EARLY-NEURO substudy manual

Only for sites <u>participating</u> in the early neuroprognostication substudy (other sites please use the "Neurological prognostication manual")

Version 1.0
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1. The prospective substudy on early neurological prognostication

The STEPCARE trial will perform a substudy on early neurological prognostication aiming to examine whether brain injury markers in blood, electroencephalogram (EEG) and head computed tomography (CT) can be used for prediction of outcome already at 24 hours post-arrest.

The hypotheses of this substudy are:

1) The combination of clinical examinations, blood levels of the brain injury marker NFL, EEG and CT predict poor outcome already at 24 h post-arrest without false positive predictions.
2) Any guideline recommended method (clinical examination/EEG/CT/SSEP) fulfilling criteria for a poor outcome according to ERC/ESICM, will have highly elevated blood levels of NFL, indicating the presence of severe brain injury.
3) Extensive sedation will not affect the prognostic accuracy of the prognostic methods EEG, CT, SSEP and NFL.

Which centers will be eligible for participation?

The EARLY-NEURO substudy will only include selected centers committed to:

1) Perform mandatory EEG and CT in all unconscious patients as early as possible after 24 h post-arrest.
2) Participate in the STEPCARE biomarker substudy.
3) Export rawdata for central blinded evaluation for EEG (European Data Transfer, EDT), SSEP and CT/MRI (DICOM format).

Please note that prediction of patient outcome and decisions on WLST will strictly adhere to the ERC/ESICM guidelines and the STEPCARE protocol, regardless of whether sites participate in the early neuroprognostication substudy or not.

Site investigators interested in recruiting their site to the biomarker and/or early prognostication substudies please contact Marion Moseby-Knappe (marion.moseby_knappe@med.lu.se) for more information.

2. Introduction

Evaluating interventions that cannot be blinded to the treating clinicians, the STEPCARE trial will employ a conservative and strict protocol for neurological prognostication based on the ERC and European Society of Intensive Care Medicine recommendations.[1, 2]

Regardless of whether sites participate in the EARLY-NEURO substudy; the clinical prediction of functional outcome will not be performed prior to 72 hours post-arrest. However, prognostic examinations should be performed according to the protocol below to allow for calculation of prognostic accuracies at this earlier timepoint.

Prognostication will be performed on *all* participants who are not awake and obeying verbal commands, and who are still in the ICU at 72 hours after randomization. The clinical examination used for prognostication should not be performed earlier than 72h after cardiac arrest but may be delayed due to practical reasons (such as weekends or national holiday). Results from additional examinations performed <72 h may be included in the assessment if performed according to ERC/ESICM recommendations.

The physician performing the prognostication will be a neurologist, intensivist or other specialist experienced in neuroprognostication after cardiac arrest and who has not been involved in patient care of this patient. The prognosticator should be blinded for group allocations, but not for relevant clinical data. Prognostication will be based on results of clinical examinations, neurophysiology, biomarkers of brain injury and imaging (Fig. 1).

