RESEARCH PROTOCOL

Treatment of electroencephalographic status epilepticus after cardiopulmonary resuscitation (TELSTAR)

a randomized controlled trial

Participants

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PROTOCOL TITLE

TELSTAR: Treatment of electroencephalographic status epilepticus after cardiopulmonary resuscitation

A randomized controlled trial

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	**ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)**
AE	**Adverse Event**
AED	**Anti-epileptic Drug**
APACHE	**Acute Physiology and Chronic Health Evaluation**
AR	**Adverse Reaction**
CA	**Competent Authority**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
CK	**Creatine Kinase**
CPC	**Cerebral Performance Category**
CV	**Curriculum Vitae**
DSMB	**Data Safety Monitoring Board**
EEG	**Electroencephalography**
ERP	**Event Related Potentials**
EU	**European Union**
EudraCT	**European drug regulatory affairs Clinical Trials**
GCP	**Good Clinical Practice**
GOS	**Glasgow Outcome Scale**
IB	**Investigator's Brochure**
IC	**Informed Consent**
IMP	**Investigational Medicinal Product**
IMPD	**Investigational Medicinal Product Dossier**
MADRS	**Montgomery and Åsberg Depression Rating Scale**
METC	**Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)**
NPO	**Neuropsychological Examination (in Dutch: neuropsychologisch onderzoek)**
PROBE	**Prospective Randomized Open label Blinded Endpoint**
(S)AE	**(Serious) Adverse Event**
SF-36	**Medical Outcomes Study 36-item short-form health survey**
SPC	**Summary of Product Characteristics (in Dutch: officiële productinfomatie IB1-tekst)**

Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
Wbp	**Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)**
WMO	**Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Rationale: Electroencephalographic status epilepticus is described in 9-35% of patients with postanoxic encephalopathy after cardiac arrest and is associated with case fatality rates of 90-100%. It is unclear whether (some) electroencephalographic seizure patterns in these patients represent a condition which can be treated with antiepileptic drugs to improve outcome, or have to be regarded as an expression of severe ischemic damage, in which treatment with antiepileptic would be futile. Therefore, both treatment *with* and treatment *without* antiepileptic drugs are considered standard modalities in these patients. We aim to compare these standard strategies and hypothesize that aggressive and early treatment of electro-encephalographic status epilepticus with antiepileptic drugs improves outcome as compared to treatment without these drugs.

Objective: To estimate the effect of medical treatment of electro-encephalographic status epilepticus on neurological outcome of patients with postanoxic encephalopathy after cardiac arrest

Study design: We propose a multicenter clinical trial with randomized treatment allocation, open label treatment and blinded endpoint evaluation (PROBE design). The intervention contrast will be aggressive medical treatment vs. no treatment of electroencephalographic status epilepticus, in addition to standard best medical management of comatose patients after cardiac arrest.

Study population: The study population will consist of adult patients with postanoxic encephalopathy after cardiac arrest, admitted to the intensive care unit, treated with hypothermia, with electroencephalographic status epilepticus on continuous EEG, who are eligible for inclusion in this trial.

Intervention: Treatment of electroencephalographic status epilepticus will be based on international guidelines for the treatment of overt status epilepticus The objective of the treatment will be to suppress all epileptiform activity in the EEG. If the electroencephalographic status epilepticus will return after tapering sedative treatment at 24 hours, the procedure will be repeated. If the status will return after 2 x 24 hours, it will be considered refractory.

Main study parameters/endpoints: The primary outcome measure will be neurological outcome defined as the score on the Cerebral Performance Category (CPC) at 3 months dichotomized as good (CPC 1-2 = no or moderate neurological disability) and poor (CPC 3-5 = severe disability, coma, or death).

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Medical treatment of electroencephalographic status epilepticus may modify the high risk of death. Otherwise, this treatment of electroencephalographic status epilepticus may lead to prolonged hospitalization of several days of comatose patients that

otherwise would have died. The risk of an increase of morbidity or mortality on the longer term is negligible.

