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Therapeutic Hypothermia and Early Waking

Waking unconscious survivors following out-of-hospital cardiac arrest to positively neurologically prognosticate

A thesis submitted in fulfilment of the requirements for the degree of Doctor of Philosophy in Health Sciences, the University of Waikato, 2024.

Abstract

Introduction: Cardiac arrest is a significant global health challenge, which leads to substantial morbidity and mortality, impacting 50 to 100 individuals per 100,000 in the general population. Ischemic heart disease is the primary cause, particularly in developed countries. Historically, survival rates following cardiac arrest with a good neurological outcome were low; however, advancements in emergency response, including early Cardio-Pulmonary Resuscitation (CPR), access to defibrillation, coronary revascularisation, intensive care and Targeted Temperature Management (TTM), have notably improved patient outcomes. The practice of TTM has evolved over the past two decades, advocating that Therapeutic Hypothermia (TH) enhances neurological outcomes; although there has been much controversy over optimal temperature ranges. Notwithstanding, international resuscitation guidelines continue to endorse TTM as a post-resuscitation neuroprotective strategy, recommending temperatures between 32° and 36° Celsius. To ensure patient comfort and prevent shivering during the administration of TTM, sedatives and neuromuscular blockers are administered, preventing an accurate neurological assessment. Despite the challenges of neurological prognostication post-cardiac arrest, current guidelines recommend a multimodal approach, including clinical examination, electrophysiological studies, biomarkers, and neuroimaging, to predict outcomes accurately.

Aim: This research sought to develop and evaluate a protocol (Therapeutic Hypothermia and eArly Waking, THAW) for early waking of unconscious Out-of-Hospital-Cardiac-Arrest (OHCA) survivors for the purpose of performing a comprehensive neurological assessment.

Methods: A mixed methods approach was used. In the development of the THAW protocol, qualitative data were obtained from a series of focus groups, which included the research team, the National Health Service Ethics committee, a clinical expert panel, OHCA survivors and their family members as well as the Essex Cardiothoracic Centre's Clinical Governance Committee. Thematic analysis was undertaken to capture the varied perspectives and insights from the different stakeholder groups to inform the THAW protocol interventions. A prospective non-randomised sampling strategy was selected for the implementation of the THAW protocol and neurological indicators collected over a 72-hour period.

Results: The THAW protocol assessed the safety and feasibility of an early waking protocol for unconscious survivors of OHCA treated with TTM at 33° Celsius, with a focus on the potential to reduce Intensive Care Unit (ICU) stay and mechanical ventilation duration through early neurological assessments. Despite an expected 50 percent mortality rate, largely due to neurological injuries, findings demonstrated that early waking and extubation with a mean mechanical ventilation duration of 21.4 hours, was feasible for 24 percent of patients, significantly reducing ICU length of stay without adverse events. Of these, seven patients (14%) were able to be transferred from the ICU to the cardiology High Dependency Unit (HDU) within the first 72 hours of their admission. The THAW protocol employed a combination of Intravenous Temperature Management (IVTM) and a counter-shivering strategy to manage core temperature, alongside physiological assessments and standard neurological exams like the Glasgow Coma Scale (GCS) and the Full Outline of UnResponsiveness (FOUR) score. Notably, the neuro biomarker and neurophysiological tests performed as part of the THAW protocol interventions, were not used to inform clinical decision-making, instead to be used in post hoc analysis to maintain objectivity.

Conclusion: The THAW protocol demonstrated the safety and feasibility of an early waking protocol in OHCA survivors undergoing TTM at 33° Celsius. Highlighting the potential to expedite neurological prognostication and reduce ICU length of stay and mechanical ventilation duration. Through careful patient selection, the implementation of IVTM with a counter-shivering strategy, early neurological assessments can be integrated into critical care practices without adverse effects on patients.

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Returning to New Zealand, being with family and friends has enabled me to focus and get this done. I know this was a full circle moment for my parents, having their son return home after 30 years of living abroad. I sincerely thank them both for their support and encouragement through some particularly stressful moments in my life.

Contribution

I, the researcher undertook all aspects of this study under the direct guidance of my supervisors. This entailed selecting the appropriate research design, the data collection and analysis, and the publishing of the findings in this thesis.

Dedication

I dedicate my research to cardiac arrest survivors, their family and friends. This journey has been an enlightening experience that has profoundly humbled me as a critical care registered nurse. It has given me a deeper appreciation for the time we have with our loved ones and the significance of those precious moments we often take for granted.

Your resilience and strength have been truly inspirational. Your openness in sharing your most personal and challenging experiences has provided invaluable insights that will undoubtedly contribute to the advancement of critical care research, for survivors of cardiac arrest. This will hopefully shift the emphasis to recovery and achieving positive outcomes.

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Chapter 1: Introduction

Don't forget, the introduction is only the beginning

Anonymous, 345 BCE

Cardiac arrest is a global problem affecting 50 to 100 per 100,000 in the general population and ischaemic heart disease remains the leading cause of death in the western world (Deo & Albert, 2012; World Health Organization, 2020), and until recently, neurologically intact survival following cardiac arrest has been poor. However, as a consequence of early Cardio-Pulmonary Resuscitation (CPR) and improved access to defibrillation, coronary revascularisation in addition to intensive care support combined with Targeted Temperature Management (TTM); survival to discharge rates have increased dramatically (Wissenberg et al., 2013).

In 2002, two seminal studies on TTM were published, which subsequently led to dramatic changes in the manner by which post-cardiac arrest care was delivered. The research identified that Therapeutic Hypothermia (TH) (32° to 34° Celsius for 12 to 24 hours with a controlled rewarming phase) resulted in improved neurological outcomes for Out-of-Hospital Cardiac Arrest (OHCA) patients (Bernard et al., 2002; HACA, 2002). However, this was later challenged (N Nielsen et al., 2013) and it was argued that there were no discernible differences in primary outcomes or mortality between patients maintained at 36° Celsius and those treated with TTM (33° Celsius). Notwithstanding, TTM as a target temperature between 32° Celsius to 36° Celsius continues to be recommended for OHCA patients by the International Liaison Committee on Resuscitation (ILCOR), American Heart Association (AHA) and American Academy of Neurology (AAN) (C. Callaway et al., 2015; Donnino et al., 2016; Geocadin et al., 2017). Therefore, TTM remains an important neuro-protective strategy for unconscious OHCA survivors due to cerebral ischemia occurring at the time of the cardiac arrest and reperfusion injury in the hours and days following ROSC (Lascarrou et al., 2019; Polderman & Varon, 2018).

To adopt TTM as a treatment strategy for unconscious OHCA survivors admitted to hospital, patients receive sedatives and Neuromuscular Blockers (NMB) to ensure patient comfort, but more importantly to prevent shivering. TTM is known to affect the pharmacodynamics and pharmacokinetics of sedatives and NMBs by increasing serum concentrations, prohibiting meaningful neurological clinical assessment and affecting the reliability of

Electroencephalogram (EEG) (Arpino & Greer, 2008; Sandorini et al., 2018). However, there are several studies which have demonstrated that TTM can be safely administered to awake patients, using an endovascular cooling device and rigorous counter shivering regimens, therefore negating the need for sedatives or NMBs (De Georgia et al., 2004; Simon R. Dixon et al., 2002; Gotberg et al., 2008; Keeble et al., 2019; Lyden et al., 2016; Noc et al., 2017). Shivering is considered counterproductive for the intended benefit of TTM as it increases metabolic activity, thereby generating heat and elevating core temperature. Furthermore, shivering is uncomfortable for the patient and can make monitoring difficult (Badjatia, Strongillis, et al., 2009; Kiekkas et al., 2005; Matthias & Indrakumar, 2014).

Of those patients who suffer an OHCA and are admitted to hospital, it is estimated that only 22 percent of patients will survive until discharged from hospital (Yan et al., 2020). Hypoxic-Ischaemic Brain Injury (HIBI) is considered the most common cause of morbidity and mortality in comatose patients following OHCA (Nolan et al., 2018; Sandorini et al., 2018; Uchino et al., 2016), which is compounded by pre-existing morbidity in approximately 75 percent of adult survivors of OHCA (Hallstrom et al., 2000; Pearn, 2000). This makes neurological prognostication challenging and therefore a multi-modal approach is recommended in all current guidelines to accurately predict neurological outcome (Nolan & Cariou, 2015; Nolan et al., 2014; Sandroni et al., 2014; Scarpino et al., 2018; Zhou et al., 2019). The guidelines recommend using a combination of predictors including clinical neurological examination, electrophysiological investigations (Electro-encephalogram [EEG] and Somatic Sensory Evoked Potential [SSEP]), serum biomarkers and neuroimaging. Both EEG and SSEP are considered useful in predicting poor outcomes (Benghanem et al., 2022; Duez et al., 2018; Sandroni et al., 2020) and EEG can provide a method of assessing the level of consciousness as well as detecting non-convulsive seizures, which can then be treated (Rothstein, 2014; Sandroni & Geocadin, 2015; E Westhall et al., 2016). Other useful predictors of neurological outcome are brain-derived proteins, Neuron-Specific Enolase (NSE) and S-100B. It has recently been described that serum concentrations of both these neuro-proteins peak within the first 24 hours in patients with a favourable to moderate neurological outcome, but continue to rise up to three days after cardiac arrest in patients with unfavourable outcomes (Pfeifer et al., 2014; Stammet et al., 2015; Stammet et al., 2017).

However, using neurological indicators to prognosticate in the unconscious cardiac arrest survivor is complex and guidelines and evidence remains mixed. The aim of this research is to assess whether it is safe and feasible to wake patients early, who have remained unconscious following out of hospital cardiac arrest, after just 12 hours to assess neurological function

whilst continuing to be treated with TTM. More specifically, the research sought to address the following questions:

1. To what extent, can early neurological assessments and accurate prognostication contribute to reducing ventilation time in OHCA patients?

2. What is the safety and efficacy of utilising Intravenous Temperature Management (IVTM) combined with counter shivering strategies in waking unconscious OHCA patients for neurological assessments?

3. How can physiological assessments be utilised to determine the suitability of waking unconscious OHCA patients early, to perform a neurological assessment?

Chapter 2: Literature review

Healing is a matter of time, but it is sometimes also a matter of opportunity.

Hippocrates (460 BCE – 375 BCE)

2.1 Introduction, literature review

Surviving an Out-Of-Hospital Cardiac Arrest (OHCA) is a formidable challenge; approximately half of those admitted to hospitals will not survive, with brain injury being the primary cause. Targeted Temperature Management (TTM), previously referred to as Mild Therapeutic Hypothermia (MTH), is a critical method which aims to reduce core body temperature, to attenuate the effects of brain injury caused by hypoxia during the 'down-time' period. However, predicting neurological outcomes remains a complex puzzle, necessitating a multi-faceted approach combining electrophysiological testing, biochemical markers, clinical examination and neuroimaging. Early identification of patients with a likely poor prognosis is paramount, though this often leaves those with potential for positive early outcomes overlooked. Standard treatment involves TTM for 24 hours, followed by a slow, careful rewarming process (Dankiewicz et al., 2019). During the administration of TTM, sedative and neuromuscular blocking agents prevent accurate neurological assessments. However, it is known that some patients can even be awake during TTM via an endovascular device, a method proven safe and feasible, when combined with an anti-shiver regimen (De Georgia et al., 2004; Simon R. Dixon et al., 2002; Erlinge et al., 2014; Gotberg et al., 2010; Islam, Hampton-Till, MohdNazri, et al., 2015; Lyden et al., 2014; Noc et al., 2017). The aim of this study is to explore whether selected OHCA patients can be awakened early (12 hours following admission to critical care), whilst still being treated with TTM at 33° Celsius for 24 hours, potentially enabling earlier positive neurological prognostication and reducing the critical care and hospital stay.

This chapter comprises three sections. The first explores the intricacies of cardiac health and the deleterious effects of cardiac arrest, focussing on the use of TTM as a treatment strategy in reducing neurological injury following cardiac arrest. The mechanism of action and neuroprotective effects of TTM as well as dosage considerations, delivery methods and the importance of preventing hyperthermia will be discussed, drawing on extant research as appropriate.

The second section of this chapter explores the essential, yet challenging aspects of neurological prognostication in the context of cardiac arrest survivors being treated with TTM. This complex process, which requires a multimodal approach, is considered instrumental in guiding clinicians' decision making on treatment strategies, as well as informing discussions with family about the patient's prognosis (Kim et al., 2019). This section will review literature on the use of neurological biomarkers, monitoring, clinical assessment (including various assessment tools) and neuroimaging as predictive tools to inform clinicians and determine patient outcomes.

In the final section of this chapter, a review of the literature on the resource impact of OHCA survivors on the Intensive Care Unit (ICU) and hospital length of stay. This will include the role of mechanical ventilation and its influence on ICU and hospital length of stay. To understand these factors and how they inform patient management decisions and identify areas for potential improvement.

Overall, this literature review seeks to provide a comprehensive overview of current knowledge and evidence-based practice on the ICU aspects and management of the unconscious survivor of OHCA. This will include neurological prognostication within the first 72 hours. The insights from this literature review are intended to inform clinical practice and protocol development and ultimately contribute to improving not only patient outcomes, but the experience for the patient and their family.

2.2 Search methodology

Articles in this literature review were obtained via computer searches from a number of medical, nursing, neurology, critical care, pharmacy and pharmacology, therapeutic hypothermia, anaesthetic databases; the majority retrieved from MEDLINE, Scopus, ScienceDirect, PubMed, SpringerLink. The Anglia Ruskin University Library, The Basildon and Thurrock University Hospital Foundation Trust Library and The Waikato District Health Board Library were used for all manual searches and online searches were undertaken using search engines Google (http://www.google.co.uk and http://www.google.co.nz), Google Scholar (http://scholar.google.co.uk and http://scholar.google.co.nz). Keywords in the searches included "therapeutic hypothermia", "targeted temperature management" "cardiac arrest', "neurological prognostication", "neurological electrophysiology", "mechanical ventilation", "neurological biomarkers", "hypoxic brain injury", "counter shivering strategies".

2.3 Definition of terms

Out-of-hospital-cardiac-arrest: Refers to the sudden cessation of the person's heart function that occurs outside of a hospital setting. During an OHCA, the heart stops beating and the person collapses, stops breathing and loses consciousness. OHCA is a medical emergency and requires immediate intervention to restore the person's heart function and prevent brain damage or death. OHCA is the leading cause of death in developed industrial countries (Berdowski et al., 2010) with survival rates varying widely depending on the location of the cardiac arrest, the underlying cause and the promptness of intervention. Survival rates are generally higher when bystanders intervene by performing Cardiopulmonary Resuscitation (CPR) and using Automated External Defibrillators (AED) until the ambulance service arrives.

Critical Care: Critical care is a highly specialised area within the hospital environment that provides life-saving interventions and treatments to patients who have life-threatening conditions, injuries or are suffering from post-operative complications. Critical care is equipped with advanced medical equipment and technology to provide monitoring, diagnostics as well as organ support. A specialised multidisciplinary team of healthcare professionals are responsible for coordinating some of the most comprehensive care planning, including the delivery of complex and technical care.

Primary Percutaneous Coronary Intervention (PPCI) Centre: Is a specialised and dedicated facility that has the equipment and trained staff to provide emergency treatment for patients experiencing an ST-Elevation Myocardial Infarction (STEMI). The PPCI centre would normally have 24-hour availability and staffed by interventional cardiologists, nurses, cardiac physiologists and radiographers, all with expertise in the diagnosis and treatment of acute coronary syndromes. In terms of the actual PPCI procedure, this involves a catheter being inserted into the patient's arterial system (usually radial artery) and advanced into the blocked coronary arteries. Where a thrombus is extracted using a suction catheter or if the coronary artery is blocked due to atherosclerosis it will be opened using a balloon. This may also require a stent to be deployed to maintain vasculature patency. PPCI is considered the gold standard treatment for STEMI patients and is associated with better outcomes and lower mortality rates compared to other treatments, such as thrombolysis or fibrinolysis.

Therapeutic Hypothermia and Targeted Temperature Management: Both of these terms refer to controlling a patient's body temperature and are often incorrectly used interchangeably. Therapeutic Hypothermia (TH) traditionally refers to the lowering of

patients' core body temperature between 32° Celsius to 34° Celsius. Whereas TTM is a broader term that incorporates the phases of induction, maintenance, rewarming and fever prevention. TTM is used as a treatment in unconscious survivors of cardiac arrest to attenuate any effects of hypoxic brain injury. TTM is a complex treatment that requires specialised equipment, monitoring and management. The treatment is typically provided in an intensive care unit by a multidisciplinary team of healthcare professionals.

Neurological prognostication: Is the process of predicting long-term outcomes for patients who have suffered a neurological injury or insult, such as during cardiac arrest. Neurological prognostication typically involves the use of clinical examination, neuroimaging, electrophysiological and biomarkers to determine the extent and severity of the injury and to predict the patient's likely functional outcomes and quality of life. The accuracy of neurological prognostication can be influenced by a variety of factors, including the timing and quality of diagnostic testing, the severity of the injury and the presence of comorbid conditions. Prognostication may also be complicated by factors such as uncertainty about the patient's prognosis and ethical and legal considerations related to end-of-life care.

Part 1: The healthy and unhealthy heart

2.4 Cardiac arrest

Cardiac arrest is characterised by a sudden loss of effective blood flow which immediately leads to a loss of consciousness and death if left untreated. The standard definition of cardiac arrest, developed by Utstein in 1991 (Cummins et al., 1991) and updated by the American Heart Association in 2004 (Jacobs et al., 2004, p. 3387) is "the cessation of cardiac mechanical activity as confirmed by the absence of signs of circulation" According to current resuscitation guidelines (American Heart Association, 2015; Australian and New Zealand Committee on Resuscitation, 2016a; J Nolan et al., 2015; Resuscitation Council United Kingdom, 2017) an absence of signs of circulation can be determined by unresponsiveness, not breathing or gasping therefore requiring chest compressions or CPR. CPR is broadly classified into basic and advanced techniques with simple airway manoeuvres, mouth-to-mouth ventilation and chest compressions being able to be performed by lay-public to advanced techniques such as endotracheal intubation, administration of intravenous medication, defibrillation and extracorporeal circulatory support provided by healthcare professionals with specialist training.

In both adults and paediatric OHCA, cardiac causes are the most prevalent (Bardai et al., 2011). Ventricular Fibrillation (VF) attributes to 50 percent of OHCA patients, whereas conversely VF and Ventricular Tachycardia (VT) is only attributed to 25 percent of In-Hospital Cardiac Arrest (IHCA).

2.4.1 Aetiology of cardiac arrest

Most observational studies and data registers are based on IHCA patients or small, often single centre, observational studies after OHCA. The patient population of interest, with respect to post-cardiac arrest and early neurological prognostication research, are those successfully resuscitated after cardiac arrest, though remain at risk of neurological morbidity or death. Percutaneous Coronary Intervention (PCI) and TTM are considered the only clinical interventions in the post resuscitation phase of OHCA that are associated with improved long-term survival (Dumas et al., 2012).

2.4.2 Incidence of cardiac arrest and outcome

The incidence of OHCA is a global problem affecting 50 to 100 people per 100,000 in the general population, with cardiovascular disease being the leading cause of death in the western world (Deo & Albert, 2012; World Health Organization, 2020) accounting for nearly 50

percent of all deaths. The global average survival rate from OHCA is seven percent (Andrew et al., 2017; Berdowski et al., 2010). Where resuscitation has been attempted, only 14 to 40 percent of patients achieve Return Of Spontaneous Circulation (ROSC) and are admitted to hospital (Arrich et al., 2009). Of those patients admitted to hospital, 7 to 30 percent are usually discharged from hospital with a good neurological outcome (Arrich et al., 2009). However, the majority of OHCA survivors who are alive after 12 months have a favourable functional and neurological outcome (Smith et al., 2015).

Adult patients suffering OHCA reportedly have a lower survival rate to hospital discharge compared to IHCA. Survival to hospital discharge is the most quoted outcome measure for both IHCA and OHCA; however, there is significant data variability in reported literature. This in part can be explained due to inclusion of all causes of cardiac arrest including trauma, differences in disease severity between the two patient populations, definition of cardiac arrest, Do-Not-Attempt-Resuscitation (DNAR) orders, as well as age. Incidence of IHCA range from one to five per 1000 admissions but with significant variation in survival rates (0 to 42%) (Sandroni et al., 2007). A recent analysis of the American Heart Association (AHA) Get With The Guidelines (GWTG) – resuscitation registry, recorded the incidence of IHCA as 4.02 per 1000 admissions with a median survival rate to hospital discharge being 18.8 percent (Chan et al., 2013). In the United Kingdom (UK), the occurrence of IHCA has been recorded as 1.6 per 1000 hospital admission with 18.4 percent surviving to hospital discharge (Nolan et al., 2014).

2.5 Temperature management

2.5.1 Targeted temperature management

TTM is the active reduction of core body temperature to prevent or attenuate secondary cellular injury following ischaemic reperfusion. There is various terminology used to describe variable temperature ranges including 'mild, moderate, severe, extreme, deep' (Safar et al., 2002), however this can be confusing. Therefore, TTM is recommended along with explicit temperature profile to provide clarity (Nunnally et al., 2011). In this thesis, patients receiving iatrogenic TTM will be referred to as receiving TTM, with inclusion of explicit numerical temperature values in parentheses.

TTM has three distinct phases: 'induction' - reduction of current temperature to a lower 'target' temperature, 'maintenance' – maintaining target temperature for a specified treatment period and 'rewarming' – controlled increase in temperature to normothermia either through active

rewarming or through intrinsic physiological control (Nunnally et al., 2011). Prevention of hyperthermia or "maintenance of normothermia" has also been described as a fourth phase (K. Polderman, 2009).

The use of hypothermia to attenuate injury has been known for thousands of years. In 2500 BC the Egyptians used low temperatures to reduce infection and inflammation. It has also been recorded that Hippocrates (460-370 BC) used snow and ice to reduce haemorrhage (Hippocrates., 460-375 BC). In 1803, the Russian method of resuscitation consisted of covering patients with snow in the hope the patient would regain a ROSC (Liss, 1986).

During the Napoleonic war in 1812, French physicians employed TH to preserve injured limbs and for its numbing effects when amputating limbs. Over a hundred years later, in 1937, Doctor Temple Fay cooled a patient to 32° Celsius for 24 hours to prevent cancer cells from multiplying. However, it was not until the 1950s that Bigelow used TH for neuroprotection (Bigelow et al., 1950). Initially, hypothermia was used under general anaesthesia before cardiac bypass to protect the brain during cardiac surgery (Bigelow et al., 1950). The in-animal study used canine and monkey models, reducing core body temperature to less than 25° Celsius during cardiac surgery. They were able to report the area of neurological injury contained less oedema, less haemorrhage and a reduced inflammatory response. In 1954, Rosomoff demonstrated that cerebral oxygen consumption reduced in dogs as the temperature was lowered from 35° Celsius to 26° Celsius (Rosomoff & Holaday, 1954). And in 1956, Marshall et al. (1956) and McMurrey et al. (1956) were able to demonstrate evidence of a reduction in histopathology and favourable functional outcomes using hypothermia (Marshall et al., 1956; McMurrey et al., 1956). These studies were able to approximate what occurs in cardiac arrest and provided a pathway for the clinical use of hypothermia in human medicine.

Benson et al. (1959) describe the first in-human use of TH following cardiac arrest (Benson et al., 1959). This study included 19 patients who were resuscitated following perioperative cardiac arrest. The body temperature of these patients was maintained between 31 and 32° Celsius. The duration of hypothermia ranged from 31 to 84 hours in the survivor group and three to eight days in the non-survivors. Six out of the 12 patients treated with hypothermia using a cooling blanket, survived without a residual neurological deficit demonstrating an improvement in survival from 14 percent (Benson et al., 1959).

Despite the potential neurological benefits of TH for OHCA survivors, there were several associated complications including arrhythmias, coagulopathy, increased infection rates,

shivering and vasospasm. This was before the existence of ICU where mechanical ventilators and cardiac monitors were available, to manage the side effects. Moreover, there were also reports of increased harm associated with paediatric drowning victims which led to TH being stopped in the early 1980s (Safar, 1988).

When several encouraging animal studies and several human feasibility studies were published in the late 1980s and early 1990s, which demonstrated the benefit of protecting the brain from hypoxia, TH re-emerged as a possible treatment modality for OHCA survivors (Leonov et al., 1990; Strerz et al., 1991). However, the benefit of TH improving survival rates and reducing poor neurological survival after witnessed VF arrest was demonstrated in two landmark Randomised Controlled Trials (RCT) published in 2002 (Bernard et al., 2002; HACA, 2002). The Hypothermia After Cardiac Arrest (HACA) study, recruited 275 patients following out-of-hospital VF arrest, who were induced with TH with a median of eight hours to reach the target temperature between 32° Celsius and 34° Celsius using surface cooling for 24 hours, followed by rewarming to normothermia (HACA, 2002). They reported 55 percent of patients who received TH, survived with a good neurological recovery compared to 38 percent after standard therapy (HACA, 2002). Bernard et al. (2002) study, recruited 77 patients, again only including out-of-hospital VF arrest patients, however TH was initiated by paramedics following ROSC using ice packs with a median of two hours to reach target temperature of 33° Celsius, this was continued for 12 hours prior to rewarming to normothermia (Bernard et al., 2002). They reported 49 percent of patients who received TH, survived with a good neurological outcome compared to 26 percent receiving standard therapy (Bernard et al., 2002). There were no serious adverse events reported following TH in either study, although it was noted that there was a trend toward increased infection rates.

Subsequently, MTH was recommended and incorporated into standard clinical practice. This led to the International Liaison Committee on Resuscitation (ILCOR), the American Heart Association (AHA) and European Resuscitation Council (ERC) recommending MTH in the management of unconscious patients following OHCA (Nolan et al., 2008). Furthermore, they also recommended that "induced hypothermia might also benefit unconscious adult patients with spontaneous circulation after out-of-hospital cardiac arrest from a non-shockable rhythm or in-hospital cardiac arrest" (Nolan et al., 2008, p. 362) and similar recommendations were provided by the International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations" (Morrison et al., 2010). However, the questions that remain unanswered include the optimal target population, temperature duration of therapy and the rate of rewarming.

A systematic review was conducted by Walters et al. (2011) of the literature for TH after cardiac arrest and explored whether TH improves mortality and morbidity compared to standard care (Walters et al., 2011). The review concluded that whilst there is evidence supporting the use of TH to improve neurological function in comatose OHCA survivors, the quality of the evidence was considered low. Temperature of patients in the control arms were not controlled, which resulted in median temperatures between 37° and 38° Celsius. Historical observational data suggests pyrexia is associated with worse neurological outcome on survival from cardiac arrest populations which show an odds ratios for a poor outcome of 2.7 for a temperature more than 37.8° Celsius (Langhelle et al., 2003) and 2.26 for every degree higher than 37° Celsius (Zeiner et al., 2001), therefore potentially increasing harm in the control group and biasing the study. It was also impossible to blind the cooling treatment and neither study reported the full details on how the decision to withdraw intensive care treatment was made, so clinicians who made the decisions on withdrawal of treatment were likely to have been aware which patients had received mild hypothermia. Furthermore, both the Bernard and HACA studies performed an interim analysis after 80 percent recruitment (n=62), with no statistical adjustment (Nielsen et al., 2011), potentially leading to an inflation of the false positive rate (Harris et al., 2008).

Nielson et al. (2011) questioned the strength of evidence in relation to the use of hypothermia after cardiac arrest (Nielsen et al., 2011) and conducted a systematic review of five randomised trials (Bernard et al., 2002; HACA, 2002; Hachimi-Idrissi et al., 2001; Laurent et al., 2005; Mori et al., 2000), performing a meta-analysis and trial sequential analysis using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (Guyatt et al., 2008). Nielsen et al. (2011) concluded that all five randomised trials, which included 478 patients were associated with substantial risk of systematic and random errors. The trial sequential analysis of these studies could not confirm or reject the intervention effect, concluding that the quality of the evidence was low and that clinical equipoise exists, recommending further investigation and research into the use of TH for OHCA (Nielsen et al., 2011).

This led to the TTM trial which set out to determine whether unconscious survivors of OHCA treated with TH is associated with a better outcome (N. Nielsen et al., 2013). This was a large international, prospective, randomised controlled trial, which recruited 939 patients, comparing target temperatures of 33° Celsius with 36° Celsius. They found both groups had similar mortality (primary end point) and neurological outcomes at 180 days (N. Nielsen et al., 2013). This resulted in considerable debate regarding the optimal target temperature for post-

cardiac arrest patients (Bernard, 2014; Polderman & Varon, 2015, 2018; Wise et al., 2014). The TTM trial led to a modification of current practice in managing OHCA with TH (Deye et al., 2016). Deye et al. (2016) later assessed changes in practice through a survey of clinicians and they concluded that approximately one-third of respondents modified their current practice, deciding to increase target temperature to 36° Celsius (Deye et al., 2016). Controversy continued and Bray et al. (2017) reported that the raised target temperature resulted in increases in adverse patient outcomes in hospitals that changed from a target temperature of 33° to 36° Celsius (Bray et al., 2017). They also reported difficulty in maintaining the target temperature at 36° Celsius, with higher rates of fever and a trend towards clinical worsening in patient outcomes (Bray et al., 2017). Furthermore, in a post-hoc analysis of the TTM-trial by Dankiowicz et al. (2017), who performed a prospective review of the data on the incidence of infectious complications, which comparing the incidence of pneumonia, severe sepsis and septic shock between both cohorts, concluded there was no association with an increased risk of infectious complications in OHCA patients treated with MTH to a target temperature of 33° Celsius compared to a target temperature of 36° Celsius (Dankiewicz et al., 2017). However, the TTM-trial did identify significant knowledge gaps in post cardiac arrest fever and temperature management, which includes optimal temperature, duration of temperature management and target population which remain to be defined.

2.5.2 The mechanisms of action of mild therapeutic hypothermia

Humans are endothermic animals, with an ability to maintain core body temperature (T_b) within a few tenths of a degree Celsius. However, humans are not able to survive temperatures of more than a few degrees from the upper limit or more than a few tenths of a degree below our lower limit. Thermoregulation is controlled by the central nervous system, but the Preoptic Anterior hypothalamus (POA) is considered the most important. Warm-sensitive POA neurons are responsible for triggering heat and cold-defence responses and are considered the pacemakers that determine the rate of spontaneous depolarisation between successive action potentials (Wechselberger et al., 2006; Zhao & Boulant, 2005).

Peripheral thermo-sensory neurons are situated directly beneath the epidermis, serving as a first line of defence against temperature variations. In contrast to central thermo-sensors, these peripheral thermo-sensors predominantly detect cold stimuli. The transmission of signals is facilitated by thin myelinated A fibres, which convey the sensory information, while unmyelinated C fibres carry signals from the less common warm sensors located slightly deeper in the dermis. Peripheral thermo-sensors exhibit a high degree of responsiveness to temperature fluctuations and can swiftly react to changes in the surrounding environment.

Additionally, there are deep-body peripheral sensors found in the oesophagus, stomach, larger intra-abdominal veins and other organs. These sensors are responsible for monitoring changes in core body temperature.

Convection, conduction, radiation and evaporation are the four basic mechanisms of heat loss. Increasing convective or conduction heat loss are the most efficient ways of inducing hypothermia. Convective heat loss accounts for approximately 20-30 percent of heat loss. There are many variables which determine the rate of heat loss, including temperature gradient, body composition and conductive properties of the environment.

Age and body mass are also known to contribute to the effectiveness of the mechanisms which control body temperature. With age, there is a decrease in sensitivity to minor temperature changes, a slower rate of metabolism, less effective vascular response and more often a lower body mass index, therefore achieving hypothermia is quicker in older patients compared to younger. Therefore, in obese patients, induction of hypothermia can take longer not only because of body mass but due to penetration of adipose tissue.

2.5.3 The neuroprotective effect of therapeutic hypothermia

Vascular, metabolic and neuronal parameters are significantly affected by brain temperature (Mrozek et al., 2012). Cerebral metabolism changes linearly with brain temperature, with six to eight percent change for every one degree Celsius of body temperature (Lanier, 1995; Rosmoff & Holaday, 1954). In previous animal models, anaesthetised dogs cooled to 28° Celsius, cerebral metabolism was reduced by 50 percent (Michenfelder & Milde, 1992). Therefore, brain oxygen consumption is dramatically reduced. Cerebral metabolic rates for glucose utilisation and lactate concentration are also dependent on temperature (Glenn et al., 2003). The cerebral metabolic rate decreases by approximately six to eight percent for one degree Celsius drop in body temperature (K. H. Polderman, 2009), therefore reducing oxygen demand protecting Adenosine Triphosphate (ATP) stores (Erecinska et al., 2003) and preventing anaerobic metabolism, specifically lactate production and development of extracellular acidosis. TH is now thought to exert its effect through several mechanisms (Polderman & Herold, 2009). Animal experiments have shown that the degree of neuroprotection is similar when either mild or deep hypothermia is used, an effect not explained by metabolism reduction alone (Polderman & Herold, 2009).

The neuroprotective effects of TH and the pathophysiological mechanism is complex. Evidence suggests that TH attenuates numerous key biochemical, metabolic and

pathophysiological events in the brain which occur after cerebral ischaemia and reperfusion injury. The cerebral metabolic rate determines cerebral perfusion; however, ischemia is characterised by a deficiency in oxygen, ATP and glucose. The release and uptake of excitotoxic compounds such as amino acids and glutamate results in the stimulation of non-N-Methly-D-aspartic Acid (NMDA) which in toxic levels causes extracellular acidosis. This leads to an increase in intracellular calcium, potassium, protease activation, as well as Nitric Oxide (NO) and Reactive Oxygen Species (ROS) synthesis (Kuffler, 2012), such as superoxide, peroxynitrite, hydrogen peroxide and hydroxyl free radicals which is common after ischaemia. TH is known to attenuate this biosynthesis, by improving ion homeostasis and decreasing cellular permeability, therefore reducing the release of excitatory amino acids, in-particular glutamate production as well as NO (K. H. Polderman, 2009) and NMDA responsible for apoptosis (Mueller-Burke et al., 2008). In a number of animal models TH has also been shown to reduce free radical production, improve delayed hypoperfusion (Karibe et al., 1994) and be involved in neuronal anti-inflammatory effects (Ceulemans et al., 2010). However, animal models have limitations when applied to humans. These include lack of co-morbidities, controlled ischaemic insults and different neuronal development patterns. Therefore, demonstration of efficacy and evaluation of dose requirement in human clinical studies is required.

There is a 50 to 65 percent reduction in metabolic rate with MTH, with an equivalent decrease in oxygen consumption and carbon dioxide reduction. There is also an increase in fat metabolism with an associated increase in free fatty acids, glycerol ketones and lactate. This is unlikely to cause a significant metabolic acidosis. Hypothermia also decreases insulin production, which can result in hyperglycaemia requiring the administration of intravenous insulin to maintain glycaemic control (K. H. Polderman, 2009).