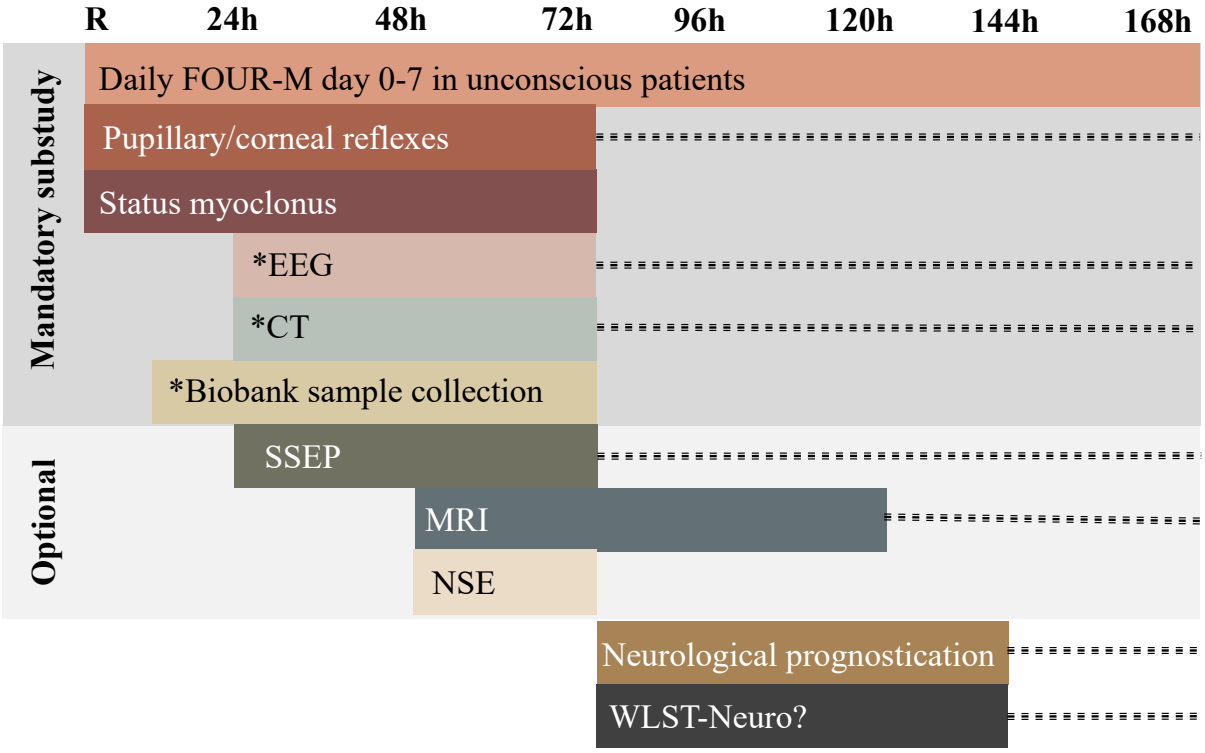

Fig. 1. Schematic overview of timepoint for prognostic examinations, neurological prognostication and withdrawal of life supporting therapies for neurological reasons (WLST-Neuro) in hours after randomization (R) for the EARLY-NEURO substudy.

The result of the prognostication will be categorized as "YES" or "NO", based on the answer to the question *"Does this patient fulfil the STEPCARE criteria for a likely poor neurological outcome?"* using the trial checklist provided. This assessment will be documented in the case report form and will be communicated to the treating clinician. Results of neurological prognostication and the potential decision to withdraw active intensive care are closely related but will be considered separate entities.

Any decision to withdraw active life support will be made by the treating physicians, together with the patient's relatives or legal surrogates, as required by local legislation. In making this decision the treating physician may use the information from the prognostication. The blinded external physician will not make any recommendation on WLST. Efforts will be made to sufficiently delay prognostication to ensure that any lingering effects of sedative agents will not affect the assessment.

3. Clinical neurological examinations

A clinical neurological exam is ***mandatory*** and should include:

- Daily assessment of the best motor response according to the Full Outline of UnResponsiveness (FOUR)-M-score[3] recorded daily until day 7 in the ICU (Fig. 2).
- Daily assessment of status myoclonus (continuous and generalized myoclonus persisting for at least 30 min) until day 7 in the ICU.
- The presence or absence of pupillary AND corneal reflexes at hospital admission, at 24 h and if applicable, at the time-point of neurological prognostication.

Absent, extensor or flexion motor response to pain (FOUR- score motor response 0-2) at 72 h or later in a patient who is considered unaffected by sedative agents, will be a prerequisite to consider the neurologic prognosis poor. Bilateral absence of pupillary and corneal reflexes at 72h after randomization or later and or the presence of an early status myoclonus (within 72 h) are criteria indicative of a poor prognosis.

