University Hospitals Plymouth NHS Trust

P25/30 somatosensory evoked potentials are associated with neurological prognosis of comatose survivors after out of hospital cardiac arrest

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This protocol describes the "Early recorded P25/30 somatosensory evoked potentials are associated with neurologic prognosis of comatose survivors after out of hospital cardiac arrest" study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the UK Policy Framework for Health and Social Care Research (2017). It will be conducted in compliance with the protocol, the Data Protection Act (2018) and other regulatory requirements as appropriate.

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GLOSSARY OF ABBREVIATIONS

BP	Blood Pressure
CI	Chief Investigator
CPC	Cerebral Performance Category
CPR	Cardiopulmonary Resuscitation
CT scan	Computerised Tomography scan
CT	Clinical Trials
CXR	Chest X-ray
DMC	Data Monitoring Committee
ECG	Electrocardiogram
EEG	Electroencephalogram
FBC	Full Blood Count
GCP	Good Clinical Practice
GCS	Glasgow Coma Scale
GP	General Practitioner
HR	Heart Rate
ICF	Informed Consent Form
ICH	International Conference of Harmonisation
ICU	Intensive Care Unit
IHCA	In Hospital Cardiac Arrest
INR	International Normalised Ratio
LFT	Liver Function Test
MRI	Magnetic Resonance Imaging
N20	Short latency [20 msec] Somatosensory Evoked Potential
NHS	National Health Service
NPV	Negative Predictive Value
NRES	National Research Ethics Service
NSE	Neuron Specific Enolase
OHCA	Out of Hospital Cardiac Arrest

P25/30	Short Latency [25-30msec] Somatosensory Evoked Potentials
PaCO2	Partial Pressure of Carbon Dioxide of an arterial blood sample
PaO2	Partial Pressure of Oxygen of an arterial blood sample
PI	Principal Investigator
PIS	Participant/ Patient Information Sheet
PEA	Pulseless Electrical Activity
PPV	Positive Predictive Value
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
ROSC	Return of Spontaneous Circulation
SaO2	Saturation of arterial Blood in Oxygen
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
SPSS	Statistical Package for Social Sciences
TSG	Trials Steering Group
TTM	Targeted Temperature Management
U&Es	Urea and Electrolytes

KEYWORDS
Somatosensory Evoked Potential, P25, P30, N20, cardiac arrest, prognosis

STUDY SUMMARY

TITLE	Early recorded P25/30 somatosensory evoked potentials are associated with neurologic prognosis of comatose survivors after out of hospital cardiac arrest.
DESIGN	Prospective, observational, non-interventional, study – prospective collection of data and interpretation. Analysis of the data and assessment of prognostic value of the P25/30 in critically ill patients post cardiac arrest.
AIMS	To be the first attempt to validate the prognostic potential of early recording [between 24-36 hours post Return Of Spontaneous Circulation (ROSC)] of P25/30 potentials in comatose survivors who are admitted to a British ICU after out of hospital cardiac arrest and who are not treated by hypothermic targeted temperature management. [Validation of the prognostication significance of P25/30 Somatosensory Evoked Potentials in predicting neurologic outcome in comatose survivors post out of hospital cardiac arrest who are treated in ICU].
OUTCOME MEASURES	Primary Endpoint: Neurologic outcome assessed by CPC score at hospital discharge. Secondary endpoints: Mortality at hospital discharge and 28 days [which occurs first], comparison of prognostic benefit of N20 and P25/30 based multimodal prognostic models.
POPULATION	Comatose survivors, after out of hospital cardiac arrest, treated in Derriford Hospital ICU, Penrose and Pencarrow wards.
ELIGIBILITY	Adults [>18 years old], out of hospital cardiac arrest, comatose after ROSC, ICU admission
DURATION	24-36 months
ESTIMATED COST	Cost for statistical analysis and full statistical support. With all University on costs the estimated cost is £4500 and with direct costs only £2300.

1. INTRODUCTION

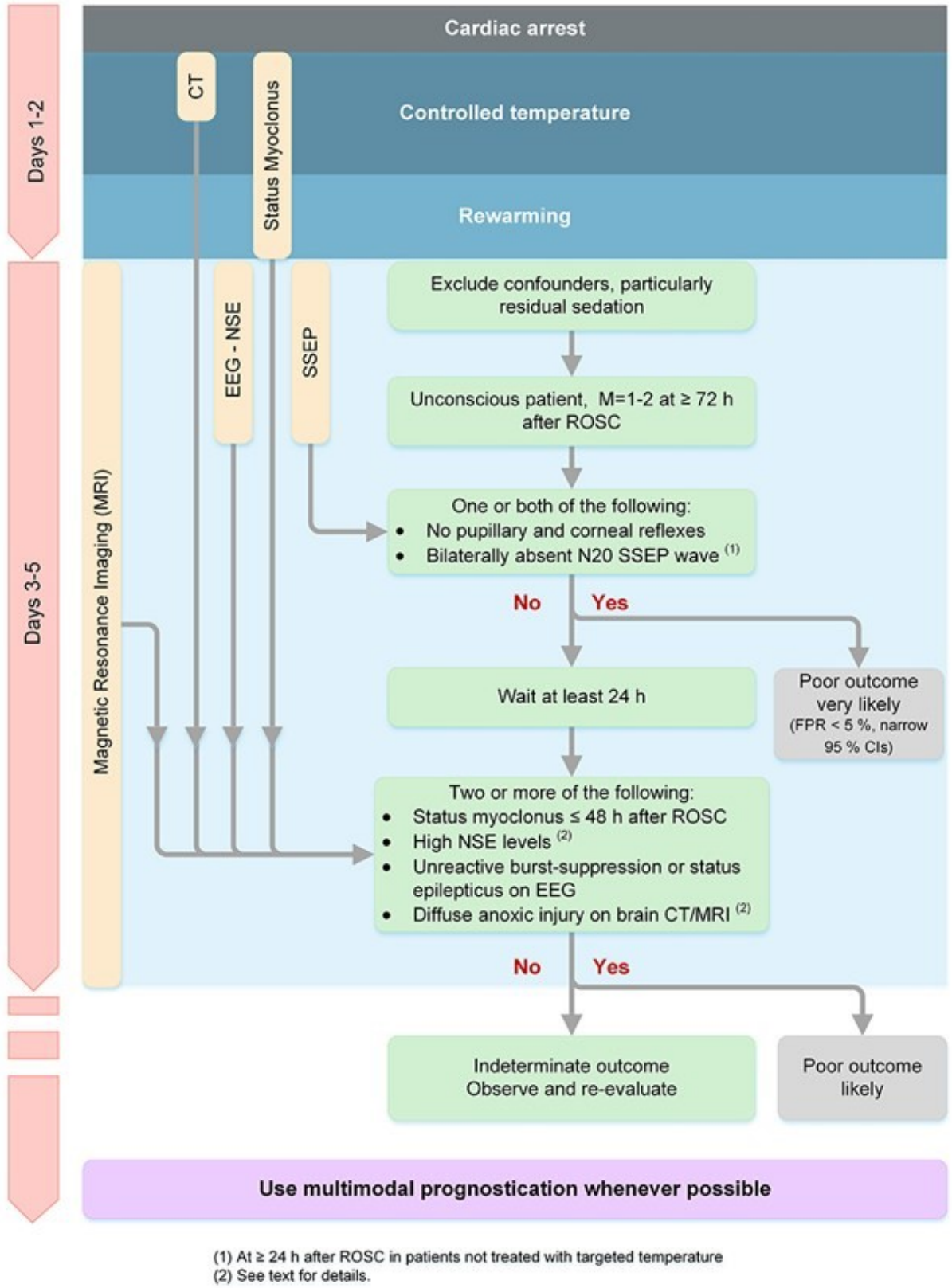
1.1 BACKGROUND

Suffering an Out of Hospital Cardiac Arrest (OHCA) is a global health problem with a yearly incidence of approximately 1:1000 people worldwide (1). In-hospital-cardiac-arrests (IHCA) affect 1-1.5 per 1000 in-patients (2). Internationally, recent survival figures for such events are 26% and 22% respectively (3,4). Much of this mortality is due to patients suffer devastating neurological damage, and so go on to receive palliative care. Locally, 200 patients were admitted to the Derriford General Intensive care in the last 3 years following an OHCA. Of those, patients who reach the intensive care, 70% died (2). Many patients who do not die will suffer varying degrees of neurological damage. Neurological outcome is most commonly measured using the Cerebral Performance Categories [CPC] [appendix figure 1] either at ICU or hospital discharge or at 3-6 months post cardiac arrest.

