Bispectral Index monitoring as an early neurological prognostic tool after an out-of-hospital cardiac arrest successfully resuscitated.
A prospective cohort study.

Final degree project
En primer lugar, agradecer al todo el equipo de la unidad coronaria del Hospital Josep Trueta, por abrirme una vez más sus puertas, por hacerme sentir como en casa. Gracias en especial al doctor Pablo Loma, por compartir sus conocimientos, su punto de vista conmigo y por su comprensión en todo momento.

A mis padres y a mi hermano, por estar siempre ahí.

“Not all those who wander are lost”.
- J.R.R. Tolkien
# 1. ABREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ATP</td>
<td>Adenosine triphosphate</td>
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<tr>
<td>BIS</td>
<td>Bispectral index</td>
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<tr>
<td>CCU</td>
<td>Coronary care unit</td>
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<td>CPR</td>
<td>Cardiopulmonary resuscitation</td>
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<td>CT</td>
<td>Computerized tomography</td>
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<td>EEG</td>
<td>Electroencephalogram</td>
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<tr>
<td>EMGi</td>
<td>Electromyogram indicator</td>
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<td>EMS</td>
<td>Emergency medical services</td>
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<td>HB</td>
<td>Hospital Universitari de Bellvitge</td>
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<td>HGT</td>
<td>Hospital Universitari Germans Trias &amp; Pujol</td>
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<tr>
<td>HJT</td>
<td>Hospital Josep Trueta</td>
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<tr>
<td>HSC</td>
<td>Hospital Universitari de la Santa Creu &amp; Sant Pau</td>
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<tr>
<td>HVH</td>
<td>Hospital de la Vall d’Hebron</td>
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<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
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<tr>
<td>NSE</td>
<td>Neuron-specific enolase</td>
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<td>OHCA</td>
<td>Out-of-hospital cardiac arrest</td>
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<tr>
<td>ROSC</td>
<td>Return of spontaneous circulation</td>
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<tr>
<td>SQI</td>
<td>Signal Quality Index</td>
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<tr>
<td>SSEP</td>
<td>Somatosensory evoked potentials</td>
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<tr>
<td>TH</td>
<td>Therapeutic hypothermia</td>
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2. ABSTRACT

Introduction: out-of-hospital cardiac arrests are one of the major complications of cardiovascular diseases. Patients who survive a cardiac arrest suffer what is known as Post-Cardiac Arrest Syndrome, which worst consequence is the post-anoxic encephalopathy, the leading cause of disability in patients after cardiac arrest. Therapeutic hypothermia, among other interventions, has proven to diminish the damage to the brain when the patient is in this situation. But, in order to avoid the painful sensation this treatment causes, patients are sedated. This makes the neurological evaluation of the patients unreliable with the tools we have until now. So, we have to wait more than 72 hours to have an accurate prognostic of the patient. In such situation, where therapeutic decisions on highly invasive acute cardiac assistance have to be taken, the actual lapse of time is unacceptable.

In the last years, researchers have been looking for new tools that make possible to give an earlier and accurate prognosis among patients who have suffered cardiac arrests successfully resuscitated undergoing therapeutic hypothermia. Bispectral index monitoring has been proposed as a proper tool to assess the neurological prognostic since it could provide us information about the cerebral perfusion probably earlier than the available tools.

Objective: the aim of this study is to describe patterns among the graphs created with Bispectral Index values of each patient and to identify if these patterns have a prognostic value in terms of neurological and functional outcomes at discharge from hospital and at follow up at 6 months and at the first year. We want to find as well a cut-off point, which in the first 24 hours allow clinicians to classify patients who had suffered a cardiac arrest successfully resuscitated according to their neurological outcomes.

Design: it will be a multi-centric prospective cohort study involving the coronary care units of Hospital Universitari Josep Trueta (Girona), Hospital Universitari de la Vall d’Hebron (Barcelona), Hospital Universitari de la Santa Creu i Sant Pau (Barcelona), Hospital Universitari de Bellvitge (Hospitalet del Llobregat) and Hospital Universitari Germans Trias i Pujol (Badalona).

Methods: 330 adult patients who have suffered an out-of-hospital cardiac arrest successfully resuscitated and undergoing therapeutic hypothermia will be included in our study. Since the moment therapeutic hypothermia starts, all of them will be connected to Bispectral index monitors by a sensor-strip located in their foreheads. We will record the first 72 hours of Bispectral index monitoring.

This study will be conducted in three years.

Key words: Bispectral index, cardiac arrest, post-anoxic encephalopathy, therapeutic hypothermia, neurological prognostication.
3. INTRODUCTION AND JUSTIFICATION

3.1 Concept of out-of-hospital cardiac arrest and epidemiology

**Out-of-hospital cardiac arrest** (OHCA) is a major complication of cardiovascular diseases and it is defined as a sudden and potentially reversible interruption of the breathing and circulation caused by any kind of cardiopathy, occurring out-of-hospital or in an emergency room, to an individual declared as dead when arriving to the hospital. It is also necessary that the time between the appearance of symptoms and the time of the death is less than an hour (1). OHCA is such an important public health problem and one of the most relevant challenges in modern cardiology. It represents about 80% to 90% of all sudden deaths (2,3).

Around 80% of OHCAs are caused by coronary diseases. The closest relation between OHCA and coronary cardiopathy leads to think that cardiovascular risk factors are also risk factors for OHCA (1,3).

Acute ischemic cardiopathy is the most frequent cause of cardiac arrest, which in 20% of cases occurs as the first manifestation of an acute coronary syndrome. First minutes of ischemia after the occlusion of a coronary artery, or one of their branches, influence the appearance of malignant arrhythmias (Table 1):

<table>
<thead>
<tr>
<th>Defibrillable rhythms</th>
<th>Non defibrillable rhythms</th>
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<tbody>
<tr>
<td>Ventricular fibrillation</td>
<td>Electromechanical dissociation</td>
</tr>
<tr>
<td>Pulseless ventricular tachycardia</td>
<td>Asystole</td>
</tr>
<tr>
<td>Initial rhythm in 85% of patients after OHCA</td>
<td>Initial rhythm in 15% of patients after OHCA</td>
</tr>
<tr>
<td>Better prognosis</td>
<td>Worst prognosis</td>
</tr>
<tr>
<td>Higher chances of survival</td>
<td>Lower chances of survival</td>
</tr>
</tbody>
</table>

Global incidences (4) of emergency medical services (EMS) attended and treated OHCAs are 95.9 cases and 62.3 per 100,000 person-years, respectively. Only in Europe, incidence is about 38 cases per 100,000 people-years, which means that there are more than 275,000 cases of OHCAs per year (5). Although in Spain incidence it is not as high as in other developed countries (28 cases per 100,000 people-years (5)), around 12% of all the natural deaths occur suddenly (6); in other words: among 24,000 to 50,000 OHCAs (7).

3.2 Complications of OHCA – Post-anoxic encephalopathy.

Successful resuscitation or return of spontaneous circulation (ROSC) after a cardiac arrest is defined as recovery of blood pressure and pulse for more than 1 hour, with or without a continuous catecholamine infusion (see METHODS – 6.4.3 Covariates for more information about ROSC) (8). Resuscitated patients from a cardiac arrest occurring out-of-hospital must be
hospitalized in a Coronary Care Unit (CCU) or in an Intensive Care Unit, where they can be monitored and treated properly since the moment they arrive to the centre.

Even survivors of OHCA are increasing, mostly due to the correct implementation of “the Chain of Survival”, most of them will die in the first three days and, in the ones who survive, brain injuries are an important cause of morbidity and mortality in the short, mid and long term. In fact, of patients admitted to hospital, only between 7 to 30% were discharged with good neurological outcomes(9). In Europe, survival to OHCA is about 10,7% for all-rhythm and a little bit higher (21,2%) for ventricular fibrillation(10), and in Spain, survival rates do not differ that much (10,1%) (11).

Complete whole-body ischemia is an unnatural pathophysiological state following cardiopulmonary resuscitation in a patient suffering OHCA. In 1972, doctor Vladimir Negovsky described the Post-Cardiac Arrest Syndrome (12), a complex combination of pathophysiological processes including brain injury, myocardial dysfunction and systemic ischemia/reperfusion response. Also, the unresolved pathological process causing the cardiac arrest can complicate all this. This syndrome starts a series of inflammatory damaging reactions to the organism that can continue some days.

Post-anoxic encephalopathy is the leading cause of disability after cardiac arrest. It is the cause of death in almost 70% of the patients after an OHCA(13). The intensity and seriousness of this situation is directly related with the time between the cardiac arrest and the cardiopulmonary resuscitation.

Anoxia is the third most frequent cause of coma, following trauma and vascular lesions. The most common causes of post-anoxic coma in adults are: cardiopulmonary arrest, stroke, respiratory arrest and carbon monoxide poisoning(14).

The spectrum of disability resulting from hypoxic-ischemic encephalopathy ranges from complete recovery to persistent coma or even death(15). Among 80% of patients successfully resuscitated after a cardiac arrest remain comatose for varying lengths of time, 40% of them progress to vegetative state(14) and the first year mortality exceeds 80%(16,17).

Damage from cerebral anoxia comes in stages (18) (Figure 1):

1. Within seconds, blood flow stops and arterial pressure of oxygen diminish. This reduction of available oxygen and glucose reduce the production of ATP, raises lactate and diminishes pH, which produce direct neuronal lesion.
2. Within minutes of anoxia, important cerebral activities are compromised and cells begin to lose structural integrity, leading to mitochondrial damage and loss of calcium haemostasis. Moreover, excess of glutamate precipitates programmed cell death (apoptosis).
3. Reperfusion limits on-going anoxic injury. But after it, additional damage (reperfusion injury) it is produced. Oxygen-free radicals accumulated after the reintroduction of oxygen to the
ischemic region and neuronal damage mediated by inflammatory cells cause this injury. Damaged vessels can as well activate coagulation’s cascade and favour thrombosis and platelet adhesion leading to a regional and multifocal under-perfusion (“No re-flow” phenomenon) and endothelial oedema. This is how damage is perpetuated.

All this process results in **heterogeneous injury to the brain**. Large projection neurons of the cerebral cortex, cerebellar Purkinje cells and the hippocampus are the most vulnerable areas. If the thalamocortical complex or extensive bilateral cortical regions are injured, dysfunction in arousal and consciousness may result. The **impairment in arousal** remains the most predominant neurologic problem during the early post-resuscitative period (19). As the brainstem can tolerate a greater degree of global ischemia, it is possible to find preservation of cranial nerve and sensory motor reflexes.
3.3 Management of post-anoxic encephalopathy.

Many actions have been taken to avoid the consequences of cardiac arrests. First, cardiopulmonary resuscitation and early defibrillation try to diminish as much as possible the time to ROSC and that way, reduce the anoxia period. Then, an in-hospital appropriate treatment plan must be implemented. Part of this standardized plan includes haemodynamic optimization, ventilation and oxygenation, an earlier treatment of the aetiology of the arrest (the realization of a coronary angiography and percutaneous coronary intervention when needed), avoiding hyperglycaemia and detecting and treating early epileptic crisis.

Moreover, in the last two decades, several studies have been carried out to optimize post-resuscitation cares and, one of the most important measures that has proven to increase the survival and to improve neurological prognosis in patients after OHCA secondary to defibrillable rhythms is mild therapeutic hypothermia (32-34°C during 12 to 24 hours)(20,21). Studies have shown that among 50 to 55% of patients undergone therapeutic hypothermia are discharged to the hospital with better outcomes; on the contrary, only 30 to 36% of the patients not treated with it were discharged with good neurological outcomes(22).

Therapeutic hypothermia (TH) has a neuroprotector effect in front of anoxic aggressions, independently of the cause. Given that the mentioned reperfusion injury happens in every comatose patient after cardiac arrest whatever the initial rhythm was, it seems reasonable to use an active treatment, even though patients with no defibrillable rhythms have worst prognosis and lower survival(23,24). Hypothermia tempers the post-cardiac arrest syndrome inflammatory cascade and aborts apoptotic pathways by reducing the release of glutamate and free radicals. It also decreases cerebral metabolic rate of oxygen, cerebral blood volume, and intracranial pressure, thereby improving the oxygen supply-and-demand mismatch(25).

So, since 2010, European Resuscitation Council and the American Heart Association guidelines recommended the application of mild therapeutic hypothermia (recommendation Class I) to every comatose patient surviving to an out-of-hospital and in-hospital sudden cardiac death secondary to any rhythm.

3.4 Prognostication among patients after OHCA.

All patients undergoing TH should receive low-dose, continuous infusions of both a sedative and analgesic agents to prevent any painful sensation and to suppress shivering. Preference should be given to agents with short half-lives like propofol or midazolam (for sedatives) and remifentanil (for analgesia), because hypothermia reduces the clearance of most of them. This strategy will facilitate neurological assessments after return to normothermia (25).

The sedation and neuromuscular blockage used during hypothermia result in pharmacologic effects that make the clinical examination unreliable. Although these medications may be weaned by 48 hours after cardiac arrest, sedatives are commonly used up to 72 hours and beyond(26). The pharmacokinetic and pharmacodynamics properties of sedatives, analgesics and
neuromuscular blocking agents are altered during hypothermia due to hepatic and renal drug clearances are decreased(27) and injured brains may be more sensitive to depressant effects of these drugs, so residual sedation can confound the accuracy of clinical examinations. Owing to the persistent presence and effects of sedatives and paralytic agents, as well as the physiologic effects of hypothermia, caution needs to be exercised when attempting to interpret the clinical examination and neurophysiologic findings.