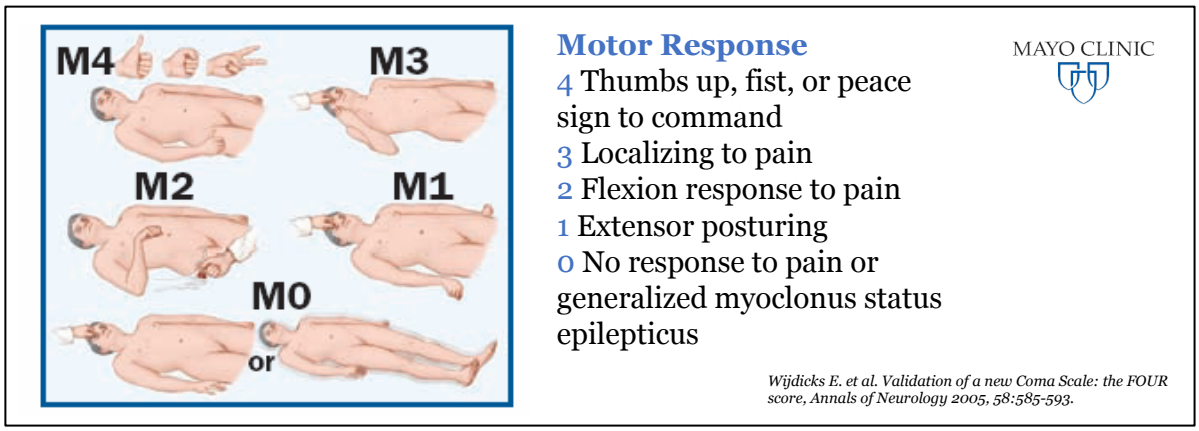

Fig. 2. Instructions for clinical examination of the FOUR Motor response. Grade the best possible response of the arms. A score of M4 indicates that the patient demonstrated at least 1 of 3 hand positions (thumbs-up, fist or peace sign) with either hand. A score of M3 indicates that the patient touched the examiner´s hand after a painful stimulus compressing the temporomandibular joint or supraorbital nerve (localization). A score of M2 indicates any flexion movement of the upper limbs. A score of M1 indicates extensor posturing. A score of M0 indicated no motor response or myoclonus status epilepticus.[3]

4. Additional prognostic examinations

Prognostication should always be multimodal and include ≥2 prognostic methods as recommended by the ERC/ESICM guidelines.[1, 2]

- For sites within the EARLY-NEURO substudy, a CT and an EEG from 24 h post-randomization is mandatory in patients still unconscious (not awake and obeying verbal commands).
- Blood samples for the biomarker substudy are mandatory and are collected at 12, 24, 48 and 72 h after randomization. Samples will be stored in a central biobank and since analyses are performed after trial completion, these biomarker results will not be available during neurological prognostication.
- The choice of additional prognostic examinations are at the discretion of the treating physicians.

4.1 EEG

An EEG as early as possible ≥24 h after randomization ***is mandatory*** for substudy patients. Either a full-montage and/or simplified continuous EEG-monitoring may be used for this purpose. Results of EEG examinations will be reported in the eCRF.

An EEG with a "highly malignant pattern" defined using the terminology of the American Clinical Neurophysiology Society, and without reactivity to sound and pain is indicative of a poor prognosis if lingering effects of sedation are ruled out.[4-6]

Highly malignant EEG patterns are:

- *burst suppression* (amplitudes <10μV constituting >50% of the recording) with or without superimposed discharges.
- *suppression* (amplitudes <10μV during the entirety of the recording) with or without discharges.

EEG-reactivity should be tested at least 2 times with an interval of more than 20 seconds in all patients and include the following:

- *Sound stimulations* - Call the patient's name, clapping hands for a few seconds. Should be repeated at least 2 times with an interval of more than 20 seconds.
- *Pain stimulations* - Recommended to include at least one proximal stimulation (i.e. sternal rubbing, jaw compression or squeezing of trapezius/deltoid).
- EEG-reactivity may include a change in amplitude or frequency, including attenuation of activity. Appearance of muscle activity or eye blink artefacts or SIRPIDs (Stimuli Induced Rhythmic, Periodic or Ictal Discharges) do not qualify as EEG-reactivity.

4.2 Brain CT

A brain computed tomography (CT) ***is mandatory*** for unconscious patients ≥24 h after randomization within the EARLY-NEURO substudy.

