizures in patients with clinical convulsions and to monitor treatment effects. To treat seizures after cardiac arrest, we suggest levetiracetam or sodium valproate as first-line antiepileptic drugs according to local treatment guidelines in addition to sedative drugs.

Prognostication and withdrawal of care

Prognostication will be performed on all participants still in the ICU after ≥ 72 hours after ICU admission. The prognostication will be based on the ERC and European Society for Intensive Care Medicine recommendations. The prognostication may be delayed due to practical reasons (such as weekend or national holiday). The physician performing the prognostication will be a neurologist, intensivist or other specialist experienced and will be blinded for group allocation, but not for relevant clinical data. Prognostication and the potential decision to withdraw active intensive care are closely related but will be considered separate entities.

The result of the prognostication will be categorised as “YES” or “NO”, based on the answer to the question “Does this patient fulfil the criteria for a likely poor neurological outcome?”. This assessment will be recorded in the case report form and will be communicated to the treating clinician.

Any decision to withdraw active life support will be made by the treating physicians, together with the patient's relatives or legal surrogates, as required by local legislation. The blinded external physician will not make any recommendation on WLST. Prognostication may need to be delayed to ensure that any lingering effects of sedative agents will not affect the assessment.

Prognostication at ≥ 72 hours will be based on two mandatory (clinical examination and EEG), and four optional (NSE, Brain CT, Brain MRI, SSEP) modalities:

Clinical examination including assessment of brainstem reflexes and response to pain and other stimuli will be performed.

Absent or extensor motor response to pain at 72h or later in a patient who is considered unaffected by sedative agents, is a prerequisite to consider the neurologic prognosis poor.

The bilateral absence of pupillary and corneal reflexes at 72h after CA or later, is a finding indicative of a poor prognosis.

The clinical examination by the ICU-staff should also include an assessment of status myoclonus (continuous and generalised myoclonus persisting for at least 30 min). A prospectively documented early status myoclonus (within 48 hours) is indicative of a poor prognosis.

An EEG performed between 36h and 72h after randomization will be performed on all participants who survive, and remain unconscious to this point, in line with standard clinical practice. If it is not possible to perform an EEG study in the specified time frame due to practical reasons (such as weekend or national holiday), the EEG should be performed as soon as possible after 72h. An EEG with a highly malignant pattern, and without reactivity to sound and pain is indicative of a poor prognosis.

If a brain-CT shows signs of global ischaemic injury, such as: generalised oedema with reduced grey/white matter differentiation and sulcal effacement, this is indicative of a poor prognosis. A CT should be considered in patients who remain unconscious to exclude other pathologies such as intracranial haemorrhage or infarction.

A brain MRI at 3-5 days may be incorporated into prognostication if it has been performed. Signs of global, diffuse, or bilateral multifocal ischaemic lesions is indicative of a poor prognosis.

High levels of Neuron-specific enolase (NSE) are indicative of a poor prognosis. If serial samples are available, and these are consistently higher than locally established levels associated with a poor outcome, this may be seen as indicative of a poor outcome.

Absent SSEP N20-responses bilaterally may be seen as indicative of a poor prognosis, if SSEP is performed more than 48h after randomisation.

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).

Study criteria for a likely poor neurologic outcome

The following criteria, evaluated at the earliest at 72 hours after randomisation or later, need to be fulfilled to establish a likely poor neurological outcome.

- Unconscious patient with absent or extensor motor response to pain (no confounders e.g. sedation)

AND at least two of the following:

- Bilaterally absent pupillary and corneal reflexes
- Bilaterally absent SSEP N20-responses
- Diffuse anoxic brain injury on CT or MRI
- Documented status myoclonus within 48h of randomisation
- High levels of serum NSE (>60ug/L at 48 h and/or 72 h)
- An EEG with a highly malignant pattern and without any observed reactivity to sound or pain. Patterns that are considered highly malignant are:
 1. Suppressed background (amplitude <10mV, 100% of the recording) without discharges.
 2. Suppressed background with superimposed continuous periodic discharges.
 3. Burst-suppression (periods of suppression with amplitude <10mV constituting 50% of the recording) without discharges.
 4. Burst-suppression with superimposed discharges.

Withdrawal of life supporting therapies (WLST)

All participants in the trial will be actively treated until at least 72 hours after randomization. There will be two exemptions from this rule.