2.5.4 Dose of therapeutic hypothermia / targeted temperature management

There remain considerable knowledge gaps regarding the dose of TH or TTM in clinical practice. Although the typical classification of TTM consists of three phases: induction, maintenance and rewarming, there is also a crucial fourth phase to consider, which is fever prevention or maintaining normothermia. This phase is often overlooked in the literature, but it is equally important to maintain the desired temperature range to avoid any potential complications associated with temperature fluctuations.

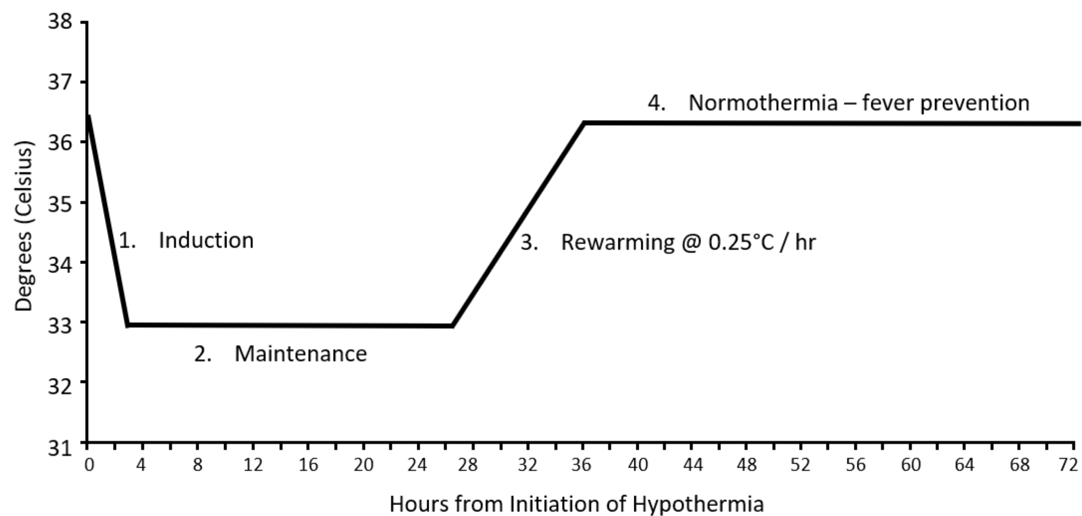


Figure 1: Phases of Therapeutic Hypothermia (Adapted from Scirica B, 2013)

The induction phase refers to the time cooling is initiated, and the time taken to reach target temperature. The optimal therapeutic window when TTM is initiated, remains contentious, although beneficial effects have been suggested when commenced less than six hours after the hypoxic ischaemic insult or ROSC (Castren et al., 2010; Mooney et al., 2011; Nagao et al., 2010; Sendelbach et al., 2012; Uribarri et al., 2015; Wolff et al., 2009). This has also been demonstrated in animal studies (Calderon et al., 2014; Eady et al., 2012; Janata et al., 2008; Perman et al., 2015; Yu et al., 2015). There is also further evidence to suggest that with a delay in implementing TTM, the beneficial effects of hypothermia are negated (Danzl & Pozos, 1994; Hossmann, 1998; Kuboyama et al., 1993; Nozari et al., 2006; Sterz et al., 2006; Takata et al., 2005). However, others have observed (Benz-Woerner et al., 2012; Lin et al., 2014) that in patients who have suffered a more severe cerebral injury may lose the ability to conserve their own body heat and reach target temperature more quickly, this appears to correlate with an unfavourable patient outcome (Haugk et al., 2011). There are notable potential side effects of TTM during the induction phase, which cause physiological changes to the circulatory and respiratory systems, as well as effects on coagulation and medication metabolism. Consequently, this causes hypotension, electrolyte disturbances, hyperglycaemia and changes to the effects of medication (Polderman, 2004; Polderman et al., 2001). To mitigate these risks, a more rapid induction phase is recommended, therefore reducing the duration of the induction phase, before reaching the stability of the maintenance phase (K. H. Polderman, 2009).

A further significant side effect, which occurs during the induction phase, is shivering. Whether accidental or intentional, shivering is the body's natural defence to hypothermia, which is to correct the homeostatic disturbance. The bodies shivering response is to increase heat production, however this can lead to a 40 to 100 percent increase in oxygen consumption (Frank et al., 1995; Matsukawa et al., 1995). Shivering is therefore an unwanted effect of TTM and needs to be aggressively managed with the administration of medications such as sedatives, analgesia and or paralysing agents. Conversely, when the core temperature is reduced to 32° Celsius there is a 50 to 65 percent reduction in oxygen and carbon dioxide production (K. H. Polderman, 2009).

The induction phase of TTM is therefore considered to be very labour-intensive for the ICU team. Having to quickly respond to changes in the patients cardiovascular and respiratory dynamics, often requiring the replacement of electrolytes, administration of fluids and medications, as well as ensuring the patient is appropriately sedated and mechanical ventilation is manipulated to prevent hyperventilation.

The maintenance phase is considered to be the stable phase of TTM, which commences when the patient reaches the desired target temperature. During this phase, the goal is to maintain a constant temperature within the desired range for a specified duration. The duration of hypothermia and stability of controlling the core temperature are the key elements of the maintenance phase. The maintenance phase is less complicated than the induction phase and carries a lower risk of electrolyte disturbances, fluid loss and requires fewer changes to be made to ventilation settings.

The desired temperature target for the maintenance phase remains uncertain. However, current international guidelines (Australian and New Zealand Committee on Resuscitation, 2016b; Donnino et al., 2015; Nolan et al., 2020; Soar et al., 2015) informed by two previous randomised control trials (HACA, 2002; N Nielsen et al., 2013), a constant temperature between 32° Celsius and 36° Celsius is recommended. However, a recent RCT by Lascarrou et al. (2019) suggested a target temperature of 33° Celsius for 24 hours led to a higher percentage of patients surviving with a favourable neurological outcome compared with targeted normothermia at 37° Celsius (Lascarrou et al., 2019).

The rewarming phase of TTM is the process of gradually increasing the patient's body temperature back to the normothermic baseline above 36.5° Celsius after a minimum of 24 hours of TTM. The recommended rate for rewarming ranges from 0.1 to 0.4° Celsius per

hour, therefore it would typically take 14 hours to reach normothermia if the patient was rewarmed at a rate of 0.25° Celsius per hour to reach 36.5° Celsius if the therapeutic temperature was 33° Celsius. The rate of rewarming is controlled to avoid rapid temperature changes that could lead to complications such as shivering, hypotension, or electrolyte imbalances. More importantly, rapid rewarming has been reported to reverse the neuroprotective effect of the hypothermic treatment or possibly even exacerbate ischemic-induced neurological injury (Hickey et al., 2003; Schmutzhard et al., 2012; Zhu et al., 2016) .

The final phase of TTM is preventing fever or maintaining normothermia, with an upper target temperature limit of 37.7° Celsius for 72 hours (Nolan et al., 2005; Soar et al., 2015). Similarly, to the benefits associated with hypothermia, fever prevention aims to attenuate the deleterious effects of hypoxia and reperfusion injury following ROSC (Granfeldt et al., 2021; Nolan et al., 2022). The most common reasons for a patient developing a fever following cardiac arrest include infection, or in response to injury or inflammation. As with the other three phases of TTM, fever prevention is most commonly achieved using either an intravascular or surface cooling device.

2.5.5 Delivery methods of therapeutic hypothermia

There are effectively two delivery methods of TH that can be categorised into either conventional or active methods. Conventional methods are typically described as including intravenous fluids, cooling pads or exposure (Bayegan et al., 2008; Bernard et al., 2012; Glover et al., 2016; Polderman & Herold, 2009). Whereas active methods are either invasive or non-invasive. Non-invasive cooling devices are described as using cooling blankets, adhesive pads, gel pads, rubber blankets and garments. Other novel approaches include intranasal or oesophageal probes whereas invasive methods include intravascular catheters, peritoneal catheters and extracorporeal circuits.

Conventional methods have been associated with a slower induction time, difficulty in maintaining set temperatures, temperature variations as well as difficulty in achieving controlled re-warming (Polderman & Herold, 2009; Seder et al., 2011; Storm, 2012; Varon & Acosta, 2008). There have also been reports of overcooling and rebound hyperthermia (Hoedemaekers et al., 2007; Shinada et al., 2014). Conventional cooling methods aim to reduce, maintain or increase brain temperature through a combination of conduction, convection, radiation and evaporation.

Standard cooling methods have consisted of rapid or bolus administration of an intravenous solution at 4° Celsius, followed by surface cooling using ice and/or cold packs. However, continuous or repeated administration of intravenous solution may induce volume overload and pulmonary oedema (Kim et al., 2014; Taccone et al., 2011). The timing and amount of ice and cold packs is normally judged by the bedside nurse and guided by the patient's temperature. However, the induction of hypothermia by means of cold-fluid infusion combined with ice-water cooling blankets is considered safe, efficacious and quick.

Fans are considered a simple and inexpensive cooling method but are not capable of inducing hypothermia (Harris et al., 2008). This includes air-circulating cooling blanket devices which are placed under and over the patient and like nasal cannula technology, these devices don't use closed-loop temperature mechanisms or biofeedback from the patient therefore aren't able to automatically adjust in response to the patient's temperature.

The gel-coated external cooling device consists of four water circulating gel coated energy transfer pads, are typically placed on the patient's back, abdomen and both thighs. They are connected to an automatic thermostat controlling the temperature of the circulating water (range 4 to 42° Celsius) based on the patient's rectal or core temperature.

Convective-immersion surface cooling uses ice-water or cold-water (2° Celsius) to rapidly induce hypothermia (Taylor et al., 2008). Howes et al. (2010) conducted a small feasibility study using the ThermoSuit® System in OHCA patients (Howes et al., 2010). The ThermoSuit circulates ice water from a perforated top-sheet across the skin surface at a rapid rate of 14 litres per minute and the authors report a 4.2° Celsius per hour rate of cooling. However, this method of cooling has not been used for maintenance of TH or indeed re-warming.

Convective head-cooling methods which incorporate the upper airways include various nasal or nasopharyngeal devices. Mellergard (1992) used a nasopharyngeal cooling device which was a Foley catheter passed through the patient's nostril where the balloon was inflated with saline and pulled back behind the choane nasi (Mellergård, 1992). Oxygen flowed through the catheter at 5 to 10 litres per minute which passed through a copper coil that was submerged in iced water. This method of cooling was not considered particularly effective as the balloon of the catheter was not positioned within the nasal cavity therefore not optimising the capacity for heat loss. Because the catheter is passed through the nose this method would not be appropriate for patients with a head injury.

Other similar methods of nasal cooling devices have been attempted including a method by Dohi and colleagues who circulated chilled air (24° Celsius) at 8 to 12 litres per minute through one nostril whilst occluding the other nostril to prevent air leaking, however they reported incidents of nasal erosion (Dohi et al., 2006). Two further studies used high flow air, through adapted nasal cannula (Andrews et al., 2005). In the second study by Harris et al. (2007), they incorporated nitric oxide to promote mucosal vasodilation and used lead weights on each side of the nose to facilitate intracranial drainage (Harris et al., 2007). However, its use would be prohibitive in patients with base of skull fractures or the possibility of facial fractures.

The Esophageal Heat Transfer Device (EHTD) is a silicone orogastric tube with three lumens. Two lumens are used for circulating water while the third lumen is available for orogastric suctioning. The EHTD is inserted 35 centimetres into the oesophagus and water which is regulated by an external heat exchanger. The water can be circulated up to 2.6 litres per minute through the closed-circuit inflow and outflow lumens. The circulating water temperature is dependent on the type of external heat exchanger but a low set temperature of 4° Celsius is possible. The position of the EHTD in the oesophagus means its proximity to the aorta, carotids, vena cava and pulmonary veins it uses heat conduction methods.

Rhinochill® is a portable, battery-powered nasal cooling device that nebulises perfluorohexane with oxygen. It is delivered through bilateral nasal cannula which are inserted into the nasal cavity, where the inert perfluorohexane evaporates promoting heat loss through convection. This is primarily intended for the induction phase of TTM and due to its portability is useful when transporting patients either pre-hospital or between in-hospital between departments. There are three pre-hospital studies and one hospital study that have examined the efficacy of utilising Rhinochill® for the induction phase of TTM in OHCA patients (Grave et al., 2016; Islam, Hampton-Till, Watson, et al., 2015; Lyon et al., 2014; Nordberg et al., 2013; Poli et al., 2014). However, perfluorohexane is expensive and because of its packaging requires regular canister changes, therefore is considered labour intensive. Rhinochill®, like other nasal devices is contraindicated in patients with a base of skull injury, possible nasal or orbital fractures or patients with an unprotected airway.

There are limited studies that have explored the use of nasal and pharyngeal cooling, which use liquid instead of gas. In a small non-randomised study conducted by Covaciu (2010) is the QuickCool™ device which comprises of a portable pump and balloon catheter which are inserted bilaterally into the nostrils and perfused with cold saline (Covaciu, 2010). There is currently one pharyngeal cooling device which has been trialled in humans (Takeda et al., 2012). This device uses a pharyngeal cooling cuff which is inserted into the pharynx after the

patient has been intubated. Cold saline (5° Celsius) is circulated under pressure (50 cmH_2O) at 500 millilitres per minute. The pharyngeal cooling cuff is thought to facilitate cooling of the carotids due to its position near the pharynx. As with other cooling devices that do not use closed-loop temperature mechanisms, temperature cannot be regulated or adjusted, similarly to the Rhinochill® device. Oesophageal, intranasal and pharyngeal devices are all contraindicated in patients with a head injury.

RapidCool® is a cap device, using thermal convection, which directs jets of cold water (1 - 4° Celsius) directly on to the scalp (Wandaller et al., 2009). Whereas there are various other designs of head-cooling devices that use a combination of water or water and alcohol and air designs, however this appears limited to experimental and clinical trials (Ugriumov et al., 1975). There have been other convective head cooling devices which is in the pilot phase of its development, is a nylon fabric hood and collar that has cold air (14.5° Celsius) flowing through an inner layer (Harris et al., 2008). The Frigicap ® which is a helmet device contains a solution of aqueous glycerol, placed around the head and neck. Prior to placing the helmet on the patient, it is kept in the refrigerator at -4° Celsius. The scalp is protected with a surgical paper cap and the material of the helmet (Hachimi-Idrissi et al., 2001). Once the cap has been placed on the patient it needs to be changed frequently as the aqueous glycerol solution warms.

There are numerous surface cooling devices, which cover the head and blankets, suits or wraps that cover the body, all functioning principally in the same way by active conduction. Surface cooling devices use water or a liquid passing through a cooling heat exchanger or thermostat bath, connected to an automated temperature control module which receives feedback from a temperature probe connected to the patient. The water/fluid circulates through a 'fabric' made of urethane laminated nylon or a thin, soft plastic which covers the head and body. There are essentially four surface cooling devices commercially available and used which include CritiCool™, Blanketrol® III, ArcticSun™ and Stryker's Altrix®. All these devices are pressurised and all have adjustable temperature ranges, ranging from 4 to 42° Celsius (Harris et al., 2009; Miller, 2009; Wang et al., 2004).

Surface cooling devices offer several benefits in terms of delivering TTM. The main advantage of these devices is they are relatively simple to apply and initiate therapy. All of these devices use a close-loop mechanism, which allows the user to set a target temperature and the cooling device will adjust the water or fluid temperature using the feedback from the patient's core temperature. This close-loop or feedback mechanism helps maintain a relatively static temperature. As surface cooling devices offer a non-invasive way of inducing TH, this

eliminates the risks associated with invasive methods, such as bleeding and infection at the vascular access site.

The disadvantages of using surface cooling devices include skin burns, skin irritation (Varon et al., 2008), as well as shivering and the inability to access the patient to carry out routine care. There can also be delays in initiating surface cooling due to the impractical nature of applying blankets, suits or wraps outside of the intensive care setting and all devices rely on a power supply therefore impractical when having to transfer the patient to the cardiac catheter lab or Computed Tomography (CT) scan. The induction phase of TTM using surface cooling devices varies between the different manufacturers, with time to reach target temperature ranging from two to eight hours. During the maintenance phase of TTM it can also be challenging to keep the patient's body temperature at the desired target temperature if the patient is not appropriately sedated. Therefore, the use of sedative and muscle relaxants is imperative (Jain et al., 2018). With thermoreceptors located in the dermis, the direct application of blankets, suits or wraps to the skin, which cool to 4° Celsius during the induction phase or in response to a temperature fluctuation during the maintenance phase, will inevitably cause the patient discomfort and shivering without adequate use of sedation and muscle relaxants (Mayer et al., 2004; Vaity et al., 2015).

Peritoneal cooling has been trialled in a safety and feasibility study (Waard et al., 2013). This method was achieved by using lactated Ringer's irrigation solution, as a continuous lavage of the peritoneal cavity, which is infused and removed through a multiple lumen catheter. This procedure is not appropriate for patients with a history of abdominal surgery, peritonitis or currently undergoing peritoneal dialysis. Patients were also excluded if they had a known history of receiving thrombolytic medication, although patient's anticoagulated for STEMI were not excluded. Using the Velomedix® system the investigators reported a median cooling rate of 4.1° Celsius per hour with a 0.45° Celsius temperature variation during the maintenance phase and controlled re-warming. This study demonstrated a quick induction phase of TTM; however, the limitations of peritoneal cooling include the length of time taken to insert the catheter and initiate cooling as well as the exclusion criteria described.

Two Japanese studies describe the use of extracorporeal cooling methods, specifically for TTM. Nago et al. (2010) describe using cardiopulmonary bypass (Extra Corporeal Membrane Oxygenator (ECMO)) for 171 patients in refractory cardiac arrest to enable coronary revascularisation and early induction of hypothermia (Nagao et al., 2010). Whereas Soga et al. (2012) describe using an extracorporeal cooling device (KTEK-3 ®) as a TTM delivery option

(Soga et al., 2012), however the focus of this study was not on comparing cooling delivery devices but instead the neurological benefit of TH. There have been other experimental studies which have trialled modified haemodiafiltration circuits normally used for renal replacement therapy. Using the return line of the circuit, which normally passes over a heat exchanger to warm the blood before returning to the patient when providing renal replacement therapy, instead is replaced with a coil that is submerged in a water-bath to cool the blood before returning to the patient (Hayashi et al., 2004). The limitation of using ECMO or any extracorporeal device whether specifically intended for cooling, is the risk of bleeding, haemorrhage, vascular injury or infection. More importantly, extracorporeal devices require highly skilled healthcare professionals to manage the extracorporeal circuit.

Endovascular cooling or more commonly referred to as Intravascular Temperature Management (IVTM), requires the insertion of a catheter into a large vein. The central venous catheter has multiple balloons on its external surface therefore providing a large surface area, which is in direct contact with the patient's blood, allowing conduction and convection heat exchange to occur. Saline circulates through the catheter which is attached to tubing that returns to a central console which has an automatic temperature control device that adjusts the temperature of the circulating saline (range 4 to 42° Celsius) based on the feedback from the patient's core temperature. The intravascular cooling device is considered the most reliable in keeping the patients within a mean target temperature range due to the direct heat-exchange between catheter and blood, resulting in a rapid transfer of cold blood circulating through the body (Bartlett et al., 2020).

The other benefit of IVTM, unlike other cooling methods is that it can been used in awake patients (De Georgia et al., 2004; Simon R. Dixon et al., 2002; Erlinge et al., 2014; Gotberg et al., 2010; Islam, Hampton-Till, MohdNazri, et al., 2015; Lyden et al., 2014; Noc et al., 2017) using a combination of counter-shivering strategies, pharmacological interventions and a surface air-warming blanket. By preventing shivering, the patient is more comfortable and expend less energy, therefore decreasing oxygen demand (N Badjatia et al., 2008). Another unwanted consequence of shivering is that it causes involuntary muscle contractions as well as increasing metabolic activity, generating heat production therefore resistance to therapeutic cooling and inability to maintain the desired set target temperature.

TTM is considered a medical intervention which used to lower the body's core temperature, which is administered through either conventional or active methods. Conventional techniques, such as the use of intravenous fluids, cooling pads and exposure, offer challenges

with slower induction times, inconsistent temperature maintenance and difficulties in achieving controlled re-warming. Moreover, they can sometimes result in overcooling and subsequent rebound hyperthermia. On the other hand, active methods can be categorised as invasive or non-invasive. Non-invasive methods encompass tools such as cooling blankets, adhesive pads and gel-coated devices, while invasive techniques involve the use of intravascular catheters and extracorporeal circuits. While fans are a cost-effective option, their efficacy in inducing hypothermia is limited. Other methods, like gel-coated external cooling devices and convective-immersion surface cooling, have shown potential, but their practical application varies. Nasal and pharyngeal cooling techniques have limited application in the OHCA setting and cannot be used in patients with head injuries.

The IVTM catheter facilitates direct heat-exchange between the catheter and the blood, leading to a rapid transfer of cold blood circulating throughout the body. IVTM is also deemed the most reliable in consistently maintaining the desired temperature range. One of its significant advantages is its potential use in awake patients. By employing counter-shivering strategies, pharmacological interventions and surface air-warming blankets, IVTM is the only method of TTM that can be delivered to awake patients. This approach also minimises the risk of resistance to therapeutic cooling and ensures the maintenance of the set target temperature. However, there exists an evidence gap concerning the use of IVTM in waking unconscious patients following cardiac arrest. While IVTM has shown promise in various settings, such as stoke and myocardial infarction, its efficacy and safety in the context of post-cardiac arrest patients who are regaining consciousness has not been researched. For a comprehensive comparison of the various TTM delivery methods (refer Table 1).

Table 1 Comparison of TTM delivery methods

	Cost			Skill required for insertion			Skill required for care			Phases of TTM										
Methods	Low	Medium	High	Basic	Intermediate	Expert	Basic	Intermediate	Expert	Induction	Maintenance	Rewarming	Fever Prevention	Transportable	Invasive	Access to patient	Auto-feedback	Workload	Precision	Possible complications not related to actual TTM
Conventional Methods																				
Ice packs	✓			✓			✓			✓	✓			✓		✓		H	P	Skin lesions, burns, discomfort, shivering and temperature fluctuations
Intravenous Cold Saline	✓			✓			✓			✓				✓		✓		H	P	Fluid overload, pulmonary oedema, electrolyte disturbances
Trans Nasal Cooling																				
Rhinochill ® Intranasal			✓		✓			✓		✓				✓		✓		H	P	White nose, periorbital emphysema
Daiken Medical – pharyngeal cooling cuff		✓				✓		✓		✓				✓		✓		H	P	Mild to moderate rhinorrhoea, headache
Trans Oesophageal Cooling																				
MediTherm Hyper/Hypothermia System ®		✓				✓			✓	✓	✓	✓	✓	✓	✓	✓		H	P	Ulcerative oesophagitis, mucosal tears, perforation, and bleeding
Blanketrol Hyper/Hypothermia System ®		✓				✓			✓	✓	✓	✓	✓	✓	✓	✓		H	P	Ulcerative oesophagitis, mucosal tears, perforation, and bleeding
Surface Coiling																				
MTRE – CritiCool ™ Surface cooling			✓		✓				✓	✓	✓	✓	✓				✓	L	G	Skin damage, burns or irritation, shivering
Gentherm – Blanketrol ® Surface cooling			✓		✓				✓	✓	✓	✓	✓				✓	L	G	Skin damage, burns or irritation, shivering
Medivance – ArticSun ™ Surface cooling			✓		✓				✓	✓	✓	✓	✓				✓	L	G	Skin damage, burns or irritation, shivering
Stryker – Altrix ® - Surface cooling			✓		✓				✓	✓	✓	✓	✓				✓	L	G	Skin damage, burns or irritation, shivering
Phillips – InnerCool STX ® Surface pads		✓					✓			✓	✓							H	P	Discomfort, skin irritation, skin abrasions, shivering, temperature fluctuations
BD – ArcticGel ™ Hydrogel surface pads		✓					✓			✓	✓							H	P	Discomfort, skin irritation, skin abrasions, shivering, temperature fluctuations
EMCOOLS – HypoCarbon ® surface pads		✓					✓			✓	✓							H	P	Discomfort, skin irritation, skin abrasions, shivering, temperature fluctuations
Endovascular																				
Zoll – Thermoguard XP ®			✓			✓			✓	✓	✓	✓	✓		✓	✓	✓	✓	E	Bleeding and infection at vascular access site
Extracorporeal																				
Getringe – Cardiohelp ECMO			✓			✓			✓	✓	✓	✓	✓	✓	✓	✓	✓	H	E	Haemorrhage, infection, vascular injury at cannulation site. Haemolysis & coagulopathy
Medtronic – Bio Console ®			✓			✓			✓	✓	✓	✓	✓	✓	✓	✓	✓	H	E	Haemorrhage, infection, vascular injury at cannulation site. Haemolysis & coagulopathy

Abbreviations: **H** = High workload L= Low workload **P** = Poor **G** = Good **E** = Excellent

2.5.6 Prevention of hyperthermia

According to the ILCOR guidelines on post resuscitation care, which recommend active fever prevention in OHCA patients who are either sedated or remain comatose for 72 hours (Soar et al., 2021). The original evidence which supported fever prevention beyond the first 12 to 24 hours was limited and derived primarily from animal studies and observational data that showed increased morbidity and mortality associated with fever during the post resuscitation period (Coimbra et al., 1996). This is primarily based on findings from two historical observational studies (Bro-Jeppesen et al., 2013; Zeiner et al., 2001) that showed an association between post cardiac arrest hyperthermia and poor outcome, as well as the TTM-1 and TTM-2 trials, which included fever prevention in both the intervention and control groups for 72 hours, as defined in both trial protocols (Dankiewicz et al., 2021; N. Nielsen et al., 2013). Whereas Kirkegaard et al. (2017) investigated the duration of temperature control, which showed no difference in patient outcomes between those receiving TTM for 24 hours versus 48 hours (Kirkegaard et al., 2017). However, a collaboration between the authors of the current ERC and European Society of Intensive Care Medicine (ESICM) recently published guidelines on temperature control after cardiac arrest in adults, were in favour of continuing with fever prevention strategies for 72 hours (Sandroni, Nolan, et al., 2022b). Acknowledging there is a lack of evidence to support such a stance, with no clinical trials comparing normothermia or fever prevention with no temperature control. There was, however, a meta-analysis performed by Vargas et al. (2015) whose findings suggest an association between patients treated with TTM having a good neurologic outcome compared to those who didn't receive TTM (Vargas et al., 2015).

It is understood that hyperthermia can be a physiological adaptive response to infection, commonly due to pulmonary aspiration after cardiac arrest, however there are other factors which may contribute to its development. These include, a response to cellular injury, activation of inflammatory cascades (Saper & Breder, 1994), or injury to the Central Nervous System (CNS), particularly the hypothalamus and focal centres in the pons, is also known to increase CNS temperature and may cause hyperthermia (Polderman & Herold, 2009). Additionally, hyperthermia can be triggered by various conditions, such as seizures, acute myocardial infarctions, venous thromboembolisms and endogenous pyrogens. Furthermore, patients with pre-arrest comorbidities, such as recent respiratory insufficiency, or coexisting sepsis may also increase the risk of developing hyperthermia following cardiac arrest (Polderman & Herold, 2009).

Hyperthermia, is relatively common in patients after cardiac arrest (Berg et al., 2013). It has been associated with poor patient outcomes, as it can worsen neurological injury (Gebhardt et al., 2013; Grossestreuer et al., 2017; Zeiner et al., 2001). Inflammatory responses triggered by hyperthermia, such as increased proinflammatory cytokines and neutrophil accumulation, are also associated with poor outcomes (Takino & Okada, 1991). Fever, specifically in patients with a neurological injury, poses a significant concern due to its potential to intensify neuronal excitotoxicity and acute neurological damage. It can increase the release of neurotransmitters, leading to accelerated production of free radicals and heightened neuronal sensitivity to excitotoxic injury (Badjatia, 2009). Furthermore, prolonged high temperatures exceeding 40° Celsius can have detrimental effects on the central nervous system and compromise the integrity of the blood-brain barrier (Diringer et al., 2004), which can result in cardiovascular, metabolic and haemodynamic instability. Therefore, it is essential to mitigate the adverse consequences of hyperthermia in OHCA survivors for the first 72 hours, incorporating strategies such as continuous core body temperature monitoring, utilisation of TTM, adequate sedation and use of muscle relaxants, as well as monitoring for early signs of infection and employing counter-shivering measures.

Temperature monitoring plays a crucial role in the early detection of hyperthermia during all phases of TTM delivery. Continuous temperature monitoring enables the healthcare professional to closely observe changes in body temperature, allowing for early detection and prompt intervention in the event of hyperthermia. There are various methods of recording temperature in the unconscious OHCA patient being treated with TTM, however both the endovascular IVTM device and the majority of surface cooling devices rely on a continuous feedback loop from the patient to enable temperature adjustments to be made to the circulating fluid. The two most common methods of recording temperature are the use of an oesophageal probe which is inserted into the oesophagus and the bladder probe, which is an integrated temperature sensor on the urinary catheter. The limitation of the oesophageal probe is the propensity for it to be displaced if a patient is vomiting and it is not well tolerated in the awake patient. Whereas the integrated temperature probe with the indwelling urinary catheter is less likely to be displaced, is better tolerated and is considered more precise when compared to other temperature measuring devices (Aykanat et al., 2021).

The biofeedback loop technology used with the endovascular and the majority of surface cooling devices used for TTM, will respond to the patient’s temperature by actively adjusting the temperature of the circulating fluid to maintain the patient’s body temperature within the desired therapeutic range. In the event the patient’s body temperature begins to increase, both

types of devices will immediately detect the temperature variation and the TTM device will compare this to the target temperature range set by the healthcare professional. In the event that the patient becomes hyperthermic, the TTM device will activate the cooling mechanism, which will include adjusting the flow rate as well as the temperature of the circulating fluid through the IVTM catheter, located in the femoral vein. With surface cooling, the circulating fluid through the cooling pads or blankets will also be adjusted as well as the flow rates.

2.5.7 Prevention of shivering during TTM

Fever management during TTM, using either the IVTM or surface devices, does provide additional clinical challenges, with shivering being the most common among them (Badjatia, 2009). Shivering is part of the bodies centrally mediated thermoregulatory defence mechanism, which can negatively affect systemic oxygen consumption, brain tissue oxygenation and intracranial pressure (N. Badjatia et al., 2008; Oddo et al., 2010). These metabolic consequences of shivering could potentially negate many of the clinical benefits of TTM. Furthermore, many anti-shivering therapies involve prolonged sedation, which can result in an extended obscuration of neurological examination and potentially lengthen the critical care stay.

During all four phases of TTM, whether using the surface or intravascular devices, both are designed to regulate the patient's temperature between ± 0.1° Celsius of the target temperature set by the clinician. During the induction and maintenance phases of TTM the device water temperature can lower to 4° Celsius to maximise conductive heat loss. Importantly, this may also occur during the fever prevention phase, in response to an increase in the patient's intrinsic temperature, whatever the cause. However, the body's natural reaction to cold is shivering—a physiological response aimed at raising the body temperature by increasing heat production. While shivering is typically beneficial, it poses challenges during TTM by elevating the metabolic demand, therefore counteracting the cooling process and potentially cause the patient discomfort. Therefore, to prevent shivering is a key element of effective TTM, which requires care to mitigate potential side effects or risks linked to the strategies utilised.

To inhibit shivering during TTM, there are a range of strategies available to healthcare professionals which can be divided into pharmacological and nonpharmacological. The use of pharmacological interventions often used, include medications such as sedatives like propofol and benzodiazepines such as midazolam (Polderman & Herold, 2009) and opioids like morphine, fentanyl, alfentanil and meperidine (Ikeda et al., 1997; Kurz et al., 1997), for both their analgesic and sedative effects. Non-depolarising neuromuscular blockers such as

rocuronium or atricurium are paralytics or muscle relaxants, typically used for endotracheal intubation but are also used for uncontrolled or severe shivering (Jain et al., 2018; Jain et al., 2023). Other pharmacological approaches used during TTM include the use of magnesium sulfate, which reduces smooth muscle tone and subsequent vasodilation (Badjatia, Strongilis, et al., 2009; Choi et al., 2011; Weant et al., 2010), as well as buspirone, which is a serotonin (5-HT1A) receptor agonist (Ikeda et al., 1997) and used in combination with low-dose meperidine, has a 2.3° Celsius reduction on the shiver threshold. The final pharmacological group is antipyretic agents, which include acetaminophen, aspirin and Non-Steroidal Anti-Inflammatory (NSAID). They are commonly used to reduce inflammation, relieve pain and lower fever by inhibiting the production of prostaglandin synthesis in the brain, increasing the hypothalamic set point (Jain et al., 2018). Determining the correct pharmacological approach is will depend on patient characteristics, the intensity and frequency of shivering, the intended target temperature as well as patient comorbidities. However, monitoring capabilities, both in terms of physiological observations but also the potential side effects of medications, relies on the experience and expertise of the clinicians and healthcare professionals responsible for the care of the patient being treated with TTM (see Table 2).