As most patients resuscitated after cardiac arrest will die of neurological complications, providing an accurate prognosis remains one of the most challenging aspects of caring for patients who receive TH. It is important to begin the conversation with families early in the hospital course, so they aware of the overall poor prognosis after cardiac arrest. If tools for having an earlier prognosis of the situation of their relatives were able, that would allow us to give families more accurate information and, above all, to take more individualized decisions in the treatment of the patient. So, we could use more aggressive diagnosis tests and treatments in those patients in which we expect better outcomes and, on the other side, we will avoid futile treatments and diagnostic tests that will not help patients whose situation is very unfavourable or even irreversible.

Before the routine use of hypothermia as a treatment for patients in coma after cardiac arrest, several prognostic parameters were widely accepted as reliable and valid for the prediction of poor neurological outcome. These parameters are:

- **Neurological examination**, which involves pupillary light response, corneal reflexes and motor response to painful stimuli.

- **Somatosensory evoked potentials** (SSEP) that involve monitoring brain response to electrical stimulation of peripheral nerves. The main response normally seen is the N20 signal in the primary somatosensory cortex 20ms after electrical stimulation of the median nerve. Its recording requires appropriate skills and experience, and care should be taken to avoid electrical interferences from muscle artefacts.

- **Electroencephalogram** (EEG) is the standard tool to assess the brain electrical activity, the global cortical function and the presence of paroxysmal activities (seizures and bursts), even when the brain function is depressed and it can’t be explored by other means, such as in coma. The lack of standardized EEG terminology continues to be a major limitation in research and practice among prognostication after cardiac arrest.

- **Biomarkers**, mainly:
  - Neuron-specific enolase (NSE), a glycolytic enzyme founded in neurons. Neuronal damage can be detected by the presence of increased levels of NSE in cerebrospinal fluid or blood.
Serum astroglial S-100B is a calcium-binding protein, enriched in astroglial cells that can cross the blood-brain barrier after hypoxic damage of the central nervous system. The predictive value of these markers is variable, and they are unhelpful before 48 hours have elapsed, due to the metabolic changes occurring immediately after an arrest and the time that takes by laboratories to perform these analyses.

- **Neuroimaging**: cranial computerized tomography (CT) scan and brain magnetic resonance imaging (MRI) have become essential tools in the diagnosis, management and prognostication of patients with acute brain injuries. In post-cardiac arrest prognostication, they can define structural damage and detect focal injury(28). Reasons for early cranial neuroimaging in post-cardiac arrest patients may be both diagnostic as well as useful for providing data that could influence clinical management. They can identify a neurologic aetiology of the arrest (subarachnoid haemorrhage or non-aneurysmal intracerebral haemorrhage) that might have caused a cardiac arrest by increasing intracerebral pressure, sympathetic storm, ischemic stroke or traumatic brain injury(29).

The *American Heart Association* made in 2015 a guidelines’ update for cardiopulmonary resuscitation and emergency cardiovascular care(23) where they manifest that the optimal time for prognostication is **upon 72 hours after normothermia** to minimize the rate of false-positive results. Moreover, they, and so many others research groups, shed light on some **problematic aspects of prognostication with the mentioned parameters** in patients undergone therapeutic hypothermia after suffering a cardiac arrest (23–25,30–33) (Table 2):
As we saw above, several studies have focused on the prognostic value of all these parameters but none could demonstrate an accurate prediction of outcome within the first 24 hours after cardiac arrest in hypothermia-treated patients. The actual lapse of time to reliably predict outcome, generally higher than 24, 48 or even 72 hours after cardiac arrest, might be too lengthy if therapeutic decisions on highly invasive acute cardiac assistance have to be taken. Moreover, these reviewed parameters only classify well those patients with the poorest outcomes (vegetative states or patients who are going to die), but we do not have any information about all the patients with mild or moderate neurological disabilities. We are not able to confirm that the absence of these indicators means that the patient is going to have good outcomes. They are only specific in
finding indicator signs that allow the physicians to diagnose when somebody is going really badly, and even in those cases, some of these parameters, like neuron-specific enolase or neuroimaging may fail. Thus, there is an unmet need for early and accurate prediction tools that give doctors the chance to take earlier decisions in the treatment of these patients and to inform properly the families about the functional, and especially the neurological, prognosis of their relatives. The ability to predict outcome early after cardiac arrest would represent a major breakthrough towards personalized medicine by adapting the treatment strategy individually to the patient. This early prediction would allow avoiding futile healthcare to patients with irreversible neurological damage while maintaining resources in patients most likely to benefit, as for example aggressive circulatory support such as coronary angiography, revascularization, mechanical circulatory support, or pulmonary thrombectomy.

3.5 Bispectral index monitoring: the ultimate tool in prognostication in patients after OHCA.

In the last few years, diverse researching groups have started the searching of new tools that made feasible to give an earlier and accurate prognosis in patients post-cardiac arrest undergoing therapeutic hypothermia. Along these lines, it has been proposed the Bispectral index (BIS) monitor (Figure 2) as a proper tool in order to reach this objective in those patients who have suffered an out-of-hospital sudden cardiac arrest and are undergoing therapeutic hypothermia.

BIS (Annex 1 – Bispectral index monitoring use instructions) is a processed electroencephalogram, approved since 1996 by the Food and Drug Administration as an aid in the assessment of the deep of anaesthesia. When used appropriately as an adjunct assessment tool, BIS monitoring helps clinicians titrate drug dosages more precisely. To process the EEG signal, processing techniques such as bispectral analysis, power spectral analysis and time domain analysis are used and combined via an algorithm(34).

The BIS monitor it is a real-time indicator that gathers information about the depth of sedation achieved by sedatives and hypnotics via a non-invasive adhesive strip placed on the patient’s forehead. Classic EEG equipment requires application of multiple head electrodes; in contrast, the BIS monitor generates digitally processed brain waves from four sensors embedded in a single adhesive strip (Figure 3):
Digital analysis of brain waves provides an objective quantitative measure of level of consciousness. The BIS monitor detects and shows certain EEG's patterns that are correlated with depth of anaesthesia (35). These processed brain waves are associated as well to a numeric value that represents the level of wakefulness on the BIS index scale. The highest value, 100, represents complete wakefulness; 0 represents maximal EEG suppression (isoelectric EEG) (34). Summarizing this information (Table 3):
Because BIS is a non-invasive tool and it does not require a previous training to interpret its results, it may be more useful than EEG or other prognostication parameters, like the ones we saw above, as a clinical monitoring tool for predicting the prognosis of post-cardiac arrest outcomes from brain damage before the first 24 hours. Since EEG is tightly linked to cerebral metabolism, BIS values and trends would reflect the adequacy of cerebral perfusion.

The BIS monitoring give us minute-by-minute information. All these values are stored in system’s memory and they are easily removable by an USB port (see Annex 1 – Bispectral index monitoring use instructions | Export Data). Since a patient is connected to BIS monitor since his admission to 72 hours or more, registers may be too long. So, when we obtain the register of each patient, we can process it with data processing programmes (Excel or SPSS®), and create the graph of this

<table>
<thead>
<tr>
<th>Sedative degree (consciousness degree)</th>
<th>Brain waves patterns</th>
<th>Level of wakefulness</th>
<th>Bispectral index values</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>Small amplitude</td>
<td>Awake</td>
<td>80-100</td>
</tr>
<tr>
<td></td>
<td>Quick frequency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild-moderate</td>
<td>Less smaller amplitude</td>
<td>The patient can respond to loud commands or mild prodding/shaking.</td>
<td>60-80</td>
</tr>
<tr>
<td></td>
<td>Quick frequency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General anaesthesia</td>
<td>Large amplitude</td>
<td>Low probability to explicit recall.</td>
<td>40-60</td>
</tr>
<tr>
<td></td>
<td>Less quicker frequency</td>
<td>Unresponsive to verbal or loud stimulus.</td>
<td></td>
</tr>
<tr>
<td>Deep anaesthesia</td>
<td>Large amplitude</td>
<td>Deep hypnotic stage</td>
<td>20-40</td>
</tr>
<tr>
<td></td>
<td>Slow frequency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brain death</td>
<td>Flat line EEG/Isoelectric EEG</td>
<td>Death</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 3. Correlation among BIS values, sedative degree, brain waves patterns and level of wakefulness. Based on (34).
patient. We think that the graphs are an easier way to interpret these registers and to check quickly the BIS values of the patient. In Figure 4 we can see how it could be the graph:

![BIS Graph](image)

**Figure 4. BIS graph.** This is the BIS graph (24 hours) from a patient who had suffered an OHCA, admitted to the Coronary Care Unit (HJT). Verbal consent of the patient was asked in order to analyse his register. This patient awakes with no neurological damage.

We do believe that BIS monitoring might be one of the definitive tools to assess the neurological prognosis of cardiac arrest patients in the early first 24 hours. As we do think about the possibilities of BIS monitoring, in 2014 C. W. E. Hoedemaekers and W. F. Abdo, in an editorial of Critical Care Medicine journal, state that maybe BIS monitoring would be “the holy grail for prognostication in patients after cardiac arrest” (36).

In the last years, some research groups have been trying to assess the value of Bispectral index monitoring among patients with cardiac arrest (37–45). All the studies they have carried through have multiple limitations, and the aim of some of these studies is different than ours (46,47). Moreover, even all these studies have taken place in intensive care units, it has not been always possible to carry them in specialized coronary care units. Because of all the mentioned, it has not been possible to achieve conclusive conclusions and results cannot be extrapolated.

We have decided to summarize below all the limitations we have found and, as well, the results some of the most relevant studies among the cited above and omit the ones that are retrospectives (46,48) and the ones which aim was different from ours (46,47) (Table 4 and Figure 5):
Table 4: Review of BIS monitoring among patients suffering out of hospital cardiac arrest (OHCA).

<table>
<thead>
<tr>
<th>Study</th>
<th>Aim</th>
<th>Type of study and sample</th>
<th>Results</th>
<th>Limitations</th>
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<tbody>
<tr>
<td>BIS helps predicting bad neurological outcome in coma survivors after cardiac arrest and induced TH</td>
<td>Determine the use of BIS as a prognostic tool in TH treated coma survivors after cardiac arrest, regardless of initial rhythm, location or cause.</td>
<td>Prospective, single-centre, unblinded, observational cohort study. 45 patients.</td>
<td>14 patients: BIS values of 0 during their ICU stay. At 6 months 11 were dead, 1 remained comatose and 2 had severe neurological sequelae. No patient of this group had good neurological outcome or improved his neurological outcome between ICU and 6-month follow-up. 31 patients: BIS values &gt; 0. At 6 months 11 died, none remained comatose, 3 had bad neurological outcome, and 17 had no or minor neurological sequelae.</td>
<td>• Only demonstrate that BIS values of 0 are indicators of poor prognosis but it cannot prove that higher values are indicators or better prognosis. • No correlation between good outcome and BIS values higher than 0 were possible.</td>
</tr>
<tr>
<td>Neurological prognostication and BIS monitoring after resuscitation from cardiac arrest</td>
<td>BIS values within the first 24 hours after resuscitation would correlate with neurological outcomes at discharge. Primary outcome: survival to hospital discharge with good neurological outcome.</td>
<td>Observational prospective cohort. All adult patients who achieved ROSC after resuscitation from OHCA and In-Hospital Cardiac Arrest and were treated with TH. 62 patients were included.</td>
<td>Statistically significant cut-off points were: Good NRL: 0 at 12h Poor NRL: 0 at 24h Good NRL: 0 at 24h Poor NRL: 0 at 24h 46 ± 16 34 ± 21 49 ± 13 30 ± 20 Sensitivity and specificity for predicting good outcomes are modest and vary (21-80% and 41 – 99%). Only a BIS value of 0 has a 100% sensitivity and specificity for poor outcomes.</td>
<td>• Discontinuation of neuromuscular blockage among the first 24 hours. • No follow-up. • Small sample size. • One centre. • Include in-hospital arrests.</td>
</tr>
<tr>
<td>The BIS index and suppression ratio are very early predictors of neurological outcomes during TH after cardiac arrest</td>
<td>To evaluate BIS and suppression ratio as very early predictors of neurological outcomes during TH after cardiac arrest.</td>
<td>Observational prospective cohorts study. 84 patients.</td>
<td>Area under the curve is 0.91 (CI 90%). Cut-off point of BIS ≤ 22 predicted poor outcome with a Likelihood Ratio of 14.2.</td>
<td>• Single centre. • Moderate sample size. • TH and sedation protocols were arbitrary among patients. • Only poor outcomes cut-off point.</td>
</tr>
<tr>
<td>Early BIS and sedation requirements during TH predict neurological recovery following cardiac arrest</td>
<td>To test that low BIS index scores and low sedative requirements during TH predict poor neurological outcomes.</td>
<td>Prospective observational study. 141 patients.</td>
<td>60% of the patients were discharged with poor neurologic outcome and had lower BIS and sedative requirements during TH compared to the 40% subjects discharged with good outcome. It seems that early prediction of neurologic recovery was best seven hours after admission, and median BIS scores at that time were 31 points lower in subjects discharged with poor outcome. Each 10-point decrease in BIS was associated with a 50% increase in the odds of poor outcome (OR 3.52 to 7.69, p &lt; 0.001).</td>
<td>• Not standardized TH and sedation protocol. • Single centre study. • It is not clear if clinicians were blinded. • Moderate sample size.</td>
</tr>
<tr>
<td>BIS to predict neurological outcomes early after cardiac arrest</td>
<td>To address the value of continuous monitoring of BIS to predict neurological outcome.</td>
<td>Prospective observational study. 96 patients.</td>
<td>Cut-off points: - Good Outcome: BIS 38 ± 9 [95% CI 26–50] Poor outcome: 17 ± 12 NRL outcomes were predicted by mean BIS with an area under the curve above 0.8. Specificity (90%) and sensitivity (96%) for 6-months NRL outcomes prediction was obtained from the 12.5 hours' cut-off value of BIS of 23 (AUC 0.88). If Specificity is fixed at 100%, cut-off value for poor Outcomes are 2,4 in the first 271 minutes (5 hours).</td>
<td>• Single centre study • Small sample • Physicians were not blinded to BIS value. • Cut-off values overlap.</td>
</tr>
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</table>

BIS: Bispectral Index; CI: Confidence Interval; ICU: Intensive Care Unit; NRL: Neurological; OHCA: Out-of-Hospital Cardiac Arrest; ROSC: Return Of Spontaneous Circulation; TH: Therapeutic hypothermia.
The studies summarized above conclude, in general, that lower Bispectral index values are related to poor outcomes. Another important fact is that among all the mentioned studies, none of them have been performed before in our country. Since features of the population may vary, we think it is also important to characterize what happens in here.