- Participants in whom further treatment is considered unethical due to irreversible organ failure, a documented medical comorbidity, or other reasons. The reason for WLST must be documented comprehensively in the CRF.
- Participants in whom brain death is established, however this will be defined as death and not WLST

The assumption of a poor neurological prognosis alone by one treating physician will not be considered sufficient to employ withdrawal of active intensive care prior to 72 hours after randomisation. After prognostication has been performed, WLST due to a presumed poor prognosis will be allowed if trial criteria for a likely poor neurological outcome are fulfilled and all effects of sedation on consciousness are ruled out. Participants who have an unclear prognosis at 72h after randomisation should be reexamined daily and WLST may be considered if neurological function does not improve and, metabolic and pharmacological reasons for prolonged coma are ruled out. If a decision of WLST is made, the time point and the main reasons for withdrawing life-supporting therapies will be recorded. However, supporting therapy may also be continued regardless of the neurological assessment of prognosis, at the discretion of the treating physician.

Follow-Up and 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 and subsequently systemic cooling at the ICU. However, study personnel making the final neurological assessment of the patient prior to discharge and at the earliest 90 days (as close as possible to 90 days but not before 90 days) follow up will be blinded as to the patient's group assignment. In addition assessment at 72 hours in regard to fulfilling criteria for withdrawal of care will be performed by a blinded assessor.

Overall survival will be reported at 30 days, 90 days and after 1 year. mRS will be assessed at hospital discharge and at 90 days and after 1 year. Long term outcomes (1-year survival and mRS at 1 year) will be presented in a separate analysis.

The formal follow-up with blinded outcome assessor will take place at 90 days after cardiac arrest. Participants will be assessed according to the mRS-scale and will be invited to a clinic visit, if possible with a relative or close friend. At these visits the specially trained, blinded assessors will perform structured interviews and administer tests according to the secondary and exploratory outcomes. The assessment will focus on cognitive function, quality-of-life, return to work, participation in society. The outcome-assessor may be an occupational therapist, physician, research nurse, psychologist or similar. Outcome-assessors will be provided with a written trial manual with detailed guidelines for performing the questionnaires and assessments.

If needed, training sessions will be provided by the trial coordinating team.

Modified Rankin Score

0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities

2	Slight disability: unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability: requiring some help, but able to walk without assistance
4	Moderately severe disability: unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

Concomitant Therapies

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

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 closest relative or 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 written consent for the use of their study data and further follow up.

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 enrol 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 with OHCA with initial shockable rhythms will be recruited by EMS personnel at the scene of the cardiac arrest. Thus, patients will be eligible for enrolment as soon as the first rhythm has been assessed. 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 post-randomization from analysis will be made by the Principal Investigator if they do not meet the study criteria and have not received the trial intervention.

Patient Inclusion Criteria

Adult patients (age >18 years) are eligible if they meet all of the following criteria:

1. Adult out-of-hospital cardiac arrest patients with initial shockable rhythm (i.e. ventricular fibrillation or pulseless ventricular tachycardia or ‘shock advised’ by an automated external defibrillator)
2. Unconsciousness defined as Glasgow Coma Scale \leq 8
3. Inclusion within 20 minutes from EMS arrival

Patient Exclusion Criteria

Patients are not eligible if they meet one or more of the following criteria:

1. Age \geq 80 years
2. Obvious non-cardiac causes to cardiac arrest (trauma, head trauma, severe bleeding, drug overdose, cerebrovascular accident, drowning, smoke inhalation, electrocution, hanging, choking due to foreign body airway obstruction, burns or exsanguination).
3. Obvious already hypothermic (e.g. found in the snow)
4. Obvious barrier to placing intra nasal catheters (e.g., intranasal obstruction)
5. Have a known Do Not Attempt to Resuscitate (DNAR) order or other limitations in care.
6. Have a known terminal disease
7. Known or clinically apparent pregnancy

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

Study Device

The investigational sites will use the RhinoChill control units and tubing sets and bottles of liquid coolant at the standard cooling rate of 40l per minute of oxygen/air flow. It is expected that at least one tubing set and 1bottles 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 systemic 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.

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.

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.

Product Accountability

Product is CE-marked and labeled by lot and serial number where appropriate.

6. EVALUATION OF SAFETY

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

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.

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.

