Neurological prognostication manual

This manual is for all sites
except those participating in the EARLY-NEURO substudy
(please see separate document)

April 17th 2023

Introduction

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]

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. 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).

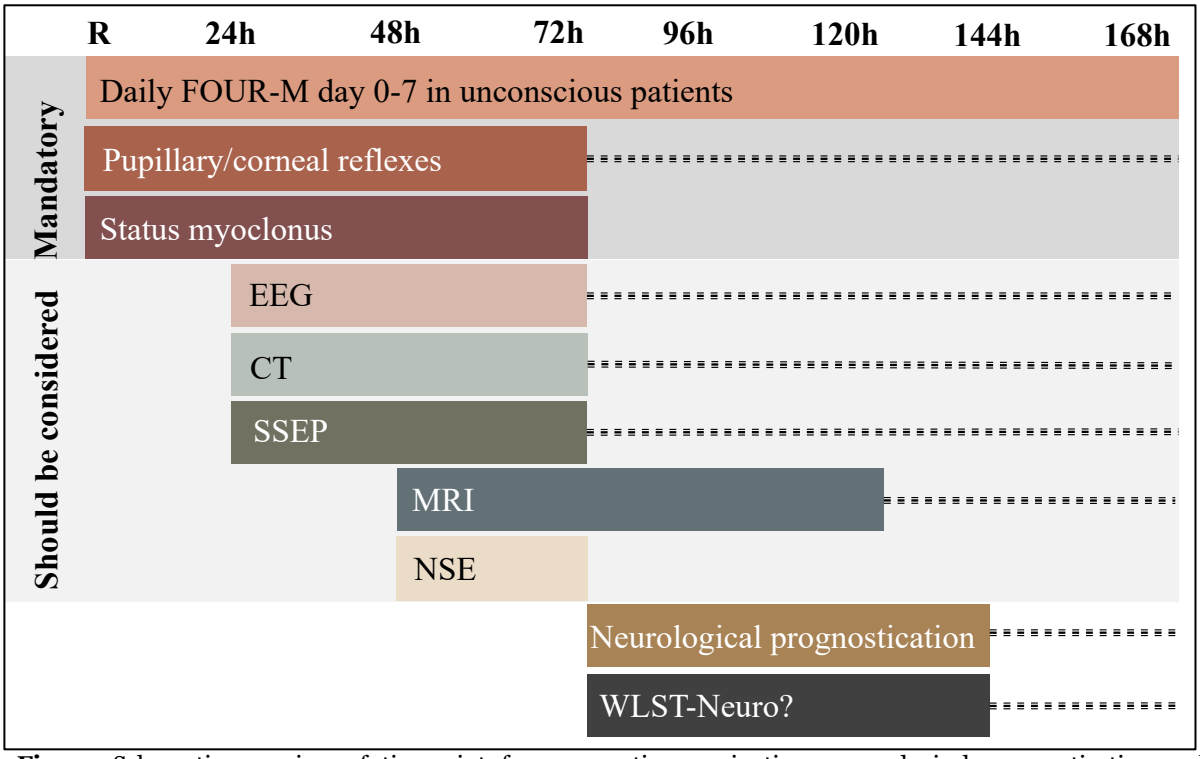

Fig. 1. Schematic overview of timepoint for prognostic examinations, neurological prognostication and withdrawal of life supporting therapies for neurological reasons (WLST-Neuro) in hours after randomization (R).

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 in the last pages of this manual. 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.

