Sedation Intervention

If needed, patients should be initially sedated to ensure safe transport, imaging, coronary angiography and other invasive procedures. Following randomization, the Richmond Agitation Scale (RASS) score and motor response will be collected every four hours.

For patients randomized to continuous sedation, sedation will be targeted to a RASS from –4 to -5 upon admission to the ICU and continued until 36h after randomization. In patients randomized to minimal sedation sedative agents should be used only as needed for clinical care.

After the 36-hour intervention period, sedation strategy for both groups will be at the discretion of the treating physician as needed for clinical care.

Sedation depth according to RASS will be recorded throughout the intervention. All patients should be assessed for pain and delirium using local protocols. Pain should be treated, according to local protocols, before a sedative agent is considered. Multimodal pain management should be adopted, including non-pharmacological techniques, acetaminophen (paracetamol), and opioids by either continuous or intermitted intravenous infusion. Pain management and treatment for delirium should follow the principles outlined by the SCCM.58

Participants in both trial groups regaining consciousness and obeying commands will be extubated and discharged according to standard local hospital criteria. Patients judged to require a tracheostomy will have this performed according to local standard practice. Discontinuation of sedation and mechanical ventilation following tracheostomy in both trial groups will be according to local hospital practice.

In both study groups, if sedative medications are required, short-acting drugs by continuous infusion (such as propofol) should be preferred to benzodiazepines (by either continuous infusion or bolus dosing) for most patients. Clinicians might consider certain patients have a particular indication for a benzodiazepine-based sedation regimen: for example, those requiring very high rates of propofol infusion, those who have demonstrated seizure activity, and those with marked hemodynamic instability. In such patients, the requirement for ongoing benzodiazepine use (vs. an alternative) should be reassessed continuously.

In both study groups, sedative medications should only be used to achieve the prescribed sedation target, and only after measures to control pain and delirium have been initiated. For patients receiving neuromuscular blocking agents the level of sedation should be titrated to avoid awareness, as per treating physician, no matter of allocation group.

Sedation – Continuous sedation for 36h

For patients randomized to continuous sedation a continuous infusion of a short-acting sedative agent (such as propofol) should be started at randomization. During the first 36 hours this infusion should be increased if the patient becomes rousable, with a RASS target

of -4 to -5 until 36h after randomization. After 36h, the sedation goal will be a RASS of -2 to 0 (unless there is a clinical indication for deeper sedation), continued until the time of liberation from mechanical ventilation, at which time all sedative medications should be discontinued as soon as judged safe.

Sedation – Minimal sedation

In patients randomized to minimal sedation sedative agents shall not be used unless needed for clinical care. During the first few hours of post-cardiac arrest care patients may require deeper sedation to facilitate safe transfers, imaging, and invasive procedures, but weaning from sedatives should be performed as early as possible, ideally within 6 hours of randomization if not at the time of ICU admission.
Patients randomized to minimal sedation will be continuously assessed for extubation as soon as possible after admission to the ICU according to local criteria. If the patient is alert, obeys commands and is otherwise stable the patient may be extubated. A patient that does not fulfill criteria for safe extubation should remain intubated and receiving sedations as needed.
No opioid or sedative medications will be given unless the patient demonstrates a requirement for analgesia or sedation to safely tolerate mechanical ventilation and/or other treatments. If such medications are required, analgesia should be administered first, according to local protocols. Multimodal pain management should be adopted, including non-pharmacological techniques, acetaminophen (paracetamol), and opioids by either continuous or intermittent intravenous administration in line with clinical guidelines. If sedation is required after pain is treated, short-acting agents (e.g., propofol) should be used, targeting a level of sedation that is as light as possible but still deep enough to enable safe treatment and adequate patient comfort. The sedation target should be RASS 0 to -2, unless there is a clinical indication for deeper sedation, in which case a deeper sedation target is acceptable.
Deeper sedation may be used in the minimal sedation arm if required to manage clinical situations such as refractory status epilepticus, myoclonus, severe hypoxemia or, confirmed or suspected raised intracranial pressure.

Sedation – Changing sedation

The clinical situation may require continuous sedation to be started in a patient in the minimal sedation group. This is at the discretion of the treating physician. If continuous sedation is started within the first 36 hours the reason for this will recorded and classified as follows:

Was continuous sedation started within 36 hours of randomization?

- No
- Yes – to facilitate general intensive care
- Yes –for seizures

Temperature Intervention

The intervention period will commence immediately after randomization. Core body temperature will be continuously measured (preferentially via a bladder catheter, but an alternative core temperature site such as esophagus and blood will be allowed).