In light of facts, even if results were more concluding, they only give us information among patients who have the poor results, but nothing is stated about patients who go well. Given that we do want to know also when a patient is going well to be more aggressive with his or her treatment in order to prevent an evolution to worst neurological states, more data about the possibilities of BIS monitoring among patients who are discharged from hospital with good neurological outcomes are needed as well.

Summarizing all the given information, nowadays in our country, we have survival rates of 10,1% among patients who suffer an out-of-hospital cardiac arrest (11). In 40% of cases, survivors evolve to a vegetative state and in the first year, the mortality rate among these patients is up to 80% (14,16,17).

Consequences of cerebral anoxia due to a cardiac arrest have been broadly studied. Therapeutic hypothermia, together with haemodynamic optimization, a correct oxygenation and a quickly revascularization, among others have been proven to diminish brain injury among these patients (20–22). But when a patient is undergone therapeutic hypothermia, sedative drugs and analgesia are needed in order to prevent any painful sensation. The sedation makes clinical examination unreliable until 72 hours or even more, depending on the features of the patient or his/her sedative requirements.

Given the general bad prognostic among patients who suffer a cardiac arrest, an early prognosis could help clinicians to take crucial therapeutic decisions among these patients. Until now, all the
neurological parameters on what we account have been proven to give us information only up to 72 hours after the arrest. That lapse of time in a situation where highly invasive acute cardiac assistance has to be taken is critical.

Because all that we have explained, we do think Bispectral index monitoring can proffer us information among neurological prognosis of the patient in the first 24 hours after the cardiac arrest because it could provide us information about cerebral perfusion in an easy to interpret way. Since it could give us information about the cerebral perfusion, it seems a feasible neurological prognostic tool in these situations.

Considering as well the features of this monitoring system to give professionals early individual information, we are inclined to think about all the possibilities Bispectral Index monitoring can provide us in order to achieve earlier prognosis in patients with such higher rates of mortality and poor prognosis reflected as a neurological severe dysfunction or death.
4. BIBLIOGRAPHY


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BISPECTRAL INDEX MONITORING AS AN EARLY NEUROLOGICAL PROGNOSTIC TOOL AFTER AN OUT-OF-HOSPITAL CARDIAC ARREST SUCCESSFULLY RESUSCITATED.


5. HYPOTHESIS AND OBJECTIVES

Main hypothesis

Patterns of Bispectral index values’ graphs among patients with an out-of-hospital cardiac arrest successfully resuscitated and that are undergone therapeutic hypothermia, allow us to establish a relation in this way:

- Patients with higher Bispectral index values, present reactive patterns that indicate good neurological and functional outcomes at discharge from hospital and at a follow up at 6 months and at a year.

- Patients with lower Bispectral index values, present areactive or flat patterns that indicate poor neurological and functional outcomes at discharge from hospital and at a follow up at 6 months and at a year.

Moreover, analysing Bispectral index values we find a cut-off point from which we can as well classify patients according to their neurological prognostic in the first 24 hours after the cardiac arrest.

Main objectives

- To identify and describe the patterns among the graphs obtained after processing Bispectral index values of adult patients who have suffered a sudden cardiac arrest successfully resuscitated, and that are undergone therapeutic hypothermia.

- To establish the prognostic value of the mentioned patterns in terms of neurological and functional outcomes at discharge from hospital and at follow up at 6 months and at the first year.

- To find a significant cut-off point in the first 24 hours of monitoring by analysing the graphs resulting from Bispectral index values, which allow clinicians to classify patients who had suffered a cardiac arrest successfully resuscitated according to their neurological outcomes.
6. MATERIALS AND METHODS

6.1 Study design
In order to be able to confirm or refuse our hypothesis, we propose a multi-centric observational prospective cohorts study conducted during three years, in Hospital Universitari de Girona Doctor Josep Trueta (HJT) together with Hospital Universitari de la Vall d’Hebron (HVH), Hospital Universitari de Bellvitge (HB), Hospital Universitari de la Santa Creu i Sant Pau (HSC) and Hospital Universitari Germans Trias & Pujol (HGT). All these hospitals account with specialized Coronary Care Units.
We will register, minute by minute, with Bispectral Index monitoring every comatose patient arriving to the Coronary Care Units after an out-of-hospital cardiac arrest successfully resuscitated. With the entire register, we will be able to transform all the registered values of each patient into a graphic with data processing programmes, such as Microsoft Excel or SPSS®.
The register of Bispectral values will be carried out for at least 48 hours after the start of therapeutic hypothermia.

For further information about the sampling process, please, check 6.3.2 Sample size.

6.2 Setting and population of the study
This research will take place in Hospital Universitari Doctor Josep Trueta, a medium-sized centre in the province of Girona, and in Hospital Universitari de la Vall d’Hebron (HVH; Barcelona), Hospital Universitari de Bellvitge (HB; Hospitalet del Llobregat), Hospital Universitari de la Santa Creu i Sant Pau (HSC; Barcelona) and Hospital Universitari Germans Trias & Pujol (HGT; Badalona).
The study population is based in a consecutive sampling of patients who have suffered out-of-hospital cardiac arrest, successfully resuscitated, admitted and hospitalised in the Coronary Care Unit of these hospitals.

6.2.1 Inclusion Criteria
- Out-of-hospital cardiac arrest successfully resuscitated, which means an achievement of return of spontaneous circulation,
- Adult patients (> 18 years old),
- Cardiac arrest caused by a cardiac aetiology,
- Any initial arrest rhythm: asystole, pulseless electrical activity, ventricular fibrillation or pulseless ventricular tachycardia,
- Uncoscious patients¹,
- Patients undergone mild therapeutic hypothermia with sedo-analgesia and neuromuscular blockage.

¹ An unconscious patient is the one who has a Glasgow coma score below or equal to 8. A coma, also called, persistent vegetative state, is a profound or deep state of unconsciousness. An individual in a state of coma is alive, but unable to move or respond to his or her environment. Individuals in such state have lost their thinking abilities and awareness of their surroundings, but retain non-cognitive function and normal sleep patterns. Spontaneous movements may occur and the eyes may open in response to external stimuli.
6.2.2 Exclusion Criteria

- In-hospital cardiac arrests,
- Death of the patient the first 24 hours,
- Patients who have active do-not-resuscitate orders,
- Non-cardiac aetiology,
- Patients not eligible for therapeutic hypothermia:
  ➞ Demonstration of spontaneous awakening with purposeful movement,
  ➞ Had a known terminal illness,
  ➞ Arrested following traumatic head injury,
  ➞ Had an initial post-arrest body temperature less than 34°C,
  ➞ Had an estimated time from arrest to ROSC greater than 60 minutes,
  ➞ Pregnant women,
  ➞ Clinically significant bleeding

6.3 Sampling

6.3.1 Patient selection

A consecutive non-probabilistic sampling method will be performed. The patients with an out-of-hospital cardiac arrest will be recruited during their attendance in the Coronary Care Units of the five hospitals when they fulfil the inclusion criteria and none of the exclusion criteria we stated above.

All the participants will be informed about the purpose of the study once they awake from coma state, and they will be invited to read and sign the information sheet and the informed consent (see Annex 2 – Informed consent). While the patient remains unconscious or if he/she awakes in a dementia, vegetative states or when the patient is in a state of brain death, their closest relatives will be in charge of read and sign the informed consent. Once the patient awakes and if he/she is able, they will be asked as well by their informed consent.

In some cases, we will need to start collecting data before having an informed consent signed, but since these data will be part of our assistance task, we will collect them in order to have a good control of the patient and help him/her in the best way. However, it is important to clarify that we will not use any of these data in our study if the patient or their relatives do not agree with the conditions of the study and they do not sign the informed consent.

6.3.2 Sample size

Given that by now, we do not know the behaviour of BIS values, which means that there is a lack of data about what is considered “higher BIS values” or “lower BIS values”, we cannot calculate the sample size.

As we have seen in the introduction, the cut-off points that have been proposed suffer overlapping between those that are supposed to be related to poor outcomes and the ones that are suppose
BISPECTRAL INDEX MONITORING AS AN EARLY NEUROLOGICAL PROGNOSTIC TOOL AFTER AN OUT-OF-HOSPITAL CARDIAC ARREST SUCCESSFULLY RESUSCITATED.

We have decided to base our sample size in the only study that gives more accurate information, which is the one carried by Burjek et al. They have done their study with a sample size of 141 patients.

Given that HJT receive among 35 to 40 OHCA patients per year, and since we do know that one of the main limitations of other studies have been the lack of bigger samples because they have not done multi-centric studies, we have decided to work in this study with four of the most important hospitals in Barcelona. Professionals in these hospitals have worked with HJT-CCU professionals in other cardiac arrest studies before. These four hospitals will be all the mentioned above.

We have data about 2015 population in Girona and in Barcelona:

- **Girona**: 753,054 people
- **Barcelona**: 5,523,922 people

So, if we make an estimation based in data about OHCA in Girona, where we have 35 to 40 cases per year, we assume that in Barcelona we will have, more or less, 290 cases of OHCA per year.

With only a year of recruitment of patients, we would have more than 300 patients. If we would do the study with only the population of Girona’s province, we will need three years, more or less, only to recruit a sample of 141 (like the one in the study we have mentioned).

So, given they have done their study with a sample size of about 141 patients, and they manifest that more studies have to be done with higher sample sizes, we have decided to carry our study with a year of recruitment in these two provinces, and we calculate we can achieve a sample size of about 300 patients.

**6.4 Variables**

We will collect all these variables since the moment the patient arrives to the Coronary Care Unit and be monitored.

**6.4.1 Independent variables**

We define as one of our independent variables the different patterns among Bispectral index values. This variable will be defined as qualitative (categorical) nominal, because we will try to define two patterns, the pattern related to good outcomes and another related to poor outcomes.

We will register, by using BIS VISTA™ MONITORING SYSTEM (see Annex 1 – BIS VISTA monitoring system use instructions for further information), every minute since the patient arrives and he or she is treated with the Unit’s protocols of therapeutic hypothermia, sedo-analgesia and neuromuscular blockage. From this register, we will obtain series of Bispectral index values going from 0 to 100. The monitoring will last, at least, the first 48 hours post-cardiac arrest.

As we explain before, these BIS values are stored in system’s memory and they are easily

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removable by an USB port. So, when we obtain the register of each patient, we will give it to an informatics technician to process it with data processing programmes (Excel or SPSS®), and create the graph of this patient. This process allow us to identify and compare all the graphs among all the registered patients, trying to find similarities between their patterns (Figure 5):

![Image of BIS graph]

**Figure 4. BIS graph.** This is the BIS graph (24 hours) from a patient who had suffered an OHCA, admitted to the Coronary Care Unit (HJT). Verbal consent of the patient was asked in order to analyse his register. The patient awakes with a cerebral performance category of 1.

Moreover, this comparison and analysis of all the graphs would allow us to find a cut-off value (another of our independent variables), which we want to prove it is as well related to neurological prognosis in a way that allow to dichotomise patients in two different groups according to their neurological and functional results:

- Patients with good outcomes would have values higher or equal than the cut-off point;
- Patients with poor outcomes would have values lower than the cut-off point.

This variable is a **quantitative continuous** one, since BIS values can achieve infinite values among 0 to 100.

### 6.4.2 Dependent variable

As we mentioned in our objectives, we want to find a relation among patterns of Bispectral values’ curves, cut-off point and neurological and functional prognosis and survival in OHCA patients undergone therapeutic hypothermia because, we do know that the main cause of mortality in these patients is post-anoxic encephalopathy.

