



Neurological Prognostication Manual - Version 1.0

OCTOBER 23, 2017

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1. Introduction

The TTM2-trial is evaluating an intervention that cannot be blinded to the treating clinicians, and will therefore employ a conservative and strict protocol for neurological prognostication and related decisions regarding limitations in level-of-care to mitigate potential bias from premature withdrawal of life-sustaining treatment. This adds complexity to the protocol but is a vital design feature that protects the internal validity of the study and was part of the previous TTM study for this reason.

The trial protocol for neuroprognostication was essentially adapted from the 2015 ERC/ESICM guidelines for postresuscitation care¹ with some minor but important modifications. These include delayed assessment for all patients until 96 hours after randomisation, modification of the criteria for a poor prognosis necessary for considering withdrawal of life-sustaining treatment (WLST) and modified criteria for highly malignant EEG-patterns.

In the TTM2-trial daily clinical neurological assessment will use The Full Outline of UnResponsiveness score (The FOUR-score), which is a simple validated tool for use in neurocritical care that improves on the Glasgow Coma Score (see section 4.1.2)

Data on blinded neuroprognostication and the treating clinical team's recommendations regarding level-of-care will be collected in the eCRF and reported in the primary study manuscript.

2. Time-point for prognostication

The first modification from the ERC/ESICM algorithm is that prognostication will be delayed for all patients until 96 hours after randomisation. All patients who are still in the ICU at this time-point should be assessed by the blinded external examiner regardless of their level-of-consciousness. This will include a substantial portion of patients who are more or less awake. Note that a clinical examination is the only mandatory investigation for awake (defined as FOUR M4) patients.

The prognostication should not be performed before 96 hours after randomisation but it may be delayed due to practical reasons (such as weekend or national holiday). Efforts should be made to prevent that any lingering effects of sedative agents affect the assessment. Short-acting sedative agents are recommended.

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

The physician performing the blinded prognostication will be a neurologist, intensivist or other specialist experienced in neuroprognostication after cardiac arrest and who has not been involved in patient care. The blinded prognosticator will be unaware of group allocation, but not of relevant clinical data such as the circumstances regarding the cardiac arrest, information on organ functions, comorbidity or investigations performed to support the prognostication. The prognosticator will report his/her judgement of the neurological prognosis by answering the question:

“Does this patient fulfil the TTM2-trial criteria for a likely poor neurological outcome?”, categorised as “YES” or “NO”.

The answer to this question and the criteria that are fulfilled will be recorded in the eCRF.

This information will be communicated to the treating physicians responsible for the care of the patient and may be used in their decisions on the further level-of-care.

The TTM2-criteria for a likely poor prognosis are conservative. The prognosis for patients not fulfilling these criteria will range from good to uncertain and many will eventually have a poor outcome. This may be discussed between the prognosticator and the treating clinical team but will not be part of the eCRF.

Although the blinded neuroprognostication and the decisions on level-of-care are closely related, they will be considered and reported as separate entities in the TTM2 trial manuscript. The blinded neuroprognosticator will not make any recommendation on WLST; this decision rests with the treating clinical team.

4. Methods for neurological prognostication

Prognostication for patients included in the TTM2 trial will be based on two mandatory, criteria and the presence of at least two out of six additional clinical findings or investigations, some of which are optional but encouraged (see section 5).

A daily clinical examination using the FOUR-score and a routine EEG on all patients who remain unconscious 48-96 hours after randomisation are components of the TTM2-trial protocol. Brain CT, brain MRI, SSEP and serum NSE are optional modalities that are encouraged but not compulsory.

4.1. Clinical examination

A clinical examination using the FOUR-score will be performed daily on all patients.

Absent or extensor motor response to pain (FOUR-score motor response 0-1; Criteria A) at 96h or later in a patient who is considered unaffected by sedative agents or metabolic effects (Criteria B), are two of the three mandatory conditions necessary for the neurologic prognosis to be considered poor.

4.1.2. The FOUR-score

The FOUR-score was developed for use in neurocritical care patients by Dr Eelco F.M. Wijdicks and colleagues at the Mayo clinic in Rochester, US. In comparison with the Glasgow Coma Scale (GCS), the FOUR-score removes the need for the verbal component and contains a more detailed investigation of brain-stem functions whilst simplifying the motor score^{2,3}

The FOUR-score is composed of 4 components, each classified from 0-4: eye response (E), motor response (M), brainstem reflexes (B) and respiration (R).