1. INTRODUCTION AND RATIONALE

Of comatose patients after cardiac arrest, 40-66% never regain consciousness as a result of diffuse postanoxic encephalopathy (Bernard et al., 2002; Krumholz et al., 1988; Zandbergen et al., 1998). In these patients, a broad spectrum of electroencephalography (EEG) changes can be observed (Cloostermans et al., 2012). Electroencephalographic status epilepticus is described is 9-35% (Cloostermans et al., 2012; Rittenberger et al., 2012; Rossetti et al., 2009) and is associated with poor outcome: case fatality was 90-100% in prospective case series, despite treatment with anti-epileptic drugs (Celesia et al., 1988; Hui et al., 2005; Kaplan & Morales, 2008; Krumholz et al., 1988; Legriel et al., 2009; Rossetti et al., 2007; Rossetti et al., 2009; San-Juan et al., 2009).

The diagnosis of status epilepticus on the electroencephalogram (EEG) in comatose patients after cardiac arrest is controversial (Brenner, 2002; Chong & Hirsch, 2005). It may consist of unequivocal seizures: generalized spike-wave discharges at 3/s or faster or clearly evolving discharges of any type at 4/s or faster, either generalized or focal (Hirsch, 2013). However, some experts also consider other rhythmic or periodic patterns, such as generalized or lateralized periodic discharges or rhythmic delta activity, as seizure activity.

It is unclear whether (some) electroencephalographic seizure patterns in patients with postanoxic encephalopathy represent a condition which can be treated with antiepileptic drugs to improve patients' outcome, or have to be regarded as an expression of severe ischemic damage, in which treatment with antiepileptic would be futile (Tjepkema-Cloostermans et al., 2013). Case series have suggested that in patients with electroencephalographic status epilepticus, preserved brainstem reactions and EEG background reactivity are associated with a favorable outcome (Rossetti et al., 2009). It is unclear whether treatment with anti-epileptic drugs reduces the risk of a poor outcome in these patients and if so, how aggressive this treatment should be. In the only prospective non-randomized intervention study, aggressive treatment up to pentobarbital induced burst-suppression resulted in a good outcome of 7% of patients with clinically overt or electroencephalographic status epilepticus (Bouwes et al., 2013). This proportion is approximately the same as reported in observational studies, irrespective of treatment (Kaplan & Morales, 2008; Legriel et al., 2009; Rossetti et al., 2007; Rossetti et al., 2009; San-Juan et al., 2009).

Despite the lack of evidence, most neurologists treat status epilepticus in comatose patients after cardiac arrest with anti-epileptic drugs. Increased detection of electroencephalographic status epilepticus by continuous EEG monitoring has led to increased prescription of anticonvulsant drugs (Abend et al., 2010; Kilbride et al., 2009). If treated at all, treatment is mostly moderate. Only approximately one third treat these patients equal to those with clinically overt status epilepticus (Abend et al., 2010; Bouwes et al., 2010). Both *aggressive* and *no* treatment of electroencephalographic status epilepticus still are considered standard modalities, where some experts believe that treatment is useless and others that it is unethical to withhold it.

Apart from the intensity of treatment, the timing of treatment probably plays an important role. As continuing status epilepticus is known to lead to brain damage in itself. Mechanisms such as excessive glutamate release are known to worsen brain damage in ongoing status epilepticus within twenty to forty minutes (Fujikawa, 2005). Also, prolonged duration of status epilepticus reduces the effect of treatment, e.g. due to receptor trafficking (Naylor et al., 2005). Therefore, rational treatment should be initiated as soon as possible. Recently, with continuous EEG monitoring starting twelve hours after cardiac arrest, we found that in approximately one quarter of patients with electroencephalographic status epilepticus, the epileptiform patterns start before 24 hours after cardiac arrest. In previous studies, EEG monitoring only started at a median of two to three days after cardiac arrest, indicating that diagnosis and subsequent treatment of electroencephalographic status epilepticus started late (Kaplan & Morales, 2008; Rossetti et al., 2007; Rossetti et al., 2009). The initiation of treatment many hours after the onset of electroencephalographic status epilepticus may be too late to prevent irreversible damage.

We conclude from this overview that evidence for effect of medical treatment of electroencephalographic status epilepticus in comatose patients after cardiac arrest is insufficient. We also conclude that if effective, treatment should probably be sufficiently aggressive and initiated as early as possible after its onset. Therefore, we aim to study the effect of aggressive and early medical treatment of electro-encephalographic status epilepticus on functional outcome of comatose patients after cardiac arrest in a randomized controlled clinical trial.

Hypothesis

Medical treatment of electro-encephalographic status epilepticus improves outcome of patients with postanoxic encephalopathy after cardiac arrest.

