# EARLY-NEURO substudy manual

## Only for sites participating in the early neuroprognostication substudy

**Version 1.0**
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## The prospective EARLY-NEURO study

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-randomization.

*The main hypotheses of the EARLY-NEURO 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-randomization without false positive predictions.
2) Patients fulfilling criteria for a poor outcome using any guideline recommended method (clinical examination/EEG/SSEP/neuroimaging), will have highly elevated blood levels of NFL, indicating the presence of severe brain injury.
3) Deep sedation will not affect the prognostic accuracy of the prognostic methods EEG, CT, SSEP and NFL.

Additional hypothesis of the EARLY-NEURO:

4) The combination of clinical examinations, blood levels of the brain injury marker p-tau$^{181}$, EEG and CT predict poor outcome already at 24 h post-randomization without false positive predictions.

*Which centers will be eligible for participation?*

The EARLY-NEURO will only include selected STEPCARE 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 raw data 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 STEPCARE protocol**, regardless of whether sites participate in the EARLY-NEURO 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.

# 1. Introduction

The STEPCARE trial will employ a conservative and strict protocol for neurological prognostication based on the European Resuscitation Council and European Society of Intensive Care Medicine recommendations (ERC/ESICM).[1, 2]

Importantly, sites that participate in the EARLY-NEURO substudy will still adhere to the STEPCARE protocol for the actual prediction of a patient´s outcome or withdrawal of care. Formal neuroprognostication performed prior to 72 hours after randomization is considered a protocol violation and must be reported as such. Please note that single prognostic examinations performed prior to 72 hours may still be included when predicting patient outcome.

In STEPCARE, 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. Please note that daily clinical examinations of all patients on the ICU including level of consciousness, observation of myoclonus and testing of brain stem reflexes are a mandatory part of the STEPCARE trial. The clinical examination used for prognostication, however, should not be performed earlier than 72 hours after randomization but may be delayed due to practical reasons (such as weekends or national holiday). Results from additional examinations performed <72 hours 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 who has not been involved in patient care of the 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).

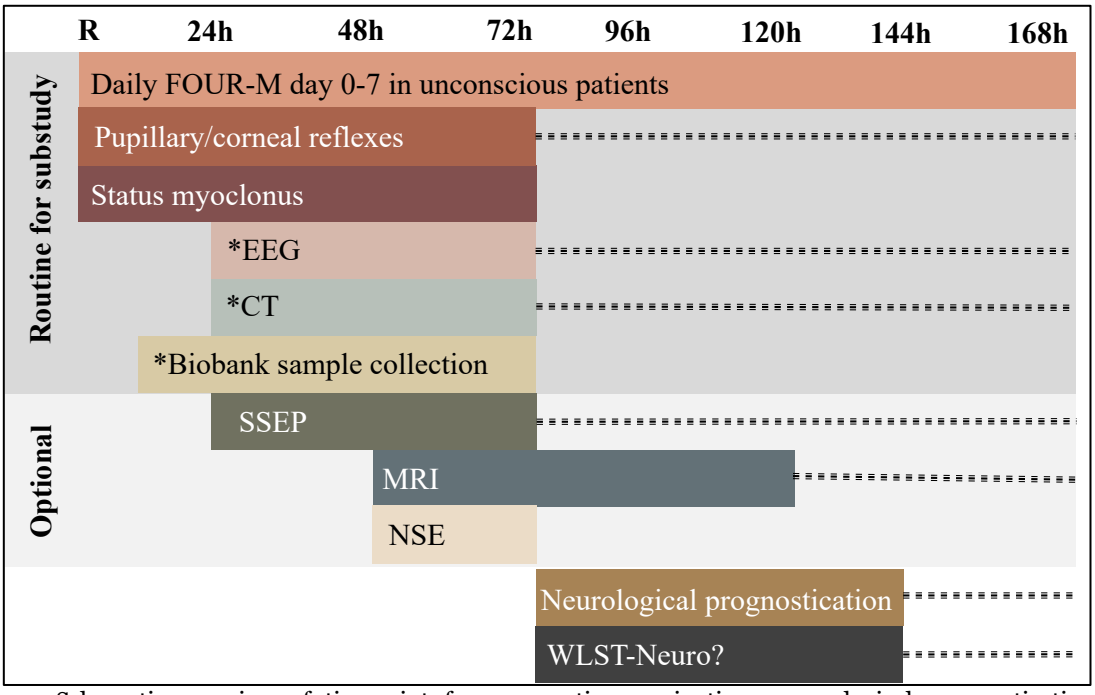


**Fig. 1.** Schematic overview of timepoint for prognostic examinations, neurological prognostication and withdrawal of life supporting therapies for neurological reasons (WLST-Neuro) in hours after randomization (R) for the EARLY-NEURO substudy.