So, to evaluate the **neurologic and functional outcomes** of each patient at discharge from Coronary care unit, and as well when we follow them up at 6 months and at a year after the episode, we will use the **Glasgow-Pittsburg Cerebral Performance Categories (CPC)** (50). These categories are the following ones:
Table 5. Cerebral Performance Categories (51)

<table>
<thead>
<tr>
<th>CPC</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPC 1 – Good cerebral performance.</td>
<td>Conscious, alert and able to work and lead a normal life. May have minor psychological or neurologic deficits (mild dysphasia, non incapacitating hemiparesis or minor cranial nerve abnormalities).</td>
</tr>
<tr>
<td>CPC 2 – Moderate cerebral disability.</td>
<td>Disabled but independent.</td>
</tr>
<tr>
<td>CPC 4 – Permanent coma/Vegetative state.</td>
<td>Unconscious. Unconscious, unaware of surroundings, no cognition. No verbal or psychologic interaction with environment. These patients suffer severe anoxic brain injury and they progress to a state of wakefulness without awareness. It is defined as:</td>
</tr>
<tr>
<td></td>
<td>▪ No evidence of awareness of themself or environment and an ability to interact with others.</td>
</tr>
<tr>
<td></td>
<td>▪ No evidence of sustained, reproducible, purposeful, or voluntary behavioral responses to visual, auditory, tactile, or noxious stimuli.</td>
</tr>
<tr>
<td></td>
<td>▪ No evidence of language comprehension or expression.</td>
</tr>
<tr>
<td></td>
<td>▪ Intermittent wakefulness displayed by the presence of sleep-wake cycles.</td>
</tr>
<tr>
<td></td>
<td>▪ Sufficiently preserved hypothalamic and brainstem autonomic function to allow survival with medical and nursing care.</td>
</tr>
<tr>
<td></td>
<td>▪ Bowel and bladder incontinence.</td>
</tr>
<tr>
<td></td>
<td>▪ Variably preserved cranial nerve reflexes and spinal reflexes.</td>
</tr>
<tr>
<td></td>
<td>It is judged to be permanent after 3 months if induced nontraumatically. Related to hypoxicischemic encephalopathy, recovery is rare after this period of time, and is associated with moderate to severe disability at best.</td>
</tr>
<tr>
<td>CPC 5 – Brain death.</td>
<td>Certified brain death or dead by traditional criteria.</td>
</tr>
</tbody>
</table>

We have decided to treat this variable as dichotomus, so CPC 1 and CPC 2 are considered good neurologic and vital outcomes, and the remaining of poor neurologic and vital outcome (CPC 3, CPC 4) or death (CPC 5).

6.4.3 Covariates

We will pick up other variables in order to ensure some of them will not be confounding factors or interactive variables. In case they were, we will control them to increase the external and internal validities of our study. We will able to minimize the effect of our confounding variables later, with a multivariate analysis (see 7.Statistical Analysis).
We will base our data collection in the **Utstein style template**, which provides a standardized uniform method for collecting and reporting cardiac arrest and resuscitation data (51).

### Sociodemographic data
- **Gender**: as this is a categorical nominal variable, we categorize it as: female or male.
- **Age**: > 18 years. It is a quantitative discrete variable and it will be measured in years.

### Medical and personal history
We have decided to collect the following variables because they can help us to suspect the etiology of the cardiac arrest and to identify factors that can get worse the prognosis of the patient if are not well treated.
- **Previous coronary artery disease**: yes/no. It is a categorical nominal variable.
- **Cardiovascular risk factors**:

<table>
<thead>
<tr>
<th>Arterial hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>According to the 2013 Clinical Practice Guideline for the management of hypertension from the European Hypertension Society and the European Cardiology Society, we consider hypertension a systolic arterial pressure ≥ 140 mmHg or diastolic arterial pressure ≥ 90 mmHg.</td>
</tr>
<tr>
<td>It is a categorical nominal variable. We will categorize it: presence/absence.</td>
</tr>
<tr>
<td><strong>Note</strong>: current treatment if it exists.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diabetes Mellitus</th>
</tr>
</thead>
<tbody>
<tr>
<td>It is defined by the World Health Organisation as the presence of classic signs of hyperglycaemia and an abnormal blood test with a plasmatic concentration of glucose ≥ 126mg/dL (or 7mmol/L) or by ≥ 200mg/dL (or 11mmol/L) 2 hours after drinking a solution with 75g of glucose.</td>
</tr>
<tr>
<td>It is a categorical nominal variable. We will categorize it: presence/absence.</td>
</tr>
<tr>
<td><strong>Note</strong>: current treatment.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dyslipidaemias</th>
</tr>
</thead>
<tbody>
<tr>
<td>According to the European Hypertension Society and the European Cardiology Society:</td>
</tr>
<tr>
<td><strong>Hypercholesterolemia</strong>: total cholesterol &gt; 250 mg/dL (6,45 mmol/L) and triglycerides &lt; 200 mg/dL. In secondary prevention and in diabetic patients, cholesterol values should be indicators when &gt; 200 mg/dL.</td>
</tr>
<tr>
<td><strong>Hypertriglyceridemia</strong>: total cholesterol &lt; 200 mg/dL (5,17 mmol/L) and triglycerides &gt; 200 mg/dL (2,26mmol/L). In secondary prevention and in diabetic patients, we consider it for values &gt; 150 mg/dL (1,69 mmol/L).</td>
</tr>
<tr>
<td><strong>Mixed hyperlipidaemia</strong>: total cholesterol &gt; 200 mg/dL (5,17 mmol/L) and triglycerides &gt; 200 mg/dL (2,26 mmol/L).</td>
</tr>
<tr>
<td>It is a categorical nominal variable. We will categorize it: hypercholesterolemia/hypertriglyceridemia/mixed/non dyslipidaemias. <strong>Note</strong>: current treatment if it exists.</td>
</tr>
</tbody>
</table>
Smoking

It is a categorical ordinal variable. We will categorize it as it follows:

- **Current smoker** (we will also quantify years and number of cigarettes in the clinical history of the patient, but we will not take it in count at the moment of the statistical analysis)
- **Non-smoker**
- **Former-smoker** (we will also quantify years and number of cigarettes in the clinical history of the patient, but we will not take it in count at the moment of the statistical analysis)

- **Other important diseases** as chronic kidney disease; chronic obstructive pulmonary disease; cancer. We will categorize it as yes/no, so it is a categorical nominal variable.
- **Previous cerebral performance categories**: we will categorize it as: 1, 2, 3 or 4. It is a categorical ordinal variable.

**Data concerning cardiac arrest and resuscitation**

The Emergency Services personnel will record these data since the moment they arrive to the scene (see Annex 3 – Emergency Services Template). These data are important because of they can be predictors of better or worst neurological outcomes and so they could be confounders or interaction variables.

- **Arrest witnessed**: we will categorize it as yes/no. It is a categorical nominal variable.
- **Cardiopulmonary Resuscitation performed by**:
  - **Bystander CPR**² – Basic CPR.
  - **Emergency personnel**³ - Advanced CPR.

  It is a categorical nominal variable.

- **Automated external defibrillation performed before EMS arrival**: yes/ no. It is a categorical nominal variable.
  
  Time of the defibrillation: hour and minute of the exact moment the defibrillation was performed, just in order to know how much time has passed since the patient suffered the arrest and the defibrillation.

- **Initial rhythm**: we will categorize it as ventricular fibrillation, pulseless ventricular tachycardia, asystole or pulseless electrical activity/Electromechanical dissociation. It is a categorical nominal variable.

- **Aetiology**: categorize it as:

² It is an attempt to perform basic CPR by someone who is not part of an organized emergency response system. In general, this will be the person who witnessed the arrest. Thus, in certain situations, physicians, nurses and paramedics may perform professional first responder CPR.

³ They are the persons who respond to a medical emergency in an official capacity as part of an organized response team. It does not include physicians, nurses or paramedics who witnesses an OHCA and initiate CPR nut do not respond as part of an organized team are not emergency personnel.
Cardiac aetiology (presumed) 4

Non-cardiac aetiology 5

It is a categorical nominal variable.

- **Time from arrest to return of spontaneous circulation** (ROSC): time since the patient suffered the cardiac arrest until he or she recovers spontaneous circulation. The *Utstein style template* accepts as ROSC the return of any spontaneous palpable pulse (detectable by manual palpation of a major artery, usually the carotid) and it does not require specific pulse duration. This pulse implies a systolic blood pressure of approximately 60 mmHg. The other signs of ROSC include breathing, coughing or movement. ROSC influences, and it is correlated, with the outcome of these patients, contributing to a poor vital and functional prognosis when it lasts for more than 20 minutes (38). Cardiopulmonary resuscitation and defibrillation have increased the chances to ROSC.

We have decided to treat this variable as a categorical nominal one, and we will dichotomize it as it follows: patients who have ROSC < 20 minutes, and patients with a ROSC ≥ 20 minutes.

It will be necessary as well to note the exact hour the patient achieves ROSC.

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**Data recorded in Coronary Care Unit (CCU)**

We decided to collect all the following variables since some of them interfere with neurological examination of the patient, making it unreliable since 24 – 48 hours after cardiac arrest, and they also could be interactive variables or confounders in the relation between BIS values, and the patterns derived of them, and neurological outcomes.

- **Lactate and pH:** lactate is produced as a consequence of anoxia post-cardiac arrest. The reduction of available oxygen and glucose reduce the production of ATP that increases lactate values (normal lactate values: 4.5 a 19.8 mg/dL), which diminishes pH values (Normal pH values: 7.35 – 7.45) leading to an acidotic state that produces direct neuronal lesion. We have decided to treat both parameters as continuous quantitative variables.

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4 Cardiac arrest is presumed to be related to heart disease. It is impractical for researchers to accurately determine the specific cause of cardiac arrest for all attempted resuscitations. Many functional factors may interact with a host of underlying structural abnormalities to initiate lethal arrhythmias. For the purposes of the *Utstein Style Template*, researchers should classify cardiac arrests as presumed cardiac aetiology if this is likely, based on available information. In the best of circumstances, this can include autopsy data and hospital records. However, this frequently becomes a diagnosis of exclusion. Patients who do not fit in the more readily defined category cardiac arrest of non-cardiac aetiology are included in this category.(61)

5 Non-cardiac causes of cardiac arrest are often obvious and easy to determine. Specific subcategories include sudden infant death syndrome, drug overdose, suicide, drowning, hypoxia, exsanguination, cerebrovascular accident, subarachnoid haemorrhage, and trauma.
Sedative, analgesic and neuromuscular blockage requirements: sedative use is required to limit awareness for patients exposed to TH. Burjek et al. (38) said that a more severe injured brain might require less sedation than a less injured brain. We will record the first dose of each drug and also every change in dosage in order to keep the patient under conditions of general anaesthesia, which is defined as an unconscious state of the patient, with analgesic effects, muscular relaxation and depressed reflexes. It is a situation of pharmacological coma in which the patient is unable to wake up when someone stimulates him or her.

We will prefer to use sedatives with short-half lives (midazolam, propofol and remifentanil). Neuromuscular blockage (we will use Cisatracurium) is induced also before cooling and then it will be continued for at least 26-36 hours, until re-warming is complete. It is necessary because the extreme degree of muscle activity, measured with electromyogram (EMG) values, in post-cardiac arrest patients related to shivering, myoclonus and even seizures could artificially increase BIS values.

The dosages will be measured and analysed as quantitative continuous variable. Our Unit has a standardized protocol of sedoanalgesia and neuromuscular blockage (Table 6):

| Sedoanalgesia and neuromuscular blockage protocols. Coronary Care Unit, HJT. |
|------------------|------------------|
| **PROPOFOL**     | Minimum dose: 4 mg/kg/h     |
|                  | Maximum dose: 12 mg/kg/h     |
| **MIDAZOLAM**    | Minimum dose: 0.12 mg/kg/h   |
|                  | Maximum dose: 0.25 mg/kg/h   |
| **REMEFENTANYL** | Minimum dose: 1 mcg/kg/h    |
|                  | Maximum dose: 12 mcg/kg/h    |
| **CISATRACURIUM**| Minimum dose: 0.06 mcg/kg/h  |
|                  | Maximum dose: 0.18 mcg/kg/h  |
| **FENTANYL**     | Start with a bolus of 100 mcg/h (mcg/h) → Rise up 50 mcg/h more. |
|                  | Minimum dose: 0.1 mcg/kg/h   |
|                  | Maximum dose: 2.5 mcg/kg/h   |

Therapeutic Hypothermia (TH): we will use Thermogard XP® hypothermia machine to treat the patients. Our aim is to keep the patient under a mild cooling since it has been the one that has shown to be protective against neurologic injuries after cardiac arrest(20,21). TH should be initiated as soon as possible after the ROSC. There is a 20% increase in mortality for every hour of delay in the initiation of TH (25).

We collect these data:
Time to TH: it concerns to the moment TH is started in the CCU. It will be written the exact hour, so we can check the hour the patient has achieved ROSC and compare it to the time TH is started. It is a quantitative continuous variable.

Target temperature: it is the temperature to which the patient will be undergone. Upon arrival to the CCU, external cooling pads are placed on the torso and thighs of the patient, who is then rapidly cooled to 32°C - 34°C, as measured by an oesophageal temperature probe. This temperature will be maintained for 24 hours via the external pad system. It is a quantitative discrete variable.

