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Neurological Prognostication Manual

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## 1. Introduction

The PRINCESS2 trial is evaluating an intervention that cannot be blinded to the hospital personnel. Therefore, a strict protocol for neurological prognostication is important to limit potential bias from premature withdrawal of life-sustaining treatment. This strategy adds complexity to the protocol but is an important design feature that protects the internal validity of the study.

Prognostication will be performed on all patients still in the ICU at ≥72 hours from randomization. The prognostication is based on the 2021 ERC/ESCIM guidelines recommendations (1).

The result of the prognostication will be the answer to the question “Does this patient fulfill the study criteria for a likely poor neurological outcome” categorized as “YES” or “NO”.

Prognostication and the potential decision to withdraw active intensive care are closely related but will be considered separate entities, and 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.

## 2. Time-point for prognostication

Prognostication should be made at the earliest 72 h after randomization, and as close as possible to 72 hours from admission. The prognostication may need to be delayed due to practical reasons (such as weekend or national holiday) or to ensure that no lingering effects of sedative agents affect the assessment.

Note that all patients, including awake patients, should be evaluated.

## 3. The role and qualifications of physician performing the blinded prognostication

The physician performing the blinded prognostication might be a neurologist, intensivist or other specialist experienced in neuroprognostication after cardiac arrest. The prognosticator should be blinded for group allocation, but not for relevant clinical data (e.g circumstances regarding the cardiac arrest, information on organ functions, comorbidity or investigations performed to support the prognostication).

The result of the prognostication will be the answer to the question “Does this patient fulfill the study criteria for a likely poor neurological outcome” categorized as “YES” or “NO”.

The answer to this question will be recorded in the CRF and will be communicated to the treating physician, but no recommendations of withdrawal of life support or not will be made.

## 4. Methods for neurological prognostication

Prognostication at ≥72 hours will be based on two mandatory (clinical examination and EEG), and four optional (NSE, Brain CT, Brain MRI, SSEP) modalities. Note that EEG is not mandatory in patients regaining full consciousness before 72 hours from randomization.

### 4.1 Clinical examination

Clinical examination including assessment of brainstem reflexes and response to pain and other stimuli will be performed.

Absent or extensor motor response to pain at 72h or later in a patient who is considered unaffected by sedative agents, is a prerequisite to consider the neurologic prognosis poor(2).

The bilateral absence of pupillary and corneal reflexes at 72h after CA or later, is a finding indicative of a poor prognosis(2).

The clinical examination by the ICU-staff should also include an assessment of status myoclonus (continuous and generalized myoclonus persisting for at least 30 min). A prospectively documented early status myoclonus (within 48 hours) is indicative of a poor prognosis (3).

### 5.2 EEG

A routine EEG should be performed between 36h and 72h after randomization on all participants who survive, and remain unconscious to this point, in line with standard clinical practice. If it is not possible to perform an EEG in the specified time frame due to practical reasons (such as weekend or national holiday), the EEG should be performed as soon as possible after 72h. An EEG with a highly malignant pattern, and without reactivity to sound and pain is indicative of a poor prognosis.

It is recommended to ask for highly malignant pattern and reactivity in the EEG-referral and to ensure that the local EEG-specialist is aware of the following criteria. Patterns that are considered highly malignant are(4):

1. Suppressed background (amplitude <10mV, 100% of the recording) without discharges
2. Suppressed background with superimposed continuous periodic discharges
3. Burst-suppression (periods of suppression with amplitude <10mV constituting 50% of the recording) without discharges
4. Burst-suppression with superimposed discharges

### 4.3 Brain CT

Brain CT is an optional examination but should be considered in patients who remain unconscious to exclude other pathologies such as intracranial hemorrhage or infarction.

If a brain CT shows signs of global ischaemic injury, such as: generalised oedema with reduced grey/white matter differentiation and sulcal effacement, this is indicative of a poor prognosis(5).

### 4.4 Brain MRI

Brain MRI is an optional examination. A brain MRI at 3-5 days may be incorporated into prognostication if it has been performed. Signs of global, diffuse, or bilateral multifocal ischemic lesions are indicative of a poor prognosis.

### 4.5 Neuron specific enolase

NSE-levels are optional for use in prognostication and should only be used by sites with experience. NSE sampling should be documented in the e-CRF. High levels of Neuron-specific enolase (NSE) are indicative of a poor prognosis (NSE >60ug/L at 48 h and/or 72 h)(1). If serial samples are available, and these are consistently higher than locally established levels associated with a poor outcome, this may be seen as indicative of a poor outcome.

### 4.6 Somatosensory evoked potentials (SSEP)

The use of SSEP is optional but encouraged if the methodology is available. Absent SSEP N20-responses bilaterally may be seen as indicative of a poor prognosis(1), if SSEP is performed more than 48h after randomization.