2. OBJECTIVES

Primary Objective

To estimate the effect of medical treatment of electro-encephalographic status epilepticus on neurological outcome of patients with postanoxic encephalopathy after cardiac arrest

Secondary Objectives

1) To assess mortality, cognitive functioning, quality of life, and depression of surviving patients

2) Cost-effectiveness analysis of medical treatment of electro-encephalographic status epilepticus as compared with no treatment.

3. STUDY DESIGN

We propose a multicenter clinical trial with randomized treatment allocation, open label treatment and blinded endpoint evaluation (PROBE design). The intervention contrast will be aggressive medical treatment vs. no treatment of electroencephalographic status epilepticus, in addition to standard best medical management of comatose patients after cardiac arrest, including therapeutic hypothermia (if applied in participating center).

STUDY POPULATION

4.1 Population (base) and participating centers

The study population will consist of adult patients with postanoxic encephalopathy after cardiac arrest, admitted to the intensive care unit, with electroencephalographic status epilepticus on continuous EEG, who are eligible for inclusion in this trial.

Participating centres should have adequate experience with (i) the intensive care management of patients with postanoxic encephalopathy after cardiac arrest and (ii) the use of early (<24 hours) continuous EEG monitoring in these patient with at least eight electrodes.

4.2 Inclusion criteria

-Patients after cardiac arrest with suspected postanoxic encephalopathy

-Age 18 years or older

-Continuous EEG with at least eight electrodes started within 24 hours after cardiac arrest

-Electroencephalographic status epilepticus on continuous EEG*

-Possibility to start treatment within three hours after detection of electroencephalographic status epilepticus.

*Definitions of electroencephalographic status epilepticus will be according to the standardized critical care EEG Terminology (Hirsch et al., 2013). They may consist of generalized spike-wave discharges at 3 Hz or faster, clearly evolving discharges of any type at 4 Hz or faster (either generalized or focal), or periodic discharges (generalized or lateralized). For continuous seizure activity, the minimum duration requirement is 30 minutes. Intermittent seizures of 5 minutes and longer, recurring at least twice, with seizure-free intervals shorter than 60 minutes will also be included. EEG assessment for inclusion will be left to the discretion of the treating neurologist or clinical neurophysiologist.

4.3 Exclusion criteria

-A known history of another medical condition with limited life expectancy (<6 months)

-Any progressive brain illness, such as a brain tumor or neurodegenerative disease

-Pre-admission Glasgow Outcome Scale score of 3 or lower

-Reason other than neurological condition to withdraw treatment

-Follow-up impossible due to logistic reasons, for example not living in the Netherlands

4.4 Sample size calculation

Power calculations are hampered by the absence of any data from randomized trials. With a presumed reduction of poor outcome of 7% (Bouwes et al., 2013), from 99% - 92%, alpha of 5%, power of 80%, and one tailed testing, 84 patients per treatment group are needed to be able to detect superiority of the treatment under study. To compensate for the interim analysis, two additional patients per group will be included (interim analysis according to O'Brien Fleming). This indicates an intended 172 inclusions.

An interim analysis will be performed after 86 included patients have had their primary outcome measurement. If the difference between the treatment groups at that time is significant at $p<0.00557$, the trial will be stopped because of "proof beyond reasonable doubt" that treatment with anti-epileptic drugs is superior above treatment without anti-epileptic drugs.

With an estimation of an incidence of electroencephalographic status epilepticus of 20% in patients with postanoxic coma (Cloostermans et al., 2012) the total number of patients to be monitored will be 860. With five participating hospitals, we estimate an enrollment period of four and a half years. During the trial, we aim to recruite more participating centers in order to reduce the enrollment period.

3. TREATMENT OF SUBJECTS

3.1 Investigational treatment

Intervention group

Since no treatment with anti-epileptic drugs (AED) has been proven superior to other, local protocols for the treatment of status epilepticus may vary slightly. Since we aim for a pragmatic trial, the choice of treatment of electroencephalographic status epilepticus for the intervention group is ultimately left to the discretion of the treating neurologist, based on local protocols. However, to prevent large differences with respect to the intensity of treatment, the following recommendations are made. These recommendations are based on international guidelines on treatment of overt status epilepticus (Brophy et al., 2012; Rossetti et al., 2011).