If a brain-CT shows signs of severe hypoxic ischemic injury, such as: generalized oedema with reduced grey/white matter differentiation and sulcal effacement, this is indicative of a poor prognosis, regardless of the time-point of examination.[7, 8]

4.3 Brain MRI

A brain magnetic resonance imaging (MRI) may be incorporated into prognostication if it has been performed. Signs of diffuse and extensive hypoxic injury on MRI is indicative of a poor prognosis at 2-5 days post-arrest.[1, 2]

4.4 Neuron specific enolase

High serial blood levels of NSE (> 60 ng/mL at 48 h and/or 72 h) are indicative of a poor prognosis.[1, 2] Hemolysis, malignancies, and other intracranial pathologies are potential confounders and should be excluded.

4.5 SSEP

Somatosensory evoked potentials (SSEP) N20-responses may be used for prognostication if the technical quality is adequate. Absent SSEP N20-responses bilaterally ≥24 h are indicative of a poor prognosis.[1, 2]

5 Trial criteria for a likely poor neurological outcome

In the trial the prognosis is considered *likely poor* if criteria A, B and C are all fulfilled (Fig. 3):

A. Confounding factors such as severe metabolic derangement and lingering sedation has been ruled out. The ERC/ESICM recommend awaiting 5 half-lives of the sedative with the longest half-life prior to clinical evaluation.[1, 2]
B. The patient has no response, a stereotypic extensor response or a stereotypic flexor response (FOUR-M ≤2) to bilateral central and peripheral painful stimulation at ≥ 72 h after randomization.
C. At least two of the below mentioned signs of a poor prognosis are present:

C1. Bilateral absence of pupillary AND corneal reflexes at 72 h after randomization or later
C2. Bilaterally absent SSEP N20-responses more than 24 h post-randomization.
C3. A highly malignant EEG-pattern ≥24 h without reactivity to sound and painful stimulation without lingering effects of sedation.
C4. Serial blood-NSE above >60 ng/mL at 48 h and/or 72 h without hemolysis or malignancies as potential confounders.
C5. A documented early generalized status myoclonus within 72 h.
C6. Neuroimaging (CT at any time or MRI 2-5 days post-arrest) with signs of diffuse and extensive hypoxic injury.