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 (attached in the final pages of this manual). The neurological 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.

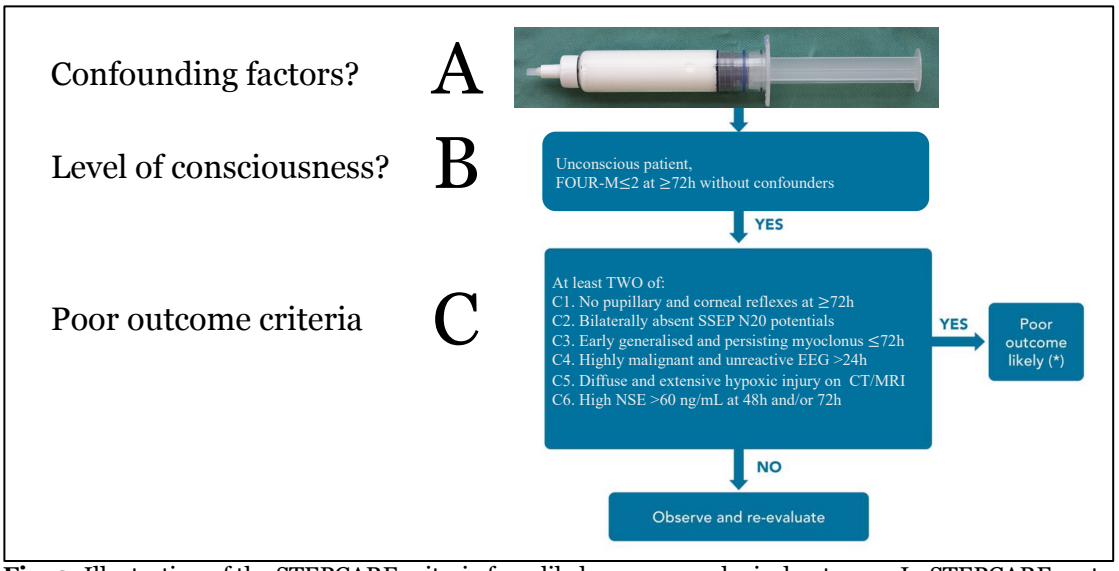


**Fig. 2.** Illustration of the STEPCARE criteria for a likely poor neurological outcome. In STEPCARE, outcome is considered poor if the patient fulfils criteria A, B and C later than 72 hours after randomization.

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 as early as possible at least 24 h post-randomization are routinely performed 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 is at the discretion of the treating physicians.

## A. Confounding factors

Prior to neurological prognostication, it is essential that confounding factors such as severe metabolic derangement and lingering sedation have been excluded. The ERC/ESICM recommend awaiting 5 half-lives of the sedative with the longest half-life prior to clinical evaluation. For Propofol, this is approximately 24 hours.[1, 2]

## B. Level of consciousness >72 hours after randomization

If confounding factors have been excluded, the next step of prognostication is to examine the patient's level of consciousness using the Full Outline of Unresponsiveness motor score (FOUR-M) (Fig. 3). Absent, extensor or flexion motor response to pain (FOUR-M 0-2) at 72 hours or later will be a prerequisite to continue with the poor outcome criteria C. Please note that the presence of a generalized myoclonus status myoclonus (within 72 hours) is classified as FOUR-M 0.