The objective of treatment with AED is to suppress all epileptiform activity. There is no clear proof that induction of a burst-suppression pattern is of additional value and induction of burst suppression is therefore not obligate. If the electroencephalographic status epilepticus returns after tapering sedative treatment at 24 hours, the procedure will be repeated. If the status returns after 2 x 24 hours, it will be considered refractory.

Decisions regarding limitation or withdrawal of treatment will be done in accordance with the Dutch guideline on postanoxic coma (“Richtlijn prognose van post-anoxisch coma”). Reasons for withdrawal of treatment will be documented.

Step 1.

A benzodiazepine (make a choice): lorazepam or midazolam (initial loading dose followed by continuous infusion, where dosing regimes are based on national and local protocols for status epilepticus treatment)

PLUS

Fenytoine bolus i.v. 15-20 mg/kg in 30 minutes, followed by 150 mg 2 dd 1, and adapted depending on serum levels (including free fraction). If fenytoine is contraindicated, use valproate or levetiracetam, as recommended in step 2.

Step 2 (if step 1 fails to suppress epileptiform activity).

Propofol infusion with a maximum of 8 mg/kg/hour, which is a higher dose than typically advised (i.e. 5 mg/kg/h), as the duration of treatment is limited. Serum Creatine Kinase (CK) and development of metabolic acidosis should be controlled.

PLUS

A second anti-epileptic drug in addition to fenytoin:

Option 1: levetiracetam bolus 1500 mg, followed by 1000 mg 2 dd 1 intravenously

Option 2: valproic acid bolus 10-20 mg/kg in 30 min, followed by15 mg/kg/day in 2 dosages intravenously. Serum levels should be measured, as the combination of fenytoin and valproic acid may result in a reduction of serum levels of fenytoin.

Step 3 (if step 1 and 2 fail to suppress epileptiform activity).

Thiopental, initial dosage 12,5 mg/kg/hr for the first 6 hours followed by 5 mg/kg/hr for 6 hours. After these loading dosages treatment should be guided by the EEG pattern.

Control group:

The non-intervention group will be treated conform standard guidelines of treatment of comatose patients after cardiac arrest, but without anti-epileptic drugs or EEG based deep sedation. Treatment to suppress clinical myoclonia or seizures with a low dose of sedative medication is left to the discretion of the treating physician.

Decisions regarding limitation or withdrawal of treatment will be done in accordance with the Dutch guideline on postanoxic coma ("Richtlijn prognose van post-anoxisch coma"). Reasons for withdrawal of treatment will be documented.

3.2 Use of co-intervention (if applicable)

n.a.

3.3 Escape medication (if applicable)

n.a.

4. INVESTIGATIONAL PRODUCT

4.1 Name and description of investigational product(s)

Potentially used drugs for the treatment of electroencephalographic status epilepticus are the following medications, which are all in the Dutch guideline for treatment of status epilepticus. Summaries of Product Characteristics (SPC) of all these are enclosed.

Fenytoin	SPC h11547
Valproate	SPC h14996
Levetiracetam	SPC h108443_fsuk
Propofol	SPC 27043
Midazolam	SPC h22595
Thiopental	SPC h11772

4.2 Summary of findings from non-clinical studies

Please see the enclosed SPC documents of the various medications

4.3 Summary of findings from clinical studies

Please see the enclosed SPC documents of the various medications

4.4 Summary of known and potential risks and benefits

Please see the enclosed SPC documents of the various medications

4.5 Description and justification of route of administration and dosage

All medication will be given intravenously, as is the regular route of administration in patients with a status epilepticus. Dosing will be based on the medications' effect in terms of suppression of epileptiform activity, as is the regular way of dosing these medications in patients with a status epilepticus. Dosages will not be higher than the standard recommendations for these patients.

4.6 Preparation and labelling of Investigational Medicinal Product

After randomization, treatment is open label, without blinding, and all modalities are part of routine treatment of patients with status epilepticus. Therefore, there will be no specific preparation or additional labelling of these medications.

4.7 Drug accountability

Since treatment is open label and part of routine treatment of the patients under study in both treatment groups, guided by local protocols, there will be no additional rules for shipment, receipt, disposition, return, or destruction of the used medication.

5. NON-INVESTIGATIONAL PRODUCT

n.a.