Up to 20% of patients suffering a cardiac arrest will still be in a coma at one week post Return Of Spontaneous Circulation [ROSC]. Some of these patients will make a good recovery (5). Predicting devastating irreversible neurological damage often takes time and requires a multimodal approach using clinical testing, electrophysiological tests, blood biomarkers, and radiological imaging. In the most recent guidelines issued by the Resuscitation Council UK in 2015 a specific prognostication algorithm is provided to facilitate the integration of these clinical signs and investigations in available in order to achieve the best possible prognostic accuracy [Figure 1].

Importantly, early and accurate detection of patients with severe cerebral damage prevents unnecessary patient suffering and assists with clear communication with relatives, reducing their distress. There are a number of known factors that are associated with a poor outcome: Age, non-witnessed arrest, lack of bystander cardiopulmonary resuscitation [CPR], presence of a non-shockable rhythm [Asystole or Pulseless Electrical Activity (PEA)], Anoxia time [time lapsed from cardiac arrest until ROSC], requirement for adrenaline, a low pH and PaCO2 on admission (6). None of these prognostic markers have sufficient sensitivity or specificity to make accurate prognostic decisions. Many of the clinical signs [pupils' reactivity to light, Glasgow Coma Scale (GCS), reflexes, presence of myoclonus] and laboratory / radiological tests [Computerised Tomography (CT) scans, Electroencephalogram (EEG), Neuron Specific Enolase (NSE), Magnetic Resonance Imaging (MRI) scan] also suffer similar uncertainty – either when used alone or in combination in the context of a multimodal approach – especially early in an admission. One exception is the Short-latency Somatosensory Evoked Potentials (SSEPs). During this test, specific electrical signals are recorded in specific area of the brain [cortex]. These electrical signals are produced after stimulation of a nerve on the hand. This test establishes presence or absence of intact brain electrical activity. At 20 milliseconds after median nerve stimulation, a response, an electrical signal, should be recorded in the corresponding area of the brain which is called sensory cortex. This electrical signal is called N20. Total absence of N20s is strongly correlated with a poor outcome.

Figure 1: Resuscitation Council UK Post cardiac arrest prognostication algorithm



However, the presence of N20s does not equate with a good outcome. Many patients with unilaterally or bilaterally present N20s may still have devastating neurological damage.

Kim *et al* (8) tested the prognostic use of SSEPs in comatose survivors after OHCA, highlighting an alternative electrical signal [formally called evoked potential], the P25/30. This is a similar electrical signal recorded during the same SSEP test after wrist nerve stimulation. This electrical signal is recorded on the same recording sheet with the N20 during the SSEP and follows the N20 approximately 5msec later [Figure 2]. This electrical signal although recorded during the same test with the N20 has been ignored for many years, regarding its potential prognostic significance for the neurological outcome of the comatose patients after cardiac arrest. The authors of this study retrospectively examined bilateral P25/30 in 116 consecutive patients 3-4 days after ROSC. Neurological outcome was recorded at hospital discharge. Their results suggest bilaterally absent P25/30 had a superior prognostic value to N20. All patients with absent P25/30 had a poor neurological outcome. Fewer patients with devastating brain injuries had present P25/30 compared to the presence of N20.

During a retrospective review of 43 cases with cardiac arrest admitted to Derriford ICU between 2015 and 2018 and in whom N20 testing was performed, the results were similar to the Kim *et al* study.

Therefore a study that would attempt to validate the proposals below is justified.

1. The prognostic value of P25/30 SSEP when recorded early [between 24-36 hours post ROSC] in comatose survivors after OHCA who are admitted to ICU

2. Test the superiority of early [between 24-36 hours post ROSC] P25/30 SSEP recording in predicting poor neurologic outcome against the early N20 SSEP recording.

This study would be the first to test this hypothesis in British ICU patients.

To summarise, the Short-latency Somatosensory Evoked Potentials (SSEPs) is one of the most promising ways available in predicting the neurological outcome in comatose patients after OHCA. This is a bedside test whereby a nerve in the wrist is stimulated and electrodes on the scalp detect the brains response to this stimulus. This response is presented as electrical signals recorded on a recording sheet. These electrical signals are called SSEPs and can be interpreted by specialist scientists, the neurophysiologists. If these electrical signals in the brain are not present (SSEP absent), it is well recognised to be a very reliable sign that the brain has suffered irreversible, devastating damage (7). Unfortunately, if the scalp electrodes do detect brain electrical signals, it does not equate with a good outcome. Many patients with present SSEP may still have devastating brain damage. Published data to date has focused on the brain electrical signals 20 milliseconds following the wrist stimulus (N20). However, recent data looked at electrical signals 25-30 miliseconds following the wrist stimulation (P25/30) recorded on the same recording sheet. The new electrical signals showed the potential for more consistent association with the prediction of the neurological outcome not only when they are absent but also when they are present.

Based on preliminary, retrospectively reviewed data in our intensive care unit; The results concur with the findings of the aforementioned results of the international medical literature.

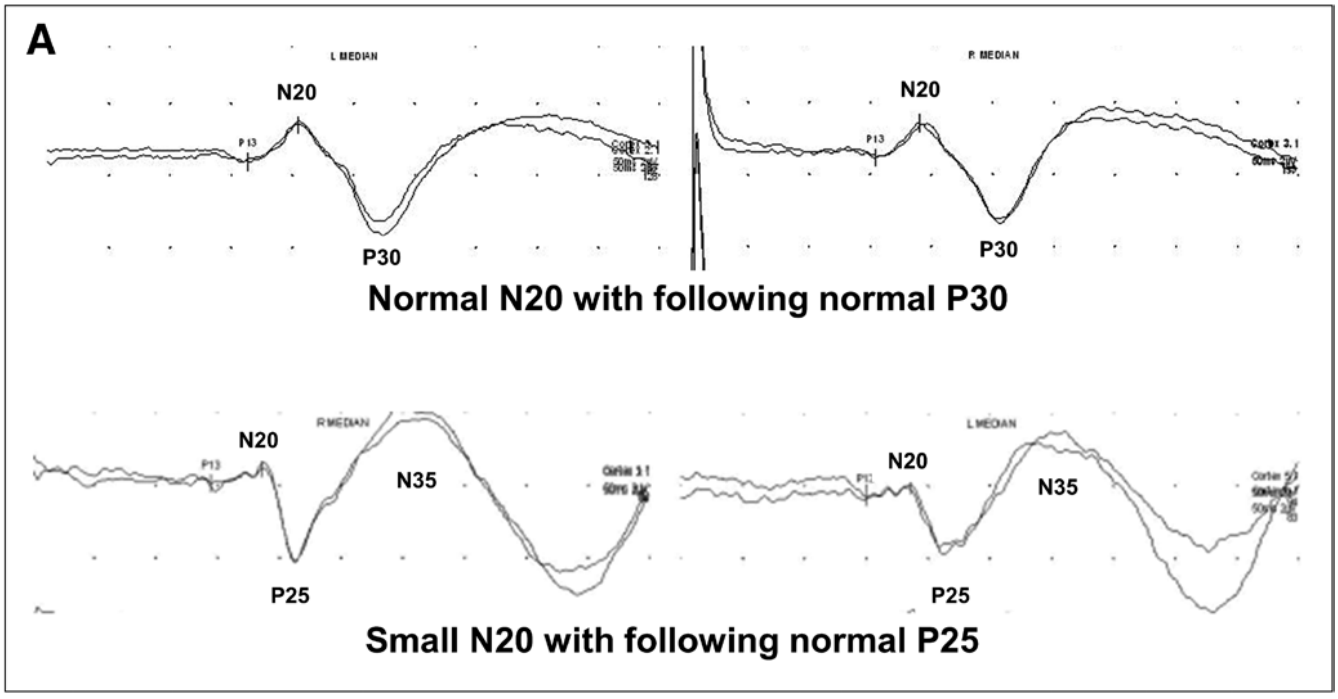
Therefore, we would propose to analyse:

1. The prognostic value of P25/30 SSEP when recorded early [between 24-36 hours post ROSC] in comatose survivors after cardiac arrest who are admitted to ICU

2. Test the superiority of early [between 24-36 hours post ROSC] P25/30 SSEP recording in predicting poor neurologic outcome against the early N20 SSEP recording.

This study would be the first to test this hypothesis in British ICU patients.

Figure 2. Example of recording sheet where N20 and P25/30 electrical signals are present and recorded [Kim et al. Crit Care Med 2018;]



1.2 RATIONALE FOR CURRENT STUDY

Research Question: Could the early [between 24-36 hours post ROSC] recorded P25/30 Somatosensory Evoked Potentials be used to predict the neurologic outcome in comatose survivors post out of hospital cardiac arrest who are admitted to ICU and who are not treated by hypothermic targeted temperature management? Could the early recording of P25/30 SSEPs be of superior prognostic value compared to the early recording of N20 SSEP?