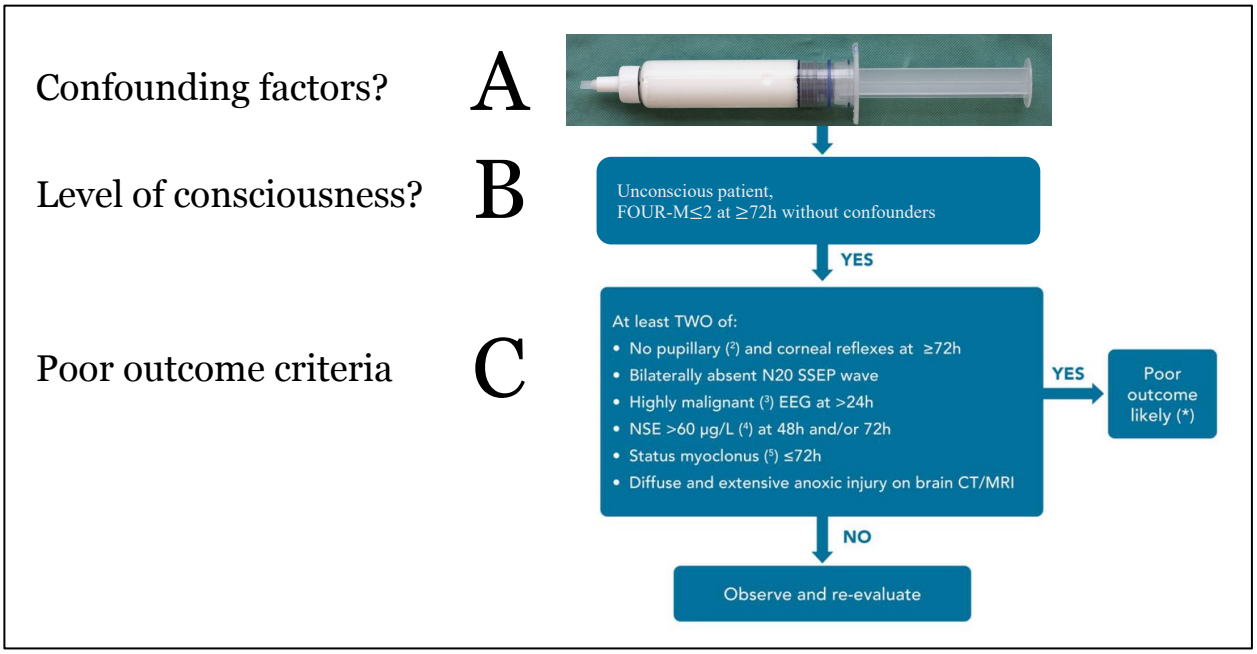

Fig. 3. STEPCARE criteria for a "poor outcome likely" adapted from the ERC/ESICM guideline algorithm.[1, 2]

Note: *Participants with suspected ongoing status myoclonus at the time of assessment should still be assessed for a response to pain. An increase in the frequency or amplitude of myoclonic jerks when a painful stimulus is applied should not be considered as a motor response. If the participant localizes to pain or EEG-background is continuous, the prognosis should not be stated as "poor outcome likely", as this state may be compatible with a diagnosis of Lance-Adams syndrome.*

6 Withdrawal of life supporting therapies (WLST)

All participants in the trial will be actively treated until **72 hours** after randomization. There will be two exceptions from this rule.

1. Participants in whom further treatment is considered unethical due to irreversible organ failure; or, following inclusion in the trial, information becomes available such as an advanced medical comorbidity (e.g., generalized malignant disease) or a pre-existing Advance Care Directive that prohibits treatment.
2. Participants in whom brain death is established according to local legislation, however this will be defined as death and not WLST. We recommend that the clinical diagnosis of brain death should be avoided during the first 24 hours after ROSC and be supported by radiological evidence of herniation and loss of intracerebral blood-flow when there is any doubt about the diagnosis.

The assumption of a poor neurological prognosis alone will not be considered sufficient to employ withdrawal of active intensive care prior to 72 hours after randomization. After prognostication has been performed, WLST due to a presumed poor prognosis will be allowed as per the treating clinician if the STEPCARE criteria for a likely poor neurological outcome are fulfilled.

Participants who have an unclear prognosis at 72 h after randomization should be reexamined daily and WLST may be considered if neurological function does not improve and, metabolic and pharmacological reasons for prolonged unconsciousness are ruled out. If a decision of WLST is made, the time point and the main reasons for withdrawing life-supporting therapies will be documented. However, supporting therapy may also be continued regardless of the neurological assessment of prognosis, at the discretion of the treating physician.

7 Brain death

Participants in whom brain death is established will be registered as dead when a conclusive assessment, based on national criteria, has been made. If death is due to brain death this will be registered.

8 References

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3. Wijdicks EF, Bamlet WR, Maramattom BV, Manno EM, McClelland RL. Validation of a new coma scale: The FOUR score. Annals of neurology 2005;58:585-593.
4. Backman S, Cronberg T, Friberg H, et al. Highly malignant routine EEG predicts poor prognosis after cardiac arrest in the Target Temperature Management trial. Resuscitation 2018;131:24-28.
5. Westhall E, Rossetti AO, van Rootselaar AF, et al. Standardized EEG interpretation accurately predicts prognosis after cardiac arrest. Neurology 2016;86:1482-1490.
6. Hirsch LJ, Fong MWK, Leitinger M, et al. American Clinical Neurophysiology Society's Standardized Critical Care EEG Terminology: 2021 Version. J Clin Neurophysiol 2021;38:1-29.
7. Lang M, Nielsen N, Ullen S, et al. A pilot study of methods for prediction of poor outcome by head computed tomography after cardiac arrest. Resuscitation 2022;179:61-70.
8. Streitberger KJ, Endisch C, Ploner CJ, et al. Timing of brain computed tomography and accuracy of outcome prediction after cardiac arrest. Resuscitation 2019;145:8-14.