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. barotrauma) will be recorded on in a special section of the CRF from ROSC through the first 24 hours from inclusion. Abnormal laboratory values are expected in these patients, and these are not to be recorded as AEs. The date of occurrence, severity, duration, management, technical issues and relationship to cooling with the RhinoChill Device will be recorded.

Serious Adverse Event Reporting

All SAEs that occur within seven days after enrolment must be followed until resolution; this includes those patients that were terminated early or withdrew. These must be reported to the study sponsor at The Karolinska Institutet (see contact information with email and phone to the principal investigator and study coordinator on the first page of the protocol) and at the same time to the company BrainCool AB as soon as possible, preferably within 24 hours of their occurrence as well as following their resolution. SAEs will be reported in a separate CRF.

SAEs in both groups (thus not specifically device related) that should be reported are:

- New cardiac arrest after enrollment.
- Arrhythmias resulting hemodynamic compromise
- Bradycardia necessitating pacing
- Cerebrovascular lesion during ICU stay (bleeding or infarction)
- Sepsis and septic shock, according to the 3rd international consensus definitions for sepsis and septic shock
- Moderate or severe bleeding, according to the GUSTO criteria
- Device related skin complications (blistering or skin necrosis)
- Other, unexpected serious adverse events

The Principal Investigator, Per Nordberg and senior adviser professor Leif Svensson at the Department of Clinical Science and education, Karolinska Institutet, will review all SAE reports as soon as possible with regard to their causal relationship to use of the cooling method.

Reporting to the regulatory authorities will be performed per European vigilance requirements and other local requirements. This is a responsibility of the PI.

7. RISK EVALUATION

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. This occurred in about 7 % of the patients in the PRINCESS trial.

Mucosal irritation/dryness caused by high oxygen flows during cooling that would resolve with over the counter medications or on its own. Has not been reported in surviving patients from the PRINCE and PRINCESS trials.

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. This occurred in about 13% of the patients in the PRINCESS trial.

Para-sinus emphysema: gas entrapment in the sinus region that will resolve on its own; associated with chronic sinusitis. Has been reported in 2 patients.

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; Has not been reported in surviving patients from the PRINCE and PRINCESS trials.

Frostbite/necrosis to the nasal tissues caused by excessive local cooling that might require intervention; Has not been reported in surviving patients from the PRINCE and PRINCESS trials.

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: Has not been reported in surviving patients from the PRINCE and PRINCESS trials

Hypoxia: depletion of oxygen supply due to saturation with PFH requiring prolonged mechanical ventilation with 100% oxygen; Has not been observed in the ICU data.

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. Major nosebleed was reported in 4 patients in the PRINCESS Trial where cooling had to be interrupted.

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; Has not been reported in surviving patients from the PRINCESS trial

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; One case of pneumocephalus was reported in the PRINCESS trial, which resolved without intervention and the patient survived with good neurologic function.

Air embolus: air circulating in the blood that results in clinical sequelae that are life threatening and may be amenable to surgical intervention; Has not been reported in patients from the PRINCE and PRINCESS trials

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; Has not been reported in patients from the PRINCE and PRINCESS trials

Burns: due to oxygen-enhanced fire/explosion that could be life threatening, requiring prolonged hospital stay and potential surgical intervention; Has not been reported.

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. Has not been reported in patients from the PRINCE and PRINCESS trials

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.

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.

Potential Benefits of the Procedure

The brain protective effect of hypothermia is most likely depending on the timing and effect of the cooling initiation. The RhinoChill has been demonstrated as feasible and effective to shorten time to target temperature in OHCA patients in two randomized trials including a total of 877 patients. Outcome data from these trials suggest a benefit in survival with good and complete neurologic outcome in patients with initial shockable rhythms. In secondary analysis, a time to initiation of cooling within 20 minutes from the cardiac arrest was beneficial.

8. STATISTICAL CONSIDERATIONS

Power calculation

This study is powered to detect clinically significant changes in survival with complete neurologic recovery (mRS 0-1) at 90 days after cardiac arrest.

Sample size calculation was based on the preceding clinical trials (i.e. PRINCESS and other recent trials in OHCA such as TTM2). In PRINCESS, the survival rate with CPC 1-2 at 90 days in VF-patients was 34.8% vs 25.9% and in CPC 1 at 90 days 32.6% vs 20%.

Among patients with VF that was admitted alive, the survival with CPC 1-2 at 90 days was 57.8% vs 44.9% and in CPC 1 at 90 days 54.2% vs 33.6%.