Table 2: Pharmacological anti-shivering strategies

Medication	When to administer	BSAS Score	Dose	Goal of Intervention	Comorbidity Considerations
Rocuronium	Severe shivering	4	0.3 – 0.9 mg/kg	NMB for uncontrolled shivering	No specific rate adjustments
Atracurium	Severe shivering	4	1-2 mcg/kg/min	NMB for uncontrolled shivering	No specific rate adjustments
Propofol	Moderate to severe shivering	3-4	25-75 mcg/kg/min	Deep sedation	Reduce dose in patients with impaired liver function
Midazolam	Moderate to severe shivering	3-4	0.03-0.2 mg/kg IV loading dose 0.02-0.1 mg/kg/hr infusion	Moderate to deep sedation	Reduce dose in elderly or patients with respiratory or hepatic impairment
Fentanyl	Moderate to severe shivering	3-4	25-100 mcg loading dose 25-100 mcg/hr infusion	Mild sedation	Reduce dose in elderly or patients with renal or hepatic impairment
Alfentanil	Moderate to severe shivering	3-4	10-50 mcg/kg IV loading dose 0.5-1 mcg/kg/min infusion	Mild sedation	Reduce dose in elderly or patients with renal or hepatic impairment
Magnesium	Moderate to severe shivering	3-4	2-4 g IV over 15-30 minutes 0.5-1 g/hr infusion	Prevention of shivering	Reduce dose in elderly or patients with renal impairment
Morphine	Moderate shivering	2-3	2-10 mg/hr	Moderate sedation	Reduce dose in elderly or patients with respiratory or hepatic impairment
Meperidine	Moderate shivering	2-3	25-100 mg IV infusion	Moderate sedation	Reduce dose in elderly or patients with renal or hepatic impairment
Buspirone	Mild to moderate shivering	1-2	30 mg PO/PR/NGT Q8	Prevention of shivering	Use with caution in patients with renal or hepatic impairment
Acetaminophen	No shivering	0	650-1000 mg PO/PR/NGT Q4-6	Prevention of shivering	Use with caution in patients with renal or hepatic impairment

Abbreviations: **BSAS Score** = Bedside Shivering Assessment Tool; **Q4-6** = four to six hours; **NMB** = neuromuscular blockade; **mcg** = micrograms; **min** = minute; **Q8** = eight hours; **mg** = milligrams; **hr** = hour; **kg** = kilograms; **PO** = per oral; **g** = grams; **PR** = per rectal; **IV** = intravenous; **NG** = nasogastric

Note: All pharmacological interventions in the context of a TTM counter-shivering strategy would be prescribed by an Anaesthetist or Critical Care Physician

2.5.8 Prevention of shivering using non-pharmacological methods

The nonpharmacological interventions used as counter-shivering strategies are limited to either increasing the core body temperature or cutaneous warming. Increasing the core body temperature using the IVTM device would be considered counterintuitive as it would negate the intended benefit of TTM. Therefore, to maintain a therapeutic target core temperature and to actively treat shivering using nonpharmacological interventions, the use of heated forced-air blanket (Bair Hugger®) or warm blankets placed over the surface of the patient, effectively deceives the body's cutaneous thermoreceptors into suppressing the urge to shiver while the core body temperature is reduced using the IVTM device. This method has been successfully trialled in conscious patients who have suffered Cerebral Vascular Accident (CVA), Acute Myocardial Infarction (AMI) and cardiac arrest (De Georgia et al., 2004; Simon R. Dixon et al., 2002; Erlinge et al., 2014; Gotberg et al., 2010; Islam, Hampton-Till, MohdNazri, et al., 2015; Lyden et al., 2014; Noc et al., 2017). Furthermore, a prospective study conducted by Badjatia et al. (2009) demonstrated that the addition of a forced-air warming blanket, with a maximum temperature of 43°C, effectively reduced the metabolic consequences of shivering in neurologically impaired patients (Badjatia, Strongilis, et al., 2009). While the nonpharmacological interventions, particularly the use of heated forced-air blankets as a counter shivering strategy during the delivery of TTM, in conscious patients suffering from CVA, AMI and cardiac arrest, there remains an evidence gap when it comes to its possible application in unconscious survivors of OHCA. Noting the significant difference between the treatment duration of TTM in these studies (De Georgia et al., 2004; Simon R. Dixon et al., 2002; Erlinge et al., 2014; Gotberg et al., 2010; Islam, Hampton-Till, MohdNazri, et al., 2015; Lyden et al., 2014; Noc et al., 2017) compared to the 72 hours for unconscious OHCA survivors, as well as the physiological differences between conscious and unconscious patients, especially in the context of OHCA, which may lead to a varied response. To determine whether the effectiveness of the counter shivering observed in conscious patients, is equally as effective in unconscious patients.

In summary, the current guidelines by the ERC and the ESICM advocate for a 72-hour fever prevention in OHCA patients who remain sedated or in a comatose state. This recommendation is based on a limited body of evidence. The rationale behind this is the understanding that hyperthermia following a cardiac arrest can amplify neurological injuries. Such injuries, if not managed promptly and effectively, can lead to severe long-term complications or even mortality. As a result, the ERC and ESICM has adopted strategies such as continuous temperature monitoring, TTM, sedation, the use of muscle relaxants and counter-shivering measures. However, the use of sedatives, opioids and other agents, while

beneficial in ensuring patient comfort and enhancing the tolerance to TTM, inadvertently impedes the ability to conduct a thorough neurological assessment. The inability to evaluate neurological function in this period means that early signs of recovery or improvement in patients who might have a favourable neurological prognosis go undetected.

The prevailing focus of the ERC and ESICM guidelines seems to be on the cohort of OHCA patients who are anticipated to have a poor neurological outcome. This approach, while cautious, might inadvertently disadvantage a subset of patients who could potentially have a positive neurological trajectory. The current guidelines do not sufficiently address the possibility of waking these patients early for a neurological assessment while continuing with TTM and fever prevention measures.

This presents a significant evidence gap. If early neurological assessments could be performed without compromising the benefits of TTM and fever prevention, this may enable other treatment strategies. Such strategies could optimise patient outcomes by allowing for early interventions in patients showing promising signs of recovery. It is imperative to ensure that every patient receives the most appropriate care based on their individual prognosis, rather than a one-size-fits-all approach.

Part 2: Positive neurological prognostication after cardiac arrest

2.6 The impact of cardiac arrest on neurological functioning

Neurological prognostication after cardiac arrest plays a fundamental role in determining the long-term outcomes and guiding medical decision making for patients who have experienced an OHCA. Cardiac arrest is characterised by the sudden cessation of heart function, which leads to a severe lack of blood flow to the brain, resulting in neurological injury. Assessing the prognosis of neurological recovery in these patients is a complex and multidimensional process that involves integrating various clinical assessments, imaging and neurophysiological findings. Accurate prognostication allows healthcare professionals to provide timely and appropriate care, optimise resource allocation and support the patient's family in making informed decisions regarding treatment and potential withdrawal of life-sustaining treatment. In this context, understanding the principles and challenges of neurological prognostication after cardiac arrest are essential for healthcare professionals involved in the management of these critically ill patients.

The global survival rate from OHCA, until hospital discharge is 8.8 percent (Yan et al., 2020). It is estimated that approximately 50 percent of OHCA survivors suffer from cognitive impairment (Sauvé et al., 1996; Tiainen et al., 2003; van Alem et al., 2004). There is a direct correlation between the severity of cognitive impairment and duration of the cardiac arrest or no-flow time (Esdaille et al., 2020; Polanowska et al., 2014). Cognitive impairment affects short-term memory, immediate and delayed recall as well as attention deficits and executive function disorders are also frequently observed (Jaszke-Psonka et al., 2016). Furthermore, possible progression to dementia, depression, decreased quality of life and social participation are some of the more profound and debilitating forms of cognitive impairment experienced by approximately 30 percent of survivors (Buanes et al., 2015; Cronberg et al., 2009; Polanowska et al., 2014; Sulzgruber et al., 2015; Wachelder et al., 2009).

With poor neurological function associated to Post-Cardiac Arrest Syndrome (PCAS), caused by the body's physiological response to protracted ischemia (Neumar et al., 2008), PCAS is considered to be the most significant cause of post cardiac arrest mortality and morbidity (Laver et al., 2004). Neurological prognostication after cardiac arrest has seen significant advancements over the past decade, influenced by a better understanding of PCAS (Negovsky,

1988; Nolan et al., 2008; Penketh & Nolan, 2023), as well as technological improvements and new insights into patient recovery, which includes neurological prognostication, physical recovery along with the psychological and emotional recovery. It also includes the long-term outcomes for OHCA survivors as well as their families and exactly what is meant by a successful recovery and factors that might influence timing of prognostic decision making. The importance of not just the immediate pre-hospital phase of the patient journey but the importance of the treatment bundle on admission to hospital. A key development is the multimodal approach to neurological prognostication, which integrates clinical examination, electrophysiological tests, biomarkers and imaging to produce a comprehensive and reliable prediction of neurological outcomes. Technological advancements, particularly in Magnetic Resonance Imaging (MRI), such as Diffusion-Weighted MRI (DWI), have also been increasingly used for prognosis after cardiac arrest, providing detailed information about brain injury (Park et al., 2020; Park et al., 2023).

2.7 Neurological prognostication

The adoption of TTM as part of the post-resuscitation care bundle, requires patients to be sedated for tolerance and comfort (N Badjatia et al., 2008) of the TTM treatment, at which time patients are administered sedatives and neuromuscular blocking agents, as a counter-shivering strategy for patients who experience moderate to severe shivering. However, these pharmacological adjuncts interfere with the ability to accurately neurologically prognosticate (Samaniego et al., 2011). Therefore, to ensure the accuracy of the neurological assessment, it is important to wait until the completion of the TTM treatment, when the use of sedatives and muscle relaxants are no longer required, and the residual effects of these medications have dissipated. The current ERC and ESICM guidelines, recommend patients be sedated for 36 hours during the induction and maintenance phase of TTM (Nolan et al., 2021). However, a recent study by Ceric et al. (2023) found that patients being treated with TTM, only 0.7 percent were awake on the first day and 3.3 percent were awake on the second day of therapy. Ceric et al. (2023) found that most patients being treated with TTM had increased titration of sedatives over the initial 48 hours, which led to patients having a significantly longer duration of mechanical ventilation (Ceric et al., 2023).

According to the ERC and ESICM 2021 guidelines on post-resuscitation care (Nolan et al., 2021), supported by evidence derived from a systematic review on prognostication and the 2020 International Liaison Committee on Resuscitation Consensus on Science with Treatment Recommendations (ILCOR CoSTR) (Sandroni et al., 2020; Soar et al., 2020), there are four

key elements that constitute a multimodal approach which should be performed for the purposes of neurological prognostication. The four key elements of the multimodal approach are described in Table 3.

Table 3 Four key elements for neurological prognostication

Key element	Description
Clinical examination	Assessing the patient's motor function in terms of reactions or movements in response to a given stimulus, typically a painful stimulus, assessing the quality, nature and purposefulness of the patient's motor response. The assessment of pupillary and corneal reflexes. The final component of the clinical examination is to determine the presence of myoclonus confirmed on EEG.
Neurophysiology	Performing an EEG to detect suppressed background activity with or without periodic discharges and burst suppression, which would be considered highly malignant and indicative of a poor prognosis. The presence of clear seizures on EEG within the first 72 hours is also associated with a poor prognosis. Perform SSEP bilateral absence of somatosensory evoked cortical N20-potentials are additional indicators of a poor prognosis.
Biomarkers	Serial measurements of NSE can be utilised if there is an upward trend in NSE values >60 micrograms per litre between 24 and 48 hours or 72 hours indicates a poor prognosis for the patient.
Neuroimaging	The presence of generalised brain oedema, characterised by a significant reduction in the grey matter/white matter ratio on brain CT or extensive diffusion restriction on brain MRI, can be indicative of a poor neurological outcome.

The ERC and ESICM 2021 guidelines on post-resuscitation care, cover a wide range of topics with a primary focus on optimising care to improve patient outcomes, however the prognostic indicators are centred on predicting poor neurological outcomes after 72 hours (Nolan et al., 2021).

The 2005 ERC guidelines were essentially the first to emphasise the importance of post-resuscitation care as a critical component in improving survival and neurological outcomes following cardiac arrest (Nolan et al., 2005). These guidelines emphasised a multidisciplinary approach to post-cardiac arrest care, including TTM, haemodynamic optimisation, early coronary reperfusion and neurological prognostication. Furthermore, the guidelines recognised that post-cardiac arrest care extends beyond the immediate resuscitation phase and encompasses the subsequent management and support of patients and how this plays a pivotal role in improving outcomes for cardiac arrest survivors (Nolan et al., 2005). Subsequently, there has been a notable and perhaps disproportionate focus on poor neurological

prognostication for survivors of OHCA, likely due to the ethical and legal implications associated with decision making regarding life sustaining treatment, including withdrawal of care and do-not-resuscitate orders (Dragancea et al., 2015; Elmer et al., 2016; Wilkinson, 2009). Furthermore, to understand whether the likelihood of poor neurological outcome is likely to cause severe cognitive impairment or leave the patient in a Persistent Vegetative State (PVS) can assist with guiding treatment and end-of-life decision making as well as resource allocation (C. W. Callaway et al., 2015; Cronberg et al., 2013; Sandroni et al., 2014). While the accurate prediction of neurological outcomes is undoubtedly crucial for medical decision-making and providing appropriate support to patients and their families, it is equally imperative to shift the emphasis towards early positive prognostication. By adopting a proactive approach that identifies favourable prognostic indicators, that clinicians and healthcare professionals can not only provide timely interventions, but also optimise a quicker recovery for patients, potentially reducing mechanical ventilation time as well as critical care and hospital length of stay.

2.7.1 Extending the four elements of the multimodal approach to include positive prognostic parameters

The 2021 ERC and ESICM guidelines (Nolan et al., 2021) have identified four key elements to assist clinicians with neurological prognostication, however the emphasis of these guidelines is determining patients with a poor prognosis following OHCA. While the four elements are instrumental in predicting poor outcomes, there is an opportunity to consider additional parameters, specifically for the purpose of positive prognostication. These include: (1) neurological assessment to evaluate the patient's level of consciousness, responsiveness to stimuli, motor function, as well as evidence of any seizures; (2) physiological parameters (3) clinical course, to include aetiology of cardiac arrest, the duration of the cardiac arrest or downtime, initial rhythm and whether the patient has been revascularised; (4) comorbidities, including any long term or terminal conditions; and (5) review of diagnostic tests, which would include the neurophysiology, blood tests including specific biomarkers and radiological images. Recognising the potential of these additional parameters not only extends our understanding of patient recovery but emphasises the importance of a holistic approach to prognostication. The intrinsic value of these additional prognostic indicators and how they can complement and enhance the existing guidelines, offering clinicians a more comprehensive toolkit for patient assessment and care planning.

2.7.2 Neurological assessment

There are two, relatively simple neurological assessment tools to evaluate the level of consciousness and neurological function in OHCA patients, the Glasgow Coma Scale (GCS)

(Teasdale & Jennett, 1974) and the Full Outline of UnResponsiveness (FOUR) score (Wijdicks et al., 2005). The GCS is a standardised assessment tool used to evaluate the level of consciousness and neurological function in patients with acute brain injury or altered mental status. It consists of three components: eye opening response, verbal response and motor response. Each component is assigned a score and the sum of these scores provides an overall GCS score ranging from three (indicating deep coma) to 15 (indicating full consciousness). The GCS evaluates the patient's ability to open their eyes in response to stimuli, respond verbally (such as following commands or speaking) and exhibit purposeful movements. However, one limitation of the GCS is that it may not be as accurate or reliable in assessing unconscious patients, especially those who are intubated or have other barriers to verbal communication. The scale allows for an objective and standardised assessment of neurological function, aiding in the initial evaluation, ongoing monitoring and communication among healthcare professionals. The GCS score helps gauge the severity of brain injury, monitor changes over time and guide treatment decisions.

The FOUR score is the other neurological assessment tool, which is designed to provide a more comprehensive evaluation of the level of consciousness and neurological function in patients with impaired consciousness, compared to GCS. It expands upon the GCS by incorporating additional parameters to assess both brainstem and cortical function. The FOUR score assesses eye response for eye-opening and eye movement, motor response for response to noxious stimuli, brainstem reflexes including pupillary responses, ocular movements and corneal reflexes and respiration pattern for spontaneous breathing, abnormal breathing, or apnoea. Each component is assigned a score from 0 to four and the sum of these scores provides an overall FOUR score.

By incorporating brainstem reflexes and respiratory assessment in addition to the traditional GCS parameters, the FOUR score allows for a more detailed and nuanced evaluation of neurological function (Kasprowicz et al., 2016). It provides additional information about brainstem function and respiratory patterns, which can be valuable in determining prognosis and potential for recovery in patients with impaired consciousness. The FOUR score serves as a useful tool in assessing and monitoring the neurological status of patients following cardiac arrest (Wijdicks et al., 2015).

A study by Hifumi et al. (2015) found that the GCS is an independent predictor of good neurologic outcome at 90 days for OHCA patients treated with TTM (Hifumi et al., 2015). However, a limitation of this study is the GCS was taken at the time of arrival of the OHCA

patient to the emergency department, before sedatives and muscle relaxants had been administered, therefore, would not be applicable in patients who had been sedated and intubated in the pre-hospital setting. Schefold et al. (2009) discusses the use of the GCS as a predictor of outcomes in OHCA patients treated with TTM following cessation of sedation discovering that the majority of patients who underwent TTM did not require ongoing sedation after the rewarming process (Schefold et al., 2009). Schefold et al. (2009) revealed that monitoring the GCS starting from the day after TTM had been stopped, proved to be a valuable method for predicting neurological outcomes (Schefold et al., 2009). Furthermore, that over time, the sensitivity and specificity of GCS monitoring increased, indicating its effectiveness in predicting outcomes. The results indicated that a GCS score greater than 4 on the first day following the termination TTM along with a GCS score greater than 6 over the subsequent three days, were associated with favourable neurological outcomes. These outcomes were defined based on Cerebral Performance Category (CPC) 1 and 2 at the time of discharge from the ICU (Schefold et al., 2009). Furthermore, Schefold et al. (2009) study found that among the three components of the GCS, motor responses appeared to be particularly important for prognosis in patients treated with TTM (Schefold et al., 2009).

2.7.3 Physiological assessment

Patients admitted to the ICU following OHCA, present numerous challenges, not just in terms of potential neurological complications, or the need for Advanced Life Support (ALS) interventions, but also haemodynamic instability (Laurent et al., 2002), respiratory compromise (Kilgannon et al., 2010), metabolic disturbances (Kilgannon et al., 2010), as well as multiple-organ dysfunction (Neumar et al., 2008) and often require management of potential complications associated with the resuscitation. Optimising patient outcomes following cardiac arrest necessitates a focus by the healthcare team on ensuring patient homeostasis. Homeostasis refers to the balance and stability of various physiological processes within the body. By actively managing and restoring homeostasis, the healthcare team can enhance patient outcomes in several ways. Ensuring cardiovascular stability, including proper oxygenation and circulation, which improves vital organ function and tissue perfusion (Gaieski et al., 2009; Laurent et al., 2002; Nolan & Cariou, 2015; Sunde et al., 2007; Walters et al., 2011). Achieving respiratory stability ensures adequate oxygenation and removal of carbon dioxide (Kilgannon et al., 2010). Maintaining metabolic homeostasis, such as controlling blood glucose levels and managing acid-base balance, supports cellular function and overall physiological equilibrium (Russo et al., 2018). Renal stability, through adequate fluid balance and management of electrolytes, helps maintain proper renal function and optimise fluid removal (Geri et al., 2015; Grand et al., 2019). By focusing on these aspects of homeostasis, the

healthcare team can create an optimal environment for patient recovery, reducing the risk of complications and enhance overall patient outcomes following OHCA.

OHCA patients are at risk of developing cardiovascular failure or cardiogenic shock which has potentially lethal consequences due to PCAS induced myocardial dysfunction and the accompanying systemic inflammatory response triggered by global ischemia and reperfusion (Laurent et al., 2002). One of the key therapeutic goals for the healthcare team is to identify and treat PCAS induced myocardial dysfunction (Gaieski et al., 2009; Laurent et al., 2002). For patients experiencing hypotension, the initial approach would involve optimising right-heart filling pressures by administering intravenous fluids. Studies have shown that relatively large volumes of fluid can be well-tolerated by OHCA patients to maintain right atrial pressures within the desired range of 8-12 millimetres of mercury (Gaieski et al., 2009; Laurent et al., 2002).

Dysrhythmias, commonly caused by focal cardiac ischemia, can be managed by maintaining normal electrolyte concentrations using standard intravenous electrolyte replacement, antiarrhythmic medications as well as electrical or cardioversion therapies. Inotropic and vasopressor agents would normally be considered if haemodynamic goals are not achieved despite optimised preload or fluid replacement therapy (Ameloot et al., 2017; Jakkula et al., 2018). Global myocardial dysfunction is generally reversible and responsive to inotropes, but the severity and duration of dysfunction may impact survival (Bro-Jeppesen et al., 2014). Vasopressors may be required to address impaired vasoregulation (Bro-Jeppesen et al., 2014). The choice of inotrope or vasopressor is guided by haemodynamic parameters, echocardiographic assessments and indirect indicators of tissue oxygen delivery, such as Central Venous Oxygen Saturation ($ScvO_2$), Mixed Venous Oxygen Saturation (SvO_2), Arterial Oxygen Saturation (SaO_2), as well as lactate, base excess and Capillary Refill Time (CRT) (Deakin et al., 2010; Nolan et al., 2008). Dobutamine and noradrenaline, either alone or in combination, are commonly used in the treatment of cardiovascular dysfunction in the post-cardiac arrest phase (Laurent et al., 2002). However, there is inadequate evidence which evaluates the impact of dobutamine and noradrenaline on patient outcomes for OHCA survivors (Deakin et al., 2010).

Heart rate is considered an important factor associated with outcomes in OHCA patients. However, sinus bradycardia during TTM has been reported to be associated with lower mortality and less severe organ dysfunction (Bro-Jeppesen et al., 2014; Dankiewicz et al., 2021; Thomsen et al., 2016). Furthermore, a lower mean heart rate at 48 and 72 hours after

resuscitation is associated with improved neurological outcomes at 12 months, particularly in patients who were not treated with TTM (Dankiewicz et al., 2021). Hypothermia during TTM can affect heart rate through various mechanisms, which lead to a progressive decrease in heart rate as a result of alterations in cardiac pacemaker cell depolarisation, conduction of myocardial impulses, action potential duration and autonomic nervous system function (Dankiewicz et al., 2021). Therefore, it has been suggested that sinus bradycardia during TTM may serve as a marker of preserved autonomic response and its absence could indicate a more severe PCAS and greater neurological injury (Bro-Jeppesen et al., 2014; Dankiewicz et al., 2021). Although, there is an association between heart rate and prognosis, there has not been a prospective trial that has evaluated strategies to specifically reduce heart rate during post-resuscitation care.

Overall, heart rate, particularly sinus bradycardia during TTM, has been linked to positive patient outcomes for OHCA survivors. However, there remains an evidence gap to better understand the relationship between heart rate, autonomic function and prognosis, as well as to explore potential strategies for heart rate management in post-resuscitation care.

2.7.4 Clinical course

Understanding the clinical course of patients who have experienced an OHCA involves considering several key factors. These include the aetiology of the cardiac arrest, the duration of the arrest or downtime, the initial rhythm observed and whether the patient has undergone revascularisation. Lee et al. (2020) conducted a study investigating the relationship between downtime duration and neurological outcomes in witnessed OHCA patients who received TTM (Lee et al., 2020). Lee et al. (2020) study found that as downtime increased, the probability of favourable neurological outcomes decreased (Lee et al., 2020). However, 19 percent of patients with a downtime exceeding 30 minutes had a favourable neurological outcome. This depended on several factors, including the patient's age, whether the primary rhythm was shockable, whether the patient received CPR from a bystander, whether the cause of the cardiac arrest was cardiac-related, whether the patient underwent a PCI and lastly, whether the downtime was less than 40 minutes. These findings challenge the conventional approach of terminating resuscitation efforts after a specific timeframe. Lee et al. (2020) study highlights the importance of obtaining reliable information about the duration of cardiac arrest to accurately understand its impact on clinical outcomes (Lee et al., 2020). Additionally, factors such as the initial rhythm observed and the implementation of revascularisation strategies through procedures like PCI have also been associated with improved neurological outcomes (Bougouin et al., 2018; Jeong et al., 2017). By considering these various aspects of the clinical

course, healthcare professionals can make informed decisions regarding management strategies for cardiac arrest patients.

Historically, resuscitation efforts in the pre-hospital setting have been terminated after 20-30 minutes of ALS if there was no response to resuscitation efforts, if the cardiac arrest had not been witnessed by either bystander or emergency services personnel (Camp-Rogers et al., 2013). However, the appropriate duration of CPR remains uncertain (Kim et al., 2016). A large observational study conducted by Reynolds et al. (2016) reported similar findings to that of Lee et al. (2020). Reynolds et al. (2020) study indicated that 99 percent of OHCA patients achieving favourable outcomes achieved ROSC within 37 minutes, furthermore, this extended to 41 minutes among those with a witnessed cardiac arrest and 47 minutes for those patients that received bystander CPR (Reynolds et al., 2016). Similarly, a study by Nagao et al. (2016) also recommended continuing prehospital resuscitation efforts for at least 40-45 minutes to maximise survival (Nagao et al., 2016). Thus, highlighting the consistent relationship between downtime and favourable outcomes based on factors such as initial rhythm and bystander CPR.

Besides duration of CPR, age, cardiac aetiology and Coronary Angiography (CAG) ± PCI have also been identified as additional factors associated with favourable neurological outcomes (Nikolaou et al., 2015; Patterson et al., 2018). Revascularisation, specifically through PCI plays a crucial role in the management of OHCA patients (Kajana et al., 2022; Kim et al., 2022). Revascularisation and reestablishing blood flow to the coronary arteries is essential for improving survival and long-term neurological outcomes in individuals who experience cardiac arrest (Barauskas et al., 2018). Early identification of the underlying cause of cardiac arrest, such as acute coronary occlusion, is vital in determining which patients would benefit from revascularisation (Kern et al., 2015). An early study by Spaulding et al. (1997) revealed that approximately 50 percent of OHCA survivors had an occluded coronary vessel (Spaulding et al., 1997). In patients where the post-ROSC electrocardiogram (ECG) suggests STEMI or Left Bundle Branch Block (LBBB), more than 80 percent of patients will have an acute coronary lesion (Nikolaou et al., 2015). Observational studies reviewed by the ILCOR in 2015 supported the recommendation for emergency cardiac catheterisation in patients with ROSC after OHCA and ST-segment elevation on ECG (Donnino et al., 2015). The 2017 European Society of Cardiology guidelines also recommend a PPCI strategy in patients with resuscitated cardiac arrest and ECG findings consistent with ST-segment elevation (Bougouin et al., 2018).

Conversely, CAG and PCI following ROSC in OHCA patients without ST-segment elevation requires careful assessment as coronary occlusion cannot be completely ruled out in these patients (Elfwen et al., 2018). According to Dumas et al. (2016), when determining the need for early CAG, various factors including but not limited to haemodynamic or electrical instability, ongoing myocardial ischemia, medical history, pre-arrest symptoms, initial cardiac rhythm during the arrest, post-return ROSC, ECG pattern, echocardiography findings and comorbidities (Dumas et al., 2016). However, in patients where an ischemic cause is probable, Dumas et al. (2016) suggests adopting a similar approach as in patients presenting with STEMI (Dumas et al., 2016). This is consistent with Kern et al. (2015) findings who suggest that approximately 25 percent of patients who present without ST-segment elevation, were found to have an occluded coronary artery (Kern et al., 2015). Lemkes et al. (2019) study found that patients with a low probability of an ischemic cause may benefit from delaying CAG for a few hours or days, allowing time for initial management in the ICU and early initiation of post-resuscitation care (Lemkes et al., 2019), therefore avoiding unnecessary CAG in patients with the lowest likelihood of an acute coronary lesion. The 2020 European Society of Cardiology guidelines suggest considering delayed angiography for stable OHCA patients without ST-segment elevation, that the emphasis on early identification of patients with irreversible brain injury is crucial to ensure that coronary interventions are performed only when beneficial (Cardiology, 2020). However, without a universally accepted prognostic tool within the first few hours after ROSC, makes it challenging to accurately identify such patients upon hospital admission. Early PCI is recommended for OHCA patients with STEMI, while the decision for early CAG in patients without ST-segment elevation is determined through a comprehensive evaluation of the patient's clinical condition and likelihood of ischemic aetiology.

Understanding the clinical course of cardiac arrest patients involves considering factors like age of the patient, aetiology of cardiac arrest, downtime duration, primary rhythm and revascularisation strategies such as PCI, all of which have emerged as strong predictors for long-term survival of OHCA survivors. Reynolds et al. (2016) and Nagao et al. (2016) demonstrated the intricate relationship between downtime duration and neurological outcomes (Nagao et al., 2016; Reynolds et al., 2016). Both, emphasising that while increased downtime generally correlates with decreased favourable neurological outcomes, there are instances where patients with extended downtimes still exhibit positive results. These outcomes are influenced by a number of factors, from the initial rhythm to bystander CPR. Furthermore, the role of revascularisation, especially through PCI, emerge as pivotal in enhancing survival and neurological outcomes post-cardiac arrest. The significance of early

identification of cardiac arrest causes, such as acute coronary occlusion, cannot be overstated, as it dictates the potential benefit of revascularisation. However, a significant evidence gap remains in early neurological prognostication. The absence of a universally accepted prognostic tool in the immediate hour's post-ROSC presents a challenge in accurately identifying patients who would most benefit from interventions like coronary angiography. This emphasises the imperative for the development of a tool that can bridge this evidence gap, ensuring that interventions are timely, appropriate and most beneficial for OHCA patients.

2.7.5 Comorbidities, long term or terminal conditions

To enhance patient outcomes in post-cardiac arrest care, a comprehensive understanding of illness severity scores and prognostic indicators is crucial. Various scoring tools and prognostic models have been developed to assess illness severity and predict outcomes in cardiac arrest patients. These models consider factors such as comorbidities, the duration of cardiac arrest or downtime, initial rhythm, as well as revascularisation status. By evaluating the strengths and limitations of these scores, healthcare professionals can make informed clinical decisions and develop evidence-based strategies for patient management. However, there is an evidence gap when it comes to early and positive neurological prognostication in cardiac arrest patients. By evaluating the accuracy and reliability of these scores in predicting positive neurological outcomes, will enable more precise prognostic assessments and optimised patient care in the post-cardiac arrest and ICU settings.

Numerous studies have been conducted to examine the effectiveness of various scores and prognostic models in this context. One such model is the Post-Cardiac Arrest Care (PCAC) score (Rittenberger et al., 2011). The PCAC score evaluates neurological and cardiorespiratory parameters in the early stages after ROSC. To gain a more comprehensive perspective, it is important to compare the PCAC score with other established scoring tools. The OHCA score (Adrie et al., 2006), the PROgnostication using LOGistic regression (PROLOGUE) score (Bae et al., 2021) and the Cardiac Arrest Hospital Prognosis (CAHP) score (Maupain et al., 2016), will be considered. Furthermore, Choi et al. in 2018 evaluated the performance of the Acute Physiologic and Chronic Health Evaluation (APACHE) II score, Simplified Acute Physiology Score (SAPS) II, Sequential Organ Failure Assessment (SOFA) score and the OHCA score on patients treated with TTM (Choi et al., 2018), will also be considered. By assessing the strengths and limitations of these different illness severity scores and prognostic indicators in post-cardiac arrest care, healthcare professionals can make informed clinical decisions and facilitate the development of evidence-based strategies for patient management. This

knowledge allows for more accurate prognostication, enabling appropriate allocation of resources and targeted interventions, ultimately leading to improved patient outcomes. The focus will be on their prognostic indicators, impact on clinical decision-making and identifying existing evidence gaps in positive prognostication versus poor prognosis.

The PCAC score is a simple and easily applicable tool for predicting the neurologic outcome in patients with OHCA. It utilises three prehospital variables: the presence of a witness, the initial rhythm and the duration of CPR. Rittenberger et al. (2011) aimed to assess the prognostic value of the PCAC tool in patients with OHCA and its potential for clinical decision making (Rittenberger et al., 2011). This study included 607 patients following cardiac arrest admitted to two different sites, Pittsburgh, Pennsylvania, United States. The results showed that outcomes worsened as the PCAC score increased and this association was consistent across both sites. The PCAC score remained significantly associated with survival, neurological outcome and favourable discharge disposition even after adjusting for other factors. The authors found that PCAC demonstrated significant predictive value for all outcomes.

The strengths of Rittenberger's et al. (2011) study include the large sample size, the inclusion of subjects from two different hospital settings with distinct patient populations and the confirmation of the association between PCAC and outcomes in both prospective and retrospective arms of the study. The PCAC tool has several benefits compared to other illness severity scores, as it can be applied to both in-hospital and out-of-hospital cardiac arrests and relies on easily assessable clinical characteristics. It also provides a graded estimate of the probability of good functional outcomes, which is unique to the PCAC tool. However, there are some limitations to consider. The study was conducted in a specific geographical region and the generalisability of the findings to other regions is uncertain. The derivation and validation cohorts for the PCAC tool were relatively small compared to other studies using large databases. There is also a possibility of bias in the assignment of PCAC scores due to arbitrary clinical decisions. Additionally, while the study assessed multiple outcome measures, there may be other patient-centred outcome measures that were not considered.

The study demonstrates that the PCAC tool is strongly associated with survival and functional outcomes in OHCA patients. Its ability to provide a baseline prognostic estimate early after resuscitation makes it valuable for clinical decision making and discussions with the patient's family members. The PCAC score demonstrates potential in predicting neurologic outcomes in OHCA patients, providing valuable insights for prognostication in OHCA survivors.

The OHCA score (Adrie et al., 2006), similar to the PCAC score (Rittenberger et al., 2011), predicts neurologic outcome in OHCA patients. By incorporating additional variables such as age, it offers a broader perspective on prognostication. Its simplicity and ease of use are also positive. The authors suggest that neurological recovery during the first 24 hours after cardiac arrest cannot reliably predict outcomes. Certain physical findings, such as absence of corneal and pupillary reflexes, withdrawal response to pain after 24 hours and absence of motor responses after 72 hours, indicate severe neurological impairment but do not reliably predict a good outcome. Using a combination of neurological findings, demographic variables, comorbidities and CPR variables they were able to predict mortality. Furthermore, the OHCA score demonstrated that survival with minimal neurological impairment can be predicted upon ICU admission using variables such as lactate and creatinine. This score performs better than other scores that rely solely on no-flow and low-flow intervals, with the inclusion of additional objective variables, such as initial rhythm and laboratory variables, which reduces the risk of error in estimating time intervals. Estimating the no-flow interval accurately is challenging and log-transformation minimises errors associated with longer intervals. The authors suggest that plasma lactate and creatinine levels reflect the severity of whole-body ischemia or reperfusion syndrome. Suggesting that while lactate levels alone have limited usefulness in predicting outcomes, combining lactate with other variables independently associated with outcomes improves prediction. The score may aid in identifying patient subgroups requiring aggressive treatment and optimising healthcare resource allocation. Additionally, it could be useful for evaluating cost-effectiveness of new interventions. Overall, the authors found this score accurately predicts outcomes in unselected OHCA patients admitted to the ICU, utilising easily obtainable variables at admission and offering potential benefits in clinical decision-making and resource optimisation.

The PROLOGUE score was developed as a prediction model for early prognosis in adult non-traumatic cardiac arrest patients (Bae et al., 2021). The study included 982 patients divided into derivation and validation datasets. Thirteen variables were utilised, which were age, sex, cardiac arrest details such as whether the cardiac arrest was witnessed, the low-flow duration and initial rhythm, as well as plasma levels of potassium, lactate, haemoglobin, creatinine and phosphate, along with cumulative adrenaline dose and GCS, including pupillary light reflex to predict the neurological outcome in OHCA patients.

The developed PROLOGUE model outperformed the OHCA (Adrie et al., 2006), CAHP (Maupain et al., 2016), scoring models as well as three other outcome prediction models by

Martinell et al. (2017), Hayakawa et al. (2011) and Okada et al. (2011) 5-R model in terms of discrimination (Hayakawa et al., 2011; Martinell et al., 2017; Okada et al., 2012), as all of these scoring models require no-flow duration for calculation of scores, whereas the PROLOGUE model only requires low-flow duration (Bae et al., 2021). However, calculating effective low-flow duration may not be particularly accurate, as the delivery of Basic Life Support (BLS) can vary considerably between rescuers and is difficult to assess (Martinell et al., 2017). The PROLOGUE model did show particular strength in subgroups such as witnessed OHCA and patients undergoing TTM. Furthermore, the PROLOGUE model includes the initial neurological assessments which significantly contributed to the predictive performance of the model.