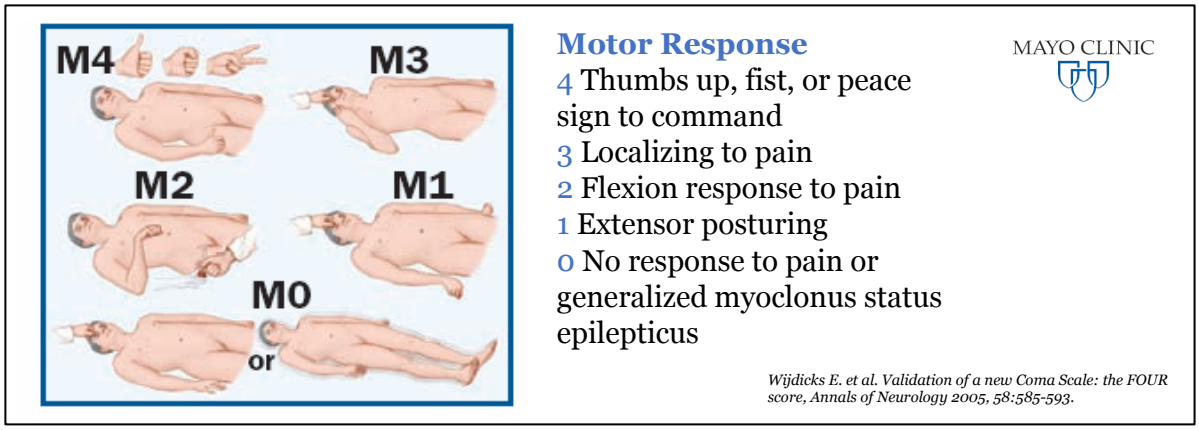


**Fig. 3.** Instructions for clinical examination of the FOUR Motor response. Grade the best possible response of the arms. M4 indicates that the patient demonstrated at least 1 of 3 hand positions (thumbs-up, fist or peace sign) with either hand. M3 indicates that the patient touched the examiner´s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

## C. Poor outcome criteria

In STEPCARE, outcome is considered poor if criteria A, B and at least two of the below mentioned criteria C of poor prognosis are present:

C1. No pupillary AND corneal reflexes ≥72 hours after randomization
C2. Bilaterally absent SSEP N20-potentials
C3. Early generalized and persisting myoclonus ≤72 hours after randomization
C4. Highly malignant and unreactive EEG-pattern >24 hours after randomization
C5. Diffuse and extensive hypoxic brain injury on CT/MRI
C6. High NSE >60 ng/mL at 48 and/or 72 hours after randomization

### C1. Pupillary and corneal reflexes

Bilaterally absent pupillary and bilaterally absent corneal reflexes ≥72 hours after randomization are indicative of a poor outcome. A pupillometer may be used if available. Please remember that sedation and muscle relaxants are potential confounders of clinical neurological examination and be careful to exclude lingering effects.

### C2. 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]

### C3. Early generalized and persisting myoclonus ≤72 hours

The presence of myoclonus is reported daily during the ICU stay until day 7. An early status myoclonus defined as a continuous and generalized myoclonus persisting for at least 30 min is predictive of a poor outcome if first documented ≤72 hours after randomization.

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 the 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.

### C4. Highly malignant and unreactive EEG-pattern

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. Note that deep sedation continues for 36 hours without sedation breaks for patients randomized to this intervention and that EEG examinations should be performed regardless. Prediction of outcome should adhere to STEPCARE protocol excluding the counfounding effects of sedation when making decisions on level-of-care. Results of EEG examinations will be reported in the eCRF. EEG recordings should be prepared for export in EDT format using the patients study ID as identification.

The STEPCARE employs a more conservative approach to EEG evaluation than the ERC/ESICM guidelines, also including reactivity to avoid false pessimistic predictions of poor outcome. 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.

### C5. Diffuse and extensive hypoxic brain injury on CT/MRI

#### CT

Within the EARLY-NEURO substudy, a brain computed tomography (CT) is part of routine examinations for unconscious patients as early as possible ≥24 hours after randomization. For all other patients, a brain CT ***should be considered***. If available, Virtual Non-Contrast sequences should be considered for CT to exclude effects of intravenous contrast after coronary angiography. We recommend removing continuous EEG electrodes during CT examinations to reduce the risk of artefacts on images. If a brain-CT shows signs of diffuse and extensive 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]

#### 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]

### C6. High Neuron-Specific enolase (NSE)

High 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.

## 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 prognosis due to hypoxic brain injury 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.

## 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.

# References


1. Nolan JP, Sandroni C, Bottiger BW, et al. European Resuscitation Council and European Society of Intensive Care Medicine Guidelines 2021: Post-resuscitation care. Resuscitation 2021;161:220-269.
2. Nolan JP, Sandroni C, Bottiger BW, et al. European Resuscitation Council and European Society of Intensive Care Medicine guidelines 2021: post-resuscitation care. Intensive Care Med 2021;47:369-421.
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.