As the study population in PRINCESS 2 will be a combination of patients that are included intra-arrest and early post ROSC the base line survival with CPC 1 that corresponds to mRS 0-1 is assumed to be 45%. To show an absolute difference of 9% (from 45 to 54%) a sample size of 485 patients in each study group is required for 80% power (2-sided $\alpha = .05$). This number would require a total sample of 970 patients to be randomized before hospital admission.

Data Collection

Data collection will be reported in the different stages of the study;

Prehospital;

Emergency department;

ICU;

Discharge;

Follow up at 30 + 90 days + 1 year.

Data will 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. For details see study CRFs for each of these phases.

1. Resuscitation parameters will be calculated for all randomized patients.
2. Early post-resuscitation cardiac performance parameters, such as ECG, cardiac biomarkers, arterial blood gas and neurologic assessment, along with core and tympanic temperatures will be calculated for those patients that survive to hospital admission.
3. At ICU a short daily CRF will be used for the first three days to collect data on organ dysfunction (SOFA score and biomarkers) and cooling intervals. Thereafter a summary of ICU measures (diagnostics, treatments etc) will be collected at discharge from the ICU.
4. Main outcome parameters will be:

Primary outcome:

- Survival with complete neurologic recovery at 90 days defined as modified Rankin scale (mRs) of 0-1.

Main secondary outcomes:

- Sustained ROSC and admitted alive
- Survival at hospital discharge
- Modified Rankin scale 0-3 at hospital discharge
- Survival at 90 days
- Modified Rankin scale 0-3 at 90 days

Tertiary outcomes

- 1-year survival
- Modified Rankin scale 0-1 at 1 year.
- Distribution of CPC scores at 90 days
- Health related outcomes (to be defined)
- Quality of life EQ5D at 90 days
- Distribution of MRs at 90 days
- Hospital free days alive at 90 days.

Statistical Analysis

A separate statistical analysis plan is attached to this protocol. In 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.

Outcome analyses will be performed as Intention to treat. The exception will be patients, in both groups, where post randomization data on the patients appear that will restrict or imply limitations in the care, such as existing DNR or severe comorbidities that upon admission to hospital will lead to restrictions in care and interrupt the study intervention. Secondary analyses will also be performed according to 'Modified Intention to treat', 'Per protocol' and 'As treated' 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 where cooling is started intra-arrest versus post-ROSC and if cooling was started within 20 minutes from the cardiac arrest.

9. STUDY MONITORING

The trial will be monitored by national monitoring offices coordinated by the study sponsor, Karolinska Institute, Stockholm, Sweden, Forum South. The frequency of on-site monitoring will depend on compliance with the protocol, number of enrolled participants and data handling. At a minimum, there will be a pre-trial meeting, mandatory monitoring after the trial and once during the trial period. Source data verification will be performed according to a monitoring plan of patient consent and key study variables which will be available only to the trial monitors before the start of the trial.

All trial sites will be provided with sufficient information to participate in the trial. This document, CRFs, instructions for registration, checklists for inclusion/exclusion and randomization, and a protocol for medical treatment will be distributed to all sites. The site investigator will be responsible for that all relevant data are entered into the electronic CRFs. The CRFs will be constructed in order to assure data quality with predefined values and ranges on all data entries.

10. DATA AND QUALITY MANAGEMENT

A digital Case Report Forms (CRFs) will be used a login will 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. 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 enrolment 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.

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.

We strongly recommend using an internal study group to ensure high quality data collection. Previous studies have successfully used an interdisciplinary internal study group that periodically reviews data masked to treatment outcome to improve study performance. They assess whether prespecified targets for performance are met for measures such as enrollment and eligibility rates, provider adherence rate, retention rate, currentness of data capture as well as key elements of concurrent care. They make recommendations about steps to be implemented to improve these rates. The group may have semi-independent membership that includes individuals who do not have leadership responsibility for the trial (e.g. site EMS provider, site study coordinator). Its main findings will be summarized in the report to an independent data safety monitoring board (DSMB) and the study EC. Both committees will assess the appropriateness of trial continuation in an EMS agency if there are serious uncorrected deficiencies in trial conduct.