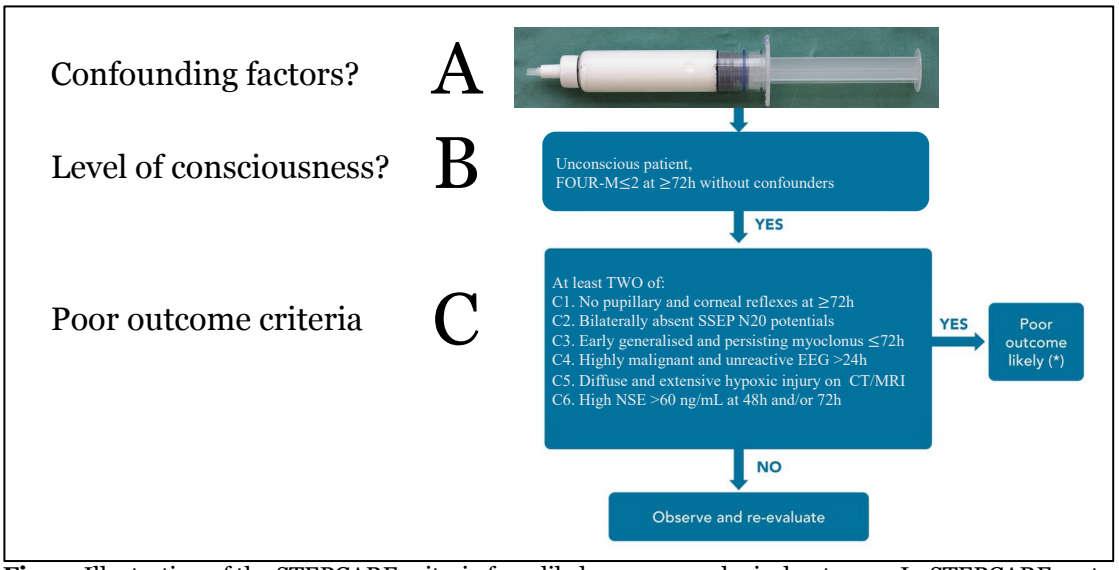

Fig. 2. Illustration of the STEPCARE criteria for a likely poor neurological outcome. In STEPCARE, outcome is considered poor if the patient fulfills criteria A, B and C later than 72 hours after randomization.

Prognostication of outcome should always be multimodal and include ≥2 prognostic methods as recommended by the ERC/ESICM guidelines.[1,2] The choice of additional prognostic examinations within the STEPCARE are at the discretion of the treating physicians unless sites participate in the EARLY-NEURO (substudy sites please see separate manual for neurological prognostication).

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.

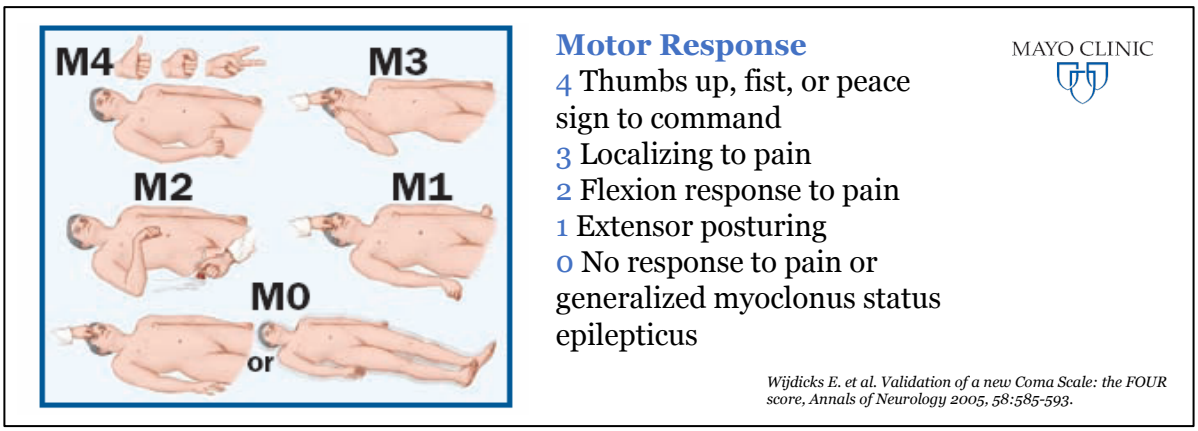

Fig. 3. Instructions for clinical examination of the FOUR Motor response. Grade the best possible response of the

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 ≥24 hours after randomization ***is recommended*** in line with ERC/ESICM guidelines.[1,2] Results of full-montage and/or simplified continuous EEG-monitoring will be reported in the eCRF.

