Statistical Analysis Plan

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Prehospital Resuscitation Intranasal Cooling Effectiveness Survival Study 2 (PRINCESS2)

NCT06025123

PRINCESS2
ULTRAFAST HYPOTHERMIA IN CARDIAC ARREST

Statistical analysis plan

PRINCESS2- Main study

2023-09-30

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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 PRINCESS2 study.

2. Objectives and outcome variables

2.1. Objectives

2.1.1. Primary Objective

- To compare complete neurological recovery (mRs 0-1) 90 days after inclusion between patients treated with trans-nasal evaporative intra-arrest cooling and subsequent systemic hypothermia at the intensive care unit (ICU) compared to standard treatment with normothermia at the ICU in patients with out-of-hospital cardiac arrest (OHCA).

2.1.2. Main secondary Objective(s)

- To compare 3-month survival between intervention and control group.
- To compare 3-months survival with favourable neurologic outcome (mRs 0-3).

2.2. Outcome variables

2.2.1. Primary outcome variable

- Survival with complete neurologic recovery at 90 days defined as modified Rankin scale of 0-1 in the modified ITT population.

2.2.2. Main secondary outcome variables

Pre-defined in the trial protocol

- Survival at 90 days with favourable neurological outcome (mRs 0-3)
- Survival at 90 days.
- Sustained ROSC rate and admission alive
- Survival at hospital discharge
- Modified Rankin scale 0-3 at hospital discharge

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

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

Inclusion 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 ≤ 8
3. Inclusion within 20 minutes from EMS arrival

Exclusion criteria

1. Age ≥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

3.3. Interventions

- Prehospital intra-arrest transnasal cooling and subsequent systemic hypothermia at ICU.
- Standard care (normothermia at ICU)

3.4. Follow-up

Neurological assessment at 3-month will be made by medical personnel.

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 and at 90 days will be blinded as to the patient's group assignment.

4. Definition of Analysis Populations

4.1. ITT (Intention-to-treat population)

The ITT population will be defined as all randomized patients with non-missing values on the primary outcome variable (mRs) and treatment allocation.

4.2. Modified ITT

The modified ITT population will be defined as all ITT patients excluding those where post randomization data on the patients appear that will restrict or imply limitations in the care, such as existing DNAR or severe comorbidities that upon admission to hospital will lead to restrictions in care and interrupt the study intervention.

4.3. PP (Per-protocol population)

All ITT patients, excluding patients which did not fulfil study criteria and in cases where patients did not receive treatment according to their allocation. In the intervention group, this include interruption or not initiated prehospital cooling and if no hypothermia treatment is initiated or interrupted at ICU.

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 in the primary analysis.

5.2.2. General considerations for descriptive statistics

Tables will present outcome data by randomised treatment group and in total for the ITT, PP.
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 ITT, PP. Predefined subgroups will be presented according to the protocol.

5.2.3. Modified Rankin scale 0-1 (mRs), primary end point

Primary analysis

The proportion with neurological intact survival, defined, as mRs 0-1 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. In addition, logistic regression analysis will be performed using study site as random effect. Proportional odds regression analysis will also be used on the outcome variable (mRs) as an ordinal variable.

In addition, Bayesian analyses will be perform using Bayesian logistic regression with both neutral N(0,1.5) and optimistic N(0.15, 1.5) [based on power calculation].

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

Subgroup analyses
The primary outcome analysis will be performed on the subgroups of patients predefined in the protocol.

5.3. Secondary efficacy analyses

5.3.1. Survival at 90-days
The 90-day survival as outcome measure (regardless of mRs score) compared between the intervention and control group.

5.3.2. mRs 0-3 at 90 days
The mRs 0-3 at 90-day will be compared between the intervention and control group.

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

5.3.4 Survival at hospital discharge.
The rate of patients discharged alive will be compared between the intervention and control group.

5.3.5 mRs 0-3 at hospital discharge
The rate of patients discharged alive with mRs 0-3 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.
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6. Analysis data base definitions

6.1. Data sources and terminology
Data will be collected from using the PRINCESS2 electronic case report form (CRF). Data will be stored in a RedCap database at Karolinska Institutet, Stockholm, Sweden.

6.2. Analysis populations

Label	Formatted values	Name	Sources	Derivation
ITT	1/0	ITT	PRINCESS2	
PP	1/0	PP	PRINCESS2	cooling never started!="Yes" & cooling stopped =”No” & ICU cooling interrupted=”No”

7. Determination of sample size

Assuming a neurological intact (mRS 0-1) survival rate among admitted patients of 45% in the control group and 54% (Cohen’s h = 0.18) in the intervention group we estimated that 483 patients would be needed in each group (966) to detect a statistically significant difference using a one-sided alpha of 0.025 and a beta of 0.2 (80% power). To adjust for 1 interim analysis (Haybittle-Peto) after 40% inclusion (approximately 400 patients), with 1 test of efficacy and 1 test of futility the sample size is inflated to 996 patients. Assuming a lost to follow-up on neurological intact survival of 2.5% the sample size will be 1022 patients.

R script for power calculation:

```
Library(rpact)
princess2samplesize <-  getDesignGroupSequential(typeOfDesign = "HP",
                        kMax = 2,
                        alpha = 0.025,
                        sided = 1,
                        beta=0.2,
                        futilityBounds = c(0),
                        informationRates = c(0.40, 1))

summary(getSampleSizeRates(princess2samplesize, pi1 = 0.54, pi2 = 0.45))
```

8. Interim Analysis Plan

An interim analysis for safety and futility will be performed after 400 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. If the z-value is over 3.0 in the interim analysis the trial can be stopped for efficacy. Similarly, if the z-value is below 0, the trial can be adviced by the DSMB to be stopped for futility. The decision to stop the trial for efficacy or futility is taken by the Steering committe.

9. Statistical software

Statistical analyses will be performed using R version 3.0.1 or later.