## 5. Study criteria for a likely poor neurological outcome

The following criteria, evaluated at the earliest at 72 hours after randomization or later, need to be fulfilled to establish a likely poor neurological outcome:

* Unconscious patient with absent or extensor motor response to pain (no confounders e.g. sedation)

AND at least TWO of the following:

* Bilaterally absent pupillary and corneal reflexes
* Bilaterally absent SSEP N20-responses
* Diffuse anoxic brain injury on CT or MRI
* Documented status myoclonus within 48h of randomisation
* High levels of serum NSE (>60ug/L at 48 h and/or 72 h)
* An EEG with a highly malignant pattern (se section 5:2) and without any observed reactivity to sound or pain.

## 6. Withdrawal of life-sustaining therapy (WLST)

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. The result from the blinded prognostication will be communicated to the treated physician and might be used as part of a potential WLST-decision.

All participants in the trial must be actively treated until at least 72 hours after randomization. There will be two exemptions from this rule:

* Participants in whom further treatment is considered unethical due to irreversible organ failure, documented medical comorbidity, or other reasons. The reason for WLST must be documented comprehensively in the CRF.
* Participants in whom brain death is established, however this will be defined as death and not WLST.

The assumption of a poor neurological prognosis alone by one treating physician will not be considered sufficient to employ withdrawal of active intensive care prior to 72 hours from randomization.

After prognostication has been performed, WLST due to a presumed poor prognosis will be allowed if trial criteria for a likely poor neurological outcome are fulfilled and all effects of sedation on consciousness are ruled out. Participants who have an unclear prognosis at 72h after randomization should be reexamined daily and WLST may be considered if neurological function does not improve and, metabolic and pharmacological reasons for prolonged coma are ruled out. If a decision of WLST is made, the time point and the main reasons for withdrawing life-supporting therapies will be recorded. 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 who are declared brain dead will be registered as dead when a conclusive assessment has been made. The diagnosis of brain death should be made and documented according to national legislation.

## 8. References

1. Nolan JP, Sandroni C, Böttiger BW, Cariou A, Cronberg T, Friberg H, et al. European Resuscitation Council and European Society of Intensive Care Medicine guidelines 2021: post-resuscitation care. Intensive Care Med. 2021;47(4):369-421.

2. Sandroni C, D'Arrigo S, Cacciola S, Hoedemaekers CWE, Kamps MJA, Oddo M, et al. Prediction of poor neurological outcome in comatose survivors of cardiac arrest: a systematic review. Intensive Care Med. 2020;46(10):1803-51.

3. Lybeck A, Friberg H, Aneman A, Hassager C, Horn J, Kjærgaard J, et al. Prognostic significance of clinical seizures after cardiac arrest and target temperature management. Resuscitation. 2017;114:146-51.

4. Westhall E, Rossetti AO, van Rootselaar AF, Wesenberg Kjaer T, Horn J, Ullén S, et al. Standardized EEG interpretation accurately predicts prognosis after cardiac arrest. Neurology. 2016;86(16):1482-90.

5. Moseby-Knappe M, Pellis T, Dragancea I, Friberg H, Nielsen N, Horn J, et al. Head computed tomography for prognostication of poor outcome in comatose patients after cardiac arrest and targeted temperature management. Resuscitation. 2017;119:89-94.

## 9. Checklist for neurologic prognostication at 72 hours from randomization

*For details, see Neurological Prognostication Manual, available at www.princess2.org*

**1. Unconscious patient with absent or extensor motor response to pain (M ≤ 3) ≥ 72 h after randomization, without any confounders:**

**Yes □ No □**

**2. Corneal and pupillary reflexes** Performed**□** Poor**□** Not conclusive **□**

**(mandatory)**

**SSEP** Performed**□** Poor **□** Not conclusive **□**

**Brain CT/Brain MRI** Performed**□** Poor **□** Not conclusive **□**

**Status myoclonus within 48 hours** Present **□** Not present **□**

**High NSE** Performed**□** Poor **□** Not conclusive **□**

**EEG (mandatory)** Performed**□** Poor **□** Not conclusive **□**

**3. Does this patient fulfil the study criteria (see below) for a likely poor neurologic outcome:**

**Yes □ No □**

*Document this answer in e-CRF*

**Study criteria for likely poor outcome**

The following criteria, evaluated at the earliest at 72 hours after randomization or later, need to be fulfilled to establish a likely poor neurological outcome:

* Unconscious patient with absent or extensor motor response to pain (no confounders e.g. sedation)

AND at least TWO of the following:

* Bilaterally absent pupillary and corneal reflexes
* Bilaterally absent SSEP N20-responses
* Diffuse anoxic brain injury on CT or MRI
* Documented status myoclonus within 48h of randomisation
* High levels of serum NSE (>60ug/L at 48 h and/or 72 h)
* An EEG with a highly malignant pattern and without any observed reactivity to sound or pain. Patterns that are considered highly malignant are:
  + Suppressed background (amplitude <10mV, 100% of the recording) without discharges
  + Suppressed background with superimposed continuous periodic discharges
  + Burst-suppression (periods of suppression with amplitude <10mV constituting 50% of the recording) without discharges
  + Burst-suppression with superimposed discharges