For participants allocated to fever management with a device, temperature management devices will be started to achieve a core body temperature of ≤37.5°C if temperature reaches the trigger of ≥37.8°C before 72h after randomization. For participants allocated to fever management without a device, fever will be managed as per standard fever treatment in the ICU, including for instance exposure and pharmacological agents.

The temperature intervention will last until 72 hours after randomization, or until extubation, whichever occurs first. After 72 hours, or earlier if the participant regains consciousness and is extubated, and after ICU discharge the management of temperature will be at the discretion of the treating physician.

Fever management with a device

Temperature will preferentially be recorded via a bladder thermometer. If the patient is oliguric, or if a bladder recording is not available then core temperature will be assessed by an esophageal or intravascular probe.
Participants who have an initial temperature between below 33°C may be actively rewarmed to 33°C, at which point active rewarming should be suspended. However, passive rewarming below 33°C may also be used, if preferred by the treating physician. Participants with an initial body temperature above 33°C will not be actively rewarmed to normothermia. To ensure that temperature does not reach 37.8°C the following conservative interventions will be allowed, at the discretion of the treating physician:

- Pharmacological treatment with Acetaminophen/Paracetamol
- Complete exposure of the patient

If conservative measures are insufficient, a device for temperature management will be used. The definition of insufficient fever control with conservative measures is:
A single recorded measurement of core body temperature ≥37.8°C, regardless of whether the temperature is deemed to be of infectious origin or a response to neurological injury within 72 hours after randomisation.
If the criterion for insufficient fever control is fulfilled a temperature management device will be applied and set at 37.5°C using:

- Approved endovascular cooling devices with closed loop systems
- Approved available surface cooling devices with closed loop systems

The treating physician may prescribe the application of a device (insert an endovascular catheter of apply a surface device) if a rise in temperature is encountered. However, the device will not be switched on until a core body temperature of ≥37.8°C is measured. Active fever control will be initiated as soon as a core body temperature reaches 37.8°C during the first 72 hours after randomization.

In a patient that wakes up, is alert, obeys command and is extubated, temperature control with a device may be discontinued even if the 72-hour mark has not been passed.

Fever management without a device

Temperature will be preferentially recorded via a bladder thermometer. If the patient is oliguric, or if a bladder recording is not available the core temperature will be assessed by an esophageal or intravascular probe.

Participants who have an initial temperature below 33°C may be actively rewarmed to 33°C, at which point active rewarming should be suspended. However, passive rewarming below 33°C may also be used, if preferred by the treating physician. Participants with an initial body temperature above 33°C will not be actively rewarmed to normothermia.

Fever management in this group should not differ from other critically ill patients in the ICU. No specific temperature target will be set. Antipyretics and non-pharmacological cooling measures may be used on the same indications as for any ICU patient. It might therefore be reasonable to use paracetamol, steroids or NSAIDS under certain circumstances but their use is not protocolized.

Fever management outside of the 72-hour intervention period

Fever management outside of the intervention should not differ from any other critically ill patient in the ICU. No specific temperature target will be set. Antipyretics and non-pharmacological cooling measure may be used on the same indications as for any ICU patient. It might therefore be reasonable to use paracetamol, steroids or NSAIDS under certain circumstances but their use is not protocolized.

Fever management after 72h in both groups will be at the discretion of the treating physician. If cooling is ongoing at the end of the intervention period, this management may continue.

Active cooling with a device may be started at any time in both groups at the discretion of the treating physician in situations of very high temperature and severely deranged physiology, similarly to situations in which a cooling device might be used in a general ICU patient.

Temperature – use of a device

The reason for a use of a device will be collected and categorized as follows

Temperature control device started

- No
- Yes – according to intervention (Temperature >37.7°C)
- Yes - Clinical team error (not according to intervention)

- Yes – Very high temperature and severely deranged physiology not responding to other treatments (not according to the intervention, but not regarded as a protocol violation)

Mean arterial pressure Intervention

All patients must have invasive monitoring of blood pressure. The intervention period will commence immediately after randomization, but titration of vasopressors to the MAP target may be delayed until the patient has completed required diagnostic work-up (e.g., CT-scan and coronary angiography) and is admitted to ICU.

Participants will be randomized to a MAP target of either >85 mmHg or >65 mmHg. The means to achieve this will be up to the treating clinician but the primary recommendation is to titrate a vasopressor unless the patient is hypovolemic, in which case judicious fluids should be prescribed.

The MAP intervention will last until 72 hours after randomization, or until extubation, whichever occurs first. After 72 hours, or earlier if the participant regains consciousness and is extubated, and after ICU discharge the management of MAP will be at the discretion of the treating physician.