A target temperature equal or upper 35°C is not considered hypothermia. Rewarming will be carried through 12 to 24 hours after the initiation of cooling. It should be slow, with a target rate of 0.25°C every hour until the patient returns to normothermia (37°C). After normothermia is achieved, the goal of therapy is to maintain a temperature of 37°C and to avoid hyperthermia. Post-CA fevers are harmful and associated with worse neurological outcomes (25). We should note the hour of rewarming.

- Bispectral index monitoring: since the moment the patient arrives to the CCU and he or she is treated with therapeutic hypothermia and sedo-analgesia and neuromuscular blockage protocols, Bispectral index monitoring must be started. As we mentioned in the INTRODUCTION, BIS monitoring allows us to record minute by minute the neurological activity of the patient and his or her levels of sedation. We will use BIS VISTA™ MONITORING SYSTEM (see Annex 1 – BIS VISTA monitoring system use instructions for further information).

Before collect and analyze BIS data, it is important to know that some things may artifact BIS monitoring values. We should be prepared to identify and respond to situations where the underlying EEG signals, and hence the BIS value, may not accurately reflect the clinical endpoints of sedation and hypnosis (Table 7):
In order to eliminate as most artifacts as possible, once we download from the system every patient’s register and an informatics technician will start processing all these data for doing the graphs, we will ask him/her to filter BIS values by two main parameters that are given by the BIS monitor itself: the Signal Quality Indicator (SQI) and the Electromyography indicator (EMGi). The **Signal Quality Indicator** (SQI) is a measure of the signal quality for the EEG channel source. It is optimal when all five bars of the SQI icon are green. When signal quality is too low to calculate the BIS value and other trend variables that are adversely affected by artefact will not be displayed on the screen. The **Electromyograph (EMG) Indicator** displays the power (in decibels) in the frequency range 70 - 110 Hz. This frequency range contains power from muscle activity as well as power from other high-frequency artefacts. When the indicator is low, it indicates that EMG activity is low. BIS monitoring conditions are optimal when the bar is empty (**Figure 5**).

<table>
<thead>
<tr>
<th>Table 7. Reported factors influencing BIS values (34).</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Factor influencing</strong></td>
</tr>
<tr>
<td>Electromyography’s artefact because of excessive muscle tone</td>
</tr>
<tr>
<td>Medical devices:</td>
</tr>
<tr>
<td>Pacemakers</td>
</tr>
<tr>
<td>Forced-air warmers applied over the head</td>
</tr>
<tr>
<td>Some types of surgery</td>
</tr>
<tr>
<td>Serious clinical conditions (because of reduction of cerebral metabolism):</td>
</tr>
<tr>
<td><strong>Cardiac arrest</strong>, hypovolemia, hypotension, cerebral ischemia/hypoperfusion, hypoglycaemia, hypothermia</td>
</tr>
<tr>
<td>Abnormal EEG states</td>
</tr>
<tr>
<td>Postictal state, dementia, cerebral palsy, brain death, severe brain injury, paradoxical arousal</td>
</tr>
<tr>
<td>Epileptiform EEG activity</td>
</tr>
</tbody>
</table>

**Figure 5.** BIS monitor.
So, we will only consider as valid those values with SQI > 90% and EMGi < 30dB (see Annex 1 – BIS VISTA monitoring system use instructions). We will have the entire register of each patient, but for us, it is important to write down the BIS index values of some key moments because we will focus specially among these values when we try to describe and identify patterns, and so on when we try to establish the earlier significant cut-off value.

The key values we consider the most important at the time of doing comparisons are:

- First BIS value with SQI = 100% and EMGi < 30dB.
- First value at target temperature with SQI > 90% and EMGi < 30dB.
- First value at rewarming time with SQI > 90% and EMGi < 30dB.
- Values at 7, 12, 24, 48 and 72 (the last one when able) hours with SQI > 90% and EMGi < 30dB.

- Initial Electroencephalogram (EEG): we will use it too evaluate every unconscious patient in order to check if he or she is suffering seizures, myoclonus or status epilepticus\(^6\). These three are observed in about 30% of patients and they typically present in the first day after the arrest. They might not be that obvious under sedo-analgesia and neuromuscular blockage. We will consider the presence or absence of one of the three of them, and categorize them as it follows:
  - Presence of seizures, myoclonus, status epilepticus.
  - Absence of seizures, myoclonus, status epilepticus.
  - Presence of persistent status epilepticus refractory to treatment.

Other data recorded in Coronary Care Unit as part of the normal procedure among OHCA patients.

We think it is necessary to explain other measures we will take as part of the normal assistance labor, but that do not be part of the statistical analysis. The following ones can be an aid in order to clarify the cause of the arrest and to the follow up of the state of the patient during the stay in the unit:

- Initial CT scan: if we cannot ensure that the cardiac arrest is due to a cardiac cause, we should perform a CT scan at the arrival of the patient in order to discover whether the cause of the arrest is not cardiologic (as the mentioned in Data concerning cardiac arrest and resuscitation). If the etiology is not cardiologic, the patient does not accomplish inclusion criteria of our study.

\(^6\) We define a seizure as a synchronic and excessive discharge of a group of neurons that, depending on their localization, it is manifested with motor, sensitive, autonomic or psychic symptoms, with or without loss of consciousness. Myoclonus is defined as spontaneous, repetitive, unrelenting, generalized and multifocal or local seizures involving the face, limbs and axial musculature that last less than 5 minutes. A status epilepticus is defined as a myoclonus but lasting more than 5 minutes. It is consider refractory when it lasts more than 30 minutes even when drugs have been used for its treatment.
- **Electrocardiogram (ECG):** every morning, an ECG will be performed in order to detect persistent malignant arrhythmias or to check the progression of a ST elevation myocardial infarction, since it is the main cause leading to cardiac arrest.

Moreover, since we cannot take withholding or withdrawal decisions by guiding us only with the results of Bispectral index monitoring, we will also perform all the parameters we have until now for the cardiac arrest prognostication, even though until now, it is known that these parameters only can give us significant information up above the 72 hours of the arrest:

- **Electroencephalogram:** if patients are not recovering consciousness 72 hours after the cessation of sedo-analgesia, we will perform another EEG in order to assess a possible brain death. Neurophysiologists will inform us about the result in order to categorize it. Small amplitudes and quick frequencies are indicators of good prognosis, while flat lines, isoelectric EEG, large amplitude, slow frequencies or burst suppression are poor prognosis’ results (31,39).

- **Somatosensory evocated potentials:** a Neurophysiologist will be requested and needed also to perform them and to interpret the results. They involve monitoring brain response to electrical stimulation of peripheral nerves. Main SSEPs include: stimulation of upper (median nerve) and lower (posterior tibial nerve) limbs, stimulation of trigeminal nerve, dermatome stimulation (lateral cutaneous nerve of tight) and spinal stimulation. The specialist, one more time, will help us to interpret the results obtained, so we can categorize the patients among the ones who had good prognosis results such as presence of bilaterally presence of the N20 SSEP wave; and the ones who do not (bilaterally absence of the N20 SSEP waves) (31).

- **CT scan:** if the cardiac arrest is due to a cardiac known aetiology, CT scan will be performed at 72 hours in a patient who is still comatose after the cessation of sedation in the order to discover if it has global cerebral oedema or reduced grey-white ratio in basal ganglia (indicators of poor prognosis) (31,33,43,44).

In our centre, we do not perform MRI to assess the prognostication of OHCA patients.

- **Neuron-specific enolase:** bedside nurses will take blood samples. In order to analyse NSE values, blood will be centrifuged at 3000 rpm for 10 minutes, and then, the sample will be frozen at -80º and stored until its analysis. The sample must not suffer hemolysis, and if it does, it will not be analyzed and blood analysis must be repeated. To analyze NSE samples, laboratory technicians will be requested and it will be used the technique of radioimmunoassay. Even absolute cut-off values appear to be unreliable, values higher than 33 ng/mL will be indicators of poor prognosis.
• **Neurologic examination:** to have a correct assessment, it should be performed after the withdrawal of sedation.

We should be pay attention to these signs:

- **Spontaneous movements:** the presence of spontaneous movements of all four limbs indicates moderate involvement of the cerebral hemispheres, especially if this is due to simple commands.

- **Response to stimuli** (voice, light, touch or pain): it can be assessed by shouting the name of the patient; opening his or her eyes and dazzling the patient; shaking or pinching him or her at specific areas (mammillary area, sternum and members, mainly). This exploration provides data on the level of impairment of consciousness and how the process is evolving. Maybe a patient is not able to respond commands but he or she can locate the painful stimulus. That is a better sign than stiffness with hyperextension of the lower limbs with flexion of the upper ones after painful stimuli, which are signs of decortication or decerebration. Both of them indicate severe impairment and are warning signs.

- The pupillary reflex to light must show a bilateral contraction of the pupils if everything is fine (it means that eye’s optic nerve and oculomotor nerve are not damaged). We have to stimulate the eye with an intense light, in a low light room, and check if it is contracted, and check if the same occurs to the other eye as well. We should keep both eyes open and direct the light to the center of the pupils and check the response. With this simple action, we evaluate the direct and consensual pupillary reflex.

- **Other reflexes** we could check:
  
  The corneal reflex (when touching the cornea with a sterile gauze) – Normal response: flicker and eye deviation must occur
  
  The oculovestibular reflex (triggered with opened eyes by turning the patient’s head quickly from one side to the other) – Normal response: eyes directed in the opposite direction to the head. If random eye’s movement occurs, patients are supposed to have brainstem injuries.

Summarizing, the data we will collect about the other prognostication tests will be categorized as “good prognostic indicator” or “poor prognostic indicator”. This will allow us to analyze as well the relation between BIS values and the other prognostication tools.
6.5 Data collection

**Emergency medical services**

For the process of data collection, communication between the EMS and the CCU will be very important. Since EMSs are the first contact with the patient, all the information they gather is crucial. For that reason, **they have a template** (see Annex 3 – Emergency Services Template), where they can fill in every data of the first minutes of the cardiac arrest so they can provide physicians in charge of treatment all the data concerning cardiac arrest itself and resuscitation.

It is very important to **ask the witness/witnesses** about the timeline and the facts’ succession because they can give us information on what happened before the EMS arrives.

Since EMSs are well trained to gather this information and to practice advanced cardiopulmonary resuscitation, we consider to **make an only informative reunion to explain them what are we going to do in this study and why it is so important they compile the data as accurate as possible**, so we ensure no information biases in our study.

Once EMS confirm an OHCA, they should immediately contact to the hospital in order to activate Cardiac Arrest’s Code.

**In-hospital care - Coronary Care Unit**

Coronary Care Unit it is an essential part of cardiology’s service and it is mean to take care of cardiac patients that require monitoring, nursing cares and a medical capacity of response higher than the available in a conventional ward of cardiology.

Hospital Josep Trueta’s CCU consists in 8 individual bedrooms, all full equipped with **continuous monitoring** (ECG, pulsioxymetry monitoring), **intubation machines and ventilation systems**, **catheterism material**, at least 2 **intravenous pump bombs** per room and **technology for urgent cardiac assistance**, such as echocardiogram machines, defibrillators, temporary pacemakers’ generators and a code cart. Every room has an individual video-vigilance system, which allows nurses and physicians to control each patient every moment.

This unit has a specialized system from which the clinicians can keep control of every patient. It is call **Centricity** and it allows physicians to keep an accurate control of vital signs and dosages of drugs, to have a quick access to results of blood analysis and to write down all the medical information gathered from the patient, so every physician from the unit can check it. Bedside nurses have as well a specialized programme (**Gacela**).

In HJT, the unit’s team consists in **three adjunct physicians** (Dr. Pablo de Loma-Osorio, Dr. Jaime Aboal and Dr. Maria Núñez) and a vary number of **medical residents**, that can stay in the unit, not only Cardiology residents, but Anaesthesia, Intensive Care, Internal medicine, Pneumology residents, among others. There is also one specialized **bedside nurse** for each two patients.
Previous to the beginning of the study, professional in charge of each centre will inform the entire cardiology equip about the study by explaining them the protocol, so they aware of the data we will need to collect and how to act when a patient with inclusion criteria arrives to the unit. Since every physician and cardiology resident of the entire cardiology service can be on duty, they must be aware of the study in order to act properly in case an OHCA patient arrives while they are on duty.

The warning EMSs give to the hospital, allows the Unit to prepare a room with every tool needed, including therapeutic hypothermia machine and Bispectral index monitor. As well, the interventional cardiology haemodynamic unit has to be ready to practice an urgent revascularization when needed.

Once the first interventions to keep the patient stable are performed and the patient is in the room, first tests should be carried through. All the personal will have to work together for data collection. In one hand, bedside nurses in the CCUs are well trained and prepare to perform correctly blood analysis, ECGs and chest radiographies when required. They will be always present every time the physician in charge of the patient goes to check him or her progress so they aware every change in medication and sedo-analgesia dosage.

Physicians will send to the laboratory requests in order they perform include the levels of lactate and pH since the first day to the day they turn to normal values, and as well, a blood analysis in order to check neuron-specific enolase at the third day of admission.

Every patient arriving to the CCU will be monitored, so we will have continuous data about vital signs including:

- Arterial pressure (mmHg),
- Cardiac frequency (beats per minute),
- Respiratory frequency (breaths per minute),
- Oxygen saturation (%),
- Diuresis (mL/day),
- Temperature (°C),
- Glycaemia (mg/dL).