To facilitate training, all centres will be provided with an instruction DVD and booklets on the FOUR score.

As an exception to the original version of the FOUR-score, the term myoclonus status epilepticus will not be used in the TTM2-trial and the best motor response of the arms will be reported also in patients with continuous myoclonus.

4.1.3. Seizures and myoclonus

The daily clinical examination by the ICU-staff should also include an assessment of seizures, myoclonus and status myoclonus; status myoclonus is defined as continuous and generalised myoclonus persisting for at least 30 min). A prospectively documented early status myoclonus (within 48 hours) is indicative of a poor prognosis.⁴ Information from daily examinations including evaluation of status myoclonus should be available to the blinded physician performing the evaluation.

Treatment of seizures is left to the discretion of the clinicians caring for the patients⁵ and not part of the TTM2-trial protocol. If prolonged sedation is used to suppress clinical seizures or epileptic activity in the EEG, prognostication should still be performed at around 96 hours after randomisation and the results registered in the eCRF. However, the TTM2-criteria demand that confounders are excluded. Confounders include severe metabolic derangement and lingering effects of sedation. Therefore, a patient still under influence of sedation cannot fulfil the TTM2-criteria for a likely poor prognosis.

FOUR Score

Eye Response

- 4 Eyelids open or opened, tracking or blinking to command
- 3 Eyelids open but not tracking
- 2 Eyelids closed but opens to loud voice
- 1 Eyelids closed but opens to pain
- 0 Eyelids remain closed with pain

Motor Response

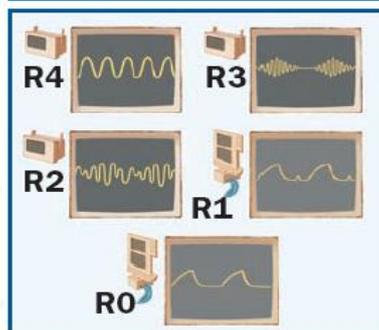
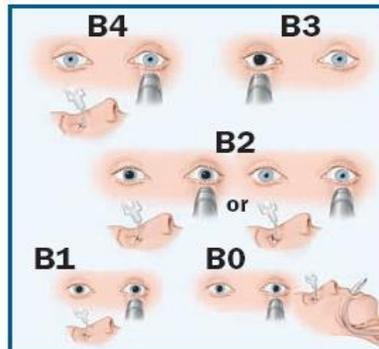
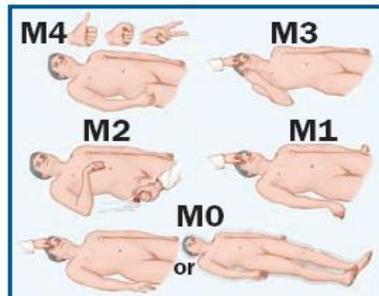
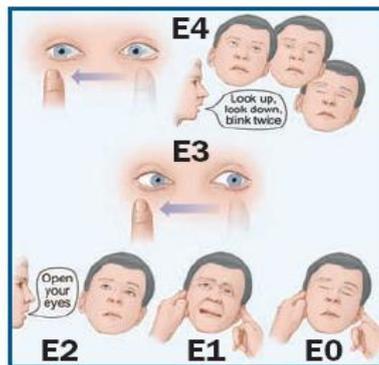
- 4 Thumbs up, fist, or peace sign to command
- 3 Localizing to pain
- 2 Flexion response to pain
- 1 Extensor posturing
- 0 No response to pain or generalized myoclonus status epilepticus

Brainstem Reflexes

- 4 Pupil and corneal reflexes present
- 3 One pupil wide and fixed
- 2 Pupil or corneal reflexes absent
- 1 Pupil and corneal reflexes absent
- 0 Absent pupil, corneal, and cough reflex

Respiration

- 4 Not intubated, regular breathing pattern
- 3 Not intubated, Cheyne-Stokes breathing pattern
- 2 Not intubated, irregular breathing pattern
- 1 Breathes above ventilator rate
- 0 Breathes at ventilator rate or apnea



Instructions for the Assessment of the Individual Categories of the FOUR Score

Eye Response (E)

Grade the best possible response after at least 3 trials in an attempt to elicit the best level of alertness. A score of **E4** indicates at least 3 voluntary excursions. If eyes are closed, the examiner should open them and examine tracking of a finger or object. Tracking with the opening of 1 eyelid will suffice in cases of eyelid edema or facial trauma. If tracking is absent horizontally, examine vertical tracking. Alternatively, 2 blinks on command should be documented. This will recognize a locked-in syndrome (patient is fully aware). A score of **E3** indicates the absence of voluntary tracking with open eyes. A score of **E2** indicates eyelids opening to loud voice. A score of **E1** indicates eyelids open to pain stimulus. A score of **E0** indicates no eyelids opening to pain.