6. METHODS

6.1 Study parameters/endpoints

6.1.1 Main study parameter/endpoint

The primary outcome measure will be neurological outcome defined as the score on the Cerebral Performance Category (CPC) at 3 months dichotomized as good (CPC 1-2 = no or moderate neurological disability) and poor (CPC 3-5 = severe disability, coma, or death).

6.1.2 Secondary study parameters/endpoints

Secondary outcome measures will include i) mortality; ii) the CPC scores at 6 and 12 months; iii) length of stay on the ICU; iv) duration of mechanical ventilation; v) seizure recurrence within one year; vi) quality of life as measured by the Medical Outcomes Study 36-item short-form health survey (SF36) (Ware et al., 1994), vii) depression as measured by the Montgomery and Åsberg Depression Rating Scale (MADRS) (Montgomery & Asberg, 1979), and viii) cognitive functioning as measured by detailed neuropsychological examination after 12 months.

Secondary outcome measures in survivors will be collected to thoroughly assess outcome and quality of life of survivors. These outcome measures will not be collected to test between-group differences, since the estimated number of survivors is small.

Furthermore, a limited amount of data on the use of resources will be collected for analysis of cost-effectiveness, including place of residence at one year and admission in hospitals, rehabilitations centers, and nursing homes within the first year.

6.1.3 Determinants

These are all data that will be collected as a part of routine patient care and collected in case record files: age, sex, medical history, neurological examination on admission, neurological examination on randomization, details of resuscitation, details on cause of resuscitation and cardiac rhythm, EEG pattern on randomization, daily neurological examination during admission, APACHE score, selected medication during admission, duration of ventilation, duration of admission.

6.2 Randomisation, blinding and treatment allocation

Subjects will be randomized using ALEA (Clinical Trial Center Maastricht, The Netherlands), which is an online, central randomization service. To prevent imbalance of allocated treatments, blocked randomization will be used, with a 1:1 allocation, stratified by center, and random block size ranging from 4 to 10 subjects.

Blinding of treatment allocation

It will not be possible to see the treatment allocation before the patient is randomized and registered in the study database. Neither will it be possible to withdraw the patient from the database after treatment assignment. After randomization, the treating physician will be aware of the treatment assignment.

Blinding of outcome assessment

Assessment of the primary and secondary outcome measures will be done by an investigator or research nurse that will be blinded for treatment allocation.

6.3 Study procedures

In participating hospitals, continuous EEG monitoring is part of regular patient care and is initiated as soon as possible after admission on the intensive care unit.

Baseline data will be obtained at admission as part of regular patient care and include: clinical data, EEG data, medical history, and use of medication.

After randomization, daily physical, neurological, and additional examinations will be part of routine patient care. Apart from the study treatment, patients will not be subjected to additional procedures during admission.

It is possible that treatment of electroencephalographic status epilepticus will lead to longer admission on the intensive care unit of several days. We assume this reasonable, since both strategies (treatment and no treatment of electroencephalographic status epilepticus) are current standard modalities in these patients.

Follow up in surviving patients will be done by telephone interview by a trained research nurse three months after admission. Surviving patients will be asked informed consent for participation and additional follow-up on long term outcome, including quality of life as measured by the SF36 (Ware et al., 1994), depression as measured by the MADRS (Montgomery & Asberg, 1979), and cognitive functioning as measured by detailed neuropsychological examination at one year. This will be by means of telephone interviews. Separate informed consent will be asked for

neuropsychological examination at twelve months, which will take place in the local hospital (please see F4 testbatterij NPO for details of the test battery).

6.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

6.5 Replacement of individual subjects after withdrawal

Subjects will be replaced after withdrawal for any reason.

6.6 Follow-up of subjects withdrawn from treatment

Every attempt will be made to complete the primary follow-up in these patients.

6.7 Premature termination of the study

A planned interim analysis will be performed after 86 inclusions. If the difference between the treatment groups will be significant at $p<0.00557$, the trial will be stopped because of “proof beyond reasonable doubt” that treatment with anti-epileptic drugs is superior above treatment without anti-epileptic drugs.

7. SAFETY REPORTING

7.1 Section 10 WMO event

In accordance to section 10, subsection 1, of the WMO, the investigator will inform the subjects and the reviewing accredited METC if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited METC, except insofar as suspension would jeopardise the subjects' health. The investigator will take care that all subjects are kept informed.

