PRINCESS^2

ULTRAFAST HYPOTHERMIA IN CARDIAC ARREST

Serious Adverse Events

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1. Terminology

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

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:
   - results in a life-threatening illness or injury
   - results in a permanent impairment of a body structure or a body function
   - requires in-patient hospitalization or prolongation of existing hospitalization
   - 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: 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.

Unanticipated Adverse Device Effect (UADE): 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.

Technical Device Failure: A failure of the device to perform its intended function when used in accordance with the Instructions for Use. 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.

2. Time frame

All clinically significant AE´s related to the use of RhinoChill (e.g. whitening of the nose) will be recorded from ROSC to the first 24 hours from randomization.

SAEs and UADEs should be reported if they occur prehospital, at the ER or ICU during the first 7 days from cardiac arrest.

3. Adverse events reporting

Clinically significant AE´s related to or those that appear to be related to the use of the RhinoChill should be reported in the dedicated section of the prehospital or inhospital eCRF.

4. Serious Adverse Event reporting

For this study, SAE´s are divided into common complications after cardiac arrest and unexpected SAE's. All SAEs listed below are considered as common complications after cardiac arrest and do not

need to be reported other than in the dedicated section of the standard prehospital or inhospital eCRF.

- New cardiac arrest after enrolment
- Arrhythmias resulting in 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

Unanticipated Adverse Device Effect (UADE) and other **unexpected SAE** must be reported to the site investigator and to the study sponsor at The Karolinska Institutet and to the company BrainCool AB (see section 5) as soon as possible, preferably within 24 hours of their occurrence as well as following their resolution. SAE:s such as those listed below will be reported in a separate safety eCRF:

- Device related skin complications (blistering or skin necrosis) including complications occurring during systemic cooling
- Device related bleeding requiring transfusion
- Barotrauma such as pneumocephalus
- Other, unexpected serious adverse events

All SAEs that occur within seven days after enrolment will be followed until resolution; this includes those patients that were terminated early. Reporting to the regulatory authorities will be performed per European vigilance requirements and other local requirements. This is a responsibility of the PI.

5. How to report

If you are unsure if an event should be reported as an UADE or unexpected SAE, contact the site investigator for a discussion.

Unanticipated Adverse Device Effect (UADE) and **unexpected SAE´s:** Contact the local **site investigator within 24 hours.** The site investigator will then contact the study sponsor and the company BrainCool AB. Unanticipated Adverse Device Effect (UADE) and unexpected SAE´s should also be reported in a separate part of the eCRF (Adverse events) in REDcap. When this eCRF is filled in, the study sponsor is automatically alerted. Reports should be done as rapidly as possible. If all information is not yet available (for example outcome), the report can be completed at a later date.

6. Resolution

The Principal Investigator 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 the responsibility of the PI.