However, the PROLOGUE model does have several limitations. It was a retrospective analysis conducted at a single centre, which might limit the generalisability of the findings. Additionally, 10.7 percent of patients were excluded from the analysis due to missing data and no imputation was performed, potentially affecting the results. The study focused on poor outcome at hospital discharge and did not examine long-term outcomes or patient-centred outcomes beyond discharge. Its comprehensive approach provides a more detailed prognostic assessment. However, its complexity may hinder its widespread use and clinical applicability. The CAHP score (Maupain et al., 2016) is a practical scoring system designed to predict the neurological outcome of patients after experiencing a cardiac arrest. The CAHP score incorporates a combination of demographic, clinical and biological factors, including age, initial rhythm, location of arrest, resuscitation delays and arterial pH, to provide a comprehensive and reliable assessment of the patient's prognosis. It was developed and validated using large population-based cohorts. The CAHP score demonstrates exceptional predictive performance, enabling clinicians to stratify patients into three risk categories based on their likelihood of a favourable or unfavourable outcome. Maupain's et al. (2016) study focused on developing and validating the CAHP score, which is considered a simple and objective scoring system to predict the neurological outcome of patients after cardiac arrest (Maupain et al., 2016). The development cohort consisted of 5,541 OHCA documented between May 2011 and December 2012. Among the resuscitation attempts, 76.8 percent did not achieve ROSC. The remaining 859 eligible cases were analysed and baseline characteristics were assessed. The study found seven independent predictors of poor neurological outcome: age, initial non-shockable rhythm, home setting arrest, delays in BLS, delays in BLS to ROSC, cumulative dose of adrenaline and acidosis.

Two validation cohorts were used in this study. The retrospective validation cohort included 367 OHCA patients and the prospective validation cohort included 1,129 patients. The CAHP score performed well in both internal and external validation cohorts in terms of calibration and discrimination. The CAHP score effectively stratified patients into three risk categories based on their neurological outcome. A score below 150 points was associated with a favourable outcome, while a score above 200 points indicated a high risk of an unfavourable outcome. The score demonstrated high specificity and positive predictive value in both the development and validation cohorts.

The CAHP score offers a practical and easily applicable tool for assessing prognosis in clinical practice. The score's immediate availability and requirement of routine parameters make it convenient for routine clinical practice. However, the authors of the CAHP score acknowledge limitations, such as inaccurate estimates of resuscitation delays and the need for further validation in different healthcare systems. However, the CAHP score provides a valuable tool for early prognostication of patients after cardiac arrest, enabling better resource allocation and management decisions for those patients with a more severe neurological injury. In the ICU setting, the APACHE II score, SAPS II, SOFA score tools are commonly used for illness severity assessment and mortality prediction. The APACHE II score incorporates physiological measurements, previous health status and disease-related information, providing a comprehensive evaluation. The SAPS II score utilises physiological variables, age, type of admission and disease-related factors to estimate mortality. The SOFA score assesses organ dysfunction in six systems, enabling prognostication and guiding interventions. These scores are complex but possess good predictive abilities for mortality.

Choi et al. (2018) evaluated the performance of the APACHE II, SAPS II and SOFA scoring systems in a group of patients who experienced OHCA and underwent TTM. A total of 237 patients were initially included, but 64 patients with specific conditions were later excluded. The mean age of the included patients was 53 years and 68.2 percent were male. The study assessed hospital mortality within 30 days and good neurological outcome at 30 days after ICU admission. IVTM was performed in 74 patients, while surface cooling was performed in 99 patients. The results showed that the APACHE II score, SAPS II and OHCA score had a moderate ability to discriminate outcomes following cardiac arrest. The scoring systems measured at specific time points were independently associated with mortality and poor neurological outcomes. The SAPS II at 48 hours and the APACHE II score at 0 and 48 hours, as well as the OHCA score, were moderate predictors of 30-day mortality. Similarly, the SAPS II and APACHE II score at 0 and 48 hours, along with the OHCA score, were moderate

predictors of poor neurologic outcomes. The SOFA score showed poor discrimination for both mortality and neurologic outcomes. The study also analysed whether variables other than the severity scores were related to mortality or poor CPC. Variables such as cause of cardiac arrest, interval from collapse to ROSC, initial non-shockable rhythm and initial lactate level were significant predictors of both mortality and poor neurologic outcome. However, these factors were not included in the calculation of the severity scores. Choi et al. (2018) study demonstrated that severity scoring systems, such as the APACHE II score, SAPS II and OHCA score, can provide moderate prediction accuracy in assessing outcomes in OHCA patients who underwent TTM (Choi et al., 2018). The study acknowledges certain limitations, including its single-centre design and the lack of a sample size calculation.

While the PCAC score, OHCA score, PROLOGUE score, CAHP score, APACHE II score, SAPS II score and SOFA score have demonstrated their value in predicting poor outcomes in post-cardiac arrest care, highlighting an evidence gap concerning early and positive neurological prognostication. Closing this evidence gap is crucial as it presents a unique opportunity to develop a scoring tool that accurately predicts positive neurological outcomes within the first 24 hours of the post-cardiac arrest phase. Furthermore, bridging the gap in early and positive neurological prognostication will enhance our understanding and enable more precise prognostic assessments and optimise patient management strategies. Integrating emerging technologies and standardised guidelines would enhance their clinical applicability. Ultimately, these scores are useful in determining poor prognosis as part of a comprehensive clinical framework, integrating an early prognostic tool that incorporates individual patient factors and clinical expertise, has the potential to inform decision-making early and optimise patient care for OHCA survivors in the ICU setting.

2.7.6 Neurophysiology

Approximately 80 percent of patients resuscitated from OHCA arrive at the hospital unconscious due to Post-Cardiac Arrest Brain Injury (PCABI) (Sandroni et al., 2021) making neurological prognostication difficult. Therefore, accurately predicting a poor neurological outcome is vital to prevent unnecessary treatments for those with irreversible PCABI. In 2020, the ERC and the ESICM conducted a systematic review on predictors of poor neurological outcomes. This review informed the 2021 ERC-ESICM Guidelines on Post-Resuscitation Care, which are aligned with the 2020 recommendations from the ILCOR CoSTR (Sandroni et al., 2020; Soar et al., 2020). According to these guidelines, a poor neurological outcome is likely if at least two unfavourable signs from various tests, including electroencephalogram (EEG) and Magnetic Resonance Imaging (MRI), are present. If none or only one predictor is

present, the prognosis remains uncertain, necessitating further observation (Sandroni et al., 2021).

Understanding the potential outcomes and evaluating brain function post-cardiac arrest is essential for effective patient care. Neuroprognostication is a complex process that requires a multi-modal approach, as no single test has sufficient specificity to eliminate false positives (Soar et al., 2020). The guidelines strongly advocate for this multi-modal approach, integrating various clinical and neurophysiological indicators, allowing for a more comprehensive assessment of brain function and prognosis.

Neurophysiology plays a pivotal role in the assessment and prognostication of patients with neurological injury, especially unconscious survivors of OHCA. It provides valuable insights into brain health, injury and recovery by studying the electrical activity and function of the nervous system. One of the neurophysiological tests commonly used for prognostication after cardiac arrest is EEG, which is a widely studied and utilised method for assessing brain function and diagnosing seizures in these patients (Friberg et al., 2015). The main aspects evaluated in EEG assessment include the background activity, superimposed discharges and reactivity (Friberg et al., 2015).

The EEG background continuity is a crucial factor in prognostication. Immediately after cardiac arrest, many patients exhibit a suppressed EEG background. However, within the first 24 hours, most patients who ultimately achieve a good outcome show a restitution of a continuous normal voltage EEG (M. C. Cloostermans et al., 2012; Rundgren et al., 2010). The time taken for this restoration has also been correlated with outcome (Oh et al., 2015; Westhall et al., 2018). However, sedative drugs and muscle relaxants which are used for TTM tolerance and as a counter-shivering strategy, but also for intubation and mechanical ventilation can affect the EEG background continuity and may induce a discontinuous or burst-suppression background in a dose-dependent manner (Drohan et al., 2018; Ruijter, van Putten, et al., 2019). Regarding specific EEG patterns, the guidelines provide recommendations based on their association with prognosis. A bilaterally absent N20 wave of Somatosensory Evoked Potential (SSEP) at 24 hours from ROSC, when combined with other indices, can be used to predict a poor outcome in adult patients who are comatose after cardiac arrest (Soar et al., 2020). However, the absence of EEG background reactivity alone should not be used as an indicator of a poor outcome (Soar et al., 2020). The presence of seizure activity on EEG, in combination with other indices, is suggested as a predictor of poor outcome, while burst-suppression on EEG at 24 hours from ROSC, when combined with other indices, can also indicate a poor

outcome in adult patients who are comatose and off sedation after cardiac arrest (Soar et al., 2020).

It is important to consider various EEG patterns in prognostication. A suppressed or low-voltage background during the first day after cardiac arrest is relatively common but can indicate a poor prognosis at 24 hours after ROSC (Backman et al., 2018; Benarous et al., 2019; Caporro et al., 2019; Lamartine Monteiro et al., 2016; Ruijter, Tjepkema-Cloostermans, et al., 2019; E. Westhall et al., 2016). Burst suppression, defined as 50-99 percent of the recording consisting of suppression alternating with bursts, has been categorised into synchronous (with highly epileptiform or identical bursts) and heterogeneous patterns (Ruijter, Tjepkema-Cloostermans, et al., 2019). Highly malignant patterns, including suppressed background with or without periodic discharges and burst suppression, have been associated with a poor outcome (Admiraal et al., 2019; Caporro et al., 2019; De Santis et al., 2017; Duez et al., 2019; Rossetti et al., 2017; E Westhall et al., 2016). However, it should be noted that not all patients with burst suppression or other unfavourable patterns necessarily have a poor outcome, which may be influenced by sedation use (Amorim et al., 2016; Backman et al., 2018; Benarous et al., 2019; Marleen C. Cloostermans et al., 2012; Duez et al., 2019; Leao et al., 2015; E Westhall et al., 2016; Zhou et al., 2019).

Assessing EEG reactivity, involves measuring changes in amplitude or frequency upon external stimulation, this is considered another important aspect of prognostication (Admiraal et al., 2019; Sandroni et al., 2020). The absence of EEG reactivity during the first 24 hours after cardiac arrest indicates a poor outcome with high sensitivity but low specificity, while after 24 hours, the specificity varies (Admiraal et al., 2019; Alvarez et al., 2015; Duez et al., 2019; Grippo et al., 2017). However, the prognostic performance of reactivity varies between studies and there is no universally acknowledged standard for reactivity testing (Admiraal et al., 2019; Sandroni et al., 2020).

Superimposed patterns on EEG, such as periodic discharges and sporadic epileptiform discharges, also provide insights into prognosis. Generalised Periodic Discharges (GPDs) have been associated with a poor prognosis, but their specificity is limited (Amorim et al., 2016; Backman et al., 2018; Lamartine Monteiro et al., 2016; E Westhall et al., 2016). Sporadic epileptiform discharges resemble those seen in epilepsy but without the regularity of a periodic pattern. Their appearance is related to a worse outcome, but their specificity varies (Benarous et al., 2019; Lamartine Monteiro et al., 2016; Ruijter, Tjepkema-Cloostermans, et al., 2019; Sandroni et al., 2020; Scarpino et al., 2018).

Electrographic seizures and electrographic status epilepticus are indicators of a poor outcome. Unequivocal seizures, characterised by generalised rhythmic spike-and-wave discharges or clearly evolving discharges, have a low sensitivity but high specificity for a poor outcome (Amorim et al., 2016; Benarous et al., 2019; Lamartine Monteiro et al., 2016; Rossetti et al., 2017; E Westhall et al., 2016). The term "Electrographic Status Epilepticus" (ESE) is defined as an electrographic seizure lasting for at least 10 continuous minutes or for a total duration of 20 percent of any 60-minute recording period (Hirsch et al., 2021). However, the definition of ESE varies between studies and standardised classification is needed (Alvarez et al., 2015; Amorim et al., 2016; Hirsch et al., 2021; Leao et al., 2015; Ruijter, Tjepkema-Cloostermans, et al., 2019; Zhou et al., 2019).

Automated assessment of quantitative EEG features, such as the burst suppression amplitude ratio and reactivity, has been explored in individual studies (Amorim et al., 2019; Ruijter et al., 2018). These quantitative EEG indices aim to provide objective measurements and may reduce subjectivity in EEG assessments.

In conclusion, neurological prognostication after cardiac arrest requires a multi-modal approach that incorporates clinical and neurophysiological indicators. EEG is a valuable tool for assessing brain function and prognosis. Various EEG patterns, including background activity, superimposed discharges and reactivity, provide insights into prognosis. However, the certainty of the evidence supporting these prognostication strategies is generally low.

2.7.7 Neurological biomarkers

Current ERC and ESICM guidelines (Nolan et al., 2021) recommend using serial measurements of NSE in combination with other methods to predict outcome after OHCA. NSE is an intracellular enzyme found in neurons and neuroendocrine cells. It is the most abundant enolase (a cytoplasmic glycolytic enzyme of glycolysis) which converts 2-phoshoglycerate to phosphoenolpyruvate. It is released into the bloodstream at a rate proportional to the degree of neuronal damage (Reiber, 2003). Therefore, elevated levels of serum NSE appear to correlate with the extent of brain injury poor neurologic outcome and has also been associated with persistent coma in OHCA survivors with a high specificity (Cronberg et al., 2011). However, an increase of NSE has also been associated with malignant proliferation and considered important in the diagnosis, staging and treatment of related Neurological Endocrine Tumours (Isgrò et al., 2015). Furthermore, an association has been found between elevated NSE serum levels and certain skin cancers (melanoma and Merkel cell tumour), seminoma, renal cell carcinoma, carcinoid tumours, dysgerminomas, immature teratomas, malignant pheochromocytoma, Guillain-Barré syndrome and Creutzfeldt-Jakob

disease (Isgrò et al., 2015). Elevated NSE levels are also considered a reliable measure of brain injury following ischaemic stroke, intracerebral haemorrhage, seizures, traumatic brain injury.

NSE is a biomarker that has been extensively researched, particularly for its prognostic value in OHCA patients (Sandroni et al., 2013). Recent studies have demonstrate that NSE levels can predict neurological outcomes in patients, with threshold values ranging from 33 to 120 micrograms per litre within the first 72 hours (Gillick & Rooney, 2018; Lee et al., 2022; Rafecas et al., 2020; Ryoo et al., 2020). These thresholds have been associated with specificities between 75 to 100 percent and sensitivities from 7.8 to 83.6 percent. However, Streitberger et al. (2017) identified exceptions where some patients with high NSE levels had favourable outcomes, although other reasons were identified as plausible explanations for the elevated NSE levels (Streitberger et al., 2017). Conversely, in this same study patients with low NSE levels died, however the cause of death was established to be unrelated to hypoxic and or ischaemic encephalopathy (Streitberger et al., 2017).

Generally, NSE levels decrease after 24 hours in patients with good outcomes and increase in those with poor outcomes, peaking between 48 to 96 hours. The best prediction times of poor prognosis for NSE are at 48 or 72 hours post-cardiac arrest. An increasing NSE level from 24 to 48 or 48 to 72 hours is a strong indicator of poor prognosis (Streitberger et al., 2017). Chung-Esaki et al. (2018) study found that a ratio of NSE levels at 48 to 24 hours greater than or equal to 1.7 had a 100 percent specificity for poor outcomes (Chung-Esaki et al., 2018). The other useful neurological biomarker used as a predictor of neurological outcome is S-100B, which is also implicated in neuronal differentiation, proliferation and apoptosis (Donato, 1999). S-100B is a useful biochemical marker of central nervous system injury (Kim et al., 1996), however Rosen et al. (1998) and colleagues undertook a study to validate the use of serum S-100B as a predictor of hypoxic brain injury and neurological outcome of patients following cardiac arrest (Rosen et al., 1998). They observed that all patients with serum S-100B levels above the discriminatory level of 0.2 micrograms per litre at day two died within 14 days, conversely almost 90 percent of patients survived with a level below 0.2 micrograms per litre (Rosen et al., 1998). Subsequent studies have questioned the diagnostic accuracy of S-100B due to a wide range of cut off values in determining poor outcome (Sandroni et al., 2014). A substudy of the TTM trial looked at the diagnostic performance of S-100B as an outcome predictor after OHCA and concluded high S-100B values taken at 24 hours were predictive or poor outcome but did not add value to the prognostic model used for the purposes of the TTM trial (Stammet et al., 2017). However, Jang et al. (2019) performed a prospective cohort study of OHCA treated with TTM and found the combination of

procalcitonin (PCT) and S-100B improved the prognostic performance compared to relying on a either biomarker independently (Jang et al., 2019). A more recent study by Deye et al. (2020) explored the use of protein S-100B as a tool for early prognostication in OHCA patients (Deye et al., 2020). This study included 330 unconscious adult OHCA patients who were treated with TTM. The primary endpoint of Deye et al. (2020) study, was to assess the performance of S-100B in discriminating patients with good outcome versus poor outcome at a three-month follow-up and their secondary endpoints included evaluating the performance of S-100B in the early phase after cardiac arrest and comparing it to other biomarkers. Deye et al. (2020) study showed that S-100B had a higher accuracy in early prediction of positive neurological outcome compared to other biomarkers such as lactate, pH, creatinine and NSE. That S-100B was able to discriminate between patients with good and poor outcomes as early as admission. The study also found that S-100B could be incorporated into prognosticating scores for OHCA patients (Deye et al., 2020). Overall, the study suggests that S-100B is a reliable tool for early prognostication after cardiac arrest.

In addition to NSE and S100B, there are three other emerging proteins which have been identified as showing potential to predict neurological outcomes for unconscious OHCA survivors. These include Glial Fibrillary Acidic Protein (GFAP), tau protein and Neurofilament Light chain (NfL) (Helwig et al., 2017; Humaloja et al., 2022). Similarly, to S-100B, GFAP is a protein found in astrocytes. It is considered a highly specific marker for the brain, particularly when the brain is exposed to ischemia, as a protective mechanism GFAP production increases. Healthy individuals typically do not have elevated GFAP levels. Therefore, high serum GFAP levels have been linked to various neurological events, including head trauma, cardiac arrest and stroke (Hol & Pekny, 2015; Larsson et al., 2014). Several studies, including those by Ebner et al. (2020), Larsson et al. (2014) and Helwig et al. (2017), have investigated GFAP levels following cardiac arrest (Ebner et al., 2020; Helwig et al., 2017; Larsson et al., 2014). The authors indicate that the accuracy of GFAP in forecasting neurological outcomes after a cardiac arrest is more pronounced at 48 and 72 hours than at earlier intervals (Ebner et al., 2020; Helwig et al., 2017; Larsson et al., 2014). Ebner et al. (2020) pinpointed a specific GFAP threshold for anticipating unfavourable outcomes 48 hours after the cardiac arrest, though it exhibited limited sensitivity (Ebner et al., 2020).

Neurofilament light (NfL), is a structural protein found exclusively in neurons, primarily in the cerebral white matter (Ashton et al., 2021). The role of NfL is not fully understood, but it is believed to be essential for nerve growth and rapid conduction. When neurons are damaged as a result of hypoxic brain injury, these proteins are released into both the cerebrospinal fluid

and blood. While NfL has been studied in the context of neurodegenerative diseases, its significant rise after hypoxic brain injury suggests its potential as a marker for acute, rather than chronic, neurological damage.

There are two recent studies by Moseby-Knappe et al. (2019) and Wihersaari et al. (2021) who specifically looked at NfL in the context of an outcome predictor in OHCA patients (Moseby-Knappe et al., 2019; Wihersaari et al., 2021). They were able to demonstrate that individuals with poor outcomes post-cardiac arrest had higher NfL levels, whereas those with good outcomes had lower levels, suggesting NfL's potential as a predictive biomarker 24 hours after a cardiac event. However, its immediate post-admission utility is limited due to overlapping levels in different outcomes. While NfL has shown promise in predicting outcomes compared to other biomarkers, approximately one-third of individuals with a favourable outcome also exhibited high NfL levels (Moseby-Knappe et al., 2021). Highlighting NfL as a possible early marker for positive neurological outcomes.

Total-Tau (T-Tau) is a protein, primarily found in the central nervous system's white matter. In the event of cardiac arrest, tau detach from microtubules, forming insoluble masses, which disrupt axonal signalling. Only a few studies have explored tau levels post-cardiac arrest (Mattsson et al., 2017; Mortberg et al., 2011; Randall et al., 2013). In the TTM trial cohort, tau was found to predict neurological outcomes more accurately than NSE, especially between 24 to 72 hours after the event (Mattsson et al., 2017). While initial thresholds for predicting poor prognosis seemed high, allowing a slight margin of error increased sensitivity and lowered the thresholds. Mortberg et al. (2011) and Randall et al. (2013) noted a two-phase tau release after cardiac arrest, with the later peak being lower or absent in patients with better outcomes (Mortberg et al., 2011; Randall et al., 2013). With the half-life of tau being approximately 10 hours, Humaloja et al. (2022) suggested that late elevations might indicate continued neuronal damage (Humaloja et al., 2022).

The use of neuronal biomarkers as part of a multimodal approach for neurological prognostication following cardiac arrest, continues to evolve with a growing body of evidence supporting the use of specific biomarkers. However, there is a notable evidence gap in the identification of biomarkers that can provide early and positive neurological prognostication, specifically within the first 24 hours. The majority of research and clinical emphasis has been placed on predicting poor prognosis after 72 hours following cardiac arrest. The European Resuscitation Council (ERC) and European Society of Intensive Care Medicine (ESICM)

guidelines currently only recommend the use of NSE as the primary biomarker to be considered for its prognostic value in determining poor patient outcomes.

However, the potential of other biomarkers, particularly S-100B, in predicting positive neurological outcomes within the first 24 hours, has yet to be fully explored. To consider biomarkers for the purpose of early and positive prognostication has the potential to provide clinicians with an opportunity to make informed decisions about patient care and management, particularly resource allocation. While NSE remains the gold standard as per current guidelines, the potential of S-100B to fill this evidence gap cannot be overlooked.

Emerging biomarkers like GFAP, NfL and Tau are also showing promise in their prognostic value. However, their widespread adoption has been limited due to practical challenges. These biomarkers require specialised assays for accurate measurement, which are not readily available in many clinical settings. This limitation poses a significant barrier to their routine use.

Part 3: Patient and service implications

2.8 Mechanical ventilation

There are primarily four reasons for unconscious survivors of OHCA to be mechanically ventilated: (1) To control oxygenation by monitoring and adjusting inspired oxygenation to avoid hypoxemia or hyperoxemia; (2) To control carbon dioxide levels by monitoring and adjusting ventilator parameters to avoid hypocarbia or hypercarbia; (3) To protect the patients airway from aspiration; and (4) To deliver supportive care to allow patients to receive other necessary treatments and interventions, such as the administration of TTM (Holmberg et al., 2020). However, protracted mechanical ventilation is associated with, not only potential patient harms, but has been directly associated with extended patient stay in the ICU as well as hospital length of stay, resulting in higher healthcare costs (Madahar & Beitler, 2020).

2.8.1 Risk of infection

Protracted mechanical ventilation is associated with high morbidity and mortality, as well as poor quality of life (Crocker, 2009). However, there is no specific universally accepted definition of what constitutes protracted mechanical ventilation. It can vary depending on the context and the specific patient population being considered. In general, it refers to the need for mechanical ventilation for an extended period, often exceeding days or weeks. Chastre et al. (2002) and Craven et al. (1995) refer to Ventilator-Associated Pneumonia (VAP) being attributable to any mechanically ventilated patient after just 48 hours (Chastre & Fagon, 2002; Craven & Steger, 1995). VAP is reported to occur in 10 to 40 percent of patients who are mechanically ventilated for more than two days (Antcliffe et al., 2018; Klarin et al., 2018). According to Torres et al. (2017) VAP is the second most common nosocomial infection in critically ill patients and the leading cause of death in these critically ill patients (Torres et al., 2017). Additionally, VAP can prolong the duration of mechanical ventilation, increase the length of stay in the ICU and contribute to other complications such as sepsis and organ failure. The development of VAP can also lead to the need for more aggressive antibiotic therapy, which can further increase the risk of antibiotic resistance and other adverse effects. Therefore, preventing and managing VAP is crucial in improving outcomes for patients on protracted mechanical ventilation.

2.8.2 Muscle atrophy

As a result of protracted mechanical ventilation, diaphragm atrophy and dysfunction are also frequently observed in critically ill patients (Levine et al., 2008; Tremblay & Slutsky, 2006) and

is the leading cause of difficult weaning from mechanical ventilation (Dres et al., 2017; Dube et al., 2017; Kim et al., 2011). The trajectory of diaphragm thickness varies among these patients. Goligher et al. (2015) study suggests that while some patients see a decrease of diaphragm thickness of more than 10 percent, others will remain stable and a few patients may see an increase in diaphragmatic thickness of over 10 percent (Goligher et al., 2015). Furthermore, Goligher et al. (2015) study was able to demonstrate that diaphragm thickness remains consistent post-extubation and patients who were self-ventilating, therefore a dose-response relationship was able to be established between inspiratory effort and diaphragm thickness changes over time (Goligher et al., 2015). Therefore, low diaphragm contractile activity correlates with rapid thickness decreases, whereas high contractile activity is linked to thickness increases (Goligher et al., 2015). The ventilator's driving pressure and its controlled modes have been associated with a decline in diaphragm contractile activity (Schepens & Goligher, 2019). Patients with either decreased or increased diaphragm thickness tend to have inferior diaphragm function compared to those with stable thickness (Grassi et al., 2020). The potential harm from protracted mechanical ventilation and its impact on the diaphragm, is associated with serious complications and costs which are directly linked to the duration of mechanical ventilation (Beduneau et al., 2017).

An extensive systematic review and meta-analysis conducted by Damuth et al. (2015) revealed that patients with chronic critical illness on prolonged mechanical ventilation had a 1-year mortality rate of 46 percent (Damuth et al., 2015). Additionally, these patients faced high hospital readmission rates, ranging between 35 to 73 percent. Damuth et al. (2015) demonstrated that prolonged mechanical ventilation in chronic critical illness is linked to high death rates and high readmission rates (Damuth et al., 2015).

2.8.3 Psychological impact

Patients requiring mechanical ventilation for at least 48 hours in the ICU experience not just the physiological challenges but psychological challenges as well (Merchán-Tahvanainen et al., 2017; Rotondi et al., 2002). Karnatovskaia et al. (2015) and Parker et al. (2015) report one in five survivors of critical illness, experience what they term, ICU acquired posttraumatic stress disorder, anxiety and depression (Karnatovskaia et al., 2015; Parker et al., 2015). Hunter et al. (2014) suggest that these complications have shown to persist for several years after discharge, which has resulted in some patients being unable to return to work (Hunter et al., 2020), as well as being linked to a decreased health-related quality of life (Parker et al., 2015). The process of weaning, or transitioning from mechanical to spontaneous breathing is multifaceted (Engstrom et al., 2013). While the physiological factors are evident, psychological factors are

often overlooked (Merchán-Tahvanainen et al., 2017). However, psychological factors are considered to play a significant role in achieving a successful weaning outcome for patients from a mechanical ventilator (Rose et al., 2014). During the critical weaning phase, patients experience emotions such as uncertainty, dependence, fear and frustration, all of which are considered to directly impede the success of weaning (Ariffin et al., 2020; Merchán-Tahvanainen et al., 2017). Arslanian-Eggoren and Scott (2003) describe the onset of dyspnoea can amplify anxiety, further complicating the weaning process (Arslanian-Engoren & Scott, 2003). Moreover, patients often feel vulnerable, especially when they struggle to communicate because of the endotracheal tube or when performing basic tasks (Engstrom et al., 2013).

Strategies to counteract these negative psychological experiences, include the provision of information and support to both patients and their families during the ICU stay. As highlighted by Rose et al. (2014), such interventions can significantly reduce the negative psychological experiences associated with mechanical ventilation (Rose et al., 2014). Nurses are considered to play a pivotal role in this process, not only for delivering medical care and responsibilities, but they are instrumental in providing emotional support, bridging the gap between medical procedures and the human experience (Tonnelier et al., 2005). Furthermore, early mobilisation has been identified as a potential tool in addressing the psychological challenges faced by these patients (Soderberg et al., 2022). While patients' initial memories of their ICU stay might be blurred, indicating cognitive disorientation, early mobilisation has been shown to improve cognitive clarity and recollection (Jin et al., 2021). The emotional journey that accompanies early mobilisation, transitioning from feelings of frustration and vulnerability to those of relief, control and gratitude, underscores its profound psychological benefits. This journey towards regaining control and normalcy demonstrates the importance of early interventions in mechanically ventilated patients. Moreover, Jin et al. (2021) identifies the introduction of early rehabilitation for patients, enhances both physical and mental recovery (Jin et al., 2021). Not only is early mobilisation and rehabilitation directly associated with a patient's physical recovery, there is a direct correlation with a reduction of ICU stay, but more importantly early mobilisation and rehabilitation alleviates the negative psychological symptoms associated with mechanical ventilation.

2.8.4 Financial

In relation to the economic consequences of mechanical ventilation, Kaier et al. (2019) conducted a comprehensive systematic review of the financial implications of mechanical ventilation on the daily expenses incurred in the ICU (Kaier et al., 2019). The authors focused on the daily costs of staying in the ICU and the extra costs associated with patients who

required mechanical ventilation as a result of acquiring VAP. They found that mechanical ventilation increased the daily ICU costs by 25.8 percent. Ferr et al. (2018) study also describes the significant resource utilisation and extended hospital stays associated with VAP, suggesting that VAP extends the duration of mechanical ventilation by 7.6 to 11.5 days and hospital stay by 11.5 to 13.1 days compared to similar patients without VAP (Ferrer & Torres, 2018). The economic implications of VAP are substantial, necessitating longer periods of mechanical ventilation, consequently lengthening ICU and overall hospital stays (Chacko et al., 2017; Gidey et al., 2023).

2.8.5 Implication for TTM

Weaning from mechanical ventilation is often delayed, leading to unnecessary patient discomfort, higher risks of complications and increased costs. The weaning process is considered to take up 40-50 percent of the total time a patient spends on a mechanical ventilator (Esteban et al., 2002). In the context of OHCA patients being treated with TTM, weaning from mechanical ventilation is a complex process that requires consideration of multiple factors not just the respiratory readiness of the patient. OHCA patients not only experience a significant physiological insult, but their condition is often compounded by the underlying cause of the cardiac arrest, as well as a potential hypoxic brain injury and other systemic complications. Furthermore, for the effective implementation and administration of TTM, patients need to be sedated to a level that prevents spontaneous respiration, necessitating mechanical ventilation. The pharmacological combination of sedation and muscle relaxant used during TTM, is for the purpose of ensuring patient comfort, prevents shivering (which can counteract the cooling process) and facilitation of maintaining a stable target temperature (Jain et al., 2018). As a result, weaning the patient from mechanical ventilation during the active phase of TTM could potentially compromise the efficacy of the TTM treatment and potentially expose the brain to further injury (Oddo et al., 2010). The primary concern for OHCA patients is the potential for neurological damage due to the period of reduced or absent cerebral perfusion during the cardiac arrest. Immediately after resuscitation, the brain is in a vulnerable state and any additional stress or hypoxia as a result of ventilation weaning could potentially exacerbate the neurological injury (Nolan et al., 2021; Penketh & Nolan, 2023). Weaning too early from mechanical ventilation, could also potentially expose the patient to the risk of hypoxemia, hypercapnia, or aspiration, all of which could further compromise cerebral oxygenation and perfusion (Johnson et al., 2018). Additionally, the metabolic demands of spontaneous breathing could increase intracranial pressure, potentially worsening any existing brain injury (Mtaweh et al., 2019). Furthermore, the underlying cause of the OHCA, whether it be a primary cardiac event, pulmonary issue, or

metabolic disturbance, if still unresolved, could also hinder attempts to wean a patient from mechanical ventilation (Terman et al., 2015).

In summary, mechanical ventilation is an essential intervention for critically ill patients, including those who are unconscious survivors of OHCA. Its role becomes even more pronounced when these patients undergo TTM and are sedated for an extended period of 72 hours. However, the prolonged use of mechanical ventilation is not without its challenges, with nosocomial infections being a significant concern. A significant proportion of patients are at risk of developing VAP who are mechanical ventilation for more than two days, making it a leading cause of death among the critically ill. Infection is directly correlated with extended durations of mechanical ventilation and ICU stays, often leading to severe complications like sepsis and organ failure. Diaphragm atrophy and dysfunction are also associated with protracted mechanical ventilation, further impacting on the ability to wean patients successfully. The economic burden is substantial, with mechanical ventilation escalating daily ICU costs as well as length of ICU and hospital stay. It is not just the physical implications but also the psychological challenges for patients, with a significant proportion of patients experiencing post-traumatic stress disorder, anxiety and depression, affecting patients' quality of life and ability to work.

Given these challenges, the early identification of patients with a positive prognosis becomes crucial. Recognising these patients promptly can prevent unnecessary extended mechanical ventilation, reducing the associated risks, costs and psychological impact. It ensures that patients receive appropriate care tailored to their prognosis, optimising outcomes and resource allocation. In essence, an early recognition tool would not only benefit the individual patient but also have broader implications for healthcare systems and resource allocation and management.

Table 4 Comparison of prognostic tools

Assessment Tool	Benefits	Limitations
GCS **(Glasgow Coma Scale)**	• Widely used tool that is simple and easy to use. • Cannot differentiate between brainstem reflexes and cortical activity. • Useful tool to monitor changes in neurological status over time. • Can be performed by healthcare professionals with minimal training.	• Only evaluates three parameters: eye opening, verbal response and motor response, which may not be sufficient for a comprehensive assessment of the patient's neurological status. • The scale has limited sensitivity and specificity. • Does not provide information on the underlying cause of the coma.
FOUR **(Full Outline of Unresponsiveness)**	• Assesses four domains: eye response, motor response, brainstem reflexes and respiration (not included in GCS). This provides a more comprehensive assessment of the patient's neurological status than the GCS. • Shown to have better sensitivity and specificity than the GCS for predicting patient outcome. • Allows for monitoring changes in neurological status over time.	• More complicated to use than the GCS. • Not as widely used or familiar to healthcare professionals as the GCS. • Require more training and expertise to perform than the GCS.

Table 4 Comparison of prognostic tools (continued)

Assessment Tool	Benefits	Limitations
EEG (Electroencephalogram)	• Provides direct information on the electrical activity of the brain, allowing for a more objective assessment of the patient's neurological status. • Able to identify specific patterns of brain activity that are associated with different levels of consciousness. • Used to monitor changes in brain activity over time.	• Not readily available in all healthcare settings. • Requires specialised training and expertise to perform and interpret the results.
SSEP **(Somatosensory Evoked Potentials)**	• Provides information on the integrity of sensory pathways in the brain. • Used to monitor changes in neurological status over time.	• Requires specialised equipment and expertise to perform and interpret the results.
Biomarkers **(S-100B and NSE)**	• They can be used to identify brain injury and predict patient outcomes.	• They do not provide a comprehensive assessment of the patient's neurological status.

2.9 Evidence gaps

2.9.1 Research underpinning the study

There is a notable evidence gap in the early identification of OHCA patients with a positive prognosis, therefore potentially subjecting patients to unnecessary medical interventions, particularly mechanical ventilation. Prolonged mechanical ventilation can lead to physiological and psychological complications for the patient, as well as having significant economic implications for the healthcare service. Accurate early prognostication would ensure patients receive appropriate care without exposure to unnecessary risks, emphasising the balance between physiological and psychological well-being.