Study Hypothesis: The early [between 24-36 hours post ROSC] recorded P25/30 SSEPs predicts the neurologic outcome in comatose survivors post out of hospital cardiac arrest who are admitted to ICU and who are not treated by hypothermic targeted temperature management. Early P25/30 SSEPs recording is of superior prognostic value compared to early N20 SSEP recording in the same patients.

Primary Endpoint: Neurologic outcome assessed by Cerebral Performance Category [CPC] score at hospital discharge.

Secondary endpoints: Mortality at hospital discharge and at 28 days [which occurs first], comparison of prognostic benefit of N20 and P25/30 based multimodal prognostic models.

1.3 PATIENT AND PUBLIC INVOLVEMENT

During the study design and the design of the patient/relative information sheet it was considered necessary to actively listen to patients' and patients' families' comments about the study after discussion with them and to collaborate with the patients and their families for the development of the Patient Information Sheet.

Patients and families in Derriford ICU were asked by us to read carefully the Patient Information Sheet that we had prepared based on the template provided to us by the local R&D. After having read that, we kindly invited the patients and families to provide their written constructive feedback about the information sheet and the study and to suggest areas that needed further modification or further explanation and/or to make specific suggestions or to express their possible concerns freely and honestly about particular parts of the information sheet or the study.

The feedback that was provided to us was generally positive. Patients and families felt that the study will be beneficial for the patients and it will help actively to improve the knowledge about patients' outcomes and the care of the patients.

There were suggestions to limit the number of words in the "description of the study" part and to avoid some unnecessary repetitions. All reviewers have understood the study methods, the analysis, the aim of the study and the potential benefit for the patients as they were described in the text.

They have said in details:

- "This section is too long, needs to be kept shorter if possible. Maybe adding another section which is more detailed and on the brief description section it could just be about the aim of the study" [comment about the brief introduction to the study section].
- "Take out what would I have to do section as this can be covered in the "Do I have to take part section" [Obviously this could not be done because it was part of the template].

- "Other than the points above, this is a very informative sheet and easy to understand."
- "As I was reading this information I found in some areas it was a bit long."
- "The new study will benefit patient and family members."
- "A more quicker and accurate outcome for patient."

The team actively listened to their feedback and proceeded to the improvement of the specific part of the text. The feedback was positive for all other parts of the information sheet.

The personal details of the patients and their family members that provided their feedback and were involved in this process are available by the study team but for confidentiality reasons they are not mentioned in this text.

Predicting the neurological outcome of comatose patients after out of hospital cardiac arrest that are admitted to ICU is one of the major clinical uncertainties and one of the major challenges for the modern intensive care medicine. Despite the use of many clinical markers to predict the neurological outcome after OHCA, none of these clinical markers alone or in combination have been effective, reliable, and reproducible enough, in order to provide a definitive answer to the simple but complex and challenging questions of the clinicians and the families: Will the patient be able to recover fully neurologically? Would the patient be able to achieve the level of functional independence and the quality of life they had before the cardiac arrest? Will the patient be disabled and if yes, at what degree?

These questions, although vital for the patients and their families, as well as for their physicians, cannot be definitely answered at an early stage of patient's care after cardiac arrest. Therefore, inevitably, only the prolonged period of time, which will be of variable duration, in ICU, in the hospital and in rehabilitation care homes, is required in order to reach a reliable conclusion about the final neurological outcome of the patients.

For those who will achieve a satisfactory neurological recovery, this period of time is associated with uncertainty, concerns, stress and frustration for the patients and their families as they cannot have the definite answers they seek since the very early stages of their treatment.

For those patients that they will never achieve a satisfactory neurological recovery and they will remain comatose or in vegetative state, the lack of a reliable prediction of the neurological outcome, early at the course of their illness, is associated with the provision of unnecessarily prolonged period of intensive support and futile treatment that does not result in their recovery but to the prolongation of survival in a very poor functional status which is distressing for their families and not beneficial for them.

All of the above make the need for an early and reliable prediction of patients' neurological outcome after OHCA, urgent and challenging. This definitive answer would help patients avoid prolonged futile treatments, would minimise families' uncertainties about the future outcomes and would help

clinicians reach more confident and definite decisions for their patients' complex clinical condition at the earliest possible stage of their treatment.

Derriford ICU team consists of clinicians intensivists with extensive and prolonged experience in Intensive care medicine and in the management of comatose patients after OHCA.

The Derriford ICU team, for many years, have interacted continuously with the families of the patients and have listened actively to their thoughts, their wishes, their concerns, their fears, and most importantly their need for definite answers about the one and most important question for the families: "Will our loved one be able to be functionally independent again and will their brain function be as before." And most of the time, despite the advances in modern intensive care medicine support and diagnostic tests, the answer to this question was impossible to be provided, especially during the early stages of the patients' treatment in Derriford ICU.

Thus, inevitably, both families and clinicians have gone through the same path of stepwise approach to the prognosis, which has been long and uncertain, with regards to the final outcome.

After admission to ICU post cardiac arrest, the ICU team members, including the members of this study team, have discussed extensively, repeatedly and consistently, with the patients' families and with the patients themselves [if possible], approaching and addressing their questions about neurological prognosis. Those discussions have taken place in the context of the patient/family communication meetings, bereavement meetings and bedside updates. All these hours of discussions had made absolutely clear that the main concern for the families and the patients is the lack of the definite answer about the final outcome of the brain damage that the patients suffer during cardiac arrest.

Taking into consideration all the above, the Derriford ICU team decided to proceed to the design and conduction of this research study, aiming to provide more reliable and more definite answers regarding the patients' final outcome after cardiac arrest at the earliest possible stage of their treatment in ICU.

The reason for the selection of this specific research topic and this specific research project was not only the need to provide an answer about a challenging and complex clinical uncertainty but also the need to address the uncertainties and provide answers to the families of all these patients that suffer from the consequences of cardiac arrest.

The concept of this study is not only the product of a strictly scientific approach to a challenging clinical question. The concept of this study is the product of the long and active interaction with families of all the patients that had made completely clear that their major concern and uncertainty and fear lies around the definite answer about the final outcome of the brain damage of their loved ones.

That interaction with families was a continuous source of inspiration for the Derriford ICU team in order to identify and focus on the critical questions that are associated with the outcome of the comatose patients after OHCA and to try to address those questions through a high quality research project.

Therefore, the families of the patients that are treated in comatose state on ICU after a OHCA and the patients that regain brain function during recovery, actively guided our research interest to the specific area of the neurological outcome and they made us understand what are the crucial questions that intensive care medicine research must answer about the patients after OHCA.

The longstanding interaction with the families and the patients and the continuous discussions with them, not only during the period of ICU admission but also after the ICU discharge, regardless of the outcome of the ICU care, helped our team to achieve an enormous level of experience regarding the understanding of families' and patients' needs, concerns, thoughts, wishes and fears and the ways to effectively approach all of them.

In order to address that in the maximum efficiency, during the conduction of this study, the members of the study group will actively listen to the thoughts of the next of kin and other family members if available and they will try to provide the maximum information to them not only about the study but also about the general potential benefit for the patients by research, the importance of the research in modern medicine and specifically in the specialty of Intensive Care Medicine where many clinical and prognostic uncertainties still exist.

Also, with the help of their next of kin for each one of the potential participants – before their enrolment in the study – we will explore the potential participants' likely previously expressed wishes or thoughts or opinions about the importance of medical research and the participation in medical research for the benefit of the patients.

The study group would be responsible to keep each one of the next of kin and/or the patients aware about the results of the study and the relevant publications [abstracts in conferences and scientific manuscripts in journals]. At that point the study group will invite the next of kin and/or the participants to provide their constructive feedback about the results of the study and their feelings with regards to their participation in this study. This could be an effective way to maximise the participation and involvement of the participants to the research process, from the initial discussion and consent to the results of the research study and their feedback.

Also, that kind of interaction with the next of kin and/or the patients would give the opportunity to the members of the study group to actively explore the perspectives of the participants in their study, to maximise their experience and ultimately to help them developing their research performance by integrating useful learning points from the participants' constructive feedback to the design and practical application of their future research projects.

The aforementioned process would potentially involve the participants of this study to the dynamic development of the research process in general.