If the unconscious patient has come accompanied by someone, a Unit’s physician should start the anamnesis to get all the information related to medical history of the patient. Companions play a very important role in the study due to the patient will be unconscious and not able to give us part of the information we need. We have to complete all the data about medical history.

As one of the limitations of previous studies had been the fact that the treating physician was not blinded to BIS values, sedoanalglesia and neuromuscular blockage of the patients under is charge, we have decided that, when possible, two physicians visit a patient at the same time and the one who decided the treatment, will be blinded to BIS values and sedative requirements. The other one
will be able to check BIS values and sedative requirements and to write in Centricity the evolution of the patient. So, this way, we ensure the blinding to BIS values. In case it will not be possible to keep a physician blinded to some patient, we must emphasize that **no withholding or withdrawal decisions will be taken based on BIS values.** This situation could happen because sometimes, decisions must be taken with multiple points of view.

The two physicians in charge of each patient will be responsible of collecting all the data related to the various protocols (therapeutic hypothermia, sedoanalgesia and neuromuscular blockage). The one not blinded, will write down in Centricity system all the necessary information in order to allow the creation of the database.

Since sedoanalgesia and neuromuscular blockage are monitored, to keep the control of their changes is easy, so changes of dosage will be able in this system as well for a quick look.

**Bispectral index monitoring values** will be collected since the moment TH’s protocol starts to, at least, the first 48 hours after admission. In *Annex 1 – Bispectral index monitoring use instructions* we explain how it works this monitoring and how to pick up data. Our aim is to keep patients in a general anaesthesia state (BIS values would be around 40-60). Once the patient awakes or if it passes more than 72 hours since the start of TH and sedoanalgesia protocols, BIS monitoring will be stopped and register of each patient will be collected by downloading it with an USB memory.

In our CCU, the person in charge of this activity is Dr. Júlia Pascual, a 4th year resident of cardiology. The register will be sent to an informatics technician, who will process it with Excel or SPSS in order to create a graph with all the BIS values monitored of that patient. When the study is over, we will have a graph for each patient of our study and we will be able to compare them all, to look for the patterns we explained in our hypothesis and objectives.

Tests such as EEG and SSEP will be asked to specialized neurophysiologists of our hospital, since they are the main specialists on interpret the patterns among EEG’s waves and the results of SSEP. They will be requested 2 times:

1. The first hours of admission to the hospital, to perform an initial EEG in order to reject seizures, myoclonus or status myoclonus in an unconscious patient.
2. The third day of admission to the hospital in order to have more prognostication data, since we are not able now to take withholding or withdrawal decisions only with BIS values.

Radiologists will perform Neuroimaging tests.

With all the data, we will create a database in order to note every variable of each patient. In this database, patients will be encoded with a number from 001 to 300 (that is our sample size) so we ensure no one except for the physicians in the study, can identify the patient. This is very important since we will give the BI S registers of the patients to an informatics technician and the statistical analysis will be in charge of a statistical professional.
Before using the patient’s data to our study, we will ensure the patient, if he or she awakes with CPC of 1, 2 or 3, give us his/her informed consent (see Annex 2 – Informed consent) to use his/her medical information, and all the data collected while the admission to our unit, to continue with the study. If the patient remains unconscious up to a week or presents a vegetative state, dementia or brain death when CPC is performed, we will ask the responsible of the patient for their informed consent.

6.6 Follow-up

In order to assess the evolution of the patients, visits will be programmed for them at 6 months and at a year after the episode. In these follow ups, we want to check if the CPC of the patient at discharge from the hospital has improved, has kept stable or has worsened as a long term consequence of the period of anoxia suffered. Until now, we do now that 40% of patients who are successfully resuscitated of an OHCA remain in a vegetative state after the discharge, and that the first-year mortality rate is of 80% (19, 21,22).

The same physician who had treated the patient while his/her admission to hospital after the arrest will carry out the follow-up evaluation.

Our data collection phase will not be finished until the last patient discharged from the hospital has done his last follow up. The results of these follow ups will give us more specific data of our population and they allow us to evaluate the prognostic value of BIS monitoring at a long term and not only at discharge. Since we do know that one of the main limitations among prospective cohorts studies are the loss of patients during the follow up, we have decided that if a patient will not come to his/her visits or is not able to do it, we will contact them by telephone in order to minimize the losses.
7. STATISTICAL ANALYSIS AND INTERPRETATION OF THE RESULTS

Previous to the complete analysis of our database, an informatics technician should have provided the study team with all the graphs of the patients of the study. The team study must interpret and classify the patterns they observe in the graphs in order to add to the database what pattern has each patient. Once this task is done, a statistical professional by using Statistical Package for the Social Science (SPSS) will perform all statistical analysis. We will calculate every difference over a two-sided confidence interval of 95%. Significance for all the analysis will be set at a p value < 0.05.

7.1 Creation of the graphs and description of patterns.

An informatics technician will be hired in order to create the graphs of the BIS values. With the graphs, the research team will be able to describe the patterns and relate the patterns to neurological outcomes.

Graphs will be created as it follows:
- The ordinate exe will show us the BIS values of the patient.
- The abscissa exe will show us the time in hours (so mean values among BIS registers that are given in minutes will be calculated). We will register if possible the first 72 hours of the patient connected to BIS monitor.
- The origin of coordinates will be the exact time the cardiac arrest happened.

![Figure 4. BIS graph](image)

This is the BIS graph (24 hours) from a patient who had suffered an OHCA, admitted to the Coronary Care Unit. Verbal consent of the patient was asked in order to analyse his register. This patient had a CPC 1 at discharge from hospital.
7.2 Univariate analysis
In the univariate analysis, variables will be defined as quantitative or qualitative (categorical):

- For quantitative continuous or discrete variables, we will determine whether they follow a normal distribution or no by using the Kolmogorov-Smirnov test. If a normal distribution could be assumed, we will use mean ± standard deviation. If normal distribution cannot be assumed, we will estimate the median with interquartile range.

- For qualitative variables, the results will be expressed in percentages (proportions or frequencies).

7.3 Bivariate analysis
In our study we have two main independent variables (patterns among graphs of bispectral values and cut-off point) and one dependent variable (neurological prognostication).

- “Patterns among graphs of BIS values” is a categorical nominal variable that we decided to dichotomise in:
  - Flat/areactive/descendent pattern,
  - Ascendant/reactive pattern

- “Cut-off point” is a quantitative continuous variable, since BIS values can achieve infinite values among 0 to 100.

- Neurological prognostication is a categorical nominal variable since we have decided to dichotomise it in the following way:
  Good neurological outcomes, which involve CPC 1 and 2,
  Poor neurological outcomes, which involve CPC 3, 4 and 5.

So, in order to compare the first of our independent variables with our dependent variable, we will use a Chi-square of Pearson test or the Fisher’s exact test, since both of them are categorical variables. This analysis must be done for the CPC at discharge, at 6-months follow up and at a year. The study outcomes about having a determinate pattern and the neurological outcome will be expressed with relative risk.

On the other hand, to compare our second independent variable with our dependent variable, we will use a bivariate logistic regression model, since the independent is a quantitative continuous variable and the dependent, a categorical nominal one.

Finally, to assess the ability of the different BIS values we explain in Covariates – Data collected in Coronary Care Unit (values at 7, 12, 24, 48 and 72 hours with SQI > 90% and EMGi < 30dB) to predict outcome, we will calculate Receiver Operating Characteristic (ROC) curves with a 95% confidence interval and we will compare their areas under the curve (AUC) across time-points (7, 12, 24, 48 and 72 hours) in all the patients.
Optimal cut-off point values to predict good and poor outcomes for the BIS values will be determined based on ROC analysis to maximize sensitivity and specificity by using Youden index ($J = \text{sensitivity} + \text{specificity} - 1$).

**7.4 Multivariate analysis**

A multivariate analysis will be accomplished to adjust our variables for covariables, thus we will try to avoid potential confounders that could modify the results. So, in order to analyse the relationship among our independent variable with the covariates, we will perform a multivariate regression logistic model.

**8. ETHICAL CONSIDERATIONS**

This protocol will be evaluated by the Clinical Research Ethics Committee of Hospital Josep Trueta, and as well in the clinical research ethical committees of the other four hospitals if needed. These committees will ensure the study respects the ethical principles for medical research involving human subjects established by Helsinki’s Declaration according to the 64th General Assembly (Fortaleza, Brasil, October 2013).

They as well make sure that the privacy of every participant will be protected and their personal information will be confidential to anybody else who is not directly involved in the study. If the committees have any recommendation in order to improve the procedure, they will be taken into account.

Before introducing the patient’s data into our database, they must be informed before (Annex 2 – Informed consent) about the aim of the study and its impact in neurological prognostication. As in our study, patients will be unconscious up to 48 hours at least because of sedative drugs, their legal representatives can give us their consent to include the patient into the study. Even though, if the patients awake at any time and they are not limited by neurological disabilities, they must sign themselves the informed consent or revoke it if they not agree. This is the only way to respect the principle of autonomy.

By following the “Ley Orgánica de protección de datos de carácter personal 15/1999” from 13th December, the “Real decreto 1720/2007 por el que se aprueba el reglamento de desarrollo de la Ley orgánica 15/1999” from 21st December and the “Real decreto 994/1999 de medidas de seguridad para automatizar los registros que contienen datos personales” from 11th June, we guarantee the protection of confidentiality of all participants while collecting data to carry through our study. An identification number will be used in the database elaboration instead of the patient’s name.
We take into account as well the “Real Decreto legislativo 1/2015 de aprobación de la Ley de garantías y uso racional de los medicamentos y productos sanitarios”, from 24th July.

Finally, the whole team declares that no decisions about withholding or withdrawal treatment will be taken based on Bispectral Index values. We will wait at least to 72 hours after the cardiac arrest, when all the other prognostication measures have been performed, in order to take clinical decisions that involve the limitation of therapeutic efforts.

9. STUDY LIMITATIONS

By reviewing our protocol, we have detected some potential limitations that can interfere with the extrapolation of the results:

— First of all, unlike conventional EEG, Bispectral Index (BIS) monitoring assess only the frontotemporal region. So, patients with brain injury might be misclassified or overrated when having poor neurological outcomes because of the various locations of this injury. Given that any study has been concluding, if our study proves a statistically significant relation among BIS values and neurologic prognostication, this limitation could be rejected. Another option will be to monitor each patient with BIS and continuous EEG since the moment they are admitted to the hospital in order to compare the differences among them, and so, assess if BIS values represent heterogeneous brain injury well.

— Another important limitation that comes to our mind is the sample size. In a hospital that receives approximately 35 to 40 patients with out-of-hospital cardiac arrest (OHCA) per year to achieve a sample size big enough to try to avoid this major limitation manifested by other studies, in our hospital we will need more time. Given that other studies have stated before that a major limitation had been the sample size and a one-centre study, we will solve this situation by enrolling hospitals from Barcelona’s province in order to have a bigger sample in less time.

— Other limitation in the investigation of prognostic procedure for predicting neurological outcome is early withdrawal of life-sustaining therapies. In most of the studies about BIS and neurological prognostication the treating clinicians are not blinded to the results of the test and may take treatment decisions on the basis of these results, leading to a “self-fulfilling prophecy”. In order to avoid this limitation, we have decided that the treating physician will not be able to check BIS values and sedative requirements of his/her patients. Given that sometimes this could be difficult to achieve because of the extended use of informatics programmes in order to facilitate the medical task, we have decided that the clinician in charge of a patient cannot write his/her clinical evolution. Another
clinician will accompany him/her while visiting the patient and will write the current information in the medical history of the patient. Only that way, the first clinician can be blinded. In case this option cannot be affordable in one of the participant centres, it will be specified and we must emphasize that any withholding or withdrawal treatment and diagnostic decisions will be made based on BIS values.

Limitations among the study design should be taken into account. First of all, we have tried to avoid the "selection bias" by selecting our sample based on some inclusion and exclusion criteria. Only when a patient fulfills the first ones at all and none of the exclusion ones, he/she will be included in our study. Another way of having this bias is by losing the contact with the patient during the follow up. Since we have proposed to do a 6-months and a year follow-up, in case patients do not assist to the programmed medical appointments, we will call them home in order to check how are they going or whether they could come another day. Given that most of our patients could have CPC of 3 and 4 at discharge from the hospital, and that their neurological state can progress to a worst condition, we will have the telephone number of a responsible member of the family if possible, so that way we can keep in touch with them.

Another limitation could be the sample size itself. Given the lack of conclusive data, we have been not able to calculate the sample size. Maybe, the sample we have stated we are going to recruit it is not enough to achieve as well conclusive results, but we do think it that our results could be an open-door to further studies with bigger sample sizes.

Finally, as our study accounts with multiple covariates, of which some of them we suspect they can be confounders of the relation between BIS values and neurological outcomes and can interfere in that association, we have decided to perform a multivariate logistic regression analysis to establish the independent value of BIS monitoring among neurological outcomes.
10. WORK PLAN AND CHRONOGRAM

The study will consist in 4 stages, as described below:

STAGE I – Coordination (8 months)

- **Activity 1** - first meeting was in May 2016. I met Doctor Pablo de Loma Osorio and Doctor Julia Pascual, and we decided to start the study.
- **Activity 2** – the HJT’s team organise an all-member meeting to start the project, to define the roles of each participant and to create a chronogram to clarify the different phases of the study.
- **Activity 3** – Protocol elaboration: the final protocol elaboration will be carried through the CCU’s team of HJT. The protocol will be finished by November 2016.
- **Activity 4** – ethical approval from the Clinical Research Ethics Committee in HJT. Dr. de Loma will be the responsible of this activity.
- **Activity 5** - To inform the entire cardiology services: once the Ethics Committee give us their approval, the professional/s in charge of the study in each hospital (in ours, they are Dr. de Loma and Dr. Pascual) will inform the entire Cardiology service about the aim of the study and how to carry it through. This information includes:
  - Inform about what data we need to collect,
  - Inform about protocols of therapeutic hypothermia, sedo-analgesia and neuromuscular blockage,
  - Inform about the importance of having a signed informed consent of the patient or his/her relatives.