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 <u>without reactivity</u> 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 ≥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. 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.

The STEPCARE-trial criteria for a likely poor outcome

In the STEPCARE trial the prognosis is considered likely poor if criteria A, B and C stated below are all fulfilled.

A. Confounding factors such as severe metabolic derangement and lingering sedation have been ruled out**.**

B. FOUR-Score Motor: The patient has no response**,** a stereotypic extensor response or a sterotypic flexor response to bilateral central and peripheral painful stimulation at ≥72 hours after randomization (FOUR-M 0-2)**.**

C. At least two of the below mentioned criteria of a poor prognosis are present:
C1. Bilateral absence of pupillary and corneal reflexes at 72h after randomization
C2. Bilaterally absent SSEP N20 potentials
C3. Early status myoclonus within 72h of randomization defined as a continuous and generalized myoclonus persisting for 30 minutes or more.
C4. A highly malignant EEG-pattern without reactivity to sound and painful stimulation on full-montage routine EEG or on simplified continuous EEG more than 24h after randomization and after effects of lingering sedation have been excluded:

> **i.** Suppressed background (amplitude <10 microV, >99% of the recording) with or without superimposed discharges**.**
> **ii.** Burst-suppression (periods of suppression with amplitude <10 microV constituting at least 50% of the recording) with or without superimposed discharges**.**

C5. Neuroimaging: either a CT or MRI with signs of diffuse and extensive hypoxic ischemic injury
C6. Serum-NSE higher than 60 ng/mL at either 48h or 72h after randomization

Prognostication Checklist

Date of prognostication (YY/MM/DD): _____

Time of prognostication (24h clock): _____

Criterium A, confounding factors

Confounding factors such as severe metabolic derangement and lingering sedation have been ruled out — Yes ☐ No ☐

When was the last given dose of a sedative agent prior to prognostication _____ hours

Criterium B, FOUR-Score motor >72 hours after CA

Evaluate the best motoric response to a bilaterally given painful stimulus both centrally and peripherally in patients who are not awake and obeying commands

- ☐ **4.** Makes sign (thumbs-up, fist or peace sign)
- ☐ **3.** Localizes painful stimulus
- ☐ **2.** Flexion response to pain
- ☐ **1.** Extension response to pain
- ☐ **0.** No response to pain or generalized status myoclonus

Criteria C (At least 2)

	Poor outcome likely					
C1. Corneal reflexes*	Bilaterally absent	☐	Present	☐	Not assessed	☐
C1. Pupillary reflexes*	Bilaterally absent	☐	Present	☐	Not assessed	☐
C2. SSEP N20	Bilaterally absent	☐	Present	☐	Not assessed	☐
N20 amplitudes (if available)	Left _____microvolt		Right _____microvolt		Not assessed	☐
C3. Early status myoclonus < 72h	Present	☐	Absent	☐	Not assessed	☐
C4. Routine EEG highly malignant and unreactive**	Yes	☐	No	☐	Not assessed	☐
C4. Continuous EEG highly malignant and unreactive**	Yes	☐	No	☐	Not assessed	☐
C5. CT with diffuse and extensive hypoxic brain injury***	Yes	☐	No	☐	Not assessed	☐
C5. MRI with diffuse and extensive hypoxic brain injury***	Yes	☐	No	☐	Not assessed	☐
C6. High serial NSE	Yes	☐	No	☐	Not assessed	☐
NSE concentrations (ng/mL)	**24h:**_____		**48h:**_____		**72h:**_____	

*C1: Bilaterally absent pupillary and bilaterally absent corneal reflexes is considered one criterion
**C4: Highly malignant EEG patterns can be diagnosed either with routine or continuous EEG
***C5: Neuroimaging is considered one criterion regardless of whether CT and MRI are pathological

Does this patient fulfil the STEPCARE criteria for a likely poor neurological outcome?

Yes ☐ No ☐