Motor response (M)

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** indicates no motor response or myoclonus status epilepticus.

Brainstem reflexes (B)

Grade the best possible response. Examine pupillary and corneal reflexes. Preferably, corneal reflexes are tested by instilling 2-3 drops of sterile saline on the cornea from a distance of 4-6 inches (this minimizes corneal trauma from repeated examinations). Cotton swabs can also be used. The cough reflex to tracheal suctioning is tested only when both of these reflexes are absent. A score of **B4** indicates pupil and cornea reflexes are present. A score of **B3** indicates one pupil wide and fixed. A score of **B2** indicates either pupil or cornea reflexes are absent, **B1** indicates both pupil and cornea reflexes are absent and a score of **B0** indicates pupil, cornea and cough reflex (using tracheal suctioning) are absent.

Respiration (R)

Determine spontaneous breathing pattern in a nonintubated patient, and grade simply as regular **R4**, irregular **R2**, or Cheyne-Stokes **R3** breathing. In mechanically ventilated patients, assess the pressure waveform of spontaneous respiratory pattern or the patient triggering of the ventilator **R1**. The ventilator monitor displaying respiratory patterns is used to identify the patient generated breaths on the ventilator. No adjustments are made to the ventilator while the patient is graded, but grading is done preferably with PaCO₂ within normal limits. A standard apnea (oxygen-diffusion) test may be needed when patient breathes at ventilator rate **R0**.

Wijdicks EFM, Barnikol WR, Maramattom BV, Manno EM, McClelland RL. Validation of a new Coma Scale: the FOUR score. *Annals of Neurology*. 2005; 58:585-593

4.2. EEG

A routine EEG is mandatory and should be ordered for all patients who survive and are still unconscious at 48 hours after randomisation. The EEG should be performed between 48h and 96h after randomisation but may be cancelled if the patient becomes fully awake (FOUR-score of M4) before the EEG examination occurs.

If it is not possible to perform an EEG study 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 96h.

To perform an EEG at this time-point is in line with standard clinical practice

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. Please refer to the detailed instructions for performance and data-storage of EEGs in the TTM2-trial.

Patterns that are considered highly malignant⁶ are:

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.

Continuous EEG-monitoring is part of a substudy, please refer to the EEG-substudy protocol for details.

4.3. CT brain

CT-brain is an optional examination but should be considered in patients who remain unconscious to exclude other pathologies such as intracranial haemorrhage or infarction. The results of all CT brain examinations should be recorded in the eCRF.

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.⁷

In a substudy, CT-brain is performed on all patients still unconscious at 48-96 hours, please see the CT-substudy protocol for details.

4.4. MRI brain

Brain MRI is an optional examination. If brain MRI is performed, the results should be reported in the eCRF. The best time-point to perform brain-MRI is 3-5 days after cardiac arrest. Signs of global, diffuse, or bilateral multifocal ischaemic lesions are indicative of a poor prognosis.

4.5. Neuron specific enolase in serum

High levels of Neuronspecific enolase (NSE) are indicative of a poor prognosis. Cut-off level for a reliable assessment of poor prognosis may vary with the methodology of assessment.⁸ NSE-sampling is not mandatory, but may be used by sites with experience. If serial samples are available, and these are consistently higher than locally established levels associated with a poor outcome, this may be indicative of a poor outcome. Samples with haemolysis should be disregarded. The levels and the local method of analyses should be recorded in the eCRF.

A separate biobank for centralized analyses is a part of the TTM2-trial in collaboration with the TAME-trial, see biobank instructions for details.

4.6. Somatosensory evoked potentials (SSEP)

The use of SSEP is optional but encouraged if the methodology is available. Artefacts from muscle activity are an important source of bias and the use of a neuromuscular blocking agent should always be considered when performing SSEP.⁹

Absent SSEP N20-responses bilaterally is indicative of a poor prognosis, if SSEP is performed more than 48 hours after randomisation.