The ERC and ESICM guidelines primarily focus on OHCA patients expected to have poor neurological outcomes, potentially overlooking those patients with a positive recovery trajectory. There is a significant lack of evidence concerning the feasibility of conducting early neurological assessments, for the specific purpose of identifying patients with a positive prognosis, in the context of TTM delivery. Addressing this gap would ensure that patient centred treatments that optimise outcomes for patients showing early signs of positive recovery, moving away from a deficit-based framework. While TTM has been demonstrated to be effectively delivered in conscious patients using IVTM and counter shivering strategies, its safety and efficacy for waking unconscious OHCA patients remain unexplored.

There is a significant lack of evidence which focuses on the early identification of neuronal biomarkers for positive neurological prognostication within the first 24 hours after cardiac arrest. While the ERC and ESICM guidelines emphasise NSE for predicting poor outcomes after 72 hours, the potential of other biomarkers, especially S-100B, for early positive outcomes remains insufficiently explored. Therefore, clinicians are not able make timely and informed decisions about patient care and resource allocation.

Several scoring tools, including the PCAC, OHCA, PROLOGUE, CAHP, APACHE II, SAPS II and SOFA scores, are valuable in predicting poor outcomes in post-cardiac arrest care. However, there is a significant evidence gap in tools that predict early and positive neurological outcomes within the first 24 hours post-cardiac arrest. Addressing this gap could lead to the development of a scoring system that offers precise early prognostic assessments, optimising patient management strategies. While current scores focus on poor prognosis, integrating a tool that considers early positive outcomes and individual patient factors could enhance decision-making and care for OHCA survivors in the ICU.

There is a significant lack of evidence in early identification of OHCA patients with a positive prognosis, leading to potential overuse of mechanical ventilation with its associated risks and costs. The ERC and ESICM guidelines, while valuable, primarily target patients with expected poor neurological outcomes, potentially neglecting those patients showing early signs of recovery. This highlights the need for an early neurological prognostic assessment tool that does not interfere with the delivery of TTM, including during the fever prevention phase. While IVTM combined with counter shivering strategies has been successfully trialled in conscious patients suffering from stroke and myocardial infarction, its application in waking unconscious OHCA patients remains unexplored. The early identification of neuronal biomarkers, especially S-100B, within the first 24 hours post-cardiac arrest is another area lacking sufficient research. Lastly, while several scoring tools predict poor outcomes, there is a need to develop a tool that can predict positive neurological outcomes early on, ensuring tailored care for OHCA survivors in the ICU.

2.9.2 Research questions

In developing the Therapeutic Hypothermia and eArly Waking (THAW) protocol for unconscious survivors of OHCA, this study seeks to address three research questions:

1. To what extent, can early neurological assessments and accurate prognostication contribute to reducing ventilation time in OHCA patients?

2. What is the safety and efficacy of utilising Intravenous Temperature Management (IVTM) combined with counter shivering strategies in waking unconscious OHCA patients for neurological assessments?

3. How can physiological assessments be utilised to determine the suitability of waking unconscious OHCA patients early, to perform a neurological assessment?

Chapter three describes and defends the methodologies employed to answer these questions and development of the THAW protocol.

Chapter 3: Research framework

> *In an era of demanding research questions and complex social problems, researchers need tools that engage the complexity rather than simplify it.*
>
> John W. Creswell

3.1 Introduction, research framework

Methodology is considered the theory of how research should be undertaken, emphasising the theoretical and philosophical assumptions that underpin research and there implications on the methods chosen (Bryman, 2016). Furthermore, methodology can be viewed as a comprehensive framework that includes the research design, data collection and analysis, all grounded in philosophical foundations that highlight the importance of the theoretical rationale to guide the selection and implementation of the research methods (Creswell & Clark, 2007).

The current study explores the evidence gaps in the care of waking unconscious survivors of Out of Hospital Cardiac Arrest (OHCA) through the development of an evidence-based early waking protocol, designed specifically for this patient group. This chapter presents a thorough examination of the philosophical assumptions, theoretical concepts that influenced the selection of methodology used to address the research questions of this study.

3.2 Methodological approach

This study was conducted using a mixed methods approach. Mixed methods research can be defined as "an approach to research in the social, behavioural, and health sciences in which the investigator gathers both quantitative (close-ended) and qualitative (open-ended) data, integrates the two, and then draws interpretations based on the combined strengths of both sets of data to understand research problems" (Creswell, 2015, p. 2).

3.2.1 Philosophical assumptions and paradigms

Pragmatism, as a philosophical underpinning in mixed methods research, prioritises the research problem and uses all approaches available to understand and address it. Patton (2015) discusses the "two ways in which pragmatism informs qualitative inquiry. First is inquiring into practical questions in search of useful and actionable answers. Second is making pragmatic decisions while conducting the inquiry based on real-world constraints of limited

time and resources" (Patton, 2015, p. 153). In other words, a pragmatic approach offers the flexibility to combine different research methods and modify data collection strategies as the research progresses and new findings are uncovered (Patton, 2015). This pragmatic approach aligns well with the practical demands and takes into consideration the needs of a clinical environment with an emphasis on what works in practice by bridging the gap between theory and application.

Adopting a pragmatic worldview emphasises the importance of outcomes and applications of research findings in real-world settings. Within the context of developing and implementing the Therapeutic Hypothermia and eArly Waking (THAW) protocol as a safety and feasibility study, this perspective advocates for integrating qualitative insights from clinical experts, patients, and their families, as well as hospital management, alongside quantitative data collection from the pilot study which focuses clinical outcomes. The pragmatic approach is action-oriented, focusing on the consequences of the research and its capacity to address and solve practical problems, thereby ensuring the protocol is both safe and effective for clinical use.

3.2.2 Quantitative approaches

Quantitative research, is based on deductive testing and verification, utilising numerical data collected through instruments and measurements. Through statistical analysis, quantitative research compares frequencies or measurements, identifying differences or correlations (Kumar, 2011). The primary aim of quantitative research is hypothesis validation to establish theory (Creswell, 2015). While quantitative methods offer concise and quickly collected data, it can lack depth in understanding and explanatory power (Creswell, 2015). However, advancements in technology enhance data collection, with quantitative findings crucial for determining causal relationships in fields like health research.

3.2.3 Qualitative approaches

Qualitative methodologies have encountered resistance in gaining acceptance in health research primarily because of a traditional preference for quantitative data, which is considered more objective and generalisable (Creswell, 2013; Sandelowski, 2000). However, the interpretive or narrative approach of qualitative research seeks to explore the meaning of phenomena through methods such as observation and open-ended data collection (Teddlie & Tashakkori, 2009). This involves utilising various empirical materials and adopting an inductive approach to analyse social phenomena (Creswell & Clark, 2007). Ensuring the

trustworthiness of qualitative data through triangulation and inter-rater reliability ensures the depth of understanding and research flexibility. The raw data, typically collected through interviews, undergo interpretive analysis where codes, categories, and themes are developed (Braun & Clarke, 2022).

3.2.3 Mixed methods research

Mixed methods research is recognised as a distinct methodological paradigm, which synergistically combines both quantitative and qualitative approaches within a study framework. This approach, established in the theories presented by Creswell and others, is designed to extend beyond simple data collection, but aims to integrate and interpret both forms of data concurrently to enhance the understanding of the research question (Bryman, 2016; Creswell, 2018; Teddlie & Tashakkori, 2009). Such integration allows researchers to capitalise on the strengths of each methodological approach while compensating for their individual weaknesses, thus providing a more comprehensive understanding of the research subject.

The methodological integration involves a range of techniques including triangulation, where different data sources are utilised to cross-validate findings and reduce bias, enhancing the reliability of the research (Teddlie & Tashakkori, 2009). This comprehensive approach is particularly effective in addressing complex research problems by providing a deeper, multifaceted perspective that cannot be achieved using single-method studies (Creswell, 2015). However, while mixed methods provides a number of advantages, the process of designing, conducting, executing, and interpreting mixed methods research can be challenging as a result of amalgamating diverse data sources and methodological approaches (Teddlie & Tashakkori, 2009). These challenges necessitate careful consideration of the specific strengths and limitations inherent in mixed methods research, ensuring a robust design that adequately addresses the research questions.

3.3 Exploratory sequential design

The aims of this study resulted in the selection of an exploratory mixed methods sequential design. This integrative approach combines both qualitative and quantitative research methods. The approach was deemed suitable for this study as it allows for a comprehensive exploration of the problem using qualitative methods and pilot testing of the protocol. Selecting exploratory sequential design is ideally suited for developing a complex critical care protocol to wake unconscious survivors of cardiac arrest due to the many variables that

influence patient outcomes, which include patient specific factors, clinical interventions, environmental and organisational factors, as well as post-resuscitation care and management. Therefore, qualitative exploration allows for collecting rich, detailed data directly from clinical staff, patients and family members, and importantly healthcare leaders and decision makers. This depth of understanding is critical for developing a complex critical care protocol as it allows the nuanced perspectives of all stakeholders to be heard and considered. This inclusive approach in the development of the protocol ensures a comprehensive understanding which is not only medically robust but practicable, realistic and operationally viable. Engaging with healthcare leaders and decision-makers early in the process, gains their support and endorsement, ensuring the protocol is aligned with broader organisational objectives, particularly important for resource allocation and protocol implementation. Furthermore, the inclusion of patients and their families allows for a deeper appreciation of their experiences and expectations, ensuring the protocol promotes not just clinical efficacy but also patient comfort, dignity, and psychological well-being. Additionally, the adaptive nature of qualitative research means that the development process can flexibly respond to new findings, enhancing the relevance and applicability of the protocol. Through this detailed and inclusive approach, the protocol not only aims for clinical excellence but also ensures broad acceptance and adaptability, essential for sustainable implementation in dynamic healthcare environments.

The exploratory sequential design is inherently flexible, which enables the researcher to adapt the study - protocol based on these insights. This adaptability enhances the research process, enabling an iterative refinement of the early waking protocol that aligns with the qualitative findings. Following the iterative development of the THAW protocol, it shifts into a quantitative phase where the early waking protocol is piloted in practice. This phase is crucial for testing the efficacy and generalisability of the protocol across broader patient populations, providing statistical validation of the qualitative findings and ensuring that the developed protocol is both effective and practical.

The approach additionally facilitates a comprehensive understanding of the research problem by first grounding the study in empirical, context-rich insights obtained from the focus group work and then quantitative analysis of the pilot study. This combination of qualitative depth with quantitative precision is an ideal tool for developing critical care protocols, particularly in the complex environment of post-resuscitation care with continuously evolving medical evidence and practice.

By employing a pragmatic stance, the development and implementation of the THAW protocol using a exploratory sequential mixed methods ensures it is grounded in robust scientific evidence and tailored to meet the practical realities of a complex clinical setting like critical care. The integration of quantitative and qualitative methods enhances the protocol's reliability, applicability, and overall effectiveness. The pragmatic framework supports a problem-solving approach that is crucial in bridging the gap between theory and practice, making the findings meaningful and feasible for real-world application.

3.3.1 Stakeholder influence

This study was strongly influenced by the views of the various stakeholder groups: clinical researchers, the National Health Service (NHS) ethics committee, clinical experts, Out of Hospital Cardiac Arrest (OHCA) survivors, their families, and the hospitals clinical governance group. The complexity of the healthcare landscape necessitates a methodology that accommodated flexibility to explore unanticipated issues and incorporate a broad range of insights from the various health disciplines, patients and their families. The study design was an iterative development process that engaged clinicians, incorporated ethical considerations, and provided a comprehensive understanding of patient experience and impact with clinical governance oversight.

Bammer's (2013) five-question framework "disciplining interdisciplinary" focuses on the integration of disciplinary and stakeholder knowledge (Bammer, 2013). Bammer's first question from the framework is about identifying the objective and intended recipients, for what and for whom is expected to benefit. In the context of the THAW protocol development, this would include OHCA survivors and their families with early prognosis detection, as well as the opportunities for clinicians to be involved in original research.

The second question is to determine the specific knowledge and expertise that each group brings. The clinical researchers would bring scientific rigor, influencing the selection of current evidence as well as policy and clinical protocols. They would also bring their knowledge and clinical experience, specifically from previous research undertaken, including TTM in the COOLAMI study (Noc et al., 2017) and a pilot study which involved rapid induction of TTM using the Rhinochill device in unconscious OHCA patients (Islam, Hampton-Till, Watson, et al., 2015). The clinical expert group, which included anaesthetists, cardiologists, and critical care staff, would draw on specialist knowledge, protocol development, to ensure alignment with best practice and enhancing the protocol's clinical relevance and effectiveness. Whereas the OHCA survivors and their families would provide valuable insights into the patient

experience, providing a more patient-centred perspective, particularly on patient outcomes and practical challenges.

The third question from Bammer's framework is the how, to describe the methods for integrating these diverse forms of knowledge, including who performs it and when. This would include collecting qualitative data through various focus group discussions and analysing it using general inductive and thematic analysis. Through to the implementation of the THAW protocol to assess its safety and feasibility, a pilot study would enable quantitative data collection.

The fourth question considers the contextual factors that might influence the research. As a regulatory requirement, the NHS Ethics Committee would need to approve the THAW study protocol to ensure adherence to ethical standards, particularly in dealing with unconscious patients and concerns with consent. Whereas the clinical governance group would ensure the THAW protocol met the patient safety threshold of 'do no harm' but would also consider the reputational risk for the organisation. Furthermore, they would consider the operational feasibility of integrating original research into clinical practice, in terms of clinical workload, as well as any financial implications.

Bammer's final question focuses on evaluating the research outcomes, which include the quantitative data collection from the pilot study of the THAW protocol to evaluate its safety and feasibility in practice.

Table 5 highlights the process involved in the selection of the mixed methods design. The factors which influenced the decision to choose a mixed methods approach included stakeholder views, the complexity of implementing a clinical protocol, the researcher's background and clinical experience. The study design and mixed methods research will be discussed later in the chapter.

Table 5: Steps in the development and implementation of the THAW protocol

Developmental steps
1. Concept development of the early waking protocol, to create a robust foundation utilising a multidisciplinary approach with contemporary practice knowledge and evidence base principles including human research
2. Ethical oversight and scrutiny to ensure responsible conduct of the early waking protocol. To ensure the protocol not only contributes to knowledge but does so in a manner that respects human dignity, rights, and societal values
3. Expert Panel: A collaborative platform which allows healthcare professionals from various specialties to identify their unique experiences, challenges, and insights into the development of an early waking protocol. To leverage their collective expertise, ensuring the early waking protocol resonates with real-world clinical scenarios. By drawing from their clinical experiences, to ensure that the early waking protocol would be both practical and beneficial in a clinical setting
4. Patient and Family Experience: To provide first-hand experiences, challenges, and feedback providing an authentic viewpoint, ensuring that the early waking protocol is patient-centred
5. Clinical Governance: To understand the administrative and governance aspects of clinical care in the context of an early waking protocol. By engaging with members of the hospital clinical governance, the early waking protocol is aligned and incorporates insights related to policy, quality assurance, financial sustainability as well as clinical oversight
6. Implementation: Prospective non-randomised safety and feasibility study of unconscious OHCA survivors. Eligible participants will be assessed to be woken early whilst continuing to be treated with Intravenous Temperature Management (IVTM). A comprehensive neurological assessment will be conducted to determine suitability of early waking using neurological electrophysiology, advanced examination and testing using biomarkers.

3.4 Complexity of implementing a clinical protocol

Developing and implementing a complex clinical protocol using a mixed methods approach leverages off the strengths of using both qualitative and quantitative research to enhance the protocol's effectiveness and relevance. This methodological approach is particularly beneficial in the clinical setting where both statistical data and nuanced personal experiences are critical for comprehensive protocol development and implementation.

Engaging with a wide range of stakeholders, with diverse perspectives, including clinicians, patients, family members, and regulatory bodies like the NHS Ethics Committee in the development process ensures that the protocol is not only clinically sound but also ethically robust and patient centred. Through, focus groups, and other qualitative techniques, the researcher can gain insights into patient experiences, preferences, and the socio-cultural factors influencing treatment efficacy. This deeper understanding enables the protocol to meet patient

needs effectively and ensures that the treatments are considered acceptable and practical for those who will use them.

To determine the safety and feasibility of introducing an early waking protocol, the collection of quantitative data provides a systematic way to assess the direct impacts of the protocol on clinical outcomes. Therefore, ensuring that the evaluations are objective and based on measurable evidence. By gathering detailed numerical data on a range of variables, from patient demographics, physiological parameters to specific clinical interventions and responses can establish a clear, empirical basis, thereby assessing the effectiveness and safety of the protocol. Quantitative measures such as the duration of hospital stay, the frequency of neurological assessments, and patient survival rates are critical for determining the feasibility of the protocol within real-world setting. These metrics would offer quantifiable indicators of a patient's progress and recovery, considered crucial for evaluating whether the protocol can be safely implemented. For example, analysing data related to the success rates of early waking interventions and subsequent neurological function would enable the clinical team to assess the risk-benefit ratio of the protocol interventions effectively. Furthermore, quantitative analysis enables the identification of patterns and trends that could inform clinical decision-making and the need for protocol adjustments.

The need for collecting quantitative data to measure patient outcomes is imperative to validate the clinical efficacy and safety of the interventions in a controlled, measurable manner. This approach not only underscores the feasibility of the protocol but also ensures that patient care decisions are grounded in statistically sound and clinically relevant data, ultimately promoting safe and more effective clinical practice in the care and management of OHCA survivors.

3.5 Researcher background

The researcher has worked in Australia, United Kingdom and New Zealand as a Registered Nurse for three decades in various roles within public and private healthcare sectors. The researcher currently holds a senior leadership position in a tertiary hospital with a clinical background which has been dedicated to cardiothoracic critical care. This provides the researcher with valuable insights into the intricate balance between resource limitations and the delivery of high-level, complex critical care, as with unconscious survivors of OHCA. Furthermore, to appreciate the need for efficient and effective resource management is not just a financial decision but needs to include evidenced-based practice, ensuring care is delivered to the highest standard, as well as ethical decisions about when to escalate or

terminate care. To understand how to weigh the benefits of continued treatment against the quality of life and the wishes of patients and their families, within the context of available resources.

Chapter 4: Methods

"It is the mark of an educated mind to be able to entertain a thought without accepting it."

Aristotle of Stagira 384 – 322 BC

4.1 Introduction, methods

Methods describes the procedures and techniques used to conduct a study, ensuring transparency and reproducibility. The research design, participant criteria and demographics, materials and instruments used to include a detailed account of the procedures followed. The methods used for collecting and analysing data as well as the statistical techniques applied would also be described. Any ethical considerations would also be addressed. Methods is pivotal for demonstrating the study's reliability and validity.

Chapter 4 will provide an in-depth description of the research design, elaborating on the specific techniques, procedures and tools that were used within the study. Following a sequential exploratory study design, this chapter details the methods used in the study and the processes that guided data collection, analysis and interpretation of the findings. The chapter is organised according to the sequential exploratory study design, with each key component of the design being discussed.

Initially, the qualitative phase is explained, covering the participant selection, data collection methods from focus groups, as well as the utilisation of thematic analysis to identify key themes. Subsequently, the transition to the quantitative phase is described, including the iterative process in the development of the Therapeutic Hypothermia and eArly Waking (THAW) protocol based on the qualitative findings. Finally, the implementation of the THAW protocol as a prospective, single centre, non-randomised pilot study, will be discussed in Section 4.3.3.

4.2 The population

Central to phase one of this study, was the implementation of a series of focus groups designed to capture diverse perspectives and insights. Creswell (2015) describes this as "purposeful selection of a sample of participants who can best help you understand the central phenomenon that you are exploring" (Creswell, 2015, p. 76). The decision to employ focus groups was driven by the need to facilitate open discussions, encourage multiple viewpoints, and importantly explore the expertise, experiences and perceptions of the participants. A total

of five distinct focus groups were involved in this phase. Unlike random sampling, where participants are randomly selected to ensure each member of the population has an equal chance of inclusion (Krueger & Casey, 2015), purposive sampling allows for the deliberate selection of individuals who can provide diverse perspectives, knowledge, and experience, including clinical expertise, operational insights and valuable lived experiences from Out Of Hospital Cardiac Arrest (OHCA) survivors and their family members.

The first focus group was the concept development group, which consisted of a multidisciplinary team who were actively involved in research activities. This group was pivotal in shaping the foundational concepts of the early waking protocol and included participants from various specialities including Consultant Cardiologists, Consultant Anaesthetists, Consultant Neurologists, Neuroelectrophysiologists, Senior Nurses, Registrars, Researchers and a Librarian. The diversity of clinical expertise was to ensure comprehensive insights from their respective specialities. The inclusion of Neurologists and Electrophysiologists was crucial for their expert opinion on the neurological implications and practical aspects of early patient waking following OHCA. The Librarian's role was to ensure access to the most up to date evidenced based research. The second focus group was the National Health Service (NHS) Health Research Authority, National Research Ethics Service Committee for the East of England, United Kingdom. This was mandated by the NHS for any original research being undertaken, which involved patients. The committee consisted of health professionals from diverse backgrounds, which included clinical and scientific researchers, pharmacists, a statistician and academics. Their focus was on patient safety and well-being, including that of family to ensure the early waking protocol aligned with broader ethical principles. The clinical expert focus group consisted of cardiology specialists, cardiothoracic surgeons, anaesthetists, neurologists, senior clinicians, critical care nurses, researchers and allied health staff. Their diverse clinical roles, from decision-makers to direct care providers, ensured that the protocol was contemporaneous and practically applicable. The varied insights from this multidisciplinary team fostered innovative ideas and provided a comprehensive and robust validation of the early waking protocol. The fourth focus group included OHCA survivors and their family members. Integrating their viewpoints offered a personalised understanding of the patient and family journey, capturing nuances often overlooked by healthcare professionals (Benizri et al., 2022). Their first-hand accounts of the recovery journey, challenges faced, and emotional impacts provided a holistic understanding of patient needs (Gill et al., 2016). Engaging patients and families ensured that the early waking protocol was both effective and compassionate, highlighting potential areas for improvement in communication and patient comfort during the waking process. The fifth focus group was

the clinical governance team, comprising Medical, Nursing, and Allied Leads, as well as the cardiothoracic directorate General Manager, Finance Manager, and Quality and Patient Safety Manager. This group's role was pivotal in the final stages of developing the early waking protocol. Their involvement ensured the protocol adhered to the highest standards of care, safety, and effectiveness, and was informed by the latest research. The clinical governance team's review process included identifying potential risks, ensuring appropriate mitigation, considering education and training requirements, and assessing financial and resource implications. Their participation provided organizational context and ensured alignment with the hospital's values.

The focus groups in Phase One included participants with diverse backgrounds and expertise. The cross-participation of individuals in multiple groups ensured a comprehensive and multidisciplinary approach. This sampling framework, based on purposive sampling, ensured that the early waking protocol was robust, comprehensive, and tailored to meet patient needs while being feasible for healthcare professionals to implement.

4.3 The research design

4.3.1 Overview

The research was conducted in two distinct phases. The first phase of the study was a series of focus groups which were conducted encompassing a diverse range of stakeholders including researchers, ethicists, clinical experts, patients and family, and individuals involved in clinical governance. The primary objective of these focus groups was to collaboratively develop an early waking protocol for OHCA survivors. The second phase of the study was the implementation of the early waking protocol. A preliminary "run-in" of ten patients was conducted to identify any immediate challenges. Specifically, intervention timings, team collaboration, data collection, documentation, and monitoring. This was followed by a full team debrief, prior to launching the final version of the early waking protocol and implementing into practice.

4.3.2 Phase one

This research was performed from 2014 to 2019 at the Essex Cardiothoracic Centre (ECTC), southeast of England, United Kingdom. The THAW protocol was developed through a series of focus groups, from the research group, ethics committee, OHCA survivors and their families, a clinical expert team and the hospital clinical governance group.

There were five distinct stages in the development of the THAW protocol. It was considered imperative to have a broad cross section of participants represented in each of the focus groups, to provide a multi-stakeholder, multi-perspective and multi-disciplinary contribution. The first stage of protocol development was to explore the initial concept of early neurological prognostication following OHCA. This was presented to the ECTC research group to consider current Evidenced Based Practice (EBP), current literature as well as local, national, and international policies and procedures on the contemporaneous management of unconscious survivors of OHCA. The second stage was in collaboration with the NHS ethics committee. The third stage was consultation with the clinical expert group, including the exploration of overcoming variations in clinical practice as well as introducing new diagnostic interventions and establishing standardised care, to differentiate standard care from the THAW protocol interventions, being proposed. The fourth stage considers the patient or survivor experience including that of the family, specifically communication between the clinical team to patients and their family. Finally, the fifth section describes the clinical governance process, which considers financial implications, organisational risk, clinical impact as well as the duty of care principles, pertaining to the patient and their family members, as well as the clinical staff and organisational impact in relation to the implementation of the THAW protocol.

General inductive analysis from field notes was used to develop these findings and the study design relating to the five phases of the research, as outlined in Figure 2.

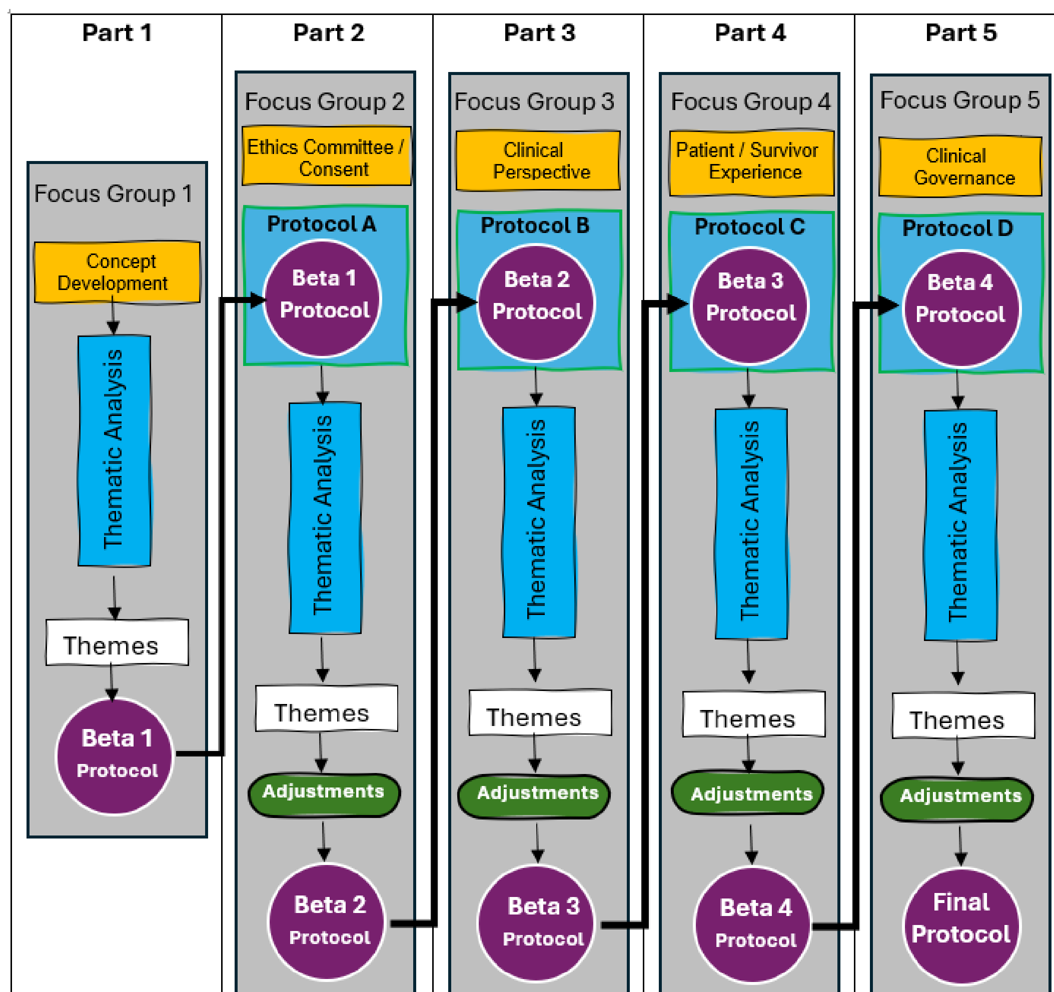


Figure 2: Phases of the THAW protocol development

4.3.3 Phase two

In Phase Two, the primary objective was the implementation of the early waking protocol. This phase commenced with a preliminary "run-in" of ten patients. A prospective non-randomised sampling strategy (or observational study) was selected for phase two of the study. All OHCA patients who presented to the ECTC would be screened on admission using the inclusion and exclusion criteria (Table 6).

This was a single-centre prospective safety and feasibility study, consecutively enrolling 50 unconscious survivors of cardiac arrest. The integration of the research intervention into standard care was separated to distinguish what constitutes the research intervention from standard care.

Standard care

- Intravenous Temperature Management (IVTM): An intravenous temperature management catheter will be inserted as soon as practicable, such as immediately preceding Primary Percutaneous Coronary Intervention (PPCI), to enable Targeted Temperature Management (TTM) to commence during PPCI. TTM will continue in the Intensive Care Unit (ICU). TTM will be maintained at 33° Celsius for 24 hours, with temperature recordings taken hourly.
- Neurological assessment: The Glasgow Coma Scale (GCS) score which includes a motor score, and brainstem reflexes (pupillary light reflexes and eye movements) was performed hourly along with FOUR score, see Appendix One.
- Sedation is administered as part of standard care to maintain a Richmond Agitation and Sedation Score (RASS) of -3 to -5 (see Appendix Two). Sedation will be re-started anytime the patient demonstrates adverse neurological signs or symptoms.
- The patient will be extubated when the patient is neurologically appropriate and fulfils the extubation criteria, see Appendix Three.
- Critical care follow-up clinic – all patients are reviewed on the ward by a member of the critical care outreach team following discharge from critical care. The patient and their relative or close friend are offered an outpatient's appointment, six to eight weeks following discharge from hospital. The follow-up clinic focuses on but not limited to a psychological assessment to provide support and advice to patients and their relative or close friend.

Early waking protocol – research intervention

1. Sedation and or paralysis is administered as part of standard care, but as part of the early waking protocol will only be administered for 12 hours instead of 24 hours to maintain a Richmond Agitation and Sedation Score (RASS of -3 to -5), see Appendix Two. Sedation will then titrated to achieve a RASS of 0 to allow a comprehensive neurological assessment to be performed. As with standard care, the patient will be re-sedated anytime they demonstrate adverse neurological signs or symptoms.
2. Once sedation and or paralysis is withdrawn, and the decision to wake early (12 hours) has been made, a recognised, conscious "anti-shiver regimen" must be instituted, see Appendix Four.
3. Diagnostic tests: Serum biochemical markers Neuron-Specific Enolase (NSE) and S-100B will be drawn when then the patient has been screened and recruited, then at six hours, 12 hours, 24 hours, 48 hours and 72 hours. These samples will be collected and sent offsite to a specialist core laboratory for analysis.
4. For the purposes of the early waking protocol Somatic Sensory Evoked Potential (SSEP) will be performed on the patient's admission to the ICU, then at six hours and 12 hours, If the patient remained unconscious SSEP was performed at 24, 48 and 72 hours. The SSEP uses scalp electrodes to assess the brain's response to an electrical stimulation of the median nerve at the wrist.

5. For the purposes of the early waking protocol a 20-minute Electroencephalogram (EEG) recording was performed on the patient's admission to the ICU, then at six hours and 12 hours. If the patient remained unconscious a 20-minute EEG recording will be performed at 24, 48 and 72 hours. The EEG is to detect burst suppression or generalised epileptiform discharges until the patient is extubated.

4.4 Data collection

4.4.1 Focus group

All focus groups were semi-structured, with the discussion agenda developed to further explore themes and approaches already raised, either in the literature, documentation or previous focus groups. This followed a participatory action research methodology. Written notes were taken at all focus groups.

4.4.2 Observation data collection

The collection of data in Phase Two was complex. Original patient data was captured in the patient's medical records. This included pre-hospital information from the ambulance service which details of timing and treatment of the OHCA. On arrival to the ECTC, the PPCI intervention was not only recorded in the medical notes but on Tomcat ™ (electronic data capture system). The patient's physiological observations were recorded hourly on the ICU chart as well as the mechanical ventilation, medication infusions including dosage and fluid balance.

All study data were recorded onto Case Report Forms (CRFs), which was in paper and electronic format. The completion of the CRF was delegated to a member of the study team (research assistant) who was listed on the Delegation of Authority Log. The Principal Investigator retained the responsibility for the accuracy and integrity of the data entered on the CRF. The CRFs were fully completed and signed prior to review by the appointed monitor for source document verification during monitoring visits. Edit checks for double entry of data was utilised to minimise the rate of error. Monitoring visits and CRF completion logs were used to track data entry in accordance with study logistics and expectations. The NSE and S100-B samples taken for each enrolled participant were assigned a randomisation / trial number that was linked to the patient information but anonymised to the biochemist. Samples were initially stored on-site but were sent to a specialist laboratory (in Sheffield) for analysis, as this was not a routine test at Basildon and Thurrock University Hospital Foundation Trust. All samples were handled in accordance with Human Tissue Act, which includes storage, transport and disposal. Neurological biomarkers test results were not available during the

patient's admission therefore the results did not influence care. A Clinical Research Organisation (CRO), in compliance with recognised Good Clinical Practices and ISO14155, conduct monitoring visits. The major function of the clinical monitor was to observe and assess compliance of the investigators and investigational site with the requirements of the clinical study protocol and Good Clinical Practices. The monitor's duties included on-site visits and review of clinical study documents and results. The monitor operated under written procedures to ensure compliance with the protocol.

4.5 Data analysis

As this is a feasibility study there is no expectation of a conclusive statistical analysis. Nevertheless, best use will be made of the data and it will analysed THAW version 2.2 14 13.08.2015 in the way required for a main study to the extent that the data are sufficient to make it technically possible. This is a pre and post study design and so the intervention will be assessed using a paired comparison of the pre and post means of the outcome measures. This will be achieved using a paired permutation t-test, and bootstrap 95 percent confidence limits will be obtained for the mean difference. Statistical analysis will be performed to meet objectives to describe time cooling was initiated, when therapeutic target temperature of 32-34° Celsius was achieved, time when sedation was stopped, and time when phased re-warming commenced. Demographics (age, sex, and race) and other baseline characteristics will be summarised using descriptive statistics.

4.5.1 Thematic analysis

The researcher first reviewed the raw data from each focus group to become familiar with its content before starting the process. Each focus group's data was then coded and recoded twice more on separate occasions. The outcomes of these coding sessions were compared to ensure consistency and reliability in the coding process.

To ensure the reliability and validity of the coding in thematic analysis, it is common practice for another researcher to verify the initial coding by independently coding some of the same data and comparing both sets to check for consistent interpretation (Miles et al., 2020). In this study, an experienced qualitative researcher with expertise in OHCA management and protocol development verified the coding. Trustworthiness in a qualitative study encompasses the elements of consistency and credibility, which are considered paramount to ensure the study's accuracy and validity (Miles et al., 2020). Inter-rater reliability of coding can be employed to assess the consistency with which the research accurately represents the social

phenomena being studied. This method ensures that multiple coders interpret the data in a similar manner, thereby validating the research findings (Flick, 2018). The themes used to develop the THAW protocol were discussed and explored by each of the focus groups, which assessed the utility of the THAW protocol.