2. STUDY OBJECTIVES

Primary objectives

1. To be the first attempt to validate the prognostic potential of early recording [between 24-36 hours post ROSC] of P25/30 potentials in comatose survivors who are admitted to a British ICU after out of hospital cardiac arrest and who are not treated hypothermic targeted temperature management.
2. To assess the Specificity, the Sensitivity, the Positive and Negative Predictive Value of the early [between 24-36 hours post ROSC] P25/30 SSEPs recording in predicting poor neurological outcome after out of hospital cardiac arrest.

Secondary Objectives

1. To test the potential prognostic superiority of early P25/30 SSEPs recording against the early N20 SSEP recording in predicting poor neurologic outcome in the same cohort of patients.
2. To test if P25/30 SSEPs are associated with higher sensitivity and negative predictive value than N20 and subsequently to test if that superiority of P25/30 is consistently associated with greater accuracy in the early detection of poor neurologic outcome [especially among those patients with unilaterally or bilaterally present N20 SSEPs].
3. Add further knowledge regarding the prognostication significance of SSEP and specifically of P25/30 potentials in comatose survivors post out of hospital cardiac arrest who are treated in ICU. Provide reliable prospective evidence of the accuracy and reproducibility of the P25/30 signal recording.

3. STUDY DESIGN

Prospective Observational, Non-interventional, Study: Analysis of the recordings of Somatosensory Evoked Potentials test which is performed for prognostication in Derriford intensive Care Unit, in comatose survivors after Out of Hospital Cardiac Arrest. The interpretation of the recordings will include the presence or absence of P25/30 SSEPs, of N20 SSEP and possible other short or long latency evoked potentials on these recordings. After the interpretation of the recordings then a test for possible correlations of the recorded P25/30 SSEPs with the neurologic prognosis of the survivors will be performed.

Estimated Study Duration: 24-36 months

Estimated Number of patients: One hundred and twenty adult Intensive Care Unit patients. In order to be included in the study, all patients must be adults, comatose survivors after out of hospital cardiac arrest who are admitted to Derriford Intensive Care Unit.

3.1 STUDY OUTCOME MEASURES

Primary Endpoint: Neurologic outcome assessed by Cerebral Performance Category [CPC] score at hospital discharge.

Secondary endpoints: Mortality at hospital discharge and at 28 days [which occurs first], comparison of prognostic benefit of N20 and P25/30 SSEPs-based multimodal prognostic models.

4. PARTICIPANT ENTRY

4.1 RECRUITMENT AND CONDUCTION OF THE STUDY

The general management of adult comatose survivors after OHCA, who are admitted to the Derriford ICU, consists of provision of organ support as required [mechanical ventilation, cardiovascular support, renal replacement therapy], targeted temperature management aiming to maintain patients in normothermic condition for the first 72 hours, continuous invasive and non-invasive multimodal monitoring [vital signs, respiratory and haemodynamic monitoring, neurologic monitoring] and treatment of the underlying cause of cardiac arrest [if known-diagnosed]. The patients remain sedated for the first 36 hours to facilitate brain protection, optimisation of patient's organ function parameters and achievement of targeted temperature within very strict temperature limits [For the first 24 hours temperature target is 36^{o}C and for the next 48 hours the temperature target is 36-37^{o}C]. The targeted temperature management is achieved with the use of external cooling devices. The neurologic prognostication of the post cardiac arrest patients is mainly based on a multimodal approach guided by the clinical picture of the patient [Level of consciousness, Glasgow Coma Scale, presence or absence of reflexes and focal neurologic signs], the results of the CT imaging studies [CT or MRI of the Head], the results of the Electroencephalogram and SomatoSensory Evoked Potentials [SSEPs] recording which usually are performed after the first 24 hours post ROSC. The SSEPs recording are performed in all comatose survivors after OHCA who are admitted to Derriford ICU as an integral part of their normal care. The recording and the analysis of the recording are conducted by the members of the neurophysiology team in Derriford Hospital. The main aim of that routine, established and used for the last 3 years, prognostication test is to assess the presence or absence of the N20 SSEP in comatose survivors after out of hospital cardiac arrest. According to the international medical literature and the national guidelines, N20 presence is associated with unknown [ranging from full neurological recovery to severely disabled status] neurological prognosis, whereas N20 absence is always reliably associated with poor neurologic prognosis.

During our study, we will interpret further the results of the SSEP recordings not only for N20 but also for the presence or absence of the P25/30 SSEPs and we will test if they are related with patients' neurological prognosis. No consent is required for the SSEP recording as this is a part of the normal clinical care of the patients in Derriford ICU and has been already used for years in daily clinical practice of our unit, as a useful tool for the neurologic prognostication of post cardiac arrest patients.

During the study, consent will be required only for the additional interpretation of the SSEP recording sheet, regarding the presence or absence of P25/30 SSEPs and their potential prognostic significance. Nothing in the post cardiac arrest ICU management changes because of the study as no additional intervention and no additional tests will be introduced further to the normal care of the ICU patients that is established currently [figure 3].

Explaining that in further details: On the admission to Derriford ICU [Penrose and Pencarrow wards], all adult comatose survivors after OHCA will be managed according to the already established routine Derriford ICU protocol for the management of all patients after out of hospital cardiac arrest.

According to the current ICU routine care protocol: the patients will remain sedated for the first 36 hours as per ICU policy. As per normal ICU care, the sedatives that will be administered as a continuous infusion will be propofol [at a rate of 1-4mg/kg/h] and fentanyl [at a rate of 50-200mcg/h]. Midazolam infusion would be used only if the use of propofol is could not be tolerated due to severe haemodynamic instability or adverse effects to propofol developed. Neuromuscular Blocking agents [Atracurium or Rocuronium] may intermittently or continuously be administered to the patients, if required, for the management of their ventilation and / or for the control of severe rigor during the targeted temperature management and / or for the control of myoclonus or convulsions.

The reasons that the patients remain sedated for the first 36 hours are to facilitate brain protection, to optimise patient's organ function parameters and to achieve targeted temperature management within very strict temperature limits.

According to the Targeted Temperature Management protocol of the Derriford ICU, the body temperature will be maintained at 36^{o}C for the first 24 hours and between 36-37^{o}C for the next 48 hours up to a total of 72 hours. As per ICU management practice, organ support as required [mechanical ventilation, cardiovascular support, renal replacement therapy], continuous invasive and non-invasive multimodal monitoring [vital signs, respiratory and haemodynamic monitoring, neurologic monitoring] and treatment of the underlying cause of cardiac arrest [if known-diagnosed] will be provided. The targeted temperature management is achieved with the use of external cooling devices.

Between the 24 hours and the 36 hours after ROSC, the usual SSEP recording will take place in ICU by members of the neurophysiology team. The recording will be performed, as usual and normal ICU care without any modification for the study, while patients are on sedation [as described above]. The use of neuromuscular blocking agents will be applicable if indicated for any of the aforementioned clinical reasons or in order to achieve the best recording quality [clear recording of SSEP baseline in patients to facilitate the optimal interpretation of the recording mainly in patients with tremor or myoclonus] if that is not possible to be achieved while patients are on sedation. A single dose of Atracurium or Rocuronium will be administered for this purpose only if this is absolutely necessary. The Neurophysiology team members may request the use of neuromuscular blocking agent if they

think that the quality of their recording is poor. It will be the decision of the ICU consultant in charge if the neuromuscular blocking agent could be administered.

Within the first 24 hours in the ICU the patients will be assessed by the members of the research study team regarding their eligibility to be enrolled in the study. If the patients meet the specific inclusion and exclusion criteria for the study, their next of kin [NOK] will be approached by a member of the research team [who is also a member of the ICU clinical team] at ICU. All NOK will be spoken to in person. A full explanation of the study design, of the study protocol and of the study objectives, as well as a specific relative information leaflet containing all the information for the study, will be provided. The provision of informed consent by the NOK will be requested if patients meet the eligibility criteria for study enrolment. The meeting with the NOK may be done ideally before the SSEP recording or, in case of non-availability of the NOK, after the SSEP recording.

During the informed consent process, the members of the study group will actively listen to the thoughts of the next of kin, and they will try to provide the maximum information to them not only about the study but also about the general potential benefit for the patients by research, the importance of the research in modern medicine and specifically in the specialty of Intensive Care Medicine where many clinical and prognostic uncertainties still exist.

The next of kin for each potential participant will be asked to consent for the participation of the patients in the study, after being fully informed both verbally and by the provision of the relevant Trial Participant Information Sheet and a copy of the Trial Informed consent form that can be found in the appendix of this document. The patient will also be given the contact details of the ICU Research Nurse, should they wish to seek further information about the study. In most cases, the next of kin of potential participants will have at least 24 hours to decide whether or not to participate in the study.