7.2 AEs, SAEs and SUSARs

7.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the experimental intervention. Adverse events will not be recorded, except those that meet the criteria for 'Serious Adverse Event' (see section 7.2.2).

7.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that at any dose:

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect;
- Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a serious adverse experience when, based upon appropriate medical judgement, the event may jeopardize the subject or may require an intervention to prevent one of the outcomes listed above.

Since case fatality in the patient population under study is known to be 90-100%, line listing of Serious Adverse Events including deaths will be performed, with reporting once per six months. An exception will be made for Suspected Unexpected Serious Adverse Reactions, for which expedited reporting will take place (see section 7.2.3), The reporting of SAEs will be limited to events that occur during the intensive treatment period (the period in which patients are exposed to the treatment under

study) and all deaths within the follow-up period of one year. Reporting of SAEs will be the responsibility of the study coordinator and the primary investigator.

SAEs will be reported as line listings through the web portal *ToetsingOnline* to the accredited METC that approved the protocol.

7.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Adverse reactions are all untoward and unintended responses to an investigational product related to any dose administered.

Unexpected adverse reactions are SUSARs if the following three conditions are met:

1. the event must be serious (see chapter 7.2.2);
2. there must be a certain degree of probability that the event is a harmful and an undesirable reaction to the medicinal product under investigation, regardless of the administered dose;
3. the adverse reaction must be unexpected, that is to say, the nature and severity of the adverse reaction are not in agreement with the product information as recorded in:
   - Summary of Product Characteristics (SPC) for an authorised medicinal product;
   - Investigator's Brochure for an unauthorised medicinal product.

The investigator / sponsor will report expedited the following SUSARs through the web portal *ToetsingOnline* to the METC:

- SUSARs that have arisen in the clinical trial that was assessed by the METC;
- SUSARs that have arisen in other clinical trials of the same investigator / sponsor and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the clinical trial that was assessed by the METC.

The expedited reporting of SUSARs through the web portal ToetsingOnline is sufficient as notification to the competent authority.

The expedited reporting will occur not later than 15 days after the investigator / sponsor has first knowledge of the adverse reactions. For fatal or life threatening cases the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

Besides the expedited reporting to the METC through the web portal *toetsingonline* SUSARs will be reported to the independent Data Safety Monitoring Board, within 48 hours after the event (see also section 7.5)

7.3 Annual safety report

In addition to the expedited reporting of SUSARs, the investigator / sponsor will submit, once a year throughout the clinical trial, a safety report to the accredited METC.
This safety report consists of:

- a list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions, ordered by organ system, per study;
- a report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

Annual safety reports will be submitted through the web portal *ToetsingOnline* to the accredited METC.

7.4 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. SAEs need to be reported till end of study within the Netherlands, as defined in the protocol

7.5 Data Safety Monitoring Board (DSMB)

The trial will be monitored by an independent data monitoring committee. The data monitoring committee will be chaired by a neurologist, and further include an intensivist and a biostatistician. Details on the composition of the DSMB and rules on analysis and reporting are included in K5: “DSMB charter”.

The DSMB will review data for safety after every 43 included patients from the study have had their primary outcome measurement. For that purpose, the DSMB will receive after every 43 inclusions by email reports of SAEs, poor outcomes, and deaths per centre. At that time, the DSMB will review general aspects of the trial, including patient recruitment,

patient inclusion, and unexpected events. Because of the expected high proportion of patients with a poor outcome in the patient group under study, and the consequent overlap between safety endpoints and the primary endpoint, the evaluation of safety by the DSMB at that time will be qualitative. In addition, suspected unexpected serious adverse reactions (SUSARs) will be reported <48 hours.

Summary of key efficacy endpoints (primary outcomes, mortality) will be provided for a planned interim analysis after 86 inclusions. The study may be stopped because of 'proof beyond reasonable doubt' or because of safety concerns. Proof beyond reasonable doubt indicates a statistically significant difference between the treatment groups at $p<0.00557$ after 86 inclusions.

The advice(s) of the DSMB will only be sent to the investigator / sponsor of the study. Should the investigator / sponsor decide not to fully implement the advice of the DSMB, the investigator / sponsor will send the advice to the reviewing METC, including a note to substantiate why (part of) the advice of the DSMB will not be followed.