4.6 Timeline

Phase One began September 2014. All focus groups were facilitated by the researcher. The focus group that consisted only of the researchers met as follows: 19 September 2014, 17 October 2014, 14 November 2014, 16 January 2015, 13 February 2015, 20 March 2015. The number of people at the focus group meetings was usually 10. The ethics committee focus group was a single meeting on the 12 June 2015. There were 10 people present, not including the researcher and supervisor. Ethics approval was also received for the Therapeutic and Hypothermia and eArly Waking (THAW) trial from Basildon and Thurrock University Hospital and Foundation Trust on 13 July 2015. The clinical expert focus group meetings were held on 4 November 2015, of which there were three separate meetings, 15 June 2016, 20 July 2016 and two separate meetings were held on the 10 August 2016. The final clinical expert focus group was held on the 15 February 2017. This was two separate meetings, including the cardiology specialists across all disciplines and the second meeting was a combined critical care meeting with the anaesthetic and nursing team.

The initial patient and family focus group meeting was in February 2016, this was followed up with a post implementation meeting in May 2017. The first clinical governance group meeting the protocol was presented occurred in February 2015. This was early in the protocol development phase and was prior to the protocol being submitted to ethics. The next clinical governance group meeting, where the early waking protocol was presented, discussed and approved was December 2016.

Phase two of the study, it was estimated the ECTC would admit approximately 80 patients post OHCA per year. Therefore, a recruitment rate of 80 percent based on the availability of the research team, the estimated study period was 18 months. The THAW study commenced on the 26 February 2017 and data collection ceased on 23 January 2018 (total study period of 11 months). The study ran continuously over this period although patients were only recruited when all of the research team were available.

4.7 Reliability and validity

4.7.1 Qualitative data

The raw data captured at each focus group meeting was read by the researcher prior to coding to become familiar with the data content. The coding was cross-checked for consistency on multiple occasions. To enhance the reliability and validity of the thematic analysis, another experienced researcher in healthcare and previously involved in protocol development verified the coding. The aim was to ensure consistency in data interpretation between researchers. The study emphasises the importance of meeting the expectations of its diverse readership, including health researchers, clinicians, patients, and management. Trustworthiness in the study's qualitative approach was highlighted, focusing on consistency and credibility. Inter-rater reliability ensured accurate representation of the researched phenomena.

4.7.2 Quantitative data

To ensure the reliability and validity of the quantitative data in this feasibility study, several key principles were applied. Despite the expectation of limited statistical conclusions, the data were analysed using version 2.2 of the THAW protocol. Reliability was addressed through internal consistency by ensuring standardised instruments and protocols were used for measurements in various aspects of the study. For early neurological assessments and prognostication, standardised tools such as the GCS and RASS scores were employed consistently across all patients, with detailed timing intervals of when to perform these assessments. This ensured uniform evaluations and consistent measurement of neurological status, irrespective of the evaluator. In examining the safety and efficacy of IVTM combined with counter-shivering strategies, validated devices and standardised methods for temperature and shivering monitoring were used. The application and assessment of IVTM and counter-shivering interventions ensured these strategies were consistently applied. Internal consistency was maintained by validating the instruments used, ensuring they accurately reflected physiological responses to IVTM and shivering management. For physiological assessments determining the suitability of waking unconscious OHCA patients early, standardised monitoring equipment and devices were used, ensuring regular and consistent assessment intervals. This approach ensured that the metrics used consistently measured the same physiological responses, providing reliable data on patient suitability for early waking. By strict adherence to these standardised instruments and protocols, the study ensured the reliability of its findings.

Statistical validity was reinforced by using appropriate statistical methods like paired permutation t-tests and bootstrap confidence limits, ensuring the sample size and statistical tests were correctly applied and interpreted. Descriptive statistics summarised demographics and baseline characteristics, providing a reliable overview of the study population. By adhering to these principles, the study ensured the data's reliability and validity, making the most of the collected data even within a feasibility study framework.

4.8 Ethical approval and informed consent

The United Kingdom, National Health Service, Research Ethics Committee gave ethics approval for this study on 30 June 2015 (Ref 15/EE/0173). Submitted to on date, see Appendix

4.9 Methods, summary

The "Methods" section details the study's procedures and techniques, ensuring transparency and reproducibility, and covers the research design, participant criteria, materials, and data collection and analysis methods. This section is vital for demonstrating the study's reliability and validity. Chapter 4 elaborates on the sequential exploratory design used, detailing both qualitative and quantitative phases, including focus groups and the development and implementation of the THAW protocol. Various stakeholder focus groups, such as clinical experts and OHCA survivors, contributed diverse insights to the protocol. Ensuring trustworthiness through consistency and credibility, the study employed inter-rater reliability for coding verification. Ethical approval was obtained from the NHS Research Ethics Committee.

Chapter 5: Protocol development findings

"Doubt is the origin of wisdom."

René Descartes 1596 – 1650

The following chapter has been adapted from the following publication:

- Watson, N., Potter, M., Karamasis, G., Damian, M., Pottinger, R., Clesham, G., ... & Keeble, T. R. (2018). Is it feasible and safe to wake cardiac arrest patients receiving mild therapeutic hypothermia after 12 hours to enable early neuro-prognostication? The therapeutic hypothermia and early waking trial protocol. Therapeutic Hypothermia and Temperature Management, 8(3), 150-155.

5.1 Introduction

The following chapter is divided into five respective sections. The first section the development of the initial concept idea, early neurological prognostication following OHCA, was presented to the Essex Cardiothoracic Centre (ECTC) research group. To consider current Evidenced Based Practice (EBP), current literature as well as local, national and international policies and procedures on the contemporaneous management of unconscious survivors of Out of Hospital Cardiac Arrest (OHCA). The second section discusses the development of the THAW protocol in collaboration with the National Health Service (NHS) ethics committee. The third section presents the findings from the clinical expert focus group, including the exploration of overcoming variations in clinical practice as well as introducing new diagnostic interventions and establishing standardised care, to differentiate standard care from the THAW protocol interventions, being proposed. The fourth section considers the patient or survivor experience including that of the family, specifically communication between the clinical team to patients and their family. Finally, the fifth section describes the clinical governance process, which considers financial implications, organisational risk, clinical impact as well as the duty of care principles, pertaining to the patient and their family members, as well as the clinical staff and organisational impact in relation to the implementation of the THAW protocol. Through the five stages of the THAW protocol development, it was considered imperative to have a broad cross section of participants represented in each of the focus groups, to provide a multi-stakeholder, multi-perspective and multi-disciplinary contribution.

5.2 Part 1 – Concept development of the THAW protocol

This section describes the development of the original research concept idea of establishing a clearly defined pathway for the management of unconscious survivors of OHCA admitted to ECTC to enable early neurological prognostication. Furthermore, it was intended that the pathway would provide critical care clinicians with a clear and consistent framework for early clinical decision making in terms of providing an appropriate plan of care that best aligned with anticipated neurological outcomes for OHCA patients.

In Part 1 of the study (Figure 3), key clinical and non-clinical staff with a specific interest in cardiothoracic research participated in a meeting to consider the development of a protocol that focused on positive prognostication as opposed to patients with a poor prognosis.

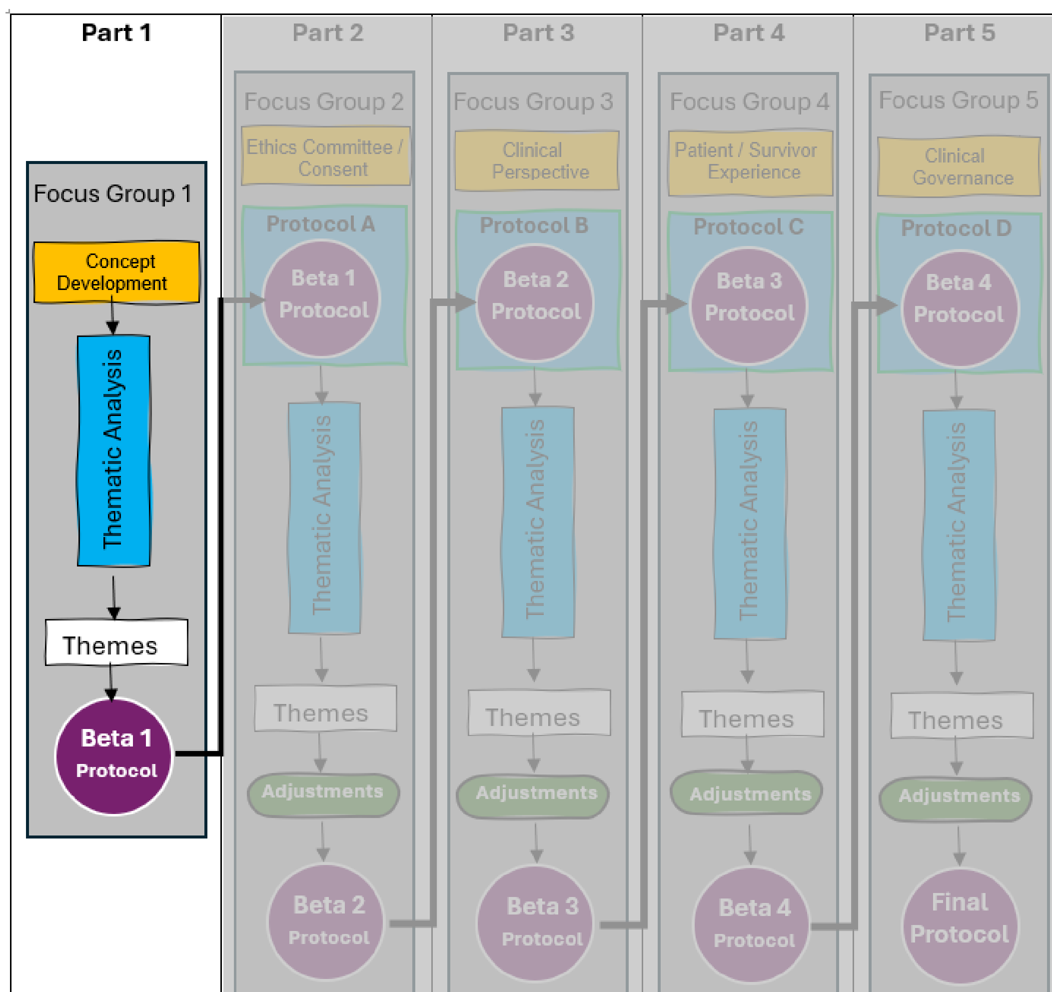


Figure 3: Part 1 – Concept development of the THAW protocol

5.2.1 Study participants, Part 1

In the first stage of the study, the participants were from several specialties as illustrated in Table 10.

Table 6 Profile of participants

Discipline	Professional Background	Age	Years Experience
Medicine	Cardiology Registrar	32	7
	Cardiology Research Registrar	31	6
	Cardiothoracic Surgical Registrar	38	13
	Consultant Anaesthetist 1	36	11
	Consultant Anaesthetist 2	47	22
	Consultant Cardiologist 1	43	18
	Consultant Cardiologist 2	41	16
	Consultant Cardiologist 3	39	14
	Consultant Cardiologist 4	58	33
	Consultant Neurologist 1	54	29
	Consultant Neurologist 2	57	30
	Director of Intensive Internal Medicine	59	32
Allied	Clinical Psychologist	35	10
	Neurological Electrophysiologist 1	61	36
	Neurological Electrophysiologist 2	64	39
Nursing	Cathlab Manager 2	49	28
	Critical Care Outreach Nurse 1	48	27
Research	Researcher 1	21	1
Other	Librarian	51	28

5.2.2 Themes from the THAW protocol concept development

As shown in Figure 4, thematic analysis concerning the concept development of the THAW protocol resulted in five extant themes, derived from 13 categories and 43 codes.

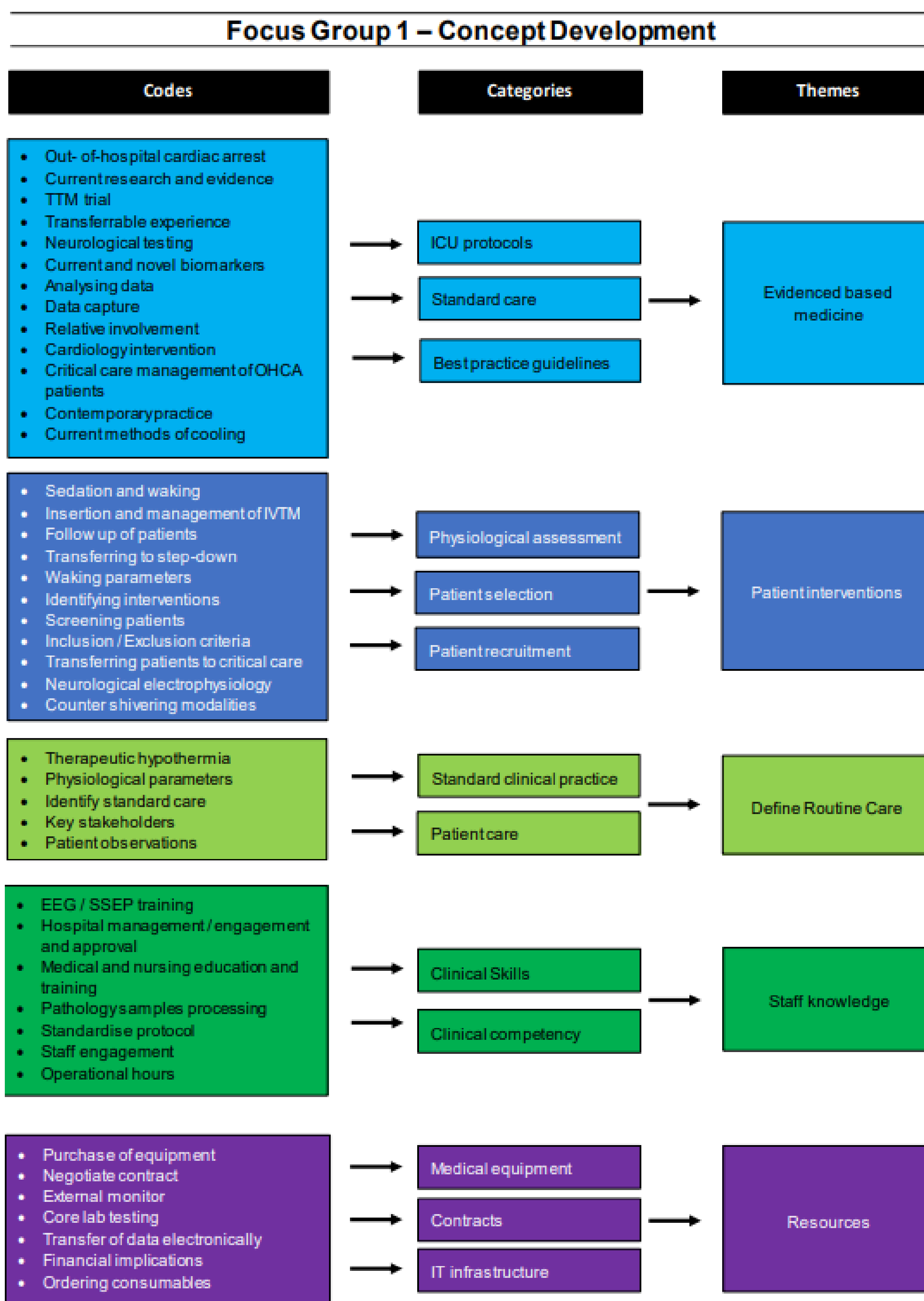


Figure 4: Thematic analysis of the THAW protocol concept development

Theme 1: Evidence based medicine

Intensive care protocols

When referring to ICU protocols in this section, it specifically pertains to those implemented at the ECTC. To highlight that these protocols were not developed in isolation, they were based on contemporaneous evidence and the latest literature. The ICU practices at the ECTC aligned with current scientific research and expert consensus, with an emphasis on patient safety and best practice principles. The research team participants not only considered current literature, but local, national and international policies and procedures on the contemporaneous management of unconscious survivors of OHCA.

The research participants involved in the concept development of the THAW protocol discussed the parallels between the management of OHCA survivors and the approach for post-operative cardiothoracic surgical patients. The research participants discussed the similarities with organ support, neurological assessment and critical care management strategies of these two patient groups. Highlighting that both contexts required careful monitoring, physiological as well as neurological assessments to determine the ideal moment for waking and extubation.

> *When I think about organ support, neurological assessment and our critical care strategies, are we emphasising the same careful monitoring and evaluations to decide the best timing for waking and extubation?*

Consultant Cardiologist 1

> *Are we drawing a parallel between the management of our OHCA survivors and the post-operative cardiothoracic surgical patients?*

Consultant Cardiologist 3

Historically, cardiothoracic surgical patients were assessed after a protracted recovery period in critical care, with a comprehensive physiological and neurological assessment being performed to enable the critical care team to decide a patient's readiness to be woken and extubated. However, this practice has evolved over recent decades with advances in critical care technology, monitoring equipment, medical management and practices, as well as standardised critical care protocols. Consequently, the post-operative recovery period for cardiothoracic surgical patients has significantly reduced. For example, the enhanced recovery model or fast-track cardiac care (Wong et al., 2016), where suitably appropriate patients have their anaesthetic medication reversed whilst still in the operating theatre, therefore patients

being woken and extubated before being transferred to critical care, inevitably leading to a shorter critical care and hospital length-of-stay.

> *Considering our approach to cardiothoracic surgical patients, have we shifted our practices significantly due to advances in critical care technology and standardised protocols?*
>
> Cardiology Registrar

> *Reflecting on our practices over the decades, do you think ICPs have streamlined our post-operative management for cardiothoracic surgical patients? And do we think this could be applied to our OHCA patients?*
>
> Consultant Cardiologist 1

Patients with extended operating procedure times or extended periods on cardiopulmonary bypass, would be transferred to the critical care immediately post-operatively, where they would be managed by the critical care team using a protocolised bundle of care, with defined physiological parameters, measures and targets, allowing the critical care team to what is now commonly phrased as warm, wake and wean. In essence, a bundle of care or pre-determined integrated care pathway that the critical care team utilises in managing the post-operative phase for cardiothoracic surgical patients.

> *How impactful do we believe the standardised critical care protocols have been in reducing the post-operative recovery period for our cardiothoracic surgical patients?*
>
> Consultant Cardiologist 4

Best practice guidelines

From an examination of the post-operative surgical ICP emerges the universality of certain critical care principles that are also described in the European Resuscitation Council (ERC) and European Society of Intensive Care Medicine (ESICM) guidelines on post-resuscitation care (Nolan et al., 2021). Both the surgical ICP, ERC and ESICM post-resuscitation guidelines prioritise continuous cardiac and hemodynamic monitoring, recognising the potential for cardiac instability. Furthermore, the emphasis on neurological monitoring is equally significant, given that both post-surgical and OHCA patients face risks of neurological compromise, whether from the surgery itself or the period of cardiac arrest. Ventilation and oxygenation strategies, including requirements for intubation and mechanical ventilation, are consistent in addressing respiratory needs for both patient groups. Hemodynamic support, use of vasopressors and inotropes, is also a common characteristic as is temperature management, notably TH, are relevant in both contexts. Systematic neurological assessments, routine fluid and electrolyte management, pharmacological approaches including sedation and

analgesia regimes, as well as early mobilisation and rehabilitation. Thus, the evidence-based post-operative surgical ICP and the ERC and ESICM guidelines (Nolan et al., 2021) for post-resuscitation care, despite serving different patient populations, share foundational critical care practices, irrespective of the clinical scenario.

The advances in the cardiac ICP have meant that patients who would have historically occupied a critical care bed for days or possibly weeks following cardiac surgery, now occupy a critical care bed for an average length-of-stay of 2.4 days before being transferred to a step-down area or ward prior to being discharged from hospital. Therefore, the development of the THAW protocol that focused on positive prognostication and based on foundational critical care practices was agreed by the research participants.

> *Given the shift towards post-op care bundles, which we know have improved patient outcomes, reduced ICU and hospital length of stay for our post-operative cardiothoracic patients, I think developing a similar protocol or ICP for the management of OHCA survivors would be beneficial.*

Consultant Cardiologist 3

Standard care

There was not a clear and consistent approach to Targeted Temperature Management (TTM) treatment of OHCA patients. With consultant anaesthetist's determining treatment plans that best aligned with their personal viewpoint. There was a divide in those who supported TTM and those who did not, which would lead to inconsistencies in whether OHCA patients were treated with TTM. To remove the ambiguity of whether to treat with TTM, there was a consensus amongst the clinicians to incorporate TTM management into the OHCA pathway unless contraindicated.

> *I think it would be useful for us to standardise our management of OHCA patient's. Particularly around IVTM, neurological assessment, blood tests. This would provide consistency and remove variation of practice. This would also familiarise everyone with equipment.*

Cardiology Registrar

Theme 2: Patient interventions

Physiological assessment

In determining a patient's readiness to be woken following an induced coma and extubated in critical care relies on a clinical assessment against established criteria. The assessment is undertaken by a clinician i.e. a Critical Care Registered Nurse (CCRN) or an Anaesthetic

Doctor. It was established that the THAW protocol should specify pre-determined physiological parameters which include neurological, cardiovascular, respiratory and metabolic thresholds that must be met before a patient can be considered appropriate for extubation. These parameters would apply to all patients being considered for extubation irrespective of the underlying reason for the patient being intubated.

> *I recognise the importance of rigorous clinical assessments in determining a patient's readiness for extubation, do we identify specific physiological criteria that need to be met?*
>
> Consultant Anaesthetist 1

The complexity with the unconscious survivor of cardiac arrest is the down time or time taken before there is a Return of Spontaneous Circulation (ROSC). Time taken to establish ROSC directly correlates with neurological recovery. Therefore, to establish the extent of neurological injury, this can only be fully appreciated once the sedation has been stopped. However, there are several neurological diagnostic tests that can be carried out whilst the patient remains unconscious or sedated to indicate neurological injury, which include neurological electrophysiology, electroencephalogram (EEG) and Somatosensory Evoked Potential (SSEP) both of these tests can be used to not only detect abnormalities in brain waves or electrical activity but absence of pathological patterns and reactivity to external stimuli can represent normal brain activity and potentially a positive prognosis. Furthermore, neurological biomarkers expressed in plasma as well as radiological, either Computed Tomography (CT) or Magnetic Resonance Imaging (MRI), compliment the clinical and electrophysiological assessments in providing a comprehensive overview of brain health and function. These tools, when utilised synergistically, offer clinicians a multifaceted approach to diagnose, monitor and prognosticate neurological conditions. However, these complex diagnostic tests are not readily available outside of hospitals that provide specialised neurological services, which includes equipment, as well as trained personnel to perform the test(s) and interpret the results.

> *Drawing from the established evidence in the ERC and ESICM guidelines, it's undeniable that EEG and SSEP are pivotal in assessing OHCA survivors. Given their recognised importance, I think we need to prioritise integrating these diagnostic tools into our protocol. But we will need to consider accessibility, interpretation.*
>
> Consultant Neurologist 1

Patient selection

All participating clinicians agreed that there was ambiguity about whether to treat OHCA patients with TTM., which has led to inconsistent management.

> *We would need to review all the current literature on Out-of-Hospital-Cardiac-Arrest Management and determine what everyone is doing following TTM.*

Consultant Cardiologist 1

There was significant reservation amongst participating clinicians and the manager about direct referral of OHCA patients from the ambulance staff to the ECTC. Primarily because of the potential for patients with a non-cardiac cause being inadvertently admitted. The implications of inappropriate admissions would negatively impact critical care bed capacity, therefore the surgical programme, placing the regional tertiary service at risk. Furthermore, with limited critical care bed capacity at local district hospitals would also make repatriation more difficult.

> *I would like to see us map out the patient journey from the perspective of the patient, which would include the referral pathway from the ambulance service to us here at the CTC through the cathlab, to critical care and finally to the ward and discharge home. It would be good if we could incorporate the acceptance criteria for PPCI to prevent the need for secondary transfers.*

Cardiology Registrar

> *As a 24-hour PPCI centre we need to consider how we can ensure continuity of service provision to this cohort of patients. We need to be cognisant of the fact this will potentially open the doors to all cardiac arrest patients being referred to the CTC which may overwhelm us, so we will need to have very clear acceptance criteria to ensure that only cardiac arrest patients, where the aetiology is clearly cardiac are accepted.*

Cathlab Manager 2

As a consequence of the discussion and analysis, it was highlighted that it was important to differentiate between standard care and the THAW protocol interventions. To define standard care, an OHCA pathway was developed from admission, coronary intervention, through to critical care management and discharge home or repatriation (Figure 5) and explored with participants.

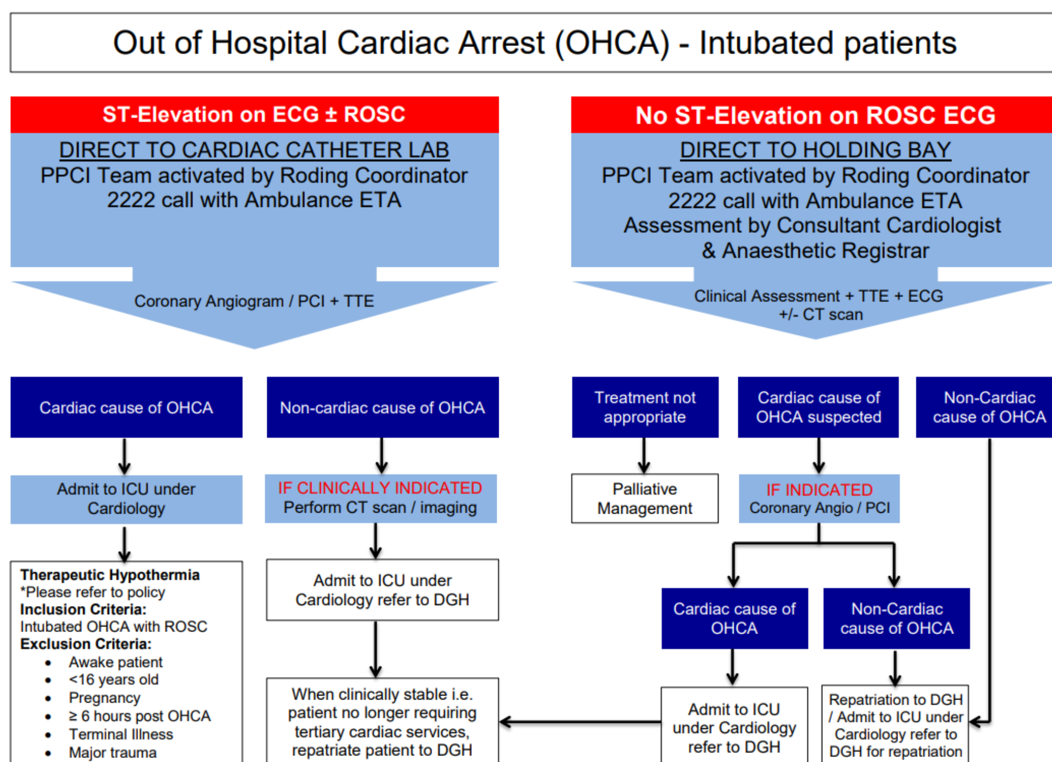


Figure 5: Developed pathway for unconscious OHCA patients

The pathway incorporates the NHS Primary Percutaneous Coronary Intervention (PPCI) activation pathway, which is also utilised for OHCA patients to ensure only patients with a likely cardiac cause for the cardiac arrest are admitted to the ECTC. Patients who do not meet the PPCI criteria would be diverted to their local hospital. This pathway identifies patients having an acute ST Elevation Myocardial Infarction (STEMI), in which case the recommendation is for PPCI, which is minimally a diagnostic angiogram, but may proceed to angioplasty and or deployment of stent.

Patient recruitment

The research group participants wanted to ensure the recruitment criteria for the THAW protocol, was clearly defined with patient safety being the priority. The inclusion and exclusion criteria were specifically aimed at only unconscious OHCA survivors, where the aetiology of the cardiac arrest was known or most likely to be cardiac in origin. The research group participants wanted to ensure the THAW protocol exclusion criteria would eliminate potential confounding factors such as patients with Do Not Attempt Resuscitation (DNAR) orders, a terminal illness and any patient who was pregnant, due to the potential ethical issues and or associated risks. Furthermore, it was also considered important to exclude patients with

known conditions such as coagulation disorders, oxygen dependency, or patients where medications used during the early waking phase would be contraindicated.

> *Are there any specific pharmacological considerations in excluding patients on certain medications, especially during the early waking phase?*
>
> Consultant Anaesthetist 2

> *How can we ensure that patient information, past medical history etc., particularly DNAR orders or known medical conditions are known before we recruit?*
>
> Director of Intensive Care Medicine

> *How will be responsible for screening?*
>
> Critical Care Outreach Nurse

Certain patients might be unsuitable for the catheter due to anatomical reasons, due to minimum height requirement might be linked to the catheter's size and the patient's vascular anatomy, ensuring effective and safe catheter deployment. By clearly identifying the inclusion and exclusion criteria ensures patient safety and aligns with current best practice.

Theme 3: Define routine care

Standard clinical practice

Participating clinicians generally agreed there maybe variations in practice that not all treating clinicians necessarily support OHCA patients receiving TTM, which would result in inconsistency in care delivery.

> *We obviously support therapeutic hypothermia but we have to acknowledge that a couple of our anaesthetic colleagues don't, so we will need to think this through.*
>
> Consultant Cardiologist 1

To ensure consistency in the management of OHCA patients, it was considered by the clinicians that the decision to treat with TTM should be standardised and the decision should be made by the consultant cardiologist. The treatment should be prescribed and commence in the cardiac catheter lab.

> *Let's standardise IVTM as routine management for our OHCA patients. If we include this in our OHCA pathway, this will need to go through governance which will ensure that we have agreement from all of our key stakeholders.*
>
> Consultant Cardiologist 3

Participating clinicians agreed that there needed to be a standardised approach for the management of OHCA patients to enable clear differentiation from the THAW protocol interventions.

> *It will be important for us to clearly differentiate between standard care and the intervention, so we will need to standardise our management of OHCA patients. We will need to put a protocol together and submit to ethics for approval.*

Consultant Cardiologist 4

Participating clinicians agreed it was important to include neuro biomarkers as a prognostic indicator but were unfamiliar with current evidence to support which had the strongest correlation. Furthermore, there were concerns expressed about the logistics of processing samples as well as concerns about utilising the biomarkers to guide treatment. The ECTC, like most cardiothoracic critical care units, in the United Kingdom, care for a combination of cardiac surgical and complex cardiology patients requiring a minimum of advanced mechanical ventilator support and or two organ support for example renal or cardiovascular organ support. The limitation of being a standalone centre is access to specialist services such as advanced neurological diagnostic testing, including on-site neurological electrophysiology and the ability to process neurological serum biomarkers. Both in terms of availability or access to diagnostic equipment and appropriately trained health professionals to perform the investigations and to interpret the results of those investigations.

> *We need to look at what neuro biomarkers are indicative of neurological injury following cardiac arrest and any that are emerging that we might want to include. There may be an issue with processing some of these tests on-site so let's work out exactly which tests we want, then we can reach out to biochemistry. If these biomarkers can't be processed on-site, that will be ok as we won't be using these results to change or inform decision making anyway.*

Consultant Cardiologist 2

Due to the apprehension, there was a consensus by the participating clinicians about using neuro-biomarkers to direct treatment decision making. Balancing innovation with clinical prudence, the decision was made not to use neuro- biomarkers to inform treatment decisions. Instead, samples would be tested offsite in a specialised core lab. While this meant immediate clinical decisions would not be influenced by the laboratory results of the neuro-biomarkers, the data would be invaluable for the post hoc analysis, therefore extending the evidence repository of knowledge and potential for future integration.

> *We know that NSE and S100B have shown promise in determining poor outcomes but there is currently limited evidence on there use on positively prognosticating, I'm not sure we should be using them for clinical decision making.*

Consultant Cardiologist 1

> *I agree I also think that in view of the fact we wouldn't be able to process these on-site anyway, that the samples would need to be sent to either Queens Square, we should review the results in our post-hoc analysis.*

Consultant Neurologist 1

Clinicians identified the sedative affect and protracted half-life of morphine compared to that of fentanyl, which was particularly relevant in the context of early waking and neurological assessment.

> *I think we need to look at what sedatives and paralysing agents we are using for these patients as these are different from what we used for the COOLAMI trial. Particularly if we want wake early to assess their neurological function whilst they are still being cooled.*

Consultant Anaesthetist 1

Theme 4: Staff knowledge

Clinical skills

Clinicians expressed concerns about having no on-site neurophysiology capability. There was knowledge of expertise elsewhere and consideration was given to whether there was capacity to support the delivery of a 24-hour, seven-day week service. Other options included upskilling research or critical care staff to perform EEG and SSEP.

> *I'm concerned about the advanced neurological assessments and tests that are being proposed, particularly if we are going to consider doing EEGs, SSEPs, CT and or MRI as we don't currently have the neuro electrophysiology on site.*

Consultant Anaesthetist 4

> *We will need to consider the logistics of how and who is going to perform these tests, what equipment that we are going to need and who is going to interpret the results. Particularly if we are not just looking at this from the perspective of a research project but potentially from a sustainable model that could be adopted by other standalone cardiac centres. Perhaps we need to reach out to a Consultant Neurologist with an interest in cardiac arrest who might like to partner with us.*

Consultant Cardiologist 2

There were some concerns raised in relation to the training required to change from surface cooling to IVTM. Specifically, around the counter-shivering strategies of having a patient awake or waking the patient whilst maintaining TTM.

> *A concern I have is that we currently use Blanketrol which we can't wake patients on. The use of IVTM has only been used on a select few therefore critical care staff are not familiar with using IVTM.*

Critical Care Outreach Nurse 1

Some clinicians considered it was unrealistic for a team to be trained and competent at performing neurophysiology tests, that it would be preferable to be limited to two staff members. Recognising that training a large team would be potentially over burdensome for some. There was also the potential for quality control to be affected and issues for staff being able to maintain competence, when considering the unpredictability of admissions and staff shift patterns.

> *I believe it's too ambitious to train multiple people on performing EEG and SSEP. We need to ensure the quality of these tests. I would suggest let's limit this to two researchers. We will need to explore a neuro electrophysiologist who is prepared to train and sign them off as competent, to provide some quality assurance.*

Consultant Cardiologist 2

There needed to be a balance between the number of staff trained and competent to perform the neurophysiology tests at the same time be able to maintain the level of service to perform neurophysiology tests whenever there was an OHCA admission that had been recruited onto the THAW trial. With each neurophysiology test taking approximately an hour, the test would need to be performed on the arrival of the patient to critical care, then repeated three times within the first 24 hours, followed by an additional two tests at 24 hourly intervals for the following two days for each patient.

