PRINCESS^2

ULTRAFAST HYPOTHERMIA IN CARDIAC ARREST

Protocol Deviation Instructions

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1. What is a protocol deviation?

Major deviations from the PRINCESS2 investigational plan should be reported. This includes cases where the intervention cannot be performed due to contraindication, limitations in care or system malfunction, but also major deviations from target temperature or required minimum time for sedation.

Protocol deviations should be recorded in the eCRF. As a general rule, try to follow the PRINCESS2 treatment protocol and collect as much data as possible.

1.1 What not to report

- Short periods of inadequate temperature control after target temperature is reached (for example a pause in TTM-treatment for an emergency CT-scan)

1.2 What to report

- Patient **not receiving intervention due to patient status**. Examples might include:
  - Exclusion criteria that became known after randomization (for example prior limitations in care or a terminal disease) that leads to starting palliative care
  - Contraindication for hypothermia (e.g severe bleeding)
  - A randomized patient being awake and following commands prehospital or at arrival to hospital (to the degree that extubation is possible) and prehospital intervention (transnasal cooling) thereby not started/interrupted and systemic cooling not performed. Since intervention is not performed or was interrupted a protocol deviation must be completed no matter which group the patient has been randomized to.
- Patients **not receiving the intervention due to technical issues** with the RhinoChill system or the systemic temperature management system (and no backup available). This also applies to patients in the control group when a device is indicated for treatment of fever.
- Patients **not receiving intervention/interruption of intervention due to a device-related serious adverse event** (also report as device-related serious adverse event, se separate document, available at www.princess2.org)
- Patients who receive the **wrong temperature intervention** (randomised to hypothermia but not cooled or randomised to normothermia but still cooled)
- Participants (in both groups) **not sedated for 40 hours**
- Withdrawal of life sustaining therapies (WLST) based on poor neurological outcome **before prognostication at 72 hours** has been performed.

2. How to report a protocol deviation

Any protocol deviation should be documented in the eCRF (inhospital part) along with an explanation for the deviation in the comments field.

If the protocol deviation is due to a Serious Adverse Device Event or any unexpected serious adverse event, this will need to be reported to the site investigator and in a special section of the CRF (adverse events). The principal investigator will then be alerted. See separate instruction for reporting SAE, available at www.princess2.org.

The site investigator will analyse 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.

3. Difficult cases

Initial care after cardiac arrest may be chaotic, and information regarding the patient can be lacking. Borderline cases regarding eligibility and protocol deviations are unavoidable. When possible, the intervention should be completed if there aren't ethical or medical reasons for discontinuation. When in doubt about reporting a protocol deviation please contact the site investigator.