Method of SSEP recording – Neurophysiology Data Acquisition and Interpretation

The following protocol of N20 SSEP recordings, currently used in Derriford ICU, will be applied for the purpose of the study. N20 and P25/30 SSEPs are expected to be recorded and then during the study interpretation of the results the presence or absence of either or both and the correlation between them will be assessed

Neurophysiology protocol of Somatosensory Evoked Potentials [upper limb Median/ Ulnar] in Derriford ICU following Out Of Hospital Cardiac Arrest.

This protocol has been used successfully for SSEP recording in Derriford ICU since 2015. This is part of the usual, established Derriford ICU policy for the management of the comatose survivors after out of hospital cardiac arrest and is not added or at any way modified, because of the study. The study purpose is the interpretation of the recording sheet of the SSEP test in order to answer the question whether the P25/30 potential that is recorded along with the N20 may have prognostic significance for the patients' neurological outcome.

The protocol of the SSEP recording is described below in details:

Deymed evoked potential system is used

Open Acquisition

Open EP protocol and select SEP from list

Select Median 4 Channel Right or Left depending on side being tested

Press On which brings up live trace to monitor

Turn up stimulation until a visible thumb twitch is seen, then select average; wait until at least 500 samples has been performed on each channel.

Measure wave forms accordingly using the measuring tool, - to print the waveforms press Quick report this will bring up document to print and then press the print icon.

A note of the patient's height if known should be made in cm.

Any sedative medication being used must be recorded on the request form. Patient should be paralysed with muscle relaxant agent to minimise EMG/movement artefact

Stimulation is routinely performed of the median or ulnar nerve in the hand; however this can be modified where necessary.

Machine Settings:	Stimulus Settings	Amplifiers (Default)
	Duration 0.1ms Rate 2.9Hz	Sensitivity 20-50uV/division Low frequency Filter 20Hz High Frequency Filter 2KHz Notch Off Artefact rejection On 20uV Divisions (Channel must be selected individually) Impedance Value must be below 5Kohm.

The machine settings may be altered as the physiologist doing the test sees fit

Electrode Placement	Position	Label (headbox)
Mid clavicle	Erb's point	Channel 4 Ipsilateral/contralateral Erbs
Nape of neck	CV2	Channel 2
Over prominent spinous process	CV7	Channel 3
	Cortex (2cm posterior to Cz and 6cm lateral on contralateral hemisphere)	Channel 1 C3/ C4
	Fz reference	Fz + input
	Ground strap on limb tested	Ground (linked)

Montage	Channel 1	Fz – C3/C4
	Channel 2	Fz/Front neck ref – Cervical C2
	Channel 3	Fz/Front of neck – Cervical C7
	Channel 4	Fz/Ips/ContErb – Erbs Ips/Cont

Sweep time: 100ms

Recording procedure

SSEPs must be recorded after at least 24hours following ROSC. Usually to be performed between 24-36 hours after ROSC.

Temperature must be recorded; mild to moderate hypothermia ≥36^{0}C does not abolish the cortical N20 responses. Cortical responses have been proven to remain until a nasopharyngeal temp of 20'C is reached.

The N20 remains present even at a sedation level sufficient to induce an iso-electric EEG.

Running the test

The established, used for many years in Derriford ICU, SSEP recording protocol is used. No changes in terms of either the method of recording or the length of the test would be done as a result of the study. Besides, the study does not have to do anything with the SSEP recording but with the further interpretation only of the recording paper for evidence of other potentials that could be used for prognosis.

The patient is positioned to reduce muscle artefact. If this is not possible and muscle artefact is high muscle relaxants may need to be prescribed to improve quality of recording and quality of SEP, especially in cases where it is thought to be absent.

The level of stimulation is subjective and needs to elicit a visible twitch of the appropriate muscle. Therefore this should be achieved prior to administration of muscle relaxant

Averaging begins once adequate stimulation is achieved, a minimum of 500 trials is required, and this must be increased where necessary. A minimum of two trials must be recorded to check for reproducibility.

Interpretation of the recording regarding N20s at the bedside for clinical purposes. This is part of the current established normal ICU care and is not part of the study.

Cortical N20 response is to be described as bilaterally absent (which is a good predictor of poor neurological outcome), or in other cases in may be present on one or both sides.

If the cortical N20 response is absent, the presence of the peripheral N9 and N13 response must be present to ensure that the response has arrived at the cortex. Cervical lesions need to be excluded if Cortical N20 response is absent. Immediately after SSEP recording, each recording will be interpreted for N20 and the result will be disclosed to the ICU clinicians as currently happens in the context of the ICU clinical policy and the Resuscitation Council UK Guidelines.

After SSEP recording

After the SSEP recording the result of the N20 potential will be disclosed to the ICU clinical team as it happens currently as per the established Derriford ICU care and that will not be part of the study.

In the context of the research study:

For those patients who informed consent is obtained from their next of kins and are enrolled in the study, a copy of each recording will be produced for the study purposes by one member of the study team who is not participating in the interpretation of the recording. This copy will be anonymised by giving a specific number for the study. The date of the recording and the time will be available on the copy. The specific study number of each recording will correspond to the specific patient and will be kept on a list not accessible by the neurophysiology study team members who will perform the interpretation of the recording for the study purposes.

After each copy has been anonymised and added in the study databank, the anonymised copy will become available to the first and to the second interpreter [both members of the study team (neurophysiology)] who will interpret the recordings with regards to the presence and absence of the N20 and P25/30 SSEPs and they will record the results of their interpretation in the results databank. The two interpreters will be blinded for the personal and the clinical details of the patient. Also each one of the interpreters will not be aware about the result of the interpretation of the other. The ICU clinicians will not be aware about the results of the P25/30 interpretation as this will be part of the study and should not be disclosed to them during the conduction of the study. In this way, the P25/30 interpretation results will be impossible to affect the treatment of the patients and / or any of the clinical decisions made about them by the ICU clinicians who will strictly be kept unaware about the results of the P25/30 SSEPs.

In the unlikely event that there was a discrepancy in interpretation of the SSEP recording between the two delegated interpreters, then a third member [not a member of the study team] of the Neurophysiology team would be asked to review the anonymised recording only in order to decide about the result. The data of the patients as well as the date of recording and the results of the interpretation of the two study team interpreters would not be disclosed to the third independent interpreter.

Interpretation of the SSEP recording for study purposes in details

Cortical N20 response is to be described as bilaterally absent (which is a good predictor of poor neurological outcome), or in other cases in may be present on one or both sides.

If the cortical N20 response is absent, the presence of the peripheral N9 and N13 response must be present to ensure that the response has arrived at the cortex. Cervical lesions need to be excluded if Cortical N20 response is absent.

The results of the SSEP from the patients enrolled to the study will be additionally interpreted for the presence or absence of the P25/30 waveforms. The additional interpretation for the study purposes will be as follows:

1. Check that baseline is clear and stable.
2. Check that all measured components are reproducible (should be possible to superimpose waves)
3. Check that peripheral nerve (N9) potential is present
4. Check that cervical spinal (N13) potential is present
5. Check that scalp (N20) potential is present and higher than 0.5 microvolts.
6. Check that scalp (P25/30) potential is present and higher than 0.5 microvolts..
7. As the P25/30 pottential could be generated in the absence of N20 as they come from two distinct areas of the brain cortex, the presence of either the P25/30 or the N20 would be confirmed when the amplitude of each one is equal or higher than the amplitude threshold [0.5 microvolts] used for the analysis of the SSEPs. The presence and the amplitude of P25/30 will not be dependent on the presence of N20 in the same recording as each one of them can exist in the absence of the other
8. Measurement of the amplitude of recorded P25/30 and N20 and their combinations. Test if there is a correlation of the recorded amplitudes and their ratio [P25/30 to N20] with the positive predictive value of N20 for the favourable neurological outcome.