They will also inform the Emergency Medical Services of all the hospitals of Girona and Barcelona provinces in order to ask them to please fulfil as much information of their templates as possible.

Finally, neurophysiologists and radiologists will be as well informed, so they are aware they will be requested the first day and the third day of each patient’s admission.

By giving the appropriate information, we ensure the study will be adequately conducted.

STAGE II - Study conduct (2 years)

- **Activity 6** – Database elaboration: in order to avoid confidentiality problems, we will create a common database, in which numbers will codify the patients. In the database, we will include all the variables we want to be analysed. The person who fulfil the database in our unit and who is in charge of keeping it updated will be Dr. Pascual. The statistician can control this process.
- **Activity 7** – Data collection: it will start on December 2016 and finishes in
December 2018 considering that we have to follow up all the patients until a year after the discharge from hospital.

We will only accept in our study patients who fulfil inclusion criteria and none of the exclusion ones. Moreover, the patients have to sign the **informed consent** in order to avoid us to use their data in our study.

Of every patient included, we will download the correspondent BIS monitoring register in order to keep them codified with the same number than we used for the patient in the database.

During these years, we will meet with the other professionals once a year in Girona or in Barcelona, in order to inform the other hospitals about how is it going. If any doubt appears, we will keep in touch by e-mail if it is not possible to organize a meeting.

**STAGE III – Data analysis (6 months)**

- **Activity 8** – **Creation of the graphs and description of the patterns**: we will hire an informatics technician to create the graphs with the BIS values of every patient. The five teams will meet in order to describe what patterns we have found and in order to add the correspondent pattern to each patient in the database.

- **Activity 9** - **Statistical analysis**: data will be analysed by a statistician. He or she will process all the data and create all the graphs of BIS values of each patient. We must emphasize that every participant hospital will employ the same statistician in order to maintain a uniform way of working data.

- **Activity 10** – **Interpretation and discussion of the results**: all the teams will meet in order to discuss the findings and to evaluate whether the results have been the ones we expected.

**STAGE IV – Publication and dissemination of the results**

- **Activity 10** – publication of the results: final research findings and the conclusions derived from them will be sent to be published in journal articles.

- **Activity 11** – dissemination of the results: it comprises the attendance to conferences of the Spanish cardiology society in order to present the results of the study.
### BISPECTRAL INDEX MONITORING AS AN EARLY NEUROLOGICAL PROGNOSTIC TOOL AFTER AN OUT-OF-HOSPITAL CARDIAC ARREST SUCCESSFULLY RESUSCITATED

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<td>HJT's team.</td>
<td>Dr. Loma-Osorio and the Clinical Research Ethics Committee (HJT).</td>
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<td>- Interpretation &amp; discussion of the results</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>STAGE 4: PUBLICATION AND DISSEMINATION OF THE RESULTS</strong></td>
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<td></td>
</tr>
<tr>
<td>- Publication of the results</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>- Dissemination of the results - Spanish Society of Cardiology Journal</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>PERSONNEL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HJT, HVH, HGT, HB &amp; HSC.</td>
</tr>
</tbody>
</table>
11. FEASIBILITY

This study will take place in five centres from Girona, Badalona, Barcelona and Hospitalet del Llobregat, which have specialists in care of critic cardiologic patients. These professionals have been working together before in other study about cardiac arrest (7).

All centres are full equipped with the necessary material in order to follow step by step the proposed protocol. That includes therapeutic hypothermia machines and BIS monitoring machines as well. The five hospitals are used to work with them and as well, all of them count on perfectly trained bedside nurses in critical cardiologic cares.

By the collaboration of these 5 centres, we will ensure our study will not last more than 3 years. If the study were carried only with Girona’s population, it will last more than 7 years in order to fulfil the sample size we wanted to reach.

Focusing on the main researcher of our study, Pablo de Loma-Osorio is a cardiologist in HJT since 2007. He has a super-specialization by the European Society of Cardiology in Critical cardiologic cares (2007) and a Master degree in Comprehensive assistance to critical patients and emergencies (2006-2008, Universitat de Barcelona). As a researcher, he has more than 15 publications and more than 20 abstracts published about the acute coronary syndromes and critical cares among these patients. He also works as researcher in many clinical assays (VISTA-16, PITAGORAS, TRACER, VIVIFY...). He is member of Societat Catalana de Cardiologia, Sociedad Española de Cardiologia and of European Society of Cardiology (where he is member of the working group on Acute cardiac care since 2006).

About budget (for further information, please, check 12. BUDGET), we consider it will not be a huge problem to carry out the study we propose. The majority of the budget is due to the publication and diffusion of the results of the study (12,400 €). The budget is as well increased as a consequence of the prize of the sensors needed to the BIS monitoring (3500 €) together with the price of some extra monitors (1 more per unit, if needed).

Finally, additional clinician personnel are not needed. However, we will hire an informatics technician, who will create the graphs, and a statistician.

Given all this information, we do think the study we proposed can be carried though without many problems.
12. **BUDGET**

**12.1 Personnel**

Most of the activities of our working plan do not require extra-costs since most of them are carried through by professionals of our hospital as part of their assistance labour. We will only need a statistician in order to perform statistical analysis and the informatics technician to create the graphs.

**12.2 Materials**

On one hand, regarding the material availability, we do not have to buy every machine we need in order to perform all the tests due to they are available in all the hospitals that are going to participate in the study, because most of them were previously used as part of the current protocols of action in cases of OHCA. The costs attributable to their use are included in routine clinical practice expenses.

On the other hand, given that Bispectral index monitoring is broadly used in the operating room when the patients are under sedatives in order to control the levels of sedation, the 5 hospitals count on 2 or 3 BIS monitors to their coronary care units. In case, they need an extra-BIS monitor, they can buy one more (it is specified in the Budget below).

We have included in the budget the price of the sensors we will put on the forehead of each patient, given that they are disposable.

Laboratory tests we will need to perform (blood analysis, including neuron-specific enolase), are made by routine at the third day of admission after an OHCA, so their price has not been included in our budget. The same happens with neuroimaging and neurophysiology tests.

**12.3 Meetings**

Various informative and coordination meetings will be needed in order to check how is going the study in each of the 5 participant hospitals. These meeting will be useful as well to explain the difficulties founded by researchers. In each meeting, two professionals of the CCU of each hospital will be representing the entire unit.

Meetings will be once a year, one in Girona (HJT) and one in a Hospital Universitari de la Vall d’Hebron. It will be as well two last meetings in Barcelona in order to discuss and interpret the results.

Summary of the meetings:

- First, Dr. Loma-Osorio and Dr.Pascual will visit HVH, where they will meet the responsible professionals of each hospital (4 train’s tickets). There, they will explain the aim of the study. When the protocol will be ready, copies of it will be sent to the other hospitals.
- Annual meeting with the professionals (one in 2017 – Girona, 16 train tickets; and one in 2018 – Barcelona, 4 train tickets).
- Two last meetings in order to discuss the results and interpret the patterns (20 train’s tickets).

12.4 Redaction and diffusion of the article

The research team will be in charge of the redaction of the article in Spanish and its translation to English. Once the article will be ready, it will be sent to some journals as the ones of Sociedad Española de Cardiología, European Society of Cardiology and Resuscitation.

The results of our study will be presented in Sociedad Española de Cardiología and European Society of Cardiology congresses. The budget below includes these expenses.

<table>
<thead>
<tr>
<th>Price per unit</th>
<th>Units</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STAGE I – COORDINATION</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protocol impression</td>
<td>20 €</td>
<td>10</td>
</tr>
<tr>
<td><strong>STAGE II – STUDY CONDUCT</strong></td>
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<td></td>
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<tr>
<td>Bispectral index monitoring</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bispectral Index monitoring (if needed)</td>
<td>300 €</td>
<td>5</td>
</tr>
<tr>
<td>Bispectral index sensors (25 sensors/box)</td>
<td>250 €/box</td>
<td>14</td>
</tr>
<tr>
<td>Meetings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transport to Barcelona-Girona/Girona-Barcelona</td>
<td>32 €</td>
<td>24</td>
</tr>
<tr>
<td>Informed consent photocopies</td>
<td>0,04 €</td>
<td>400</td>
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<tr>
<td><strong>STAGE III – DATA ANALYSIS</strong></td>
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<tr>
<td>Informatics technician salary</td>
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<td>50 (h)</td>
</tr>
<tr>
<td>Statistician salary</td>
<td>30 €</td>
<td>100 (h)</td>
</tr>
<tr>
<td>Meetings to discuss the results</td>
<td>32 €</td>
<td>20</td>
</tr>
<tr>
<td><strong>STAGE IV – PUBLICATION AND DISSEMINATION OF THE RESULTS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Publication in journals</td>
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<td>3</td>
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<tr>
<td>Attendance to SEC and ESC congresses</td>
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<td></td>
</tr>
<tr>
<td>SEC: 1,200 €</td>
<td>2</td>
<td>2,400 €</td>
</tr>
<tr>
<td>ESC: 2,000 €</td>
<td>2</td>
<td>4,000 €</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
13. IMPACT ON THE NATIONAL HEALTH SYSTEM

As we have mentioned above, out-of-hospital cardiac arrests are an important public health problem. In Spain, we do have around 50,000 cases per year and survival rates are about 10% of the cases. Among the survivors, most of them progress to a vegetative state due to the period of anoxia following the arrest, which is the leading cause of disability after an episode.

Until now, the prognostication tools we have are not able to give us conclusive information about the neurological prognosis of out-of-hospital cardiac arrest patients in less than 72 hours. This lack of time between the moment of the arrest and the time the physicians are certain to the neurological condition of the patients, might be to long in order to take clinical decisions.

Bispectral index monitoring is rising as a possible early neurological prognostication tool, which might help physicians to take earlier decisions about the treatment of cardiac arrest patients. Given the lack of conclusive data among its use in these patients, we propose to carry out this study.

This study would be the first about Bispectral index monitoring among out-of-hospital cardiac arrest patients carried out in Spain, and the first in the world in trying to describe the patterns (or trends) among Bispectral index values. Its results could provide better knowledge about the role of this monitoring system in these patients, which have such higher poor prognosis rates.

Given that the Bispectral index monitor only give us information about the pattern that BIS values are following by an hour, if the results of our study are concluding, an option could be to develop a software that transforms quickly the BIS values among the first 24 hours of register of each patient. Another option could be to make an improvement to the actual BIS monitor in order to allow it to show the observer the entire pattern of the day while the BIS values are registering.

If we find as well a cut-off point, its use, together with the information the patterns give us, could be more determining to allow professionals to take earlier decisions, which include to use more aggressive diagnosis tests and treatments in those patients who are expected to have good neurological outcomes and, by the contraire, to avoid futile treatments and these aggressive diagnostic tests among those patients whose situation is unfavourable. The possibility of having an earlier prognosis, could allow physicians to inform the families with more certainty among the first day after the arrest.

Our results could be an open door to other research teams to prove with their populations our findings by replicating our study, so we can evaluate what happens in the rest of the populations.

With our study, we will try to improve the limitations that other studies have defined, so we will be able to individualize the clinical care of these patients in order to improve their outcomes, in the best of cases, or to avoid the suffering when the situation is irreversible.
It consists of the following basic components:

- **BIS VISTA monitor**,
- **BISx**: it receives, filters, and processes patient EEG signals. It is located close to the patient’s head where the EEG signal is less subject to interference from other medical equipment;
- **Patient interface cable (PIC)**,
- **BIS sensor**: is the single use component of the BIS Monitoring System and should be replaced after each use.
- **Detachable power cord**.

Figures Annex 1.1 A, B, C: BIS VISTA monitoring system components. Images provided by Covidien-Medtronic.

http://www.medtronics.com/covidien/products
First of all, when attaching the sensor to the forehead of the patient, the monitor automatically will perform a **sensor checking** to test the impedance of each electrode to verify that it is within an acceptable range for monitoring.

Once the sensor check has successfully completed, monitoring begins and the corresponding information appears on the screen (FIGURA):

- **BIS value**: this number is displayed and continuously updated during all display modes as long as signal quality is sufficient.
- **BIS trend graph**: it is a graphic indicator of the trends of BIS values. It only gives us an hour of register.
- **Signal Quality Indicator (SQI)**: is a measure of the signal quality for the EEG channel source. It is optimal when all five bars of the SQI icon are green. When signal quality is too low to calculate the BIS value and other trend variables that are adversely affected by artefact will not be displayed on the screen.
- **Electromyograph (EMG) Indicator**: displays the power (in decibels) in the frequency range 70 - 110 Hz. This frequency range contains power from muscle activity as well as power from other high-frequency artefacts. When the **indicator is low**, it indicates that EMG activity is low. BIS monitoring conditions are optimal when the bar is empty.
If a target range for BIS has been set, the target area displays as either a colored bar or two horizontal lines showing the upper and lower target ranges (depending on the user setting).
If the BIS value falls outside of the target range, a message displays in the Message Region of the screen, and if an audible alarm was requested in the target range set up screen, the alarm sounds (unless alarms have been silenced). The alarm continues to sound until the BIS value returns to the target range or the alarm is silenced.
During periods of poor signal quality, an artefact bar appears along the horizontal axis at the bottom of the graph. **When signal quality is considered too low to calculate a BIS value, the bar becomes bright yellow and any trend variables that are adversely affected by artifact will not be displayed.**

### EXPORT DATA
This selection allows the user to send data to a removable drive via the USB port at the rear of the monitor. The registers can be presented as Excel pages.