Achieving the MAP target

Titration of vasopressors to the MAP target may be delayed until the patient has completed the required (clinician defined) initial diagnostic work-up (e.g., CT-scan and coronary angiography) and is admitted to ICU.

In both groups the means of achieving the targeted MAP will be up to the treating clinician according to local protocols. The most common vasoactive and inotropic drugs in the cardiac intensive care unit include noradrenaline, adrenaline, phenylephrine, vasopressin, milrinone, dobutamine, dopamine and levosimendan.

Fluid therapy should be guided by standard procedures for hemodynamic support such as fluid responsiveness, urinary output, hemodynamic and laboratory values and echocardiography. In case of suspected hypovolemia and fluid responsiveness (based on for example stroke volume variation or the results of a passive leg raising test), a fluid bolus may be administered. Excessive fluid loading should only be performed after careful consideration.59

If the target is not achievable despite adjustment of vasoactive/inotropic therapies, then a lower target may be accepted, and the reason will be recorded.

If the MAP is higher than the allocated target and the patient is on vasopressors, then the vasopressor should be titrated down to achieve the target.

Hypertensive urgencies occurring in the absence of vasoactive medications will be managed in accordance with usual practice in both the low MAP and high MAP arms.

Low MAP target

Participants allocated to targeting a MAP of 65 mmHg will have their vasopressor infusions titrated until a MAP of at least 65 mmHg is achieved for the first 72 hours after randomization. In case of suspected hypovolemia fluid boluses of a crystalloid may be administered.

The MAP target should not be continued in participants ready to be discharged from ICU before 72 hours.

If the patient is extubated the MAP target will be up to the treating clinician. If the patients is reintubated before 72 hours the MAP target will be 65 mmHg.

After the 72-hour intervention period, the MAP target is decided by the treating clinician.
7.3.3 High MAP target

Participants allocated to a MAP target of at least 85 mmHg will have their vasopressor infusions increased until a MAP of at least 85 mmHg is achieved for the first 72 hours after randomization. In case of suspected hypovolemia crystalloid fluid may be administered.

The MAP target should not be continued in participants ready to be discharged from ICU before 72 hours.

If the patient is extubated the MAP target will be up to the treating clinician. If the patients is reintubated before 72 hours the MAP target will be 85 mmHg

After the 72-hour intervention period, the MAP target is decided by the treating clinician.

Adjusting the MAP target

The overall intention is to achieve the MAP target throughout as much of the 72h intervention period as possible; the clinical situation may however require an adjustment of the MAP-target.

If necessary, the MAP target should be adjusted in increments or decrements of 5 mmHg. Subsequently, if there is a change in the clinical status of the patient, further attempts to achieve the targeted MAP may be considered.

The reason for the deviation from the allocated target will be collected and categorized according to the description below.

MAP-target changed or abandoned before extubation or 72h?

- No

- Yes –Lower target - Escalation of vasoactive treatment not achieving a higher MAP

- Yes – Lower target because of cardiac reasons.

(Cardiac reasons include severe arrhythmias, worsening pulmonary oedema, worsening cardiogenic shock, LVOT-obstruction, aortic insufficiency, or other reasons where the clinician suspects that an increase in vasopressor dose is causing a clinically important decline in cardiac output)

- Yes – Lower target because of major surgery
- Yes – Lower target because of intracranial bleeding.
- Yes – Lower target because of bleeding (extracranial)
- Yes – Lower target because of other reason

- Yes – Higher target because clinical team forgot
- Yes – Higher target because of renal perfusion
- Yes – Higher target because of ischemic stroke or critical carotid stenosis
- Yes – Higher target because of other reasons.

Discontinuation and reinstitution of the interventions

For participants that are de-sedated and extubated before the end of the intervention period of 72 hours for the temperature and MAP intervention, and where the interventions have been discontinued, the interventions should be reinstituted in the event of re-intubation/re-sedation if within the intervention period. After 72 hours the targets for temperature and MAP are to the discretion of the physician.

If the participant is evaluated for likely brain death according to national criteria, the sedation, temperature, and MAP targets will be at the clinicians discretion.

General ICU care

General ICU-care should be delivered similarly in all allocation groups according to local standardized care plans at the discretion of the treating physicians. Management of respiration, metabolic disturbances, ulcer-, and deep venous thrombosis-prophylaxis and other aspects of intensive care should be according to local protocols, at the discretion of the treating physician. Cardiac interventions will also be guided by local protocols, however participating centers will need to have access to around-the-clock invasive management, either on-site or at a nearby hospital also part of the trial. Cardiac catheterization (coronary angiography) should not be delayed by the trial interventions. Apart from the interventions adhering to international and national guidelines for post-resuscitation care is recommended.