Explanation clarification between the usual Derriford ICU post cardiac arrest care and what additionally will be done for the research study purposes

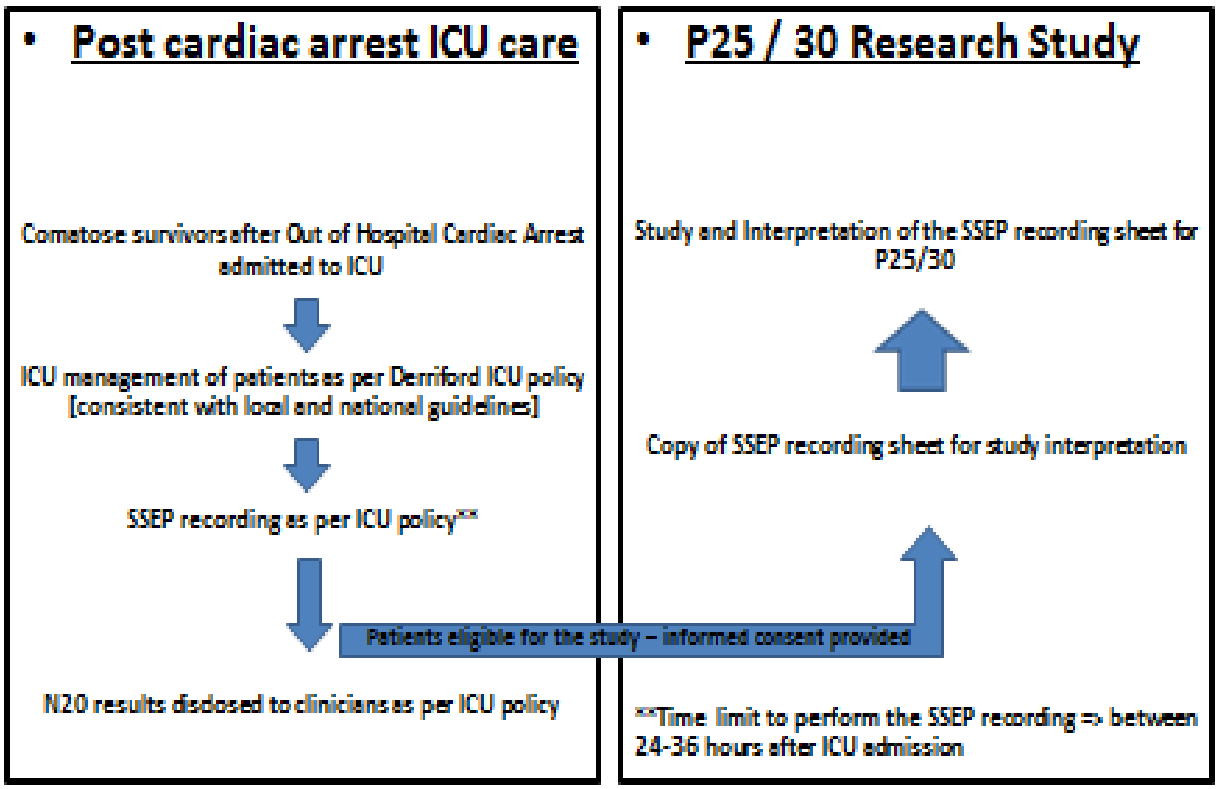


Figure 3. Explanation-clarification of the usual Derriford ICU post cardiac arrest care and what additionally will be done for the research study purposes

During the conduction of the study the patient's confidentiality and the unbiased analysis / interpretation of the SSEP recordings of the patients will be continuously ensured by the fact that once enrolled in the study their personal data will be replaced by a study number that will be representative of them. Only the members of the team that collect the data and do not take part in any interpretation of the results of the SSEPs and are not involved as clinicians in the clinical care of the patient will be aware about the correspondence between the study number and the personal and clinical details of each patient. The members of the study team that will be SSEP interpreters will be blinded for any clinical and personal data of the patients and the clinical ICU team will be not aware about the result of the P25/30 study interpretation.

After the SSEP recording has been conducted, between 24 and 36 hours post ROSC, the patients will be followed up by members of the study team. Those members of the team will assess the patients, by CPC and by performing full neurologic clinical examination, on the day of ICU discharge and on the

day of their discharge from Derriford Hospital. The online system SALUS of Derriford hospital will be used to follow up the patients after their discharge from ICU and before their discharge from the hospital.

The study team has already worked collaboratively with the IT and SALUS teams members and they have developed an effective way of patients follow up for the study purposes.

Through SALUS system, the members of the study team responsible for the patients follow up will be notified for the planned patients' discharge date in order the patients to be assessed by a study team member before they leave the hospital. The neurologic outcome, assessed with the Cerebral Performance Category [see figure 1 on the Appendix], will be recorded on the day of Hospital discharge [within the last 24 hours before discharge].

If a study participant died on ICU as a result of severe brain dysfunction or after the decision of ICU Consultant to be withdrawn from invasive organ support due to extremely poor prognosis and futility of further continuation of treatment, then, the discharge CPC would be the most recently recorded, after the patient have remained consistently off sedation [for a period of time varied for different sedatives or combination of sedatives].

Specifically, in a case that the ICU Consultant in charge considered withdrawing the invasive organ support in one of the study participants due to extremely poor prognosis, then the ICU consultant should notify the ICU research nurse in order one member of the team to perform the CPC score recording. The assessment by CPC must always take place before the decision for withdrawal of treatment is implemented and strictly before the palliative pathway is initiated. If the study team members failed to be notified by the ICU consultant about the withdrawal of treatment and the Palliative pathway is initiated before patient's CPC and neurologic examination recorded then the patient will be excluded from the study.

If a participant died unexpectedly from another cause rather than severe brain dysfunction and / or withdrawal of invasive organ support, then the most recent CPC before death [if possible to be recorded] will be based on the last available clinical assessment off sedation and will be considered as indicative of neurologic outcome for the patients. In case the CPC could not be assessed, the patient would be excluded from the study analysis.

If patients die on ICU while still on sedation and before being possible to assess their CPC then they will be excluded from the study analysis as the assessment of their outcome based on CPC will not be possible.

The Results of the CPC assessment and the outcome of the patients will be stored in the general study databank for further analysis.

The members of the study team with the help of the Derriford Hospital IT team have already created a study team folder on the hospital computer system. Rights to access the study folder have been

provided by Derriford hospital IT only and strictly to the study team members. The access to the folder is password protected. Each member of the study team must protect the patients' confidentiality and treat the data safely as per Good Clinical Practice and Research Governance Principles.

The study folder will contain four separate databanks: The first databank will contain the personal data of the patients [Name, Age, Hospital number, next of kin, and contact details] and their corresponding study numbers by which the patients will be known to all the members of the study team. During the conduction of the study, specific members of the study team will be responsible for the creation and management of this databank and only they will have access to this during the conduction of the study.

The second databank will contain all the clinical data that will be recorded for each patient [represented by a study number on this databank] on the day of ICU admission, the day of ICU discharge and the day of hospital discharge [see below for further information regarding clinical data expected to be collected for each patient].

The third databank will contain the results of the interpretation of the SSEP recordings with regards to P25/30 and N20 SSEPs. This databank will be accessible during the study conduction only by the study team members who will be the interpreters of the SSEP recording.

The fourth databank will contain the results of the neurologic outcome of the patients, in the form of Cerebral Performance Category recorded on ICU discharge day and on hospital discharge day.

At the End of the study, all data will be merged and statistically analysed and from the result of this analysis one or more relevant manuscripts must be submitted to a peer-review journal within the first 4 months after the completion of the study.

For each one of the patients-participants, the following clinical data must be collected prospectively, during the conduction of the study [at different stages i.e. at the time of enrolment and follow up] and must be kept safely in an anonymised form in a suitable database [see above for explanation]. The principles of patients' confidentiality and privacy must be applied at all times.

1. Age
2. Gender
3. Comorbidities [Scored by Charlson Comorbidity Index (see figure 3 on the Appendix)]
4. Pre-admission performance status [Assessed by the ECOG/WHO performance status score (see figure 2 on Appendix)]
5. Cardiac Arrest Rhythm [Rhythm that was initially recorded after cardiac arrest, usually at scene]
6. Bystander – witness of cardiac arrest and Cardiopulmonary resuscitation

7. Anoxic time [total time between cardiac arrest was noted and ROSC]. If multiple episodes of cardiac arrest then the sum of all anoxic times to be considered.
8. GCS before intubation [total or with components if available]
9. Aetiology of cardiac arrest [cardiac or non-cardiac or unknown]
10. CT scan report if performed because it was clinically indicated
11. Cerebral performance category at ICU discharge and Hospital discharge.
12. Date of death, number of days post ROSC that death occurred
13. ICU length of stay, hospital length of stay
14. Time of SSEP performed [hours post ROSC]
15. Time between ROSC and ICU admission,
16. First 24 hours post ROSC: mean SpO2, mean PaO2, mean PaCO2, mean HR, mean BP, mean Glucose levels, mean Lactate levels, mean pH, mean BE, Urea and Creatinine levels, liver function tests: ALT, INR, Bil and ammonia in patients with pre-admission acute or chronic hepatic dysfunction], Plasma Na levels, Temperature, SOFA Score, APACHE II score.

No particulars tests needed for the study purposes. The aforementioned tests are performed and the aforementioned clinical data are recorded for all patients admitted to Derriford ICU after out of hospital cardiac arrest as part of daily clinical practice.