5. TTM2 criteria for a likely poor neurological outcome

In the TTM2 trial the prognosis is considered *likely poor* if criteria A, B and C are all fulfilled;

- A. Confounding factors such as severe metabolic derangement and lingering sedation has been ruled out
- B. The patient has no response or a stereotypic extensor response to bilateral central and peripheral painful stimulation at ≥ 96 hours after randomisation.
- C. At least two of the below mentioned signs of a poor prognosis are present:
 - C.1. Bilateral absence of pupillary and corneal reflexes at 96h after CA or later
 - C.2. A prospectively documented early status myoclonus (within 48 hours)
 - C.3. A highly malignant EEG-pattern according to the TTM2 definition without reactivity to sound and painful stimulation.
 - C.4. CT brain with signs of global ischaemic injury, such as: generalised oedema with reduced grey/white matter differentiation and sulcal effacement or MRI-brain with signs of global, diffuse, or bilateral multifocal ischaemic lesions.
 - C.5. Serial serum-NSE samples consistently higher than locally established levels associated with a poor outcome
 - C.6. Bilaterally Absent SSEP N20-responses more than 48 hours after randomisation.

6. Withdrawal of life supporting therapies (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. In making this decision the treating physician may use the information from the blinded prognostication and other factors that are relevant in such a decision.

All participants in the trial will be actively treated until 96 hours after randomisation. There will be two exemptions from this rule:

- Participants in whom further treatment is considered unethical due to irreversible organ failure, a documented medical comorbidity, or other reasons
- Participants in whom brain death is established. This will be defined as death and not WLST.

The assumption of a poor neurological prognosis by the treating clinical team will not be considered sufficient to employ withdrawal of active intensive care prior to 96 hours after randomisation.

After blinded prognostication has been performed, > 96 h after randomization, WLST due to a presumed poor neurological prognosis will be allowed if the TTM2-trial criteria for a likely poor neurological outcome are fulfilled. Participants who have an unclear prognosis at the blinded assessment should be re-examined daily using the FOUR-score and WLST may be considered if neurological function does not improve and if metabolic and pharmacological reasons for prolonged coma can be ruled out. If a decision of WLST is made, the time point and the main reasons for withdrawing life-supporting therapies will be recorded. 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 due to cerebral herniation will be registered as dead when a conclusive assessment has been made. If death is due to brain death, this will be registered. The diagnosis of brain death should be made and documented according to national legislation

8. References

1. Nolan JP, Soar J, Cariou A, et al. European Resuscitation Council and European Society of Intensive Care Medicine 2015 guidelines for post-resuscitation care. *Intensive Care Med* 2015;41:2039-56.
2. Wijdicks EF, Bamlet WR, Maramattom BV, Manno EM, McClelland RL. Validation of a new coma scale: The FOUR score. *Annals of neurology* 2005;58:585-93.
3. Fugate JE, Rabinstein AA, Claassen DO, White RD, Wijdicks EF. The FOUR score predicts outcome in patients after cardiac arrest. *Neurocrit Care* 2010;13:205-10.
4. Lybeck A, Friberg H, Aneman A, et al. Prognostic significance of clinical seizures after cardiac arrest and target temperature management. *Resuscitation* 2017;114:146-51.
5. Reynolds AS, Claassen J. Treatment of Seizures and Postanoxic Status Epilepticus. *Semin Neurol* 2017;37:33-9.
6. Westhall E, Rossetti AO, van Rootselaar AF, et al. Standardized EEG interpretation accurately predicts prognosis after cardiac arrest. *Neurology* 2016;86:1482-90.
7. Moseby-Knappe M, Pellis T, Dragancea I, et al. Head computed tomography for prognostication of poor outcome in comatose patients after cardiac arrest and targeted temperature management. *Resuscitation* 2017.
8. Stammet P. Blood Biomarkers of Hypoxic-Ischemic Brain Injury after Cardiac Arrest. *Semin Neurol* 2017;37:75-80.
9. Horn J, Tjepkema-Cloostermans MC. Somatosensory Evoked Potentials in Patients with Hypoxic-Ischemic Brain Injury. *Semin Neurol* 2017;37:60-5.