The various types of data that may be exported are listed below:

- **Live Data:** when selected, live case data (BIS values, SQI, EMG and unfiltered EEG waveforms) are exported named using the format LMMDDHHMM (‘L’ stands for Live Data, MM is the two-digit month, DD the two-digit day, HH is the two-digit hour and MM the two-digit minute that the data were exported).
- **History Data:** when selected, case data stored in the BISx are exported. BIS values, SQI and EMG are reported at one-minute intervals. History data files are named using the format HMMDDHHMM (initial ‘H’ stands for History data, followed by the mentioned above).

In order to export data, the system must be powered ON and the BISx must be connected to the monitor.

To export data:
1. Press the Export Data touch key. The display shows the data types available for export.
2. Press the desired data type; then press Begin Export.
3. When the export status screen displays “100% complete,” the drive may be removed from the back of the monitor. To stop Live Export, press [Stop Export] before removing the drive. Do not remove drive while export is in progress.

### BISx DATA MEMORY
The duration of BISx data stored is approximately **1200 hours (50 days)** of continuous monitoring.

When the BISx memory is full, the oldest data are automatically erased as new data are stored. Memory will be retained even if the monitor battery has been discharged and remains when the monitor and BISx are powered off.
ANNEX 2 - INFORMED CONSENT FOR THE STUDY OF BISPECTRAL INDEX MONITORING AMONG PATIENTS SUFFERING OHCA IN HJT.

Principal researchers: Pablo de Loma-Osorio Ricón, Júlia Pascual Mayans & Estefania Morales Perez.

We appreciate your collaboration in our study, which takes place at the Coronary Care unit of Hospital Universitari Josep Trueta, in Girona.

Your collaboration will help to improve our knowledge of neurological prognostication among patients after an out-of-hospital cardiac arrest. We do know that, when the heart arrests, the whole-body circulation arrests with it. That means that the blood flux does not arrive either to the brain and that can cause cerebral injuries that can worsen the neurological outcomes of the patient. In order to diminish the brain damage, the patients are treated with therapeutic hypothermia under general anaesthesia, which have proven to decrease the level of damage.

In the last years, clinicians have realized that there is a lack of accurate prognostication tools that helps us to identify what patients, which after suffering a resuscitated cardiac arrest, can benefit of more aggressive treatments and diagnostic tests and in what patients these measures can be futile. Since all our patients will be under sedatives, neurological examination is not reliable. The other tools we have until now cannot help us to get information among the first 24 hours of admission of the patient, what would be ideal.

Given that the existent tools we have only give us accurate information up above the 72 hours after the episode, that time might be too lengthy in a process where rapid decisions must be taken in order to individualize the treatment of each patient.

So, following this, the main objective of this project is to evaluate if Bispectral index monitoring, a non-invasive tool, can help us to have an early neurological prognostication.

How does Bispectral index monitoring work?
Bispectral index monitoring is a non-invasive tool that has been broadly study among patients that have been undergone sedation. It consists in a monitor connected to a sensor that is placed in the forehead of the patient and it can measure the level of consciousness of the patient. Due to Bispectral index monitoring give information about the current electroencephalogram of the patient, which is linked to cerebral activity, the information provided by Bispectral index could reflect the adequacy of cerebral perfusion.

We are currently conducting a study that aims to register Bispectral index values of the patients suffering cardiac arrests, together with other medical data, in order to evaluate the relation we suspect that Bispectral index values can give us early information about the prognosis of the patients.
You must know that every data we collect, are collected as well as part of the routinely assistance process in these cases but we only use them if you give us your consent. All the personal information collected or generated by this study will be protected accordance to law. To this end, we use the measures detailed below:

During your participation in the study:
• We will inform you about the objectives of the project and answer any questions that you may have,
• To participate in our study, you will not receive any financial reward,
• The data recorded in your file, can be treated statistically for the purpose of research,
• The data may provided and processed anonymously to a third party who may use it only for research purposes and in any case, your name will be shown in the publication of the results,
• The treatment you will receive in our unit, will be the same as other person not participating in the study,
• The Coronary Care Unit of Hospital Universitary Josep Trueta certifies that all the information received, will be codified in order to avoid the patient’s identification to people external to our Cardiology service,
• Your privacy is protected by national (LO15/1999, LGC5/2002, Ley de Investigación Biomédica 14/2007) and international (95/46/CE) laws. This will avoid access to your medical information with the purpose of exposing your data with adverse economical, legal, psychological or social effects.
• You will be able to know the research studies in which your clinical data have been used and we will provide you with the results of these studies related to your disease if you wanted to,
• The Hospital Universitari Josep Trueta is commited not to sell your clinical data,

DONOR’S STATEMENT
I have been informed, by the health professional, about what is mentioned below:
• About the advantages and disadvantages of this procedure,
• About the site of collection and processing of the clinical data,
• About the purpose for using my clinical data (public health or statistical studies that meet the law requirements, the Advisory Comitiee of experts in ethical, economic, environmental, legal and social, and the scientific committee),
• That my data will be provided anonymized to the investigators who work with them,
• That at any time I can revoke my consent and request the destruction of my data (LO15/1999),
• That at any time I can request the information about the studies where my data have been used,
• I understood all the information and I have been able to ask all the questions that I thought appropriate,
I agree to be contacted by personnel from cardiology service in Hospital Josep Trueta in order to get additional information when needed:

YES _____
NO ______

Please, sign parts A, B or C as appropriate:

HEALTH’S PROFESSIONAL’S STATEMENT REGARDING PROPERLY INFORMING THE PATIENT:

Name: Signature:

A. Adult with full mental capacity

Patient’s name: Patient’s signature:

B. Patient with diminished mental capacity

Patient’s name:

Legal representative’s name:

Legal representative’s signature:

C. Deceased patient:

Deceased patient’s name:

Legal representative’s name:

Legal representative’s signature:

To contact with the responsible, you can find us at the 6th floor, Coronary Care Unit, in Hospital Josep Trueta, Girona.

We use the informed consent in English in order to keep similarities with the rest of the protocol but there are Catalan and Spanish versions as well. In case of need of other languages, we have a translator in the hospital.
## ANNEX 3 – EMERGENCY SERVICES’ TEMPLATE.

### EMERGENCIES MÉDIQUES

<table>
<thead>
<tr>
<th>Unitat</th>
<th>Metge</th>
<th>Infermer</th>
<th>TTS/TES/Pilot</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Núm. Afectat</th>
<th>Data de servei</th>
<th>Hora activació</th>
</tr>
</thead>
</table>

**Motiu de l’alerta:**

**Lloc d’assistència:**

- [ ] Via pública
- [ ] Lloc públic
- [ ] Domicili
- [ ] Centre Sanitàri

**Adreça:**

**Dades del pacient:**

- NOM...
- Cognoms...
- Edat...
- Sexe D H DNI/Pasaport...
- CIP...
- Matrícula vehicle...
- Companyia...
- Núm. Polissa...
- Nom de l’empresa...
- Mútua...
- Núm. Afiliació...

**ANAMNESI:**

- AL·LEGIES: [ ] No [ ] Sí
- AP: [ ] No [ ] DM [ ] HTA [ ] DL [ ] Anticoagul [ ] IC [ ] Asma [ ] MPDC [ ] Insuf. renal

### EXPLORACIÓ FÍSICA I

#### A.VIA AEREA

- [ ] Permeable
- [ ] No permeable

#### B. VENTILACIÓ

- Eupnea
- Estridor
- Patró respiratiu irregular

#### C. CIRCULACIÓ

- Apnea
- Tiatge
- Mob. anormal del tòrax
- Hemorragia externa

#### D. NEUROLÒGIC

- Conscient
- Inconscient
- Distorção
- Atget
- Agressiu
- Relax estrènitures

### EXPLORACIÓ FÍSICA II

#### APERÈLL RESPIRATORI

- Auscultació pulmonar
- Moviment ventilationi
- Abdot
- Extensa
- Roncs
- Espiració allargada
- Matèries

#### APERÈLL CARDIOVASCULAR

- Auscultació cardíaca
- Drop
- Articular
- Galop
- Torsos esmorzals
- Bufs
- Freu pericàrdic

#### APERÈLL LOCOMOTOR

- A. Amputació
- Ax. Ascensament
- C. Contusió
- D. Dolor
- E. Erosió
- F. Frac. oberta
- G. Frac. tancada
- H. Hemorragia
- I. Luxació
- J. Cremades

### NEUROLÒGIC

- NORMAL
- FOCALITAT NEUROLÒGICA
- Meninisme
- Alter. motora
- ROMS patològics
- Dismetria

### ABDOMEN

- NORMAL
- ANORMAL
- Viscerimogènia
- Masses
- Peritoneum
- Punció percutària lumbar

### MONITORIZACIÓ DE CONSTANTS

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<tr>
<th>Hora</th>
<th>Ta Dret</th>
<th>Ta Estat</th>
<th>FC</th>
<th>FR</th>
<th>SAD</th>
<th>FIO</th>
<th>ECO</th>
<th>Peak flow</th>
<th>Temp</th>
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### ECG

**FREQUÈNCIA:** bpm

**ESCALES DE VALORACIÓ**

**HORA**

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<th>ITP</th>
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<th>Malalties</th>
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**OBSEVACIONS**

Generalitat de Catalunya
Departament de Salut
INFORME D’ATENCIÓ
UNITAT DE SUPORT VITAL AVANÇAT

TRACTAMENT: Procediments

Permeabilització VA/Extracció CE
Neteja VA/Aspiració secrecions
Cànuca orofaringia
Guia elèctrica/Frova
TOT núm.

Cirugia núm.
Cricototomia
Mascareta i FIO2
Baix resuscitador

VMNI
IPAP.. EPAP...
O2
VMI C A/C
VT...
PEEP...
PS... PR/PLATEAU...

HEMOSIATICA
DEA
Monitor DF
MCP extern
H.
Amperatge
Cardioversor elèctric
Energia lúxules
Baix contrapressió

BISPECTRAL INDEX MONITORING AS AN EARLY NEUROLOGICAL PROGNOSTIC TOOL AFTER AN OUT-OF-HOSPITAL CARDIAC ARREST SUCCESSFULLY RESUSCITATED.

CIRCUIT.

MANIOBRES: Mobilització / Immobilització

Mobilització prèvia
Collaret cervical
Férola de Kendrich
Antirrotatori cervical
Tauló espinal
Matales de buit
Ullera esora

CODIS I PREACTIVACIÓ HOSPITAL

Codi IAM
Codi ICTUS
Codi SWAP
Codi PPR: Priorització
Alfa Romeo... GCS...
Charlie... Hotel.......

DADES DEL TRASLLAT

Centre emissor
Servei emissor
Mestre responsable
Indicatiu Unitat
USVI
HMS
USVI

Signatura consentiment informat
Sí
No

DADES DE L’ACCIDENT

1. ANATOMIA DE LA LESIO

Fèrida penetrant
Fractura de crani
Sensat inconscient
Fractura de pelvis

2. VEHICLES IMPACTATS

Bicicleta
Ciclomotor
Motocicleta
Turisme

4. MATERIAL DE SEGURITAT

Activació airbag
Casco integral
Casco no integral
Sensat csc o mal posat
ORI i/o cadèira

3. MECANISME DE LA LESIO

Precipitació > 6 m (mens 2-3 cops al’hora)
Col·lisió automobil·ística
Atropellant
Ejercici del vehicle
Mort d’un altre passatger
Deformitat de l’habitatge
Vehicle botat

5. ALTRES ACCIDENTS

Boví
USVI
USVI

INCIDENTS EN EL TRANSPORT HOSPITALARI

Retard sortida > 20'. Motiu:

Recepció hospitalaria. Motiu:

FINALITZACIÓ DEL SERVEI

Alta médica
Trasllat hospital
Trasllat CAP/112
Trasllat involuntari
Signes negats de vida
Servei nul:

Hora

A dalt voluntària:
Signatura que confirma que accionava el trasllat i transport.

SIGNATURA RESPONSABLE DE LA UNITAT:
Mestre/a
Infermer/a

Núm. col·legiat...

Registre Utstein

Hora

ACR
RCP-B
DEA
RCP-A
Monitorització
1a DF
Vía venosa
1r fàrmac
Cirurgia esportativa
Ventilació esportativa
Final RCP: Núm DF...

Comp. mecàniques
Hipòtesia...
BISPECTRAL INDEX MONITORING AS AN EARLY NEUROLOGICAL PROGNOSTIC TOOL AFTER AN OUT-OF-HOSPITAL CARDIAC ARREST SUCCESSFULLY RESUSCITATED.