4.2 PRE-REGISTRATION EVALUATIONS

No specific laboratory tests or imaging tests results are required in order to guide the decision to enrol a patient in the study. The inclusion and exclusion criteria [as described below] are solely based on clinical assessment and history taking that would be available at the time of ICU admission.

4.3 INCLUSION CRITERIA

1. All adult comatose survivors after out of hospital cardiac arrest who are admitted to Derriford Hospital Intensive Care Unit [Penrose and Pencarrow wards]. The cause of cardiac arrest may be cardiac and/or non-cardiac or unknown at the time of enrolment.
2. All patients must be comatose before intubation [GCS equal or lower than 8].
3. All patients must be on one or more invasive organ support [e.g. Endotracheal intubation and mechanical ventilation, vasopressor and/or inotropic support, Continuous Renal Replacement Therapy Sedated and/or on neuromuscular blocking agents].
4. All patients must be sedated before and during the time of SSEP recording. If clinically indicated, neuromuscular blocking agents may also be used.
5. All patients must be on targeted temperature management as per Derriford ICU policy and protocol: For the first 24 hours after ICU admission, the target-temperature is 36°C with temperature control commencing within the first hour after critical care admission. For the

next 48 hours the temperature of the patients will be maintained between 36-37°C. The aforementioned temperature targets are achieved with external cooling devices.

6. Patients must have a CT scan of the head if severe cerebral pathology which is part of the exclusion criteria is clinically suspected.
7. Absence of all exclusion criteria

4.4 EXCLUSION CRITERIA

1. Non-comatose patients after ROSC
2. Coma secondary to Intracranial and Intracerebral haemorrhage
3. Patients with haemorrhagic shock
4. Patients with severe neurologic disability [CPC level higher than 2] during the pre-cardiac arrest period
5. Presence of active Demyelinating disease or past medical history of Demyelinating disease
6. Trauma-induced Cardiac arrest
7. Previously or during the current admission diagnosed Spinal Cord and /or brain stem lesions
8. Patients with Implantable defibrillator device [incompatibility with SSEP recordings device]

4.5 WITHDRAWAL CRITERIA

1. If during the analysis of the results will become evident that any of the exclusion criteria was present but not diagnosed during the time of enrolment
2. Decision of the patient-participant or their next of kin [who have initially consented] to withdraw from the study. All participants should be considered free to withdraw at any time from the study without giving reasons and without prejudicing further treatment
3. Patients that were lost during the follow up period
4. Patients that died within the first 24 hours
5. Patients that were transferred to other hospitals within the first 24 hours
6. Technical Error during recording of N20 and P25/30 SSEPs
7. Recordings of poor quality that it is not possible to be reliably interpreted

5. ADVERSE EVENTS

There are no active interventions to the patients during the conduction of this study

Therefore there is no potential for any adverse events to the patients associated with the conduction of the study

The conduction of the study will not have any effect on the clinical decision-making by the responsible clinicians for the participants and it will not have any effect on the treatment of the participants.

What is analysed during the study is the recorded Somatosensory Evoked Potentials. Apart from the N20 Somatosensory Evoked Potential that is analysed during that clinical test we will further analyse the recordings with regards to the presence or absence of P25/30 Somatosensory Evoked Potentials. The Physicians responsible for the treatment of the patient will not become aware about the presence or absence of P25/30 SSEPs at any point of patient's care. The care physicians will continue to become aware about the results of N20 SSEP as currently.

The neurophysiology scientists who will interpret the recordings will not become aware about the patients' clinical data at any point of the study.

6. ASSESSMENT AND FOLLOW-UP

After the SSEP recording has been conducted, between 24 and 36 hours post ROSC, the patients will be followed up by members of the study team. Those members of the team will assess the patients, by CPC and by performing full neurologic clinical examination, on the day of ICU discharge and on the day of their discharge from Derriford Hospital. The online system SALUS of Derriford hospital will be used to follow up the patients after their discharge from ICU and before their discharge from the hospital. Through SALUS system, the members of the study team responsible for the patients follow up will be notified for the planned patients' discharge date in order the patients to be assessed by a study team member before they leave the hospital. The neurologic outcome, assessed with the Cerebral Performance Category [see figure 1 on the Appendix], will be recorded on the day of Hospital discharge [within the last 24 hours before discharge].

If a study participant died on ICU as a result of severe brain dysfunction or after the decision of ICU Consultant to be withdrawn from invasive organ support due to extremely poor prognosis and futility of further continuation of treatment, then, the discharge CPC would be the most recently recorded, after the patient have remained consistently off sedation [for a period of time varied for different sedatives or combination of sedatives].

Specifically, in a case that the ICU Consultant in charge considered withdrawing the invasive organ support in one of the study participants due to extremely poor prognosis, then the ICU consultant should notify the ICU research nurse in order one member of the team to perform the CPC score recording. The assessment by CPC must always take place before the decision for withdrawal of treatment is implemented and strictly before the palliative pathway is initiated. If the study team members failed to be notified by the ICU consultant about the withdrawal of treatment and the Palliative pathway is initiated before patient's CPC and neurologic examination recorded then the patient will be excluded from the study.

If a participant died unexpectedly from another cause rather than severe brain dysfunction and / or withdrawal of invasive organ support, then the most recent CPC before death [if possible to be recorded] will be based on the last available clinical assessment off sedation and will be considered as

indicative of neurologic outcome for the patients. In case the CPC could not be assessed, the patient would be excluded from the study analysis.

If patients die on ICU while still on sedation and before being possible to assess their CPC then they will be excluded from the study analysis as the assessment of their outcome based on CPC will not be possible.

The end of the study for each of the patients-participants will be either the discharge from hospital or their death at any time after the SSEP recording.

7. STATISTICS AND DATA ANALYSIS

7.1 DESCRIPTION OF STATISTICAL METHODS

Demographic information of participants will be summarized using descriptive statistics and presented in tables to provide an exploratory overview of the study population.

Continuous measures will be summarised as means, standard deviations and ranges where the distribution appears normal, and as medians, inter-quartile ranges and ranges otherwise.

Categorical data will be summarised by frequencies and percentages.

The primary outcome measure is the CPC score at hospital discharge with discrete values ranging from 1 to 5. The score will be dichotomised as 1-2 (positive or good outcome) and 3-5 (negative or poor outcome).

Sensitivity, specificity and predictive values of P25/30 in predicting poor outcome will be computed and the results compared to that of N20. Where appropriate, parameter estimates will be presented with 95% confidence intervals. Significant demographic and clinical predictors of poor neurological outcomes will be assessed and identified using regression models.

Statistical data analysis will be undertaken once data collection from the required number of participants is completed. No interim analysis is scheduled for this study.

Analyses will be performed in SPSS version 24 (or later), supplemented where required by Stata SE version 14.2 (or later) and R.

a. THE NUMBER OF PARTICIPANTS

Sample size calculation was based on diagnostic test accuracy (adequate sensitivity) of P25/30. A previous study (Kim et al. 2018) on patients treated by hypothermic targeted temperature management showed that the sensitivity of P25/30 in predicting poor outcome is 90.12% (95% CI, 81.5–95.6%). Though the proposed study will be based on those who are not treated by hypothermic targeted temperature management, the result (90%) is the ‘best’ available information regarding pre-determined sensitivity of P25/30. From experience of the team and analysis of the past three-years

pilot data, the prevalence of poor outcome was assumed to be 75%. In order the maximum marginal error of estimate does not exceed from 5% with 95% confidence level, and adjusting for drop-out/lack of consent at 3%, the minimum required sample size will be 115. No power was assumed in the calculation of the sample size as there is no testing of hypothesis.

7.3 The Level of Statistical Significance

Whenever applicable, a 5% level of significance will be used.

7.4 Criteria for the Termination of the Trial.

As this is not an interventional study, the chance to terminate the trial is minimal.

7.5 Procedure for Accounting for Missing, Unused, and Spurious Data.

Spurious and/or missing data will be summarised and reasons for missingness given where possible. All data analyses will be based on the complete data only.

7.6 Procedures for Reporting any Deviation(s) from the Original Statistical Plan

Statistical analysis of the data will be performed at the end of the study as per Section 7.1 above. If deemed necessary, a separate statistical analysis plan (SAP) can be prepared prior to the completion of the study and approved by the oversight committee. The study team will discuss any deviation from the analysis plan and report it to the oversight committee. Any revisions to the SAP will be documented, including a brief justification and timing of revision.

7.7 Inclusion in Analysis

All eligible participants will be included in the analyses.