Prognostication Checklist

1 FOUR-score

Questions	Answers
1. Eye Response?	<input type="checkbox"/> 4. Eyelids open and tracking, or blinking on command <input type="checkbox"/> 3. Eyelids open but not tracking <input type="checkbox"/> 2. Eyelids closed but open to loud voice <input type="checkbox"/> 1. Eyelids closed but open to pain <input type="checkbox"/> 0. Eyelids remain closed with pain
2. Motor Response?	<input type="checkbox"/> 4. Makes sign (thumbs-up, fist, peace) <input type="checkbox"/> 3. Localises painful stimulus <input type="checkbox"/> 2. Flexion response to pain <input type="checkbox"/> 1. Extension response to pain <input type="checkbox"/> 0. No response to pain or myoclonus
3. Brainstem Reflexes?	<input type="checkbox"/> 4. Pupillary and corneal reflexes present <input type="checkbox"/> 3. One pupil wide and fixed <input type="checkbox"/> 2. Pupillary <i>corneal</i> reflexes absent <input type="checkbox"/> 1. Pupillary <i>and</i> corneal reflexes absent <input type="checkbox"/> 0. Absent pupillary, corneal, and cough reflex
4. Respiration?	<input type="checkbox"/> 4. Not intubated, regular breathing pattern <input type="checkbox"/> 3. Not intubated, Cheyne-Stokes breathing <input type="checkbox"/> 2. Not intubated, irregular breathing <input type="checkbox"/> 1. Intubated - breathes above ventilator settings <input type="checkbox"/> 0. Intubated - breathes below ventilator settings

2 Criteria A and B

Confounding factors such as severe metabolic derangement and lingering sedation has been ruled out

Yes No

No response or a stereotypic extensor response to bilateral central and peripheral painful stimulation at 96h after randomisation

Yes No

3 Criteria C (At least 2)

Corneal and Pupillary reflexes	Performed <input type="checkbox"/>	Poor <input type="checkbox"/>	Not conclusive <input type="checkbox"/>
Early status myoclonus (within 48h)		Present <input type="checkbox"/>	Not Present <input type="checkbox"/>
EEG	Performed <input type="checkbox"/>	Poor <input type="checkbox"/>	Not conclusive <input type="checkbox"/>
Brain CT*	Performed <input type="checkbox"/>	Poor <input type="checkbox"/>	Not conclusive <input type="checkbox"/>
Brain MRI*	Performed <input type="checkbox"/>	Poor <input type="checkbox"/>	Not conclusive <input type="checkbox"/>
High serial NSE	Performed <input type="checkbox"/>	Poor <input type="checkbox"/>	Not conclusive <input type="checkbox"/>
SSEP	Performed <input type="checkbox"/>	Poor <input type="checkbox"/>	Not conclusive <input type="checkbox"/>
EEG	Performed <input type="checkbox"/>	Poor <input type="checkbox"/>	Not conclusive <input type="checkbox"/>

*CT and MRI should be considered **one** criterion (Neuroimaging)

Does this patient fulfil the criteria for a likely poor neurological outcome? Yes No

4 The TTM2-trial criteria for a likely poor neurological outcome

In the TTM2 trial the prognosis is considered likely poor if criteria A, B and C are all fulfilled.

- A** Confounding factors such as severe metabolic derangement and lingering sedation has been ruled out.
- B** The patient has no response or a stereotypic extensor response to bilateral central and peripheral painful stimulation at ≥ 96 hours after randomisation.
- C** At least two of the below mentioned signs of a poor prognosis are present:
 - C1** Bilateral absence of pupillary and corneal reflexes at 96h after randomisation or later
 - C2** A prospectively documented early status myoclonus (within 48h of randomisation)
 - C3** A highly malignant EEG-pattern according to the TTM2 definition without reactivity to sound and painful stimulation. Patterns that are considered highly malignant are:
 - i. Suppressed background (amplitude $< 10\text{mV}$, 100% of the recording) without discharges.
 - ii. Suppressed background with superimposed continuous periodic discharges.
 - iii. Burst-suppression (periods of suppression with amplitude $< 10\text{mV}$ constituting 50% of the recording) without discharges.
 - iv. Burst-suppression with superimposed discharges.
 - C4** CT brain with signs of global ischaemic injury, such as: generalised oedema with reduced grey/white matter differentiation and sulcal effacement or MRI-brain with signs of global, diffuse, or bilateral multifocal ischaemic lesions
 - C5** Serial serum-NSE samples consistently higher than locally established levels associated with a poor outcome
 - C6** Bilaterally Absent SSEP N20-responses more than 48 hours after randomisation