> *I do have a concern for logistical reasons about only having two trained to perform EEG/SSEP, particularly if we are recruiting 24/7.*

Neurological Electrophysiologist 1

Clinical competence

There was a collective acknowledgment by clinicians about the importance of training, skills and knowledge with an emphasis on multidisciplinary working in caring for the OHCA patient.

> *We will also need to have key personnel trained for patient recruitment, enrolment as well as expertise in initiating IVTM in the cathlab. I would suggest we establish a multidisciplinary team comprising of cathlab, critical care as well as research staff who are activated on acceptance of a referral to the CTC.*

Critical Care Outreach Nurse 1

The counter-shivering techniques used in the previous 'COOLAMI' trial was on conscious patients and the TTM treatment time was limited to three hours. The notable difference is that OHCA patients have had an anoxic period and will have been in an induced coma for a minimum of 12 hours, it is unknown the extent of their brain injury, therefore how they will respond when being woken. Maintaining TTM for potentially 12 hours compared to three hours in a compliant patient will be a significant challenge.

> *With respect to the counter shivering techniques we used for COOLAMI we should replicate this is a tried and tested method. We will need to consider what the maximum dose for Pethidine as we will be maintaining TTM for 24 hours as opposed to the 3-4 hours with COOLAMI.*
>
> Consultant Cardiologist 2

Theme 5: Resources

Medical equipment

Clinical information recorded on the Cardio-Vascular Information System (CVIS), which records the cardiac interventions in the cardiac catheter lab. In critical care, physiological observations are recorded on the Mindray N19 or N22 monitors and mechanical ventilation parameters on the Maquet Servo I ventilator, both with download capability. The Zoll Thermoguard XP records the TTM data and the Maquet Datascope CS300 records the intra-aortic physiological data, both with download capability. Observational assessment data would be recorded on the critical care chart, therefore would need to be transcribed, however neurophysiology would be recorded using the Cadwell Neuromonitoing system, which recorded the neurophysiological event that would require formal reporting.

> *Data capture will be important. There will be multiple sources as well, it would be good if we can look at a way of automating this.*
>
> Critical Care Outreach Nurse 1

> *We will need to discuss this with the MEMs team to see if there is a way to download data from both monitoring and devices including the IVTM machine.*
>
> Researcher 1

Contracts

There was a sense echoed by the Consultant medical participants, acknowledging the gravity of the research. They considered that taking a proactive stance early and engaging with management would not only provide a nuanced perspective but also their support. Emphasising the need for early and continuous collaboration. The emphasis on early engagement was considered more than just a formality, but a strategic move to ensure the project's success. By involving management from the onset, the Consultant participants considered this would cultivate a sense of shared ownership, mutual understanding and genuine buy-in. The benefit of this approach would create a collaborative environment where potential challenges are anticipated and addressed collectively. Furthermore, this transparent approach would also generate a sense of commitment, to hopefully ensure that the project receives the necessary resources and support, as well as ensuring the project aligns with organisational goals, maximising its potential for success and transformative impact.

> *This is a significant research project that we are proposing, we will need to ensure that management are aware of this project and are in agreement. Let's ensure we engage with them early to elicit their response. We will obviously need their support and buy-in.`*

Consultant Cardiologist 1

There was a real sense of concern in relation to cost implications. The reality of not just the initial purchase of the EEG and SSEP hardware but also the software and consumables. Furthermore, the labour costs of those involved in performing the EEG and SSEP but also having the recordings interpreted and formally reported. In the context of the trial, there was discussion about the possibility of exploring charitable funding or applying for research funds. As a result, a local self-funding and voluntary charity group, was engaged. They were regularly involved in fundraising activities for the Essex Cardiothoracic Centre and agreed to fundraise for the purchase of the EEG and SSEP hardware. A service contract was then negotiated with the supplier of the neurophysiology equipment, as well as separate contracts for the consumables with NHS supply chain. With regards to labour costs, it was considered that THAW research activities that occurred outside of the researcher's normal contracted hours would need to rely on the good will of participating clinicians.

> *It's not just the one-off purchase cost for the EEG/SSEP machine but we will need to consider the consumables. My concern is how is this all going to be funded. I suspect there will be service packages with this which will also potentially have cost implications.*

Neurological Electrophysiologist 2

This research clearly has attributable cost implications – it will be useful to have a clear understanding of the exact costs and how these will be covered. So equipment, consumables, diagnostics, external expertise.

Consultant Anaesthetist 1

The IVTM catheter and kits cost approximately UK£1,000.00, considerably more expensive compared to the surface cooling kits at UK£350.00. However, there was no alternative as patients were not able to be woken while they are being treated with surface cooling. A competitive contract with the supplier for 60 IVTM catheters and consumables was negotiated. Furthermore, the potential for cost saving would also potentially be realised through stepping down the patient early from a level three bed in ICU, at a cost of approximately UK£2,200.00 per day to a level two bed at a cost of £800.00. Additionally, waking patients after just 12 hours instead of the traditional 36 hours, would potentially reduce the critical care length of stay by 24 hours.

Can we also consider the significant cost of the IVTM catheters, these are significantly more expensive than the Blanketrol kits. We will need to be mindful of the price difference and consider the quantifiable data to justify the additional cost.

Cathlab Manager 2

Information technology infrastructure

There was a recognition and understanding by the research group participants of the significant amount of data collection that would be required to capture and populate the Case Report Form (CRF) created for the purposes of the THAW trial, see Appendix Six. Not only did this include the admission and treatment interventions in the cardiac catheter lab, but also the hourly physiological observations in critical care, including the observational assessment data, neurophysiology tests and the pathology results. Furthermore, it also includes demographic, past medical history, as well as pre-hospital data, specifically the cardiac arrest event.

The group considered that it would be imperative to utilise the data captured on the various electronic platforms to avoid transcribing and what was described as a very labour-intensive exercise. Consideration would need to be given to identifying how to obtain the electronic information obtained from the Computer Aided Dispatch (CAD) system combined with the data from the Electronic Patient Record (EPR) used by East of England Ambulance and the Essex and Herts Air Ambulance Services, which captured pre-hospital data. Without a consultant neurologist with neuro-electrophysiology expertise onsite, reporting of EEG and

SSEPs, for convenience and the geographical location of the Consultant Neurologist agreeing to report on these tests, would require electronic export and transfer of data from these tests. The logistics of providing secure data transfer of EEG and SSEP files was a significant concern.

> *There is also the issue of core lab support for interpreting the EEGs and SSEPs. Consideration will need to be given to who is going partner with us, how will we get the EEG and SSEPs to this individual for them to interpret or is there a possibility to transfer these electronically. I think we also need to identify whether there will be an associated cost.*
>
> Consultant Neurologist 1

5.3 Part 2 – Research ethics approval

This section describes the ethics approval process with the members of the National Health Service (NHS) Research Ethics Committee (REC) panel. Their primary role is to protect the rights, safety, and well-being of research participants. The NHS REC is comprised of a mixture of registered healthcare professionals as well as 'lay' members who are not primarily involved in research or registered as healthcare professionals. The NHS REC committee independently evaluates research proposals for ethical considerations, ensuring the studies are participant-centric and operate autonomously from research sponsors, funders, and researchers.

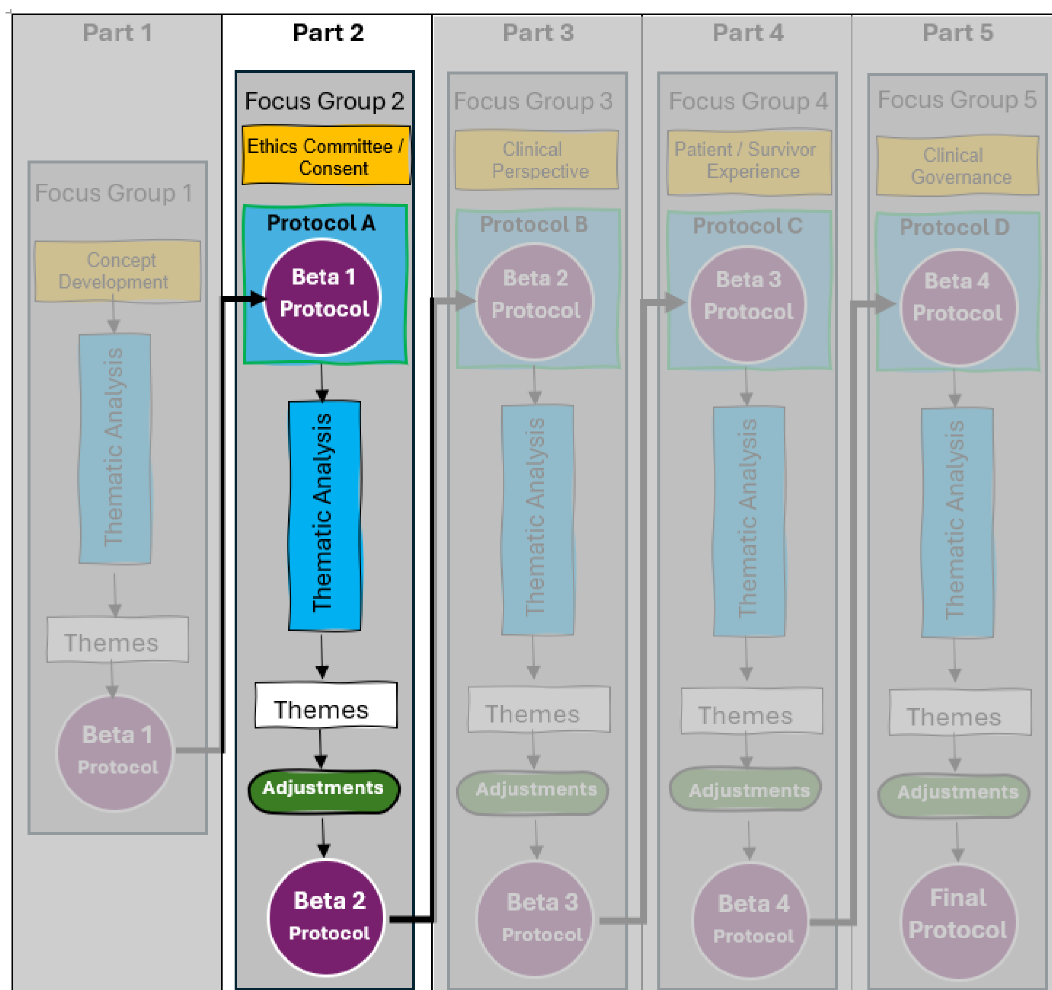


Figure 6: **Part 2 – Review of THAW protocol by the NHS research ethics committee**

5.3.1 Study participants, Part 2

In the second stage of the study, the participants were the National Health Service (NHS) Research Ethics Committee (REC) panel. They are dedicated to protecting the rights, safety and well-being of research participants. These committees, comprise of up to 15 members, which include a portion who are 'lay' members, meaning they are not primarily involved in research or registered as healthcare professionals. The NHS REC independently evaluate research proposals for ethical considerations and ensure participant-centricity, operating autonomously from research sponsors, funders and the researchers. The 10 members of the ethics committee came from diverse professional backgrounds, including clinical and scientific research, pharmacy, statistics, academia and surgery. The diverse representation provides a variety of ethical perspectives, ensuring its robustness and appropriateness. Table 11 provides a profile of the NHS REC panel.

Table 7 Profile of panel participants

Professional Background	Age	Experience
Clinical Researcher	52	27
Clinical Trials Pharmacist	27	2
Data Access and Regulatory Support Officer	32	11
Retired Research Officer	68	35
Retired Senior Research Trial Manager	66	35
Senior Medical Advisor/Scientist	41	13
Statistician	72	44
Retired Consultant Surgeon	66	36
University Lecturer in Clinical Informatics	46	9
Academic Clinical Lecturer	33	10

5.3.2 Themes from the NHS REC panel

Analysis of the NHS REC panel participants of the THAW protocol resulted in three themes, seven categories and 17 codes, as illustrate in Figure 7.

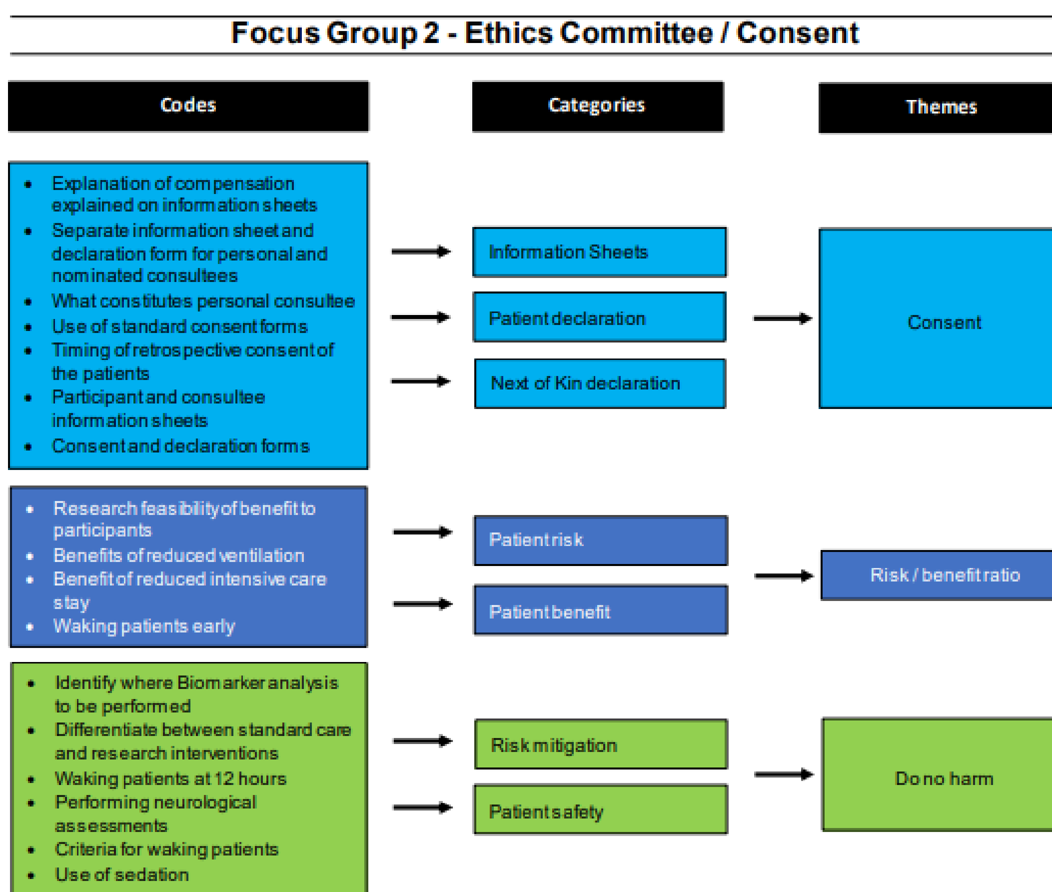


Figure 7: Thematic analysis of the NHS ethics committee

Theme 1: Consent

Information sheets

Information sheets needed to convey complex medical information to patients and their relatives. Information about the purpose of the study as well as information about participation, including the option to withdrawal from the study. The information sheet also needed to include the risks and benefits as well as guidance on actions that can be taken if something goes wrong. The information sheet needed to include details about how the participant's personal and medical records would be kept confidential and all published data would be anonymised.

The ethics committee members considered that some the medical terminology contained within the information sheets needed to include a brief explanation or to be translated into lay person language. The information sheets should be separated from the declaration forms to enable the reader to review and assimilate the information in their own time.

There should be an information sheet available for the participant or consultee with appropriate use of language for their intended audience. These should be separate from the declaration forms.

Ethics Committee Member

Patient declaration

The issue of gaining patient consent would not be possible, because patients would be unconscious on admission. Therefore, it would be necessary to get approval from next of kin. The ethics committee recommended this would need to be a signed declaration. There would need to be a verbal explanation of the THAW trial to the next of kin and they would need to be provided with an information sheet, with an opportunity to ask any questions. The declaration would need to confirm that the next of kin (personal consultee) were consulted about the patient participating in the THAW trial and from their perspective whether they considered the patient would agree to participate or not. Also, to be included on the declaration form were permission statements in relation to access to care records and data collected by the research team, as well as the collection of neurological biomarkers.

If the patient is unconscious and not able to give consent, the family or next of kin would need to confirm by means of a signed declaration that they agree to their relative / loved one to be a participant in the research trial?

Ethics Committee Member

The importance of obtaining declarations. I consider it's crucial to get a declaration from the personal consultee and ideally, within the first 24 hours.

Ethics Committee Member

This approach would help avoid any potential conflicts of interest. But we also have another concern. I was wondering what would happen if the patient, their personal consultee, or the nominated consultee decided to withdraw their consent or agreement to continue with the THAW trial.

Ethics Committee Member

We need clarity on how this decision would impact the patient's care. It's essential for us to understand the implications fully.

Ethics Committee Member

> *And let's not forget the emotional aspect of this. We must ensure that patients and their families are reassured. They need to know that their care and legal rights won't be negatively affected, no matter what decision they make about the trial.*

Ethics Committee Member

Next-of-kin declaration

The ethics committee members suggested that declarations were obtained from the personal consultee within 24 hours. In the event the patient was not able to be identified or contact was not able to be made with the personal consultee within the 24-hour timeframe, a nominated consultee, Consultant Cardiologist, who was not directly responsible for the patient, mitigating conflict of interest, would need to complete the declaration.

> *I recognised that there might be times when we can't identify the patient or reach their personal consultee within that time. So, in such cases, I would suggest having a nominated consultee, maybe a Consultant Cardiologist, who isn't directly involved in the patient's care, to step in and complete the declaration.*

Ethics Committee Member

Theme 2: Risk versus benefit ratio

Patient risk

The THAW protocol differentiates between what is considered standard care and the research protocol interventions. The standard care component of the protocol describes the use of IVTM for TTM management, neurological assessment, the use of sedatives, as well as a criteria for extubation. Whereas, the research protocol interventions are mostly diagnostic tests, that carry minimal risk to the patient. However, performing an EEG on an unconscious, intubated patient in the ICU is intricate and carries inherent risks. Movement of the head during EEG electrode application could potentially displace or dislodge the endotracheal or nasogastric tube. Electromagnetic interference from other ICU equipment may introduce artefacts into the EEG reading. Additionally, the adhesive or gel used for electrode placement could cause skin irritation. The most significant risk, however, is the misinterpretation of the EEG or SSEP results, which could lead to unnecessary treatments. A further potential risk arises during the early waking phase when sedation is reduced, and muscle relaxants are discontinued. The patient might experience muscle discomfort from resuscitation efforts or the endotracheal tube, as well as potential disorientation or confusion. There's also the possibility that the patient could be intolerant to medications given during this phase.

> *The protocol needs to be explicit in describing the specific research intervention(s) and whether these interventions have the potential to cause harm to the patient or put them at risk.*

Ethics Committee Member

Information sheets needed to convey complex medical information to patients and their relatives. Information about the purpose of the study as well as information about participation, including the option to withdrawal from the study.

> *The perceived benefits as described in the protocol for patients suitable for early waking include a reduction in the time the patient is mechanically ventilated, early assessment of possible neurological injury, potential reduction in critical care stay.*

Ethics Committee Member

With having no on-site pathology laboratory capable of processing the neurological biomarker samples these would need to be processed off-site. To ensure the integrity of blood sample handling a clear process from collection, storage to transport and processing would need to be established.

> *For the purposes of ensuring the integrity of blood sampling management there would require a clearly defined chain of command*

Ethics Committee Member

Patient Benefit

The ethics committee expressed a desire to understand the potential benefits of the protocol. Including how they extend not only to patients but also to their families. For patients who meet the physiological criteria, there is an effort to initiate early waking. Reducing the sedation level and ceasing the use of muscle relaxants allow clinicians to conduct a thorough neurological assessment. If patients show promising neurological signs, the focus shifts to a positive prognosis, leading to the discontinuation of sedation and preparation for extubation. This approach reduces mechanical ventilation duration and its associated risks. The benefits include not just a decrease in the use of sedation, muscle relaxants and mechanical ventilation, but also a potential reduction in ICU stay duration. After extubation, patients can communicate with their families, alleviating concerns about the neurological implications of their cardiac arrest.

> *How have you addressed the potential risks associated with early waking, especially in patients who might not be ready for reduced sedation?*

Ethics Committee Member

> *How will families be informed about the protocol and will they have a role in the decision-making process?*

Ethics Committee Member

> *If a patient does not show the expected benefits or if there are adverse reactions to early waking, how will the protocol be adjusted to ensure patient well-being?*

Ethics Committee Member

Theme 3: Do no harm

Risk mitigation

The ethics committee had a desire to explore how the THAW protocol mitigated the risks associated with the research interventions identified. The risks that pertain to the research interventions are primarily around the potential of misinterpretation of the neurophysiology tests EEG and SSEP. This has been mitigated by having the results interpreted off-site at a core lab, with these findings to be included only in the post-hoc analysis.

> *If an urgent or unexpected result arises from these tests, how will it be communicated and acted upon?*

Ethics Committee Member

> *Why are the findings of the EEG and SSEP tests only being included in the post-hoc analysis?*

Ethics Committee Member

The potential risks associated with waking patients early include the reduction of sedation and stopping of muscle relaxants are primarily mitigated by employing assessment tools like the Richmond Agitation and Sedation Scale (RASS), a pain scale and the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU score).

> *How will the reduction in sedation and cessation of muscle relaxants be monitored to ensure patient safety and comfort?*

Ethics Committee Member

Patient safety

The committee required clarification on any impact on care in the event of the patient, personal consultee or nominated consultee withdrawing consent or agreement for ongoing participation in the THAW trial. The importance of ensuring that patients and relatives are reassured that critical care provision and legal rights are not negatively impacted.

> *The protocol will need to clearly define between the consent and declaration with specific timeframes for completion. In the event the declaration or consent is withdrawn, the impact of their withdrawal on the care and management of the patient will need to be clearly articulated during the declaration conversation(s).*

Ethics Committee Member

5.4 Part 3 – Clinical perspective

Since the inception of the National Health Service (NHS) in 1948 there has been numerous service restructures, including a significant reduction in bed capacity by approximately 70 per cent and centralisation of specialist services. Hospital sizes have significantly increased from an average of 68 beds to just over 580 beds. Between 1974 to 2020, total bed capacity across England has reduced by 65 per cent from 400,000 to 141,000 (OECD & Union, 2022). During the same period, the population in England has increased by 27 per cent from 49.4 to 67.44 million. The reasons for reorganisation, centralisation of services and reduction in bed capacity reflects advances in both medical innovation and technology as well as workforce supply, financial limitations and urbanisation. Furthermore, most routine surgery is now undertaken as a day surgical procedure, with 80 per cent of patients having a mean length-of-stay of three days. Part 3 of the study involved Focus Group 3, which provided a clinical perspectives from a panel of expert clinicians see Figure 8.

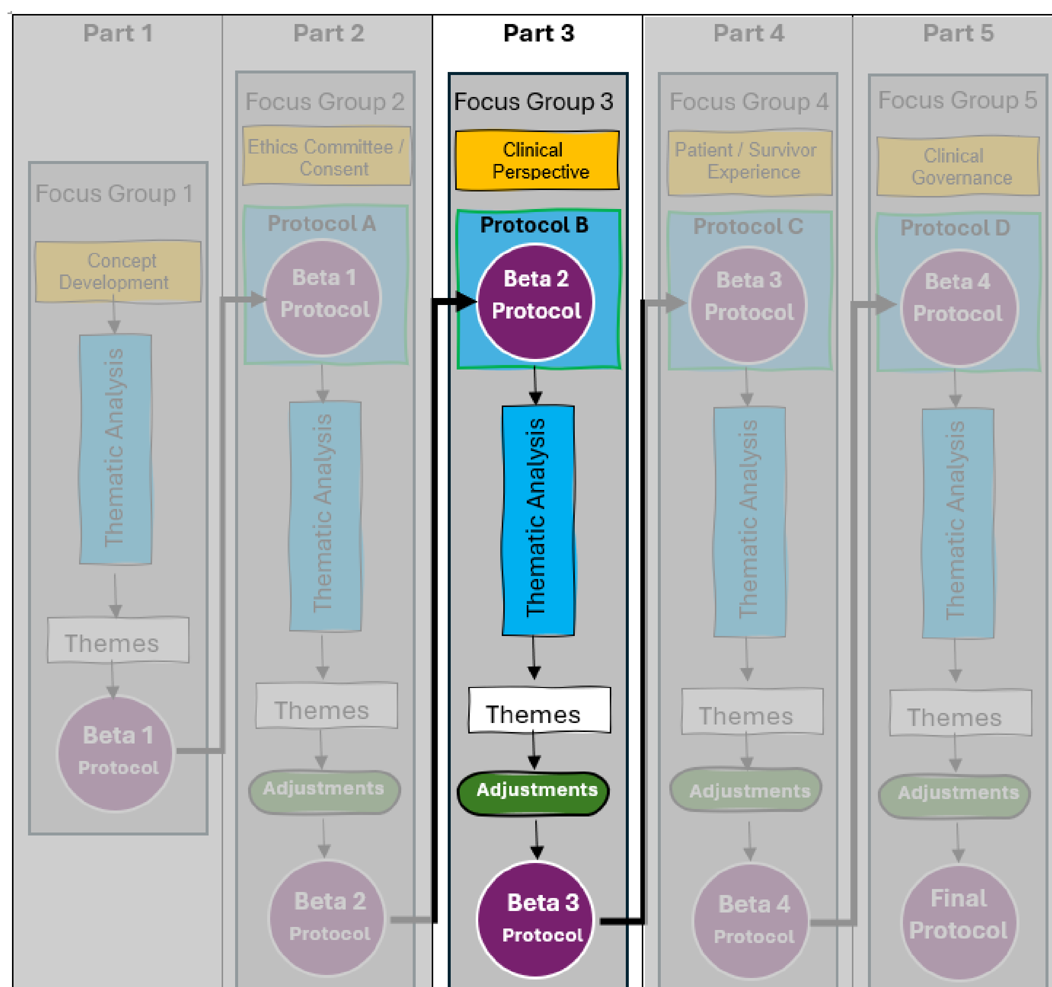


Figure 8: Part 3 – Expert panel

5.4.1 Study participants, Part 3

In the third stage of the study the participants were a panel of clinical experts that primarily worked at the Essex Cardiothoracic Centre. There were 25 participants with a medical background all specialising in either cardiology, cardiothoracic surgery, or anaesthetics. Two Consultant Neurologists, one of whom worked external to the Essex Cardiothoracic Centre but participated in the expert panel as a clinical expert on neurophysiology, the other Consultant Neurologist worked within the organisation. Ages of the medical participants ranged from 31 to 59 years and their years of experience was from six to 36 years. There were 15 participants with a nursing background, in various management roles within the cardiothoracic centre, as well as senior clinical and research roles from critical care. Their ages ranged from 38 to 58 years and their experience ranged between 17 and 37 years. The allied staff included a Clinical Psychologist with 10 years of experience, a Cardiac Physiologist, Electrophysiology Manager and Lead Perfusionist, all with significant years of experience

ranging from 23 to 31 years. Lastly, the research assistants, both relatively new to their roles, with ages 20 and 21 and each within the first year of their clinical experience.

Table 8 Profile of panel participants

Discipline	Professional Background	Age	Experience
	Cardiology Research Registrar	31	6
	Cardiothoracic Surgical Registrar	38	13
	Chair Clinical Governance	61	36
	Clinical Director	56	31
	Consultant Anaesthetist 1	36	11
	Consultant Anaesthetist 2	47	22
	Consultant Anaesthetist 3	59	34
	Consultant Anaesthetist 4	49	24
	Consultant Anaesthetist 5	43	18
	Consultant Anaesthetist 6	47	22
	Consultant Cardiologist 1	43	18
	Consultant Cardiologist 2	41	16
	Consultant Cardiologist 3	39	14
	Consultant Cardiologist 4	58	33
	Consultant Cardiologist 5	49	24
	Consultant Cardiologist 6	55	30
	Consultant Cardiologist 7	54	29
	Consultant Cardiologist 8	59	34
	Consultant Cardiologist 9	47	22
	Consultant Neurologist 1	54	29
	Consultant Neurologist 2	57	30
	Lead Cardiothoracic Surgeon	61	36
	Lead Consultant Anaesthetist	61	36
	Lead Consultant Cardiologist	52	27
Nursing	Cardiology Ward Manager	49	28
	Cathlab Manager 1	48	27
	Cathlab Manager 2	49	28
	Critical Care Outreach Nurse 1	48	27
	Critical Care Outreach Nurse 2	48	27
	Matron of Critical Care	48	27
	Nurse - Research	48	30
	Outpatients Manager	58	37
	Private Suite Manager	43	22

Discipline	Professional Background	Age	Experience
	Senior Charge Nurse Critical Care	57	26
	Senior Sister Critical Care 1	43	22
	Senior Sister Critical Care 2	52	31
	Sister Critical Care	47	26
	Surgical Ward Manager	38	17
	Theatre Manager	46	22
Allied	Clinical Psychologist	35	10
	Cardiac Physiologist	49	28
	Electrophysiology Manager	52	31
	Lead Perfusionist	47	23
Research	Researcher 1	21	1
	Researcher 2	20	1

5.4.2 Themes from the clinical expert panel

As shown in Figure 9, analysis of the clinical expert panel participants of the THAW protocol produced five themes, which arose from 13 categories and 30 codes.

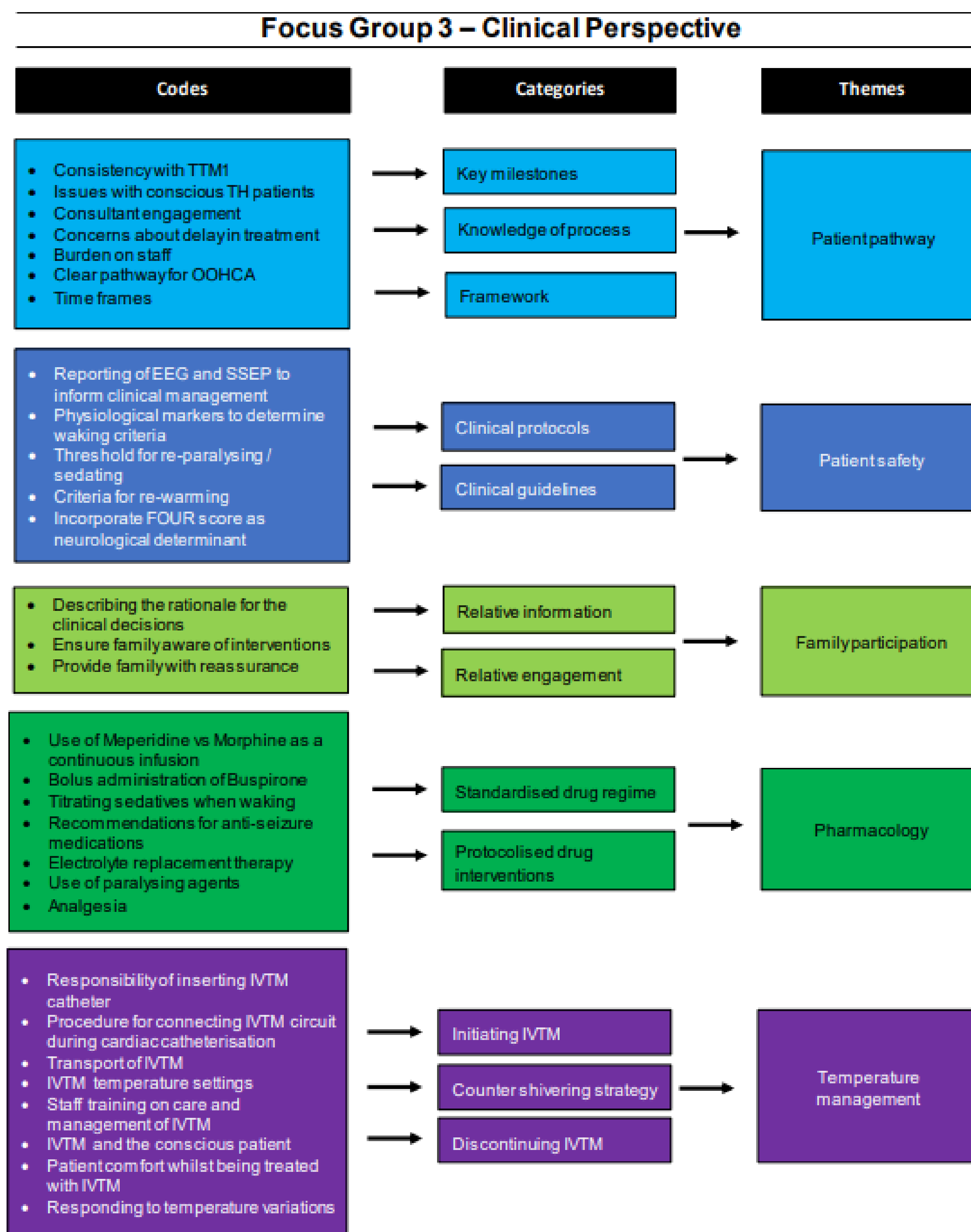


Figure 9: Thematic analysis of the clinical expert panel

Theme 1: Patient pathway

Key milestones

Following the publication of the TTM trial in 2013, there was ambivalence surrounding the application of TTM as a critical care strategy for the management of post cardiac arrest patients. The results of the trial suggested there was no significant difference in patient outcomes between patients treated with TTM compared to those kept normothermic. However, this led to a number of clinicians interpreting the results of TTM as being of no benefit, therefore abandoning TTM as a treatment strategy. With each clinician deciding whether or not to incorporate TTM as a treatment strategy, this resulted in inconsistency in the management of post cardiac arrest patients. Therefore, clinicians considered it was necessary to establish what current evidence recommended to support best practice and a consistent way forward.

> *As a result of TTM1 there is a lot of confusion and lack of consistency in approaches as to whether or not to use therapeutic hypothermia. I know of centres who have made the decision not to cool.*

Consultant Anaesthetist 1

> *We need to make a decision about whether we are going to use therapeutic hypothermia to treat our patients.*

Consultant Cardiologist 5

> *I disagree the decision of whether to support TTM will be based on evidence and best practice. If the evidence supports the use of TTM then as a consultant group, this should be incorporated into our practice.*

Consultant Cardiologist 5

Clinicians considered it necessary to attain consultant engagement but more importantly for practice to be based on best evidence. To enable early initiation of TTM Consultant Cardiologists would be responsible for IVTM catheter insertion at time of admission to cardiac catheter lab for PPCI.

> *I think we should canvass both the cardiologist and anaesthetic consultants to understand whether they support the use of TTM. Also, which consultants are prepared to insert the IVTM catheter.*

Consultant Cardiologist 5

Knowledge of process

Through previous experience with the COOLAMI study, Consultant Cardiologists were familiar with inserting the IVTM catheter and initiating cooling prior to proceeding with PPCI. Sequencing TTM before PPCI would allow the critical care team attending to connect to the ZOLL console, whilst the Consultant Cardiologist was able to proceed with the PPCI. This would allow for a sterile connection without contaminating the sterile field.

