TITLE (SHORT, 200 CHARACTERS MAX.):

LONG-TERM FUNCTIONAL OUTCOME AND HEALTH-RELATED QUALITY OF LIFE AFTER POSTANOXIC ELECTROGRAPHIC STATUS EPILEPTICUS (PSE)

MAIN HYPOTHESES TESTED (2 MAX)

Main objective: To determine early clinical and electrographic characteristics associated with favorable long-term functional outcome (Glasgow Outcome Scale Extended score 5-8) after postanoxic electrographic status epilepticus and to develop a long-term prognosis risk score.

Secondary objective: To describe long-term functional outcome and health-related quality of life after postanoxic electrographic status epilepticus

Main hypothesis:

Patients with electrographic status epilepticus with the following clinical and electrographic characteristics may have a favorable outcome:

- start after or during rewarming

- continuous background before start

- continuous background during ongoing SE at some time-point

- reactive background at some time-point

- not super-refractory to anesthetic treatment

- without signs of extensive brain injury using other prognostic tools (SSEP, brain imaging, biomarkers, lack of pupillary and corneal reflexes at 72 hours)

SINGLE CENTER [ ] , MULTICENTER [X]

Lund (Sweden)

Versailles (France)

Lausanne (Switzerland)

Bruxelles (Belgium)

Malmö (Sweden)

Helsingborg (Sweden)

Linköping (Sweden) ?

Cochin (France)

PICO

Patients: Patients successfully resuscitated after cardiac arrest

Intervention/Exposure/Prognostic factor: complicated by postanoxic electrographic status epilepticus (EEG-confirmed)

Comparison: favorable versus unfavorable long term functional outcome assessed by Glasgow Outcome Scale Extended score, EQ5D-5L values, cognitive tests and participation in society scores

Outcome: long term functional outcome at 6 and 24 months follow-up

DATA NEEDED FOR THE ANALYSIS (SPECIFY VARIABLES AND MOTIVATE ANY PROPOSED ADDITIONS TO THE ECRF)

Each comatose survivor after extra-hospital cardiac arrest (CA) hospitalized in the participating ICUs will undergo, as soon as possible after hospital admission, a bipolar cEEG recording including at least 8-channels according to the Standard international 10-20 system. Patients will be managed in accordance with the TTM2 protocol, cEEG recordings will be read by local neurophysiologists, and treatment of postanoxic status epilepticus will be at the discretion of the bedside physician. For the purpose of this ancillary TTM2 study, all continuous EEG recordings will be centrally-reinterpreted and patients categorized as having definitive or possible electrographic status epilepticus.

Definition for status epilepticus (Alternative A):

The criteria for *definitive* status epilepticus will be based on the ACNS terminology (Hirsch et al., 2013) and considered fulfilled if one of the following patterns occurred:

- Bilateral spike/sharp-and-waves at a rate of ≥ 3 Hz and constituting at least 50% of a 30 min period
- Repeating sequences of at least 10 sec with discharges or rhythmic activity of any type clearly evolving in frequency, reaching > 4 Hz and constituting at least 50% of a 30 min period.

The criteria for *possible* electrographic status epilepticus:

- Rhythmic spike/sharp-and-waves or periodic discharges at a rate of ≥ 1 Hz for at least 50% of a 30 min period (including bilateral, lateralized or focal discharges).

If a *possible* electrographic status epilepticus appear in combination with one of the following it is considered definitive status epilepticus:

- clinical ictal phenomena time-locked to discharges
- EEG and clinical improvement after intravenous AED

Definition for status epilepticus (Alternative B):

The criteria for *definitive* status epilepticus will be based on the Salzburg Criteria (Beniczky et al., 2013) and considered fulfilled if one of the following patterns occurred:

- Epileptiform discharges at a rate of > 2.5 Hz for ≥ 10 seconds and similar or repeating discharge pattern for ≥ 10 minutes
- Possible status epilepticus combined with one of the following:
    - typical spatiotemporal evolution
    - clinical ictal phenomena time-locked to discharges
    - EEG and clinical improvement after intravenous AED

The criteria for *possible* status epilepticus

- Epileptiform discharges at a rate of ≤ 2.5 Hz or rhythmic delta-theta-activity > 0.5 Hz for ≥ 10 seconds and similar or repeating discharge pattern for ≥ 10 minutes.