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 and the Steering committee. 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. DATA AND SAFETY MONITORING COMMITTEE

An interim analysis for safety and futility will be performed by an external Data and Safety Monitoring Committee (DSMC) after the first 400 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 . The DSMC will be able to request additional data if they find it necessary.

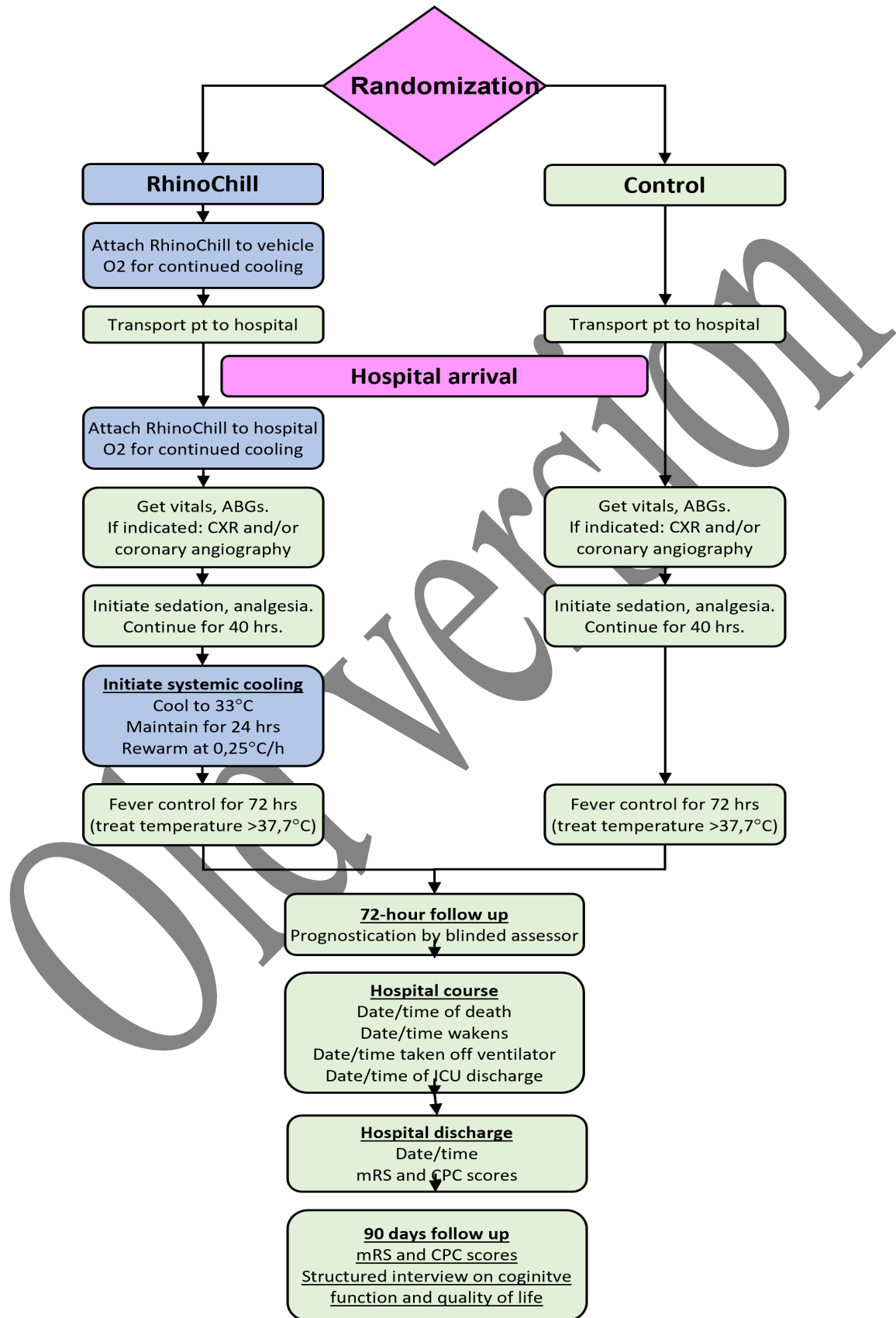
14. PUBLICATION POLICY

At the conclusion of the study, a multi-center abstract reporting the primary results will be prepared and presented at key Cardiology/Resuscitation/Intensive care 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 Per Nordberg and Fabio Taccone, will finally decide the list of authors and how these will be ordered in the final publication. The author list will include the steering group members, national investigators and additional names. Centres recruiting >30 participants will be entitled to one name, >60 two names, >100 three names, >150 four names, >220 five names in the author list (additional names). After the author list there will be added: "and the PRINCESS II trial group" and a reference to an appendix with all sites, site investigators and number of participants enrolled.