8. ARCHIVING

Data and all appropriate documentation will be stored on safe databanks as described [on section 4.1] and will be kept for a minimum of 5 years after the completion of the study. After that period of time all data will be deleted. Similarly the data will be immediately deleted if any of the study participants or their NOK who have provided informed consent to participate in the study decides retrospectively to withdraw from the study.

9. REGULATORY ISSUES

9.1 ETHICS APPROVAL

The Chief Investigator had applied for approval from the Health Research Authority [HRA] and the North West – Haydock Research Ethics Committee. The study has been approved by the HRA and the North West – Haydock Research Ethics Committee. The Investigator will ensure that this study is conducted in full conformity with relevant regulations and with UK Policy Framework for Health and Social Care Research (2017), which have their basis in the Declaration of Helsinki.

9.2 CONSENT

Consent to enter the study must be sought from each participant only after a full explanation has been given, an information leaflet offered and time allowed for consideration. Signed participant consent should be obtained. The right of the participant to refuse to participate without giving reasons must be respected. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment. In these cases the participants remain within the study for the purposes of follow-up and data analysis.

However, all the patients enrolled in the study are expected to be in coma at the time of enrolment. This is a reality about most of the ICU patients. Therefore, within the first 24 hours after ICU admission, the members of the study group will discuss with the next of kin of the patients regarding the potential participation in the study and the informed consent process.

During this process, the members of the study group will actively listen to the thoughts of the next of kin and other family members if available and they will try to provide the maximum information to them not only about the study but also about the general potential benefit for the patients by research, the importance of the research in modern medicine and specifically in the specialty of Intensive Care Medicine where many clinical and prognostic uncertainties still exist.

The next of kin for each potential participant would be asked to consent for the participation of the patients to the study after being fully informed, both verbally and by the provision of the relevant relatives' information booklet that can be found in the appendix of this document.

Also, with the help of their next of kin for each one of the potential participants – before their enrolment in the study – we will explore the potential participants' likely previously expressed wishes or thoughts or opinions about the importance of medical research and the participation in medical research for the benefit of the patients.

If the participants in the study regain full mental capacity to provide informed consent and make informed decisions after their enrolment in the study, then they will be fully informed about the study by a member of the study group and they will be asked if they agree to continue with their participation in the study. If the participants are happy to remain in the study cohort then their data will be used for analysis and publication purposes. If they decide anytime to withdraw from the study then their decision will be respected but it will be explained that that their data already collected may still be analysed as part of the study.

The same options will be available for the next of kin that would have consented initially for the participation of patients in the study. Similarly, if the next of kin at any point before the completion of the study decided to withdraw their initial consent, then their decision would be respected but it will be explained that that the patients data already collected may still be analysed as part of the study.

The study group would be responsible to keep each one of the next of kin and/or the patients aware about the results of the study and the relevant publications [abstracts in conferences and scientific manuscripts in journals]. At that point the study group will invite the next of kin and or the participants to provide their constructive feedback about the results of the study and their feelings with regards to their participation in this study. This could be an effective way to maximise the participation and involvement of the participants to the research process, from the initial discussion and consent to the results of the research study and their feedback.

Also, that kind of interaction with the next of kin and/or the patients would give the opportunity to the members of the study group to actively explore the perspectives of the participants in their study, to maximise their experience and ultimately to help them developing their research performance by integrating useful learning points from the participants' constructive feedback to the design and practical application of their future research projects.

The aforementioned process would potentially involve the participants of this study to the dynamic development of the research process in general.

9.3 CONFIDENTIALITY

The Chief Investigator will preserve the confidentiality of participants taking part in the study and will comply with the Data Protection Act (2018).

9.4 INDEMNITY

This is an NHS-sponsored research study. If an individual suffers negligent harm as a result of participating in the study, NHS indemnity covers NHS staff and those people responsible for conducting the trial who have honorary contracts with the relevant NHS Trust. In the case of non-negligent harm, the NHS is unable to agree in advance to pay compensation, but an *ex-gratia* payment may be considered in the event of a claim.

This study is non-interventional and therefore no risk for potential harm of the participants is expected to be associated with this study

9.5 SPONSOR

University Hospitals Plymouth NHS Trust will act as the main sponsor for this study.

9.6 FUNDING

There is funding from the University Hospitals Plymouth NHS Trust Charitable Funds for £2,300 for the cost of statistical analysis.

9.7 AUDITS

The study may be subject to audit and monitoring by University Hospitals Plymouth NHS Trust under their remit as sponsor and other regulatory bodies to ensure adherence to the study protocol and the UK Policy Framework for Health and Social Care Research (2017).

10. STUDY MANAGEMENT

The day-to-day management of the study will be co-ordinated through Dr Nikitas Nikitas and Mrs Nicola Broomfield, from the departments of Intensive Care Medicine and Neurophysiology, respectively.

11. PUBLICATION POLICY

The interim and final results of the study will be disseminated *via* presentations at appropriate scientific meetings and conferences and publication in appropriate peer-reviewed journals.

The research findings is planned to be disseminated in the following manner:

a) The annual meeting of the Intensive Care Society UK

b) International meetings: European Society of Intensive Care Medicine and International Symposium in Intensive Care and Emergency Medicine

c) Publication in a peer reviewed journal.

d) Feeback to study participants

The study team would be responsible to keep each one of the next of kin and/or the patients aware about the results of the study and the relevant publications [abstracts in conferences and scientific manuscript in journal]. By submitting a copy of the relevant publication [accompanied by a plain English summary/explanation of the results] to each participant and/or their next of kin, the study team will invite the next of kin and/or the participants to provide constructive feedback about the results of the study and their feelings with regards to their participation in this study.

12. REFERENCES

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APPENDIX

Additional information to the protocol, consisting of:

- Schedule of events table
- Cerebral Performance Category
- Performance status
- Comorbidities score
- Participant/patient information sheet

TABLE 1. SUMMARY OF INVESTIGATIONS, TREATMENT AND ASSESSMENTS

Investigations / Treatments / Assessments	Time performed / recorded		
	At enrolment [First 24 hours post ROSC]	ICU discharge	Hospital Discharge
History of Present Complaint and Past medical History	X		
Neurological examination	X	X	X
ECG	X		
Cardiac arrest Rhythm	X		
CXR	X		
FBC, Creatinine-U&E, LFT, INR, Ammonia [if acute or chronic hepatic dysfunction], mean Glucose levels, mean Lactate levels	X		
Mean SpO2, mean PaO2, mean PaCO2	X		
Mean HR, mean BP, mean T			
APACHE II score	X		
SOFA score	X		
Cerebral Performance Category		X	X
ECOG / WHO pre-admission performance status	X		
Charlson Comorbidity Index Scoring System	X		
Informed consent	X		

FIGURE 1. THE CEREBRAL PERFORMANCE CATEGORY SCALE [CPC]

Cerebral Performance Category [CPC] Scale	
Positive [good] Neurologic Outcomes	CPC 1: Full Recovery or Mild Disability
	CPC 2: Moderate Disability but Independent in Activities of Daily Living
Negative [poor] Neurologic Outcomes	CPC 3: Severe Disability – Dependent in Activities of Daily Living
	CPC 4: Persistent Vegetative State
	CPC 5: Death

FIGURE 2. THE ECOG/WHO PERFORMANCE STATUS SCORE

ECOG/WHO Performance Status score	
Grade	**Performance status**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g. light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only self-limited care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self- care. Totally confined to bed or chair
5	Dead

FIGURE 3. THE CHARLSON COMORBIDITY INDEX SCORING SYSTEM

Charlson Comorbidity Index Scoring System	
Score	**Condition**
1	Myocardial infarction [history, not ECG changes only] Congestive Heart Failure Peripheral Vascular Disease [includes aortic aneurysm ≥ 6cm] Cerebrovascular disease; CVA with mild or no residua or TIA Dementia Chronic Pulmonary Disease Connective Tissue Disease Peptic Ulcer Disease Mild Liver Disease [without portal hypertension, includes chronic hepatitis] Diabetes without end-organ damage [excludes diet-controlled alone]
2	Hemiplegia Moderate or severe renal disease Diabetes with end-organ damage [retinopathy, neuropathy, nephropathy, brittle diabetes] Tumour without metastases [exclude if >5y from diagnosis] Leukaemia [acute or chronic] Lymphoma
3	Moderate or severe Liver Disease
6	Metastatic Solid Tumour AIDS [not just HIV-positive]
NB. For each decade > 40 years of age, a score of 1 is added to the above score. **Abbreviations:** ECG: electrocardiogram, CVA: cerebrovascular accident, TIA: transient ischaemic attack, AIDS: acquired immunodeficiency syndrome, HIV: human immunodeficiency virus	