8. STATISTICAL ANALYSIS

8.1 Primary study parameter(s)

The primary analysis will be a single comparison between the treatment groups of the primary outcome measure after three months. This analysis will be performed according to the intention-to-treat principle. To assess the effect of treatment with anti-epileptic drugs, an absolute risk reduction of poor outcome and its corresponding 95% confidence interval will be calculated.

8.2 Secondary study parameter(s)

Baseline characteristics, raw distributions on the CPC, and scores of secondary outcome measures will be presented in a descriptive way.

For secondary outcome measures, between-group differences will be analyzed by means of independent samples t-tests, Mann-Whitney tests, or Fisher exact tests, where appropriate.

If necessary, multivariable regression analysis will be used to adjust for imbalances in main prognostic variables between intervention and control group.

8.3 Interim analysis (if applicable)

A planned interim analysis will be performed after 86 inclusions. If the difference between the treatment groups will be significant at $p<0.00557$, the trial will be stopped because of "proof beyond reasonable doubt" that one treatment is superior above the other.

9. ETHICAL CONSIDERATIONS

9.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (7th revision, Fortaleza, 2013) and in accordance with the Dutch Medical Research Involving Human Subjects Act (WMO) and local guidelines.

9.2 Recruitment and consent

Patients with electrographic status epilepticus after cardiac arrest will be recruited at intensive care units at the participating hospitals. Eligible patients will be randomized as soon as possible after the diagnosis of electroencephalographic status epilepticus, so that treatment will not be postponed. The treating intensivist / neurologist / clinical neurophysiologist will inform a patient's legal representative as soon as possible after randomization, and ask for consent for the use of anonymized clinical data and for the first telephone follow-up after 3 months. Survivors will be asked for informed consent for long term follow up separately, if their neurological condition is sufficiently good.

No consent will be obtained prior to randomization, as this procedure unnecessarily delays treatment and the possible prevention of additional brain injury. We consider prompt treatment initiation of vital importance for the effect of treatment of status epilepticus and thus for the quality of the data that will by provided by the trial. We consider it reasonable to start treatment without written informed consent, since we compare two standard treatment modalities. Furthermore, with this approach we avoid putting time pressure on patient's legal representative in making a decision on participation in this severe medical condition in the acute situation.

9.3 Objection by minors or incapacitated subjects

n.a.

9.4 Benefits and risks assessment, group relatedness

Of comatose patients after cardiac arrest with electroencephalographic status epilepticus, 90-100% dies (Celesia et al., 1988; Hui et al., 2005; Kaplan & Morales, 2008; Krumholz et al., 1988; Legriel et al., 2009; Rossetti et al., 2007; Rossetti et al., 2009; San-Juan et al., 2009). It is unclear whether (some) electroencephalographic seizure patterns in these patients represent a condition which can be treated with antiepileptic drugs to improve outcome, or rather severe ischemic damage, in which treatment is futile.

On the majority of intensive care units continuous EEG monitoring is not a part of regular care, which indicates that electroencephalographic status epilepticus is often not even diagnosed. If diagnosed, most neurologists treat with anti-epileptic drugs (Bouwes et al., 2010). However, treatment is mostly moderate and started relatively late (Abend et al., 2010; Bouwes et al., 2010). If effective, treatment should probably be aggressive and initiated as early as possible, analogous to treatment of status epilepticus in general (Fujikawa, 2005; Naylor et al., 2005). Uncontrolled case series have suggested a small reduction of mortality after aggressive treatment (Bouwes et al., 2013; Rossetti et al., 2009) and some experts believe that it is unethical to withhold such aggressive treatment. However, controlled trials are lacking and both strategies (*treatment* and *no treatment* of electroencephalographic status epilepticus) are current standard modalities in these patients.

Aggressive and early treatment of electroencephalographic status epilepticus may modify the high risk of death. Otherwise, aggressive treatment of electroencephalographic status epilepticus may lead to prolonged hospitalization of several days of comatose patients that otherwise would have died. The risk of an increase of morbidity or mortality is negligible.

9.5 Compensation for injury

Dispensation from the obligation to provide insurance is obtained, since both treatment in the experimental group and treatment in the control group are standard, daily used, modalities. The risk of increased morbidity or mortality by participation in the trial is therefore considered negligible.

9.6 Incentives

n.a.

10. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

10.1 Handling and storage of data and documents

For data collection and management, the OpenClinica® open source software (OpenClinica LLC, Waltham, MA, USA) will be used. All patients will receive a study number by which all data will be coded. The study coordinator / principal investigator will have access to the source data, if necessary. The code will be safeguarded by them.

10.2 Monitoring and Quality Assurance

In accordance with Good Clinical Practice (GCP) guidelines, there will be a monitor system. Herewith it will be verified that

(a) the rights and well-being of the included patients are protected

(b) reported trial data are accurate, complete, and verifiable from source documents.

(c) the conduct of the trial is in compliance with the currently approved protocol, with GCP, and with applicable regulatory requirements.

10.3 Amendments

A 'substantial amendment' will be defined as an amendment to the terms of the METC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the METC and to the competent authority.

Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the investigator / sponsor.

10.4 Annual progress report

The sponsor / investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events / serious adverse reactions, other problems, and amendments.

10.5 End of study report

The investigator / sponsor will notify the accredited METC and the competent authority of the end of the study within a period of 90 days. The end of the study is defined as the last patient's last visit.

In case the study is ended prematurely, the investigator / sponsor will notify the accredited METC and the competent authority within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator / sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC and the Competent Authority.

10.6 Public disclosure and publication policy

The trial has been registered in the United States National Institutes of Health Clinical Trials registry (clinicaltrials.gov, identifier NCT02056236) on February 4, 2014..

Publications will be by the executive committee, in the name of the steering committee. Pre-defined sub-studies or post-hoc analysis by participating investigators are possible after consultation of the executive committee and only after publication of the primary results of the trial.

The executive committee consists of the six investigators from the trial initiating centers (J. Hofmeijer, M.J. Blans, J. Horn, A.F. van Rootselaar, A. Beishuizen, M.J.A.M. van Putten) and the study-coordinator (B.J. Ruijter, PhD student at the University of Twente). The steering committee consists of one or two local investigators from each other participating center (C.W.E. Hoedemaekers, W.M. van den Bergh, J.W.J. Elting. S.C. Tromp, P.G. Noordzij, F.S. Taccone, N.A. Foudraine, F.H.M. Kornips), and the executive committee. The steering committee will make decisions regarding continuation of the trial and protocol changes. Decisions will be prepared by the executive committee. The chairman of the steering committee (i.e. the principal investigator) will be advised by the independent data monitoring and safety committee. The study-coordinator is responsible for running the trial on a day-to-day basis, and will report to the executive committee.

11. STRUCTURED RISK ANALYSIS

11.1 Potential issues of concern

N.a., since the trial concerns registered products to be used within the indication and not in combination with other products.

11.2 Synthesis

Of comatose patients after cardiac arrest with electroencephalographic status epilepticus, 90-100% dies (Celesia et al., 1988; Hui et al., 2005; Kaplan & Morales, 2008; Krumholz et al., 1988; Legriel et al., 2009; Rossetti et al., 2007; Rossetti et al., 2009; San-Juan et al., 2009). It is unclear whether (some) electroencephalographic seizure patterns in these patients represent a condition which can be treated with antiepileptic drugs to improve outcome, or rather severe ischemic damage, in which treatment is futile.

On the majority of intensive care units continuous EEG monitoring is not a part of regular care, which indicates that electroencephalographic status epilepticus is often not even diagnosed. If diagnosed, most neurologists treat with anti-epileptic drugs (Bouwes et al., 2010). However, treatment is mostly moderate and started relatively late (Abend et al., 2010; Bouwes et al., 2010). If effective, treatment should probably be aggressive and initiated as early as possible, analogous to treatment of status epilepticus in general (Fujikawa, 2005; Naylor et al., 2005). Uncontrolled case series have suggested a small reduction of mortality after aggressive treatment (Bouwes et al., 2013; Rossetti et al., 2009) and some experts believe that it is unethical to withhold such aggressive treatment. However, controlled trials are lacking and both strategies (*treatment* and *no treatment* of electroencephalographic status epilepticus) are current standard modalities in these patients.

Medical treatment of electroencephalographic status epilepticus may modify the high risk of death. Otherwise, medical treatment of electroencephalographic status epilepticus may lead to prolonged hospitalization of several days of comatose patients that otherwise would have died. The risk of an increase of morbidity or mortality is considered negligible.

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