TITLE (SHORT, 200 CHARACTERS MAX.):

CEREBRAL AUTONOMIC REGULATION IN MULTIMODAL MONITORING AFTER CARDIAC ARREST – A TTM2 SUBTRIAL (TTM2-CAR)

MAIN HYPOTHESES TESTED (2 MAX)

Can assessment of cerebral haemodynamics and cerebral oxygenation measured by non-invasive techniques, combined with electroencephalography and serial evoked potential studies, provide a feasible multimodal brain monitoring and prognostic tool in patients treated with TTM after cardiac arrest in the Intensive Care Unit for cardiac arrest?

Can this feasibility study indicate areas for further study where non-invasive multimodal monitoring of the brain may improve the clinical management of patients treated in the Intensive Care Unit for coma, for instance through optimization of cerebral autoregulation of CBF?

SINGLE CENTER [X]

Addenbrookes Hospital, Cambridge University Hospitals, Hills Road, Cambridge, CB2 0QQ, United Kingdom (Neurocritical Care Unit and John Farman Intensive Care Unit)

PICO

Patients: All patients after OHCA eligible for TTM2 trial

Intervention/Exposure/Prognostic factor: Noninvasive monitoring of continuous EEG, SSEP, and cerebral autonomic function via TCD and NIRS

Comparison: Observational feasibility study; the multimodal monitoring data from patients will be compared with age matched controls. These control subjects will be tested separately with the same 30-minute, non-invasive monitoring session.

Outcome: Changes in cerebral autonomic function during clinical course after ROSC. Functional outcome of the patients will be assessed at discharge from the ICU and at 6 months post admission using the modified Rankin scale and mini mental status exam.

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

The monitoring protocol will involve non-invasive measurement of arterial blood pressure (ABP via Finapress), non-invasive intracranial pressure (ICP) via transcranial Doppler ultrasound (TCD), cerebral blood flow (CBF) via TCD, perfusion using TCD and Near Infrared Spectroscopy (NIRS) plus status of autoregulation of CBF. In addition, the

patients will have an electroencephalogram (EEG), and evoked potential studies will be performed (Somatosensory evoked potentials – SSEP, and Brainstem Auditory Evoked Potentials - BAEP). Transcranial Magnetic Stimulation (TMS) will be performed in selected patients. Data will be integrated using ICM+ software® (http://www.neurosurg.cam.ac.uk/icmplus) developed in Cambridge.

We also propose MRI which could be performed at the Wolfson Brain Imaging Centre (WBIC), Addenbrooke's Hospital, Cambridge according to a protocol yet to be agreed with other imaging substudies within TTM2. The WBIC is a research facility dedicated to investigation of brain imaging in Neurosciences Critical Care. Inclusion of MRI will depend on funding of the substudy, to be agreed.

LOGISTICS – HOW WILL ADDITIONAL DATA BE GATHERED?

Data will be gathered through PhD students in the Brain Physic Laboratory, Cambridge University, supervised by Dr. M. S. Damian and Prof.. Marek Czosnyka.

BRIEF STATISTICAL ANALYSIS PLAN AND SAMPLE SIZE ESTIMATE

Sample size: Because of inclusion and exclusion criteria, we expect that we will have to screen about 80 patients per year. This number is based on total annual ICU admissions in JFICU and NCCU, Cambridge University Hospital.

Statistical Analysis: All variables will be tested for normal distribution and appropriate statistical analysis. Normality of distribution will be checked by employing Kolmogorov-Smirnov or Shapiro-Wilk test. For basic demographic and clinical variables, descriptive data analysis will be used. Analysis will also include factorial repeated measures analysis of variance (ANOVA) (time × group) and independent t-tests for primary and secondary endpoints. Intention to treat analysis will be applied. We will use the χ^2 test or Fisher Exact test (as appropriate) to compare categorical variables between the two study groups, including the primary endpoint (MRC scale), and the Mann-Whitney two-sample rank-sum test or t tests to compare continuous variables. A cumulative event curve (censored endpoints) will be estimated with the Kaplan-Meier procedure. The effect of the treatment protocol on the endpoint will be compared between groups with the log-rank test. Additional analysis will be done with logistic and Cox regression models that adjusted for the main baseline factors that predict outcomes (age, APACHE II, presence of sepsis) and the presence of the intervention. We will check the assumption of proportionality of hazard functions in our Cox regression model. Hazard ratios (HRs), together with 95% CIs, will be estimated with these models. The p value$\leq$0.05 will be considered statistically significant.

FUNDING (IF APPLICBABLE)

To be determined; partial funding through TTM2 trial substudy funding..

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