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.

Old Version

APPENDIX 1: STUDY FLOW DIAGRAM



15 References

1. Nolan JP, Sandroni C, Bottiger BW, et al. European Resuscitation Council and European Society of Intensive Care Medicine guidelines 2021: post-resuscitation care. *Intensive care medicine* 2021;47:369-421.
2. Froehler MT, Geocadin RG. Hypothermia for neuroprotection after cardiac arrest: mechanisms, clinical trials and patient care. *Journal of the neurological sciences* 2007;261:118-26.
3. Abella BS, Zhao D, Alvarado J, Hamann K, Vanden Hoek TL, Becker LB. Intra-arrest cooling improves outcomes in a murine cardiac arrest model. *Circulation* 2004;109:2786-91.
4. Nozari A, Safar P, Stezoski SW, et al. Mild hypothermia during prolonged cardiopulmonary cerebral resuscitation increases conscious survival in dogs. *Critical care medicine* 2004;32:2110-6.
5. Awad A, Taccone FS, Jonsson M, et al. Time to intra-arrest therapeutic hypothermia in out-of-hospital cardiac arrest patients and its association with neurologic outcome: a propensity matched sub-analysis of the PRINCESS trial. *Intensive care medicine* 2020;46:1361-70.
6. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *The New England journal of medicine* 2002;346:549-56.
7. Dankiewicz J, Cronberg T, Lilja G, et al. Hypothermia versus Normothermia after Out-of-Hospital Cardiac Arrest. *The New England journal of medicine* 2021;384:2283-94.
8. Castren M, Nordberg P, Svensson L, et al. Intra-arrest transnasal evaporative cooling: a randomized, prehospital, multicenter study (PRINCE: Pre-ROSC IntraNasal Cooling Effectiveness). *Circulation* 2010;122:729-36.
9. Nordberg P, Taccone FS, Truhlar A, et al. Effect of Trans-Nasal Evaporative Intra-arrest Cooling on Functional Neurologic Outcome in Out-of-Hospital Cardiac Arrest: The PRINCESS Randomized Clinical Trial. *JAMA : the journal of the American Medical Association* 2019;321:1677-85.
10. Taccone FS, Hollenberg J, Forsberg S, et al. Effect of intra-arrest trans-nasal evaporative cooling in out-of-hospital cardiac arrest: a pooled individual participant data analysis. *Critical care* 2021;25:198.
11. Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *The New England journal of medicine* 2002;346:557-63.
12. Wolfson MR, Malone DJ, Wu J, et al. Intranasal perfluorochemical spray for preferential brain cooling in sheep. *Neurocritical care* 2008;8:437-47.
13. Dodd DE, Brashear WT, Vinegar A. Metabolism and pharmacokinetics of selected halon replacement candidates. *Toxicology letters* 1993;68:37-47.
14. Tsai MS, Barbut D, Tang W, et al. Rapid head cooling initiated coincident with cardiopulmonary resuscitation improves success of defibrillation and post-resuscitation myocardial function in a porcine model of prolonged cardiac arrest. *Journal of the American College of Cardiology* 2008;51:1988-90.
15. Wang H, Barbut D, Tsai MS, Sun S, Weil MH, Tang W. Intra-arrest selective brain cooling improves success of resuscitation in a porcine model of prolonged cardiac arrest. *Resuscitation* 2010;81:617-21.
16. Guan J, Barbut D, Wang H, et al. A comparison between head cooling begun during cardiopulmonary resuscitation and surface cooling after resuscitation in a pig model of cardiac arrest. *Critical care medicine* 2008;36:S428-33.

17. Yu T, Barbut D, Ristagno G, et al. Survival and neurological outcomes after nasopharyngeal cooling or peripheral vein cold saline infusion initiated during cardiopulmonary resuscitation in a porcine model of prolonged cardiac arrest. *Critical care medicine* 2010;38:916-21.
18. Busch HJ, Eichwede F, Fodisch M, et al. Safety and feasibility of nasopharyngeal evaporative cooling in the emergency department setting in survivors of cardiac arrest. *Resuscitation* 2010;81:943-9.

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