Specific additional variables (additional module in the eCRF):

- Date and time of first identification of definitive or possible electrographic status epilepticus (as defined above)

- Date and time of first treatment of electrographic status epilepticus

- Date and time of control of electrographic status epilepticus (defined according to local routine and possible status epilepticus criteria no longer fullfilled)

- Number of antiepileptic lines to control electrographic status epilepticus

- Antiepileptic treatments received to treat electrographic status epilepticus in detail (first, second, third line; start, stop, daily maximal infusion rate)

- Anesthetic treatments with anticonvulsant properties (start, stop, daily maximal infusion rate)

- Adjuvant treatments of electrographic status epilepticus (Ketogenic diet, Magnesium infusion, Ketamine, inhalation of halogenated anaesthetics, others)

Specific additional variables (collected from the TTM2-database after the trial or separate EEG-analysis):

- Temperature at electrographic status epilepticus onset

- Occurrence and type of clinical convulsion on each day during status epilepticus

- Refractory status epilepticus (yes/no) (defined as continuous or intermittent definitive electrographic status epilepticus despite two lines of anticonvulsants)

- Super refractory status epilepticus (yes/no) (defined as ongoing or recurrent definitive electrographic status epilepticus 24 h or more after anesthetic treatment initiation)

- Electrographic status epilepticus duration (calculated from the first 30-minute period with electrographic status epilepticus to the end of the last 30-minute period of electrographic status epilepticus or to the end of monitoring if ESE was still ongoing)

- Continuous EEG background before start of electrographic status epilepticus

- Continuous EEG background at any time-point during ongoing electrographic status epilepticus

- Reactive EEG background at any time-point

LOGISTICS – HOW WILL ADDITIONAL DATA BE GATHERED?

Data related to demographics, cardiac arrest, temperature management, complications during ICU stay, neurological prognostication (clinical examination, SSEP, biomarker levels, brain imaging: CT scan and/or MRI), and outcomes measurements will be extracted from basic data collection of the TTM2 trial.

Data related to electrographic status epilepticus therapeutic management will be collected as additional data in the eCRF

Data related to EEG will be collected in a standardized form by the neurophysiologist who will perform posthoc EEG analysis.

BRIEF STATISTICAL ANALYSIS PLAN AND SAMPLE SIZE ESTIMATE

Data will be reported as median and interquartile range (IQR) or percentages among all included patients with a final diagnostic of postanoxic electrographic status epilepticus and described according to definitive and possible electrographic status epilepticus classification. Categorical variables will be compared using Fisher's exact tests and continuous variables using Wilcoxon rank-sum tests.

To identify associations between factors and a favorable long term functional outcome (Glasgow Outcome Scale Extended score of 5-8) we will perform a logistic regression. Factors included in the analysis will associate demographic characteristics, patient characteristics related to CA, patient characteristics related to postanoxic electrographic status epilepticus (time from onset to CA, temperature at onset, total duration, Number of treatment lines needed to control status epilepticus, refractory electrographic status epilepticus, super refractory electrographic status epilepticus), neurological prognostication (clinical examination, SSEP findings including N20 amplitude, biomarker levels, brain imaging: CT scan and/or MRI), complications during ICU stay (Inotropic support for post-CA shock, Renal replacement therapy for post-CA syndrome, Acute respiratory distress syndrome in post-CA syndrome, Intestinal injury in post-CA syndrome). All continuous variables will be checked for log-linearity, and dichotomized if indicated. A multivariate model will be built with variables that will yield *P* values smaller than 0.20 by univariate analysis and/or clinically relevant. Hosmer-Lemeshow goodness of fit test will be computed on final models. Association of factors with a favorable outcome will be reported in terms of odds-ratio (OR) with their 95%CI. All tests will be two sided and *P* values <0.05 will be considered as statistically significant.

Development of the risk model will be based on the use of regression coefficients of factor independently associated with long-term favorable functional outcome obtained by logistic regression. In case of a small number of survivors with favorable long term outcome after postanoxic electrographic status epilepticus, adaptive methods will be used such as penalized regression (ridge regression or lasso regression).

We will perform an internal bootstrap validation of the score on a large number of created bootstrap datasets.

Given the exploratory nature of this ancillary study, and the low of rate of survivors after postanoxic electrographic status epilepticus, it is not possible to estimate a sample size a priori.

However, eligible patients would be anticipated as follows:

- prevalence of postanoxic electrographic status epilepticus among TTM2 patients : 33%
- prevalence of survivors among patients with postanoxic electrographic status epilepticus : 10%

According to the expected recruitment of participating site to this ancillary study, we could estimate a total of N patients with postanoxic electrographic status epilepticus and n survivors.

(if you deem it necessary we may however calculate a sample size and power of this ancillary study)

Participating site	Expected TTM2 recruitment and cEEG
Lund (Sweden)	25
Versailles (France)	20
Lausanne (Switzerland)	40?
Bruxelles (Belgium)	?
Malmö (Sweden)	25
Helsingborg (Sweden)	15
Linköping (Sweden)	15?
Cochin (France)	60
Total	200-250?

FUNDING (IF APPLICABLE)

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CORRESPONDING AUTHORS NAME, INSTITUTION & E-MAIL ADDRESS:

Legriel stephane, Intensive Care Unit, Versailles Hospital, France, slegriel@ch-versailles.fr

CO-WORKERS:

Erik Westhall, Nicolas Gaspard, Andrea Rossetti, Tobias Cronberg

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