TTM2 Trial Management Manual - Version 1.0

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1. SCREENING, INCLUSION AND RANDOMISATION

- Screen **all** patients admitted to your institution with an out-of-hospital cardiac arrest who have return of spontaneous circulation (ROSC) in the TTM2 trial eCRF found at: www.ttm2trial.org (fill in site specific screening/randomisation passwords)
- Screening can be performed either in the emergency room, angiography suite, or in the intensive care unit
- For eligible patients, register cooling device type before randomisation (intravascular versus Surface)
- Randomise all eligible patients to hypothermia or fever control
- Follow your local instructions for consent procedure
- For patients eligible and randomised, print out the instruction sheet at the end of the procedure. This sheet must follow the patient during the ICU stay. Make a note in the patient charts that the patient is included in the TTM2-trial (NCT02908308) with screening number XXYYYZZZ. To allow for blinding of prognosticators and follow up personnel, DO NOT MAKE A NOTE OF WHICH GROUP THE PATIENT IS RANDOMISED TO
- Fill in the provided paper case record form on background characteristics, pre-hospital data and data on admission. It is very important to document a complete neurological status (including FOUR score) and a blood gas at admission
- Collect blood according to the biobank instructions at admission
- Coronary diagnostics/intervention and/or CT scan according to standard care

2. INTERVENTION PHASE

Sedation: The intervention period will commence immediately at randomisation and go on for 40 hours. During the intervention period all patients (both groups) should be sedated: RASS of minus 4 to minus 5 (any movement (but no eye-contact) to voice/no response to voice or physical stimulation). There is no defined protocol for sedation and analgesia but short-acting drugs or volatile anaesthesia are recommended. If a patient, despite sedation, does wake up and makes definite and meaningful contact extubation should be considered according to standard practice. Temperature management according to allocation should be continued at best effort, but as a minimum fever prevention should be continued throughout the intervention period.

Temperature recording: All patients must have a temperature probe (1st choice bladder catheter probe, 2nd Esofageal probe, 3rd Blood probe) and temperature recordings should be registered per protocol. For patients randomised to hypothermia, record the time points of first reaching target temperature of 34°C and 33°C.

Shivering: For all patients shivering should be assessed with the Bedside Shivering Assessment Scale (BSAS):

0	None - No shivering
1	Mild - Shivering localized to neck/thorax, may be seen only as artefact on ECG or felt by palpation
2	Moderate - Intermittent involvement of the upper extremities ±thorax
3	Severe - Generalized shivering or sustained upper/lower extremity shivering

The treatment goal for shivering will be to maintain a BSAS score of 0 or 1. To ensure adequate control of shivering the following protocol is recommended:

Baseline care for all patients:

- Acetaminophen/Paracetamol administered either intravenously, parenterally or rectally, according to standard dosing guidelines. Acetaminophen/ Paracetamol may be withheld at the discretion of the treating physician if liver dysfunction contraindicates the use.
- Buspirone, magnesium, clonidine, meperidine and skin counterwarming will be included, but not required, in baseline care if these interventions are part of the local protocol for management of shivering.
- If these measures are not enough:
    - 1. Sedation should be increased and
    - 2. Neuromuscular blockade should be administered (bolus or continuous) according to the treating physician.

Hypothermia management: In participants allocated to targeted temperature management at 33°C cooling should be started **immediately** when the randomisation process is over. Patients will be rapidly cooled with all available measures **including a servo-controlled device** to 33°C or <33°C (Depending on the lowest possible temp on the device) With this approach a dip under 33°C will be likely, but the strategy will allow for rapid induction. Upon reaching this first temperature goal, a maintenance phase will commence, which will end 28 hours after randomisation. During the maintenance phase the target temperature will be 33°C with a closed loop cooling device. The maintenance phase will be followed by rewarming at a maximum of 0.3°C/hour until the patient reaches 37°C.

Cooling can be induced by the following means:

- Intravenous cold (4°C) fluids. Normal saline, Hartman's solution or other similar crystalloids are recommended. The maximal volume for the initial cooling should be 30ml/kg or 2 litres.
- Approved endovascular cooling devices with closed loop (servo) systems
- Approved surface cooling devices with closed loop (servo) systems
- Approved devices for intranasal or oesophageal cooling
- Ice-packs or cooling pads
- Complete expose of the patient
- Lowering of ambient temperature
- Any combination of the above that includes a device

The target temperature should be achieved as soon as possible. Local protocols should be developed to ensure that it is feasible to reach the targeted temperature within 90 minutes or shorter in the majority of participants

Fever control management: In the normothermia group the aim will be a temperature below 37.5°C. If conservative and pharmacological measures are insufficient to prevent fever and the temperature reaches 37.8°C, cooling with a servo controlled device will be initiated with a target temperature of 37.5°C. There should be no active warming in this group unless below 33°C.

Conservative measures of fever prevention include:

- Complete exposure of the patient
- Lowering of ambient temperature
- Antipyretic medication according to local procedures

The definition of insufficient fever control is: *one single recorded measurement of a core body temperature ≥37.8°C.* If this definition is fulfilled the same measures as described under Hypothermia management above may be used. The treating physician may prescribe the application of a device (insert an endovascular catheter or apply a surface device) either prophylactically in all participants randomised to normothermia or if a rise in temperature is encountered. However the device should not be switched on until a core body temperature of ≥37.8°C is measured.

For both intervention groups: Patients with an admission temperature of below 33°C should be actively or passively rewarmed to 33°C to avoid the vulnerable body temperature zone. For patients allocated to 33°C the patients should be maintained at 33°C from when the patient reaches this temperature. For patients allocated to fever control the fever prevention measures should be instituted to aim for a temperature below 37.5

3. WHEN THE INTERVENTION PERIOD IS OVER

Sedation should be stopped or tapered according to the clinical status of the patient when the intervention period is over. Extubation should be attempted at the earliest possible time, based on standard procedures for discontinuation of mechanical ventilation. For patients who remain in the ICU and are still comatose or sedated at end of the intervention, patients in both allocation groups should be given treatment to avoid fever until 72 hours after randomisation (goal of having temperature maintained in the normal range 36.5 to 37.7°C). Any use of antipyretic medication and/or a temperature management device in this phase will be at the discretion of the treating physician.

4. TRIAL SPECIFIC BLOOD SAMPLING

Blood should be drawn according to the biobank sampling instructions at admission/randomisation and 24 hours, 48 hours and 72 hours after randomisation. Blood gasses and other blood tests should be sampled according to the separate blood sampling instruction.

5. GENERAL ICU-CARE

The general ICU-care should be delivered similarly in both allocation groups according to local standardised care plans at the discretion of the treating physicans. Fluid therapy should be guided by standard procedures for haemodynamic support (fluid responsiveness, urinary output, haemodynamic and laboratory values, echocardiography etc). Management of haemodynamics, respiration, metabolic disturbances and seizures should be according to local

protocols, at the discretion of the treating physician. Cardiac interventions should also be guided by local protocols and follow general guidelines. Cardiac catheterisation should not be delayed by the intervention, but efforts should be made to ensure temperature management according to randomisation during the procedures.