> *We will not want to delay PPCI but we also don't want to delay the initiation of cooling. I would propose the cardiologists are responsible for inserting the IVTM catheter, this could be done immediately prior to arterial catheterisation, which would allow the IVTM to be connected.*

Consultant Anaesthetist 1

There was a collective agreement from the clinicians to define the pathway for the OHCA patient, from admission to the cathlab to transfer and admission to critical care. To familiarise the multidisciplinary team with their roles and responsibilities it was suggested to simulate the patient journey.

> *I suggest we map out the sequence of events with regards to the cardiology, anaesthetic and critical care roles and responsibilities. Once we have done that, we should rehearse this as a team and then perhaps run through the process in real time and then review/debrief. Once we are comfortable with the sequence, roles and responsibilities perhaps apply to a couple of 'run in' patients.*

Consultant Anaesthetist 1

Framework

Through experience with the COOLAMI study, Consultant Cardiologists were familiar with inserting the IVTM catheter and initiating cooling prior to proceeding with PPCI. Sequencing TTM before PPCI would allow the critical care team attending to connect to the ZOLL console, whilst the Consultant Cardiologist was able to proceed with arterial cannulation and PPCI. This would allow for a sterile connection without contaminating the sterile field.

> *In terms of performing the EEG and SSEPs we've established this will be undertaken by the trained researchers, the reporting will be undertaken by our Consultant Neurophysiologist, we need to be clear that we won't be using the findings to inform care or treatment.*

Consultant Anaesthetist 1

Theme 2: Patient safety

Clinical protocols

The clinical experts had a comprehensive viewpoint on the determination of early waking through physiological parameters. They also emphasised the significance of a thorough neurological evaluation and the neurophysiologist suggested the integration of the FOUR score along with the Glasgow Coma Scale (GCS) into the assessment. Highlighting the potential sensitivity these combined scales offer towards detecting minor neurological variations. With the FOUR score being more comprehensive than GCS, in its ability to assess intubated patients and provide a more detailed analysis of brainstem reflexes.

They also stressed the importance of a systematic and rigorous approach towards decision-making for early waking. Recognising the critical nature of this decision, they proposed a two-step process. Firstly, the initial assessment should be conducted by the designated researcher, ensuring an unbiased and objective evaluation. Followed by, rather than leaving the final decision to a single individual, they advocate for a collaborative approach. The decision to proceed with early waking should be made after a consultation between the researcher and a representative from the anaesthetic team. They agreed this would ensure the safety of the clinical decision-making.

> *The physiological markers that are used for determining early waking should include a comprehensive neurological assessment. This should include the FOUR score as well as GCS. This is more sensitive to subtle neurological changes.*
>
> Consultant Neurologist 1

> *We will need some rigor around the decision making as to whether the patient is appropriate for early waking. I would suggest the initial assessment be undertaken by the researcher and the decision would be made in consultation with someone from the anaesthetic team.*
>
> Consultant Anaesthetist 1

Clinical guidelines

There was a well-defined view expressed by all the clinical expert panel, that there should be clear clinical guidelines that describe the process of identifying patients that can be considered for early waking. The clinical guideline should also describe the process for re-sedation and the reintroduction of muscle relaxants in the event of patient deterioration. With an emphasis on patient safety, ensuring that only suitably appropriate patients were attempted to be woken early, as well as providing a clear process in the event of patient deterioration, removes

ambiguity around clinical decision making. The adoption of clinical guidelines also removes any inconsistencies or delays in decision-making, that could potentially put patients at risk. By establishing clear, evidence-based guidelines, ensures that decisions such as re-sedating and paralysing the patient is clinical indicated rather than disparate individual judgments.

> *The protocol would also need to clearly define thresholds around the need to re-paralyse +/- sedate the patient in the event there was a change or deterioration in their condition.*
>
> Consultant Cardiologist 5

The expert panel discussed the importance of effective communication with patients and their families in relation to the early waking protocol. That effective communication establishes trust, reduces anxiety and ensures that families feel informed and involved. They suggested having a prepared script for patient's and family to ensure consistency in the information being relayed, therefore families would receive consistent and accurate information. Having a script also potentially prevents any inadvertent inconsistencies or omissions. It was also suggested that key individuals would provide family updates, to ensure that there was a continuous and coherent communication channel between the critical care team and the families. It was considered imperative for the researchers conducting the EEG and SSEP testing, to proactively engage and reassure family members about the safety and purpose of these tests. Furthermore, that families must be made unequivocally aware that these diagnostic procedures do not influence the subsequent course of treatment or care.

> *Like we have done with other trials I think it's important for us to have a basic script prepared for our patient's relatives and loved ones, both in terms of recruitment as well as providing updates. It would also be useful to establish who will be responsible for family updates and alternatively who this might be delegated too.*
>
> Consultant Anaesthetist 1

> *It will be important for the researches to engage with the family members and reassure the family when performing EEG and SSEP testing. It will need to be made very clear to the family that these tests will not have any impact on care or treatment.*
>
> Consultant Cardiologist 5

The expert panel acknowledged that in light of the TTM1 publication, there exists noticeable uncertainty and variability in whether or not to use TTM. They were also aware that certain centres have opted out of cooling. Therefore, there was a consensus from the expert panel, that based on the currently available evidence that the ECTC, would not only continue to treat OHCA patients with TTM but this would be considered standard practice and clinical

guidelines would be included into the hospitals policy on the management of OHCA treated at the Essex Cardiothoracic Centre.

> *As a result of TTM1 there is a lot of confusion and lack of consistency in approaches as to whether or not to use therapeutic hypothermia. I know of centres who have made the decision not to cool.*
>
> Consultant Anaesthetist

Theme 3 – Family participation

Relative information

The expert panel reflected on previous research activities, highlighting the lessons learned which identified the importance of early and regular communication to family, as well as involving family in any decision-making. That timely communication was imperative to manage family expectations and answer any immediate questions, but importantly to set the scene and prepare family for when they were reunited with their loved one in the ICU. The expert panel stressed the importance of providing a timely family update, which ideally should occur soon after the patient has been admitted to ICU. That the initial meeting and update with family, should minimally include the cardiology registrar or consultant, a member of the research team and the ICU registered nurse caring for the patient. That they would be best placed to talk through the PPCI procedure, the reason for transfer to the ICU and introduce the opportunity to participate in research of OHCA survivors.

> *What specific information should we communicate to the family during the initial update?*
>
> Cardiology Registrar

> *Who should provide the initial update and when?*
>
> Critical Care Outreach Nurse 1

Due to the complexities of the research interventions, specifically EEG monitoring and how overwhelming this might be for family members entering the patient's bed space for the first time. Furthermore, OHCA patients would typically be connected to a ventilator, invasive monitoring, but also would have multiple infusions as well as equipment to administer TTM, including the IVTM console and surface warming device. To ensure that communication to the family was consistent and clearly understood, the expert panel emphasised the importance of having patient information sheets that was written in lay person's language, without medical jargon.

> *I think it would be useful to have members from Hearts and Minds to look over the information sheets to identify any medical language that needs removing or further explanation?*
>
> Consultant Cardiologist 1

Relative engagement

Because consent would not be able to be obtained from the patient, the expert panel considered that family should be approached at the initial meeting about the possibility of the patient being included in a research trial. The researcher should provide a basic overview of the research and give the family the information sheet which would provide them with more detail about the research. The researcher would be in a position to answer any questions in relation to the research and this would be an opportunity to emphasise the research interventions would not cause any harm or discomfort to the patient and the results of these tests would not be used for the purposes of clinical decision making. The expert panel considered it was important to ensure the family had signed the declaration within the first 24 hours.

> *How do we ensure that family are adequately informed without causing unnecessary additional stress?*
>
> Nurse – Research

The expert panel considered that it was important for the researchers not to discuss or disclose any findings when undertaking the EEG and SSEP. That if the researcher was asked to comment on the EEG and SSEP recordings, by either family or clinicians, that it would be important for the researcher to reiterate that these will be formally reported off-site and that these findings would not be used for the purposes of decision making.

> *How can we ensure that our explanations of clinical decisions are easily understandable for family members?*
>
> Consultant Cardiologist 1

Theme 4 – Pharmacology

Standardised drug regimen

In the discussions with the expert panel, the use of Meperidine over Morphine was highlighted as a significant point of contention. Notably, Meperidine has been associated with an increased risk of seizure activity. However, it was essential to recognise that its judicious use in OHCA

patients might offer distinct advantages. The current evidence suggests that Meperidine, in conjunction with Buspirone, has been successfully trialled in conscious patients undergoing TTM, indicating its potential efficacy and safety in such contexts. Additionally, to counteract potential nausea the concurrent administration of Ondansetron was also recommended. There were also collaborative discussions with the pharmacy department exploring the full range of therapeutic options. The decision to include the administration of Meperidine as an infusion, it was important to provide a robust protocol that delineates the method of initiation, titration and vigilant monitoring to ensure patient safety and therapeutic effectiveness.

> *The use of Meperidine as opposed to Morphine does raise a few alarms for me as we know that Meperidine has been associated with causing an increased risk of seizure activity. It would be useful to explore all options and discuss with pharmacy.*

Consultant Anaesthetist 3

> *Using Meperidine as infusion we will need to prepare a protocol for initiating the infusion as well as titrating.*

Consultant Anaesthetist 1

> *The protocol will need to include the titrating of sedatives when waking. This will also need to include the re-introduction of these should we need to re-sedate the patient.*

Consultant Anaesthetist 6

Prescribed drug interventions

The clinical expert panel identified the variability in the prescribing of anti-seizure medications not only introduce inconsistencies with patient management and care, but potentially impact patient outcomes and will complicate the interpretation of trial results. Therefore, a recommendation was to ensure there was a consistent approach, to ensure that all patients recruited into the THAW trial received a standardised anti-seizure regime. Establishing standardised clinical guideline would facilitate this consistency, also reducing ambiguity and ensuring that all members of the treating clinical team are aligned in their treatment strategies.

> *We have typically used a variety of anti-seizure medications depending on the consultant decision making. It would be useful to have a consistent approach.*

Consultant Cardiologist 5

Theme 5 – Temperature management

Initiating IVTM

The Consultant Cardiologists, from the expert panel, identified that transitioning to Intravenous Temperature Management (IVTM) from the conventional Blanketrol system represents a substantial shift in clinical practice for TTM. Whilst the rationale for moving to IVTM is not only for its superiority to other methods of delivery it is also the only delivery method that allows patients to conscious whilst being treated with TTM. However, changing from Blanketrol to IVTM necessitates a rigorous training programme to ensure patient safety. The IVTM catheter insertion, in terms of when, is pivotal, to ensure TTM is initiated as soon as practicable and who will be responsible for inserting the catheter. Furthermore, the expert panel discussed who would be responsible for preparation of the IVTM machine, setting the correct target temperature and ensuring a sterile connection within the cathlab environment are crucial steps that demand precision as well as expertise. It wasn't just about the cathlab, but also the transfer to ICU and reconnecting the IVTM in ICU. This raised the issue of ensuring 75 percent of the nursing and medical staff needing to be trained and competent in its use before being incorporated into standard practice. Additionally, ICU staff would need to be proficient in not only basic IVTM operation but also in troubleshooting any potential issues that may arise, as they would be responsible out-of-hours. The justification for this rigorous approach was ensuring patient safety was paramount. Moving across to IVTM is a significant shift from using Blanketrol, there will need to be an intense training regimen which will need to include both catheter insertion, machine preparation and settings and sterile connection in the cathlab.

Consultant Cardiologist 5

> *There will also need to be training on transport of IVTM, reconnection in ICU as well as training of ICU staff that includes troubleshooting.*

Consultant Cardiologist 5

Counter-shivering and discontinuing IVTM strategy

There were a number of Consultant Cardiologists from the expert panel who had experience in using IVTM in awake patients, combined with counter shivering techniques. However, navigating the complexities of this approach in waking unconscious survivors following OHCA was considered significantly more challenging. Not only maintaining the target temperature for 24 hours while the patient is potentially awake for 12 of those hours but also during the 14 hours of slow re-warming, as well as the remaining 36 hours, whilst maintaining normothermia, a total of 72 hours. Delivering IVTM in awake patients presents unique challenges, particularly those associated with temperature variations and potential discomfort

from shivering. To manage this effectively, the expert panel recommended that a detailed and structured IVTM management process would need to be crafted. This would clearly identify step-by-step process for adjusting temperature variations, maintaining the desired therapeutic range and responding to any unexpected changes. The step-by-step process would also need to provide explicit instructions for scenarios such as the need to transfer a patient or discontinue IVTM, ensuring a smooth transition without compromising therapeutic goals of TTM.

> *Managing the awake patient with IVTM and counter shivering techniques is complex, there will need to be a really clear management process described for staff. This will need to include management of temperature variations as well as transfer or discontinuing IVTM.*

Consultant Cardiologist 5

5.5 Part 4 – Patient survivor experience

Part 4 highlighted in the Figure 10 involves Focus Group 4, which focuses on patient and survivor experiences.

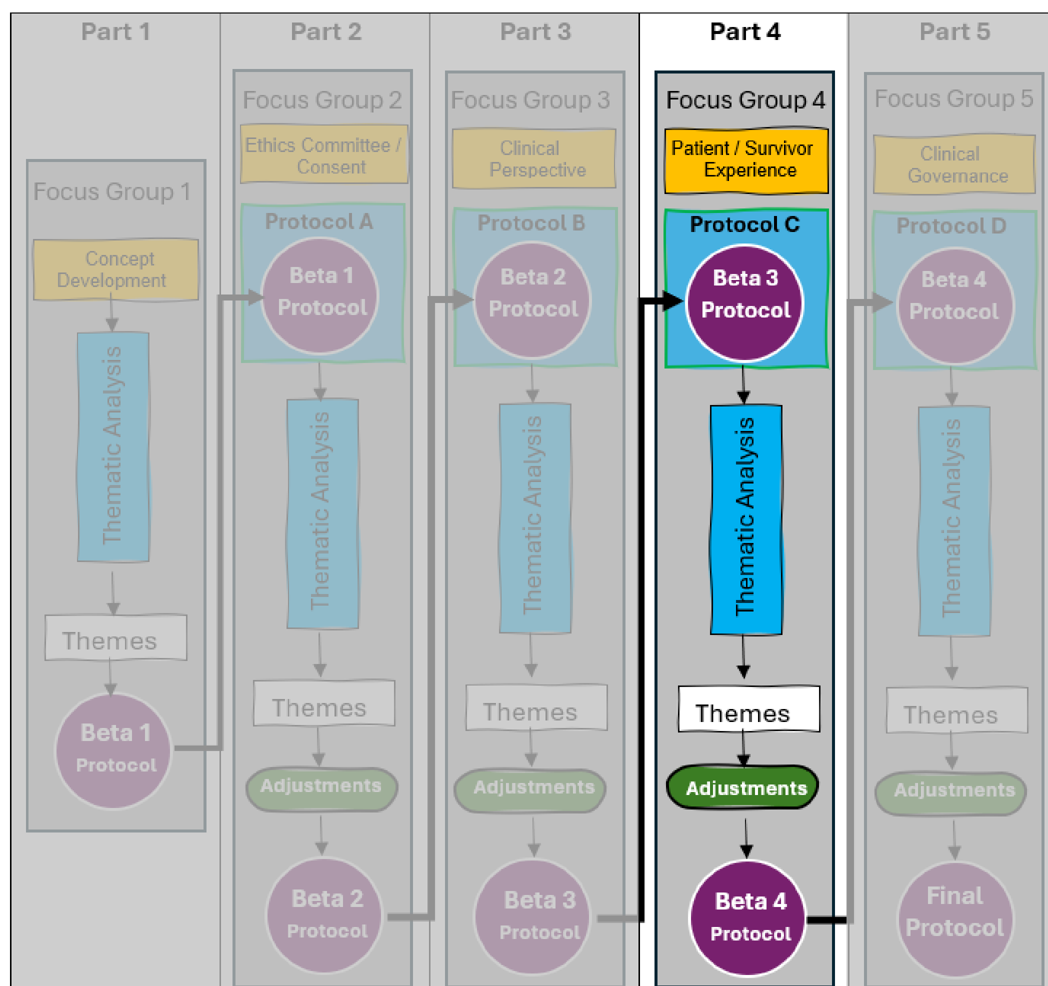


Figure 10: Part 4 – The patient and family

5.5.1 Study participants, Part 4

In the fourth stage of the study the participants were survivors of OHCA and their families. There were 20 survivors and 12 Family members. Table 13 provides a profile of the participants.

Table 9 Profile of study participants

Background	Age	Background	Age	Background	Age
Survivor 1	74	Survivor 12	78	Family 3	43
Survivor 2	60	Survivor 13	54	Family 4	61
Survivor 3	65	Survivor 14	73	Family 5	54
Survivor 4	70	Survivor 15	61	Family 6	51
Survivor 5	71	Survivor 16	66	Family 7	79
Survivor 6	69	Survivor 17	67	Family 8	87
Survivor 7	55	Survivor 18	70	Family 9	59
Survivor 8	58	Survivor 19	71	Family 10	62
Survivor 9	61	Survivor 20	56	Family 11	74
Survivor 10	48	Family 1	80	Family 12	38
Survivor 11	49	Family 2	48		

5.5.2 Themes from the survivor and family

As shown in Figure 11, analysis of the survivor and family participants in the development of the THAW protocol resulted in four themes, nine categories and 24 codes.

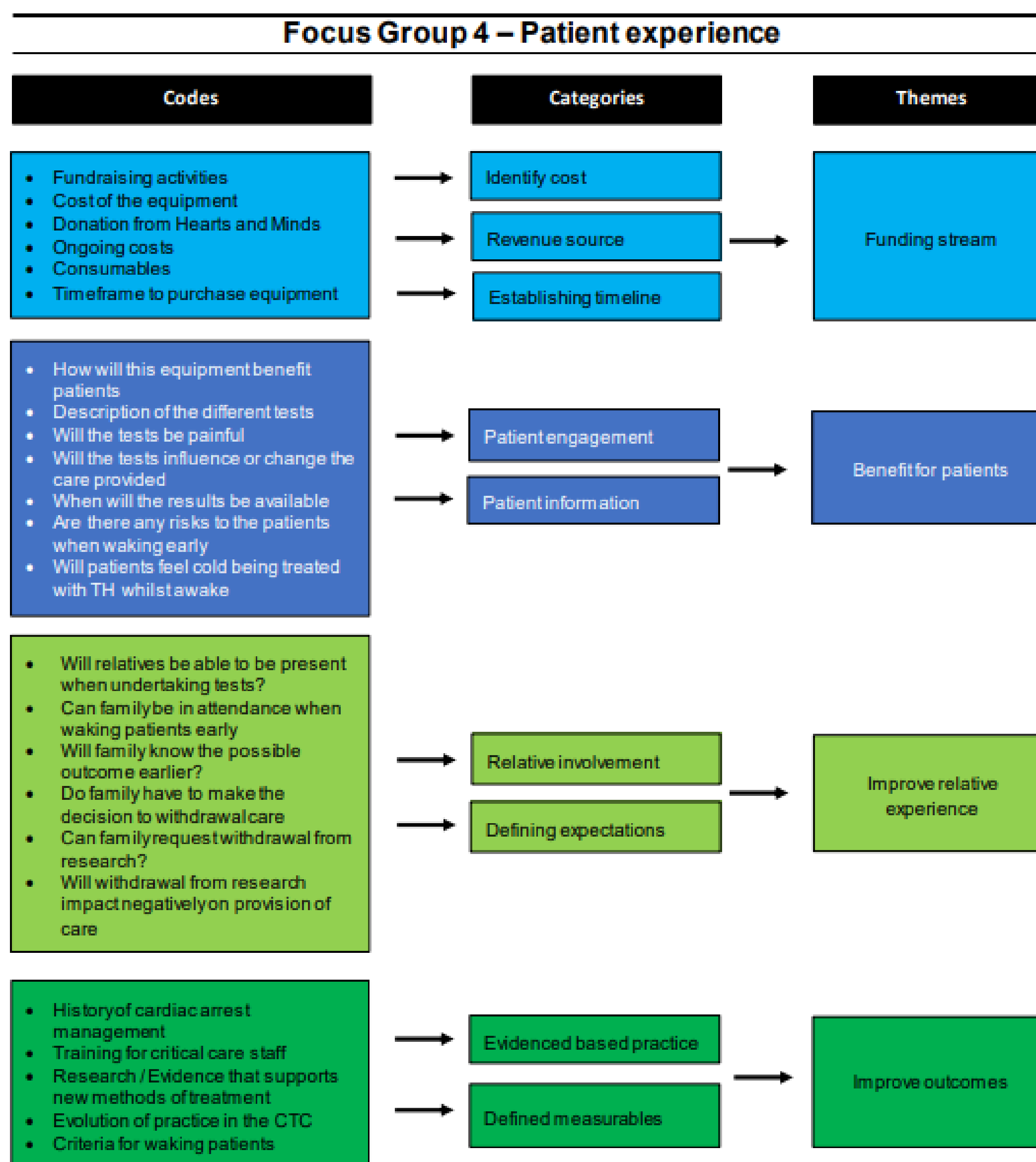


Figure 11: Thematic analysis of the survivor and relative feedback

Theme 1 – Funding stream

Identify cost

The Basildon and District, Hearts and Minds, is a charitable organisation and was established in 2012. The members of the group are heart disease sufferers, family members and carers. The group was established to increase awareness of heart disease, its causes, treatments, implications and help available, it is also to provide social and personal contact with people who share and understand their needs and problems. The group would also liaise with existing groups, organisations and institutions as well as promote and provide support on aftercare for patients, partners and carers when returning home.

Most of the Hearts and Minds members had been a patient or were the family member or carer for a patient who had received treatment at the Essex Cardiothoracic Centre. This could have been in the capacity of being an outpatient, an in-patient, recipients of the cardiac rehabilitation programme or being followed up as part of the critical care follow-up programme.

Hearts and Minds had regular monthly meetings for its members, they would often invite guest speakers to present on new and innovative treatments and therapies on cardiovascular disease. A rehabilitation nurse from the Essex Cardiothoracic Centre would also be in attendance. The members would have an opportunity to share their experiences and the rehabilitation nurse would be available to answer any questions. Not only did the meetings serve as a support group for its members, but an information session, as well as an opportunity to identify the next project to support and fundraise money for. The group had expressed an interest in fundraising for new equipment for the Essex Cardiothoracic Centre. As a significant number of the members were survivors of OHCA, therefore had lived experience of being a patient in critical care and the complex recovery journey. They were invested in supporting fundraising for equipment that would improve the experience for future OHCA survivors and their families.

The purpose of meeting with the group was to explore the patient, family and carers lived experience and perspective of surviving an OHCA. The journey for family members was often described at the point of witnessing the cardiac arrest. However, the focus was on the hospital stay, crucially the first 24 hours in critical care.

> *It's wonderful to know that our fundraising for the Essex CTC is being put to good use and making the journey for patients better.*

Survivor 1

Hearts and Minds members consider many projects for fundraising. Over the previous 10 years Hearts and Minds members had fundraised more than £70,000.00 for equipment for the Essex Cardiothoracic Centre. To remove any conflict or influence, members would vote outside of the meeting, as to whether to support this fundraising project based on the benefit or impact on patient outcome and experience.

> *We have a number of fundraising activities planned for the next few months and hope to raise £12,000. We will have to put it to the members to confirm support for this piece of equipment.*

Survivor1

Revenue source

The journey for the survivors and family who were involved in Hearts and Minds began after a life-altering experience. Like so many members of this supportive community, they describe finding solace and purpose in sharing their stories, hearing others' and realising they were not alone. The monthly meetings became integral to their healing process. Each meeting was an opportunity for survivors and their family to gain valuable insights, understand the latest advancements in cardiovascular treatments and be surrounded by individuals who truly comprehended the emotional rollercoaster they were on. The group described the ambition to fundraise for new equipment at the ECTC spoke to their personal experience. It was not just the life-saving measures taken that mattered, but also the quality of life afterwards. That having state-of-the-art equipment was integral to ensuring the best outcomes for OHCA survivors. The members considered their fundraising as more than just a charitable endeavour but described it as personal. It represented hope, advancement in care and the potential to offer others a better recovery journey. All their fundraising initiatives were a testament to the collective strength of the Hearts and Minds community and their shared commitment to transforming personal challenges into meaningful change for others.

The opportunity to leverage their lived experiences, combined with the strength as a community, to drive tangible improvements in care. By championing this initiative, they described that they were not just supporting the acquisition of equipment; that they were investing in better futures for OHCA survivors and their families.

> *Given our shared experiences and understanding of the critical recovery phase, how do you believe the addition of the EEG and SSEP equipment at ECTC will enhance the neurological assessment and ultimately, the prognosis for OHCA survivors?*

Survivor 2

Establishing timeline

The timeline for the fundraising journey for the purchase of EEG and SSEP equipment needed to begin with a connection to the cause. Their decision to embark on this fundraising initiative was brought about by their collective desire to contribute positively to the healthcare journey of future OHCA survivors and their families. With this being one of the largest fundraising efforts, the members of Hearts and Minds recognised the importance of maintaining transparency, integrity and objectivity in their decision-making process and to eliminate any possibility of conflict or undue influence, the members agreed that the deciding vote would be conducted outside of the presentation meeting. This would also ensure that

each member had the opportunity to reflect on the information, weigh up the pros and cons, therefore ensuring that the integrity of the process, which reflected the collective decision by its members. With approximately a third of the funds already collected it was estimated to take another four to six months to fundraise the remainder of the money.

> *The group will conduct a vote on whether to fundraise for the EEG and SSEP equipment outside of this meeting to ensure fairness and eliminate any potential influence.*

Survivor 1

Theme 2 – Benefit for patients

Patient engagement

To enable the members of Hearts and Minds to make an informed decision about whether they were going to support fundraising for the EEG and SSEP machine, they required a presentation to understand its use and the possible benefit to patients and their families. However, this was not just about revenue raising for new equipment this was very much about involving patients and families in the development of the THAW protocol. The direct experiences and insights of survivors and their family offers a nuanced perspective that complements the clinical expertise. Patients and families can provide firsthand accounts of how the THAW protocol might impact the health, well-being and experience of future OHCA survivors. Their feedback offers valuable insights into how the THAW protocol might benefit from further refinement or adaptation to enhance the patient and family experience.

The inclusion of patient and family perspectives ensures that the protocol is designed with a holistic understanding of the patient and family journey. While the clinical, ethical and organisational metrics are undeniably important, understanding the emotional, social and psychological aspects of being an OHCA survivor or family member, ensures the protocol is patient centred.

> *It would be good to understand what exactly the EEG/SSEP machine does.*

Survivor 11

Patient information

Some of the members and their families described the pictures of the EEG electrodes on the scalp as intimidating and overwhelming. Therefore, it was important to understand how to reduce the fear and anxiety that would be heightened in the clinical environment. Describing the placement of the EEG electrodes on the scalp was the same principle as applying electrodes on the chest to perform an ECG, enabled the members and their families a relatable, non-threatening experience. When describing performing the SSEP, which requires an electrical stimulus of the medial nerve at the wrist, it was imperative to reassure that the least amount of electrical stimulus is used to elicit a response, that it isn't painful and only performed on the unconscious patient.

> *Families would want to be reassured that the tests you are doing aren't going to be painful.*

Family 5

> *As a relative it was really important to be kept informed and up to date.*

Family 12

Theme 3 – Improve relative experience

Relative involvement

Family members who had witnessed their loved-one being woken from a coma described the importance of being informed of what to expect. The importance of being prepared for the possibility of the patient not responding appropriately or being agitated when attempting to be woken. To be reassured that any attempt for early waking would only proceed when the patient fulfils the early waking criteria and to provide reassurance that patient safety takes priority and that only patients who are clinically stable will be considered to be woken early, therefore mitigating any risk or potential harm.

> *It would also be important to explain all the risks to the family about their loved one being woken early. Not just explaining what you are doing but also what to expect when you start waking the patient.*

Family 11

> *We will confirm our support after our next meeting.*

Family 5

Defining expectations

Visitor access to critical care is controlled, meaning that when and how long visitors can visit is usually determined by fixed visiting hours. Furthermore, the number of visitors allowed to attend the bedside, at any given time is also restricted to prevent overcrowding and ease of access for clinicians to the patient and critical care equipment. Visitor access is further compounded by visitors being asked to leave the bedside when tests are being performed. Family members of OHCA survivors described their frustrations of frequently being asked to wait outside and the potential further impact on visiting because of the frequency of the THAW protocol interventions.

> *Most family members want to be at the bedside as much as possible, it's really difficult to be made to wait outside when tests are being done.*

Family 7

The relatives describe the importance of being kept informed and up to date. Particularly within the first few hours when the outcome for the patient is unknown. They describe receiving but not always retaining information from the clinical team and the need for communication to be repeated. Relatives considered it was important to have an information sheet that described the THAW protocol. To ensure the information sheet was written in lay language and it included contact details of key personnel.

> *As a relative it was really important to be kept informed and up to date.*

Family 5

Relatives reflected on their experience of patients being treated with TH felt cold to touch, therefore they were concerned that patients would be uncomfortable if they were woken early whilst still being treated with TH.

> *We were really worried when we touched "patient x" and he felt cold, we thought he was dead. Would the patients feel cold if they are woken whilst they are still being treated with cooling?*

Family 4

As the results of specific THAW trial tests will only be examined at the conclusion of the trial, they will not be included in the decision-making for withdrawal of care. Withdrawal decision-making will be determined the clinical team which considers futility of care or certified brain death. The family would be involved in all discussions but it the responsibility of the clinical team to determine withdrawal of care, not the family.

> *We thought it was the family who had to make the decision whether to carry on with treatment and make the decision whether to turn off the machines.*

Family 3

In the context of the THAW trial, the results of the serial neuro biomarkers and neuro electrophysiology tests, would not be made available to the relatives or clinicians as they would be sent off site to a core laboratory for analysis and formal reporting. The predictive prognostic value of these tests was also unknown therefore not appropriate to be used in clinical decision making or influence care. The assessment to determine whether the patient was appropriate to be woken early would be based on the extended neurological assessment and physiological stability of the patient against pre-determined parameters.

> *The sooner you are able to get an indication as to whether the brain has been affected the better, especially being able to communicate any update to the family.*

Family 7

Relatives expressed concern for the potential disparity in care for patients either not included in the THAW trial or if family decide to withdraw the patient from participation in the trial. It was therefore considered necessary to provide clarity to relatives that all OHCA patients will receive the same level of care whether a participant or not. There would also need to be a clear distinction of THAW trial interventions from standard care. That participants will undergo a series of additional non-invasive tests that will not be used to influence care. The test results will be collated from all trial participants at the conclusion of the trial and considered for their predictive prognostic value. Furthermore, participants will be assessed for appropriateness of being woken early at 12 hours, against an established criteria. Withdrawal of participation will therefore not result in any impact on the provision of standard care. Non-participants would be assessed for waking early after 36 hours, when normothermic.

> *From a relative's perspective you would want to know that you were free to withdraw consent and it wouldn't have a negative impact on your loved one's care.*

Family 1

The results of specific THAW trial interventions will only be examined at the conclusion of the trial, in a post hoc analysis, they will not be included in the decision making for withdrawal of care. Withdrawal decision making will be determined the clinical team which considers futility of care or certified brain death. The family would be involved in all discussions but it the responsibility of the clinical team to determine withdrawal of care, not the family.

Important for us to know how we can help others.

Family 9

Theme 4 – Improve outcomes

Evidence based practice

Describing the traditional management of cardiac arrest patients in critical care using surface cooling methods, necessitated sedation and paralysis to inhibit shivering and ensure effective temperature management. That the cooling period, typically extending to 36 hours, prevents clinicians performing a neurological assessment until after the patient had been rewarmed. However, the THAW protocol incorporates Intravascular Temperature Management (IVTM), with counter-shivering strategies that not only provides a more precise control over the patient's body temperature, but potentially allows for suitable patients to be woken early to assess their neurological function, while continuing to be treated with TTM. This would potentially offer family members an insight into the potential outcomes, alleviating some of the emotional burden associated with the waiting period.

I remember that when 'patient x' was in the ICU, you had these cold blankets over him and he was very cold to touch and he was in a coma for days and we didn't know whether he was going to have brain damage, with this new method are you saying that patients will be warm to touch and you will be able to know sooner whether they are going to be ok?

Family 3

The recommendations from the European Resuscitation Council (ERC) and the European Society of Intensive Care Medicine (ESICM), support the use of TTM, but they also recommend the incorporation of neurological electrophysiological monitoring, such as EEG and SSEP, as well as neuro-biomarkers as a multimodal approach to be used in the assessment of determining neurological outcomes for OHCA survivors. However, the emphasis of this multimodal approach is to identify patients with a poor prognosis, whereas the THAW protocol is to identify patients with a likely positive outcome.

Are these EEG and SSEP tests painful or uncomfortable?

Family 1

Will the results of these tests affect the treatment plan for my loved one and how?

Family 5

> *Can you explain in simple terms what EEG and SSEP tests are and how they help understand what's going on in the brain after a cardiac arrest?*

Family 10

Defined measurables

The members of Hearts and Minds expressed a keen interest in gaining a comprehensive understanding of the logistical and technical aspects of conducting EEG and SSEP tests, particularly around the qualifications and training of the individuals performing these tests. Describing the plan to train the dedicated researcher and a research assistant to conduct the EEG and SSEP tests, to ensure that trained personnel are always available, due to the unpredictability of OHCA admissions. They would carry out the series of tests from the moment of admission and subsequently at six hours, 12 hours and if necessary, at 24 hours. To ensure the highest level of competency the researcher and assistant will undergo rigorous training with a neuro-electrophysiologist, including observed sessions to assess accuracy in electrode placement and recording of the EEG and SSEP. This will provide a quality assurance measure to ensure that the data collected are reliable and accurate.

> *Who will be trained to perform the EEG and SSEP? Do you need to get in a specialist?*

Family 10

> *What happens if the tests are not done correctly? How would that affect the patient's care or recovery? Can the family be there during these tests and will someone explain what is happening and why it's necessary at the time?*

Family 10

For the interpretation of the EEG and SSEP results, the recordings will be sent to an off-site core lab, where a consultant neurophysiologist will analyse and report on the findings. This will ensure an additional layer of expertise and objectivity in interpreting the results. It was important to emphasise that during the implementation phase of the THAW protocol, the EEG and SSEP data will be recorded and sent to the core lab. That the interpretation and reporting of EEG and SSEP results will only be made available for post hoc analysis, that these results will not in any way influence or direct immediate treatment and planned care during the implementation phase of the THAW protocol. To ensure that the trial's integrity is maintained and any potential biases are eliminated.

> *How quickly after the test is done do you get the results and who looks at them to decide what needs to happen next?*

Family 7

The defined measurables were described as identifying suitable patients for early waking to assess for positive neurological signs and the feasibility of waking patients early from unconsciousness while continuing to be treated with TTM, as well as the ability to extubate patients from mechanical ventilation and the potential to step down patients from intensive care. Whether these outcomes directly correlate with improving the patient recovery trajectory and reduce the length of stay in critical care, ultimately enhancing the overall patient care and resource utilisation in the intensive care setting.

> *Does waking up early and doing these tests improve the chances of a full recovery, or just speed up the process?*

Family 12

5.6 Part 5 – Clinical governance

The final Part Five focuses on the concluding stages of the THAW protocol development. Focus Group 5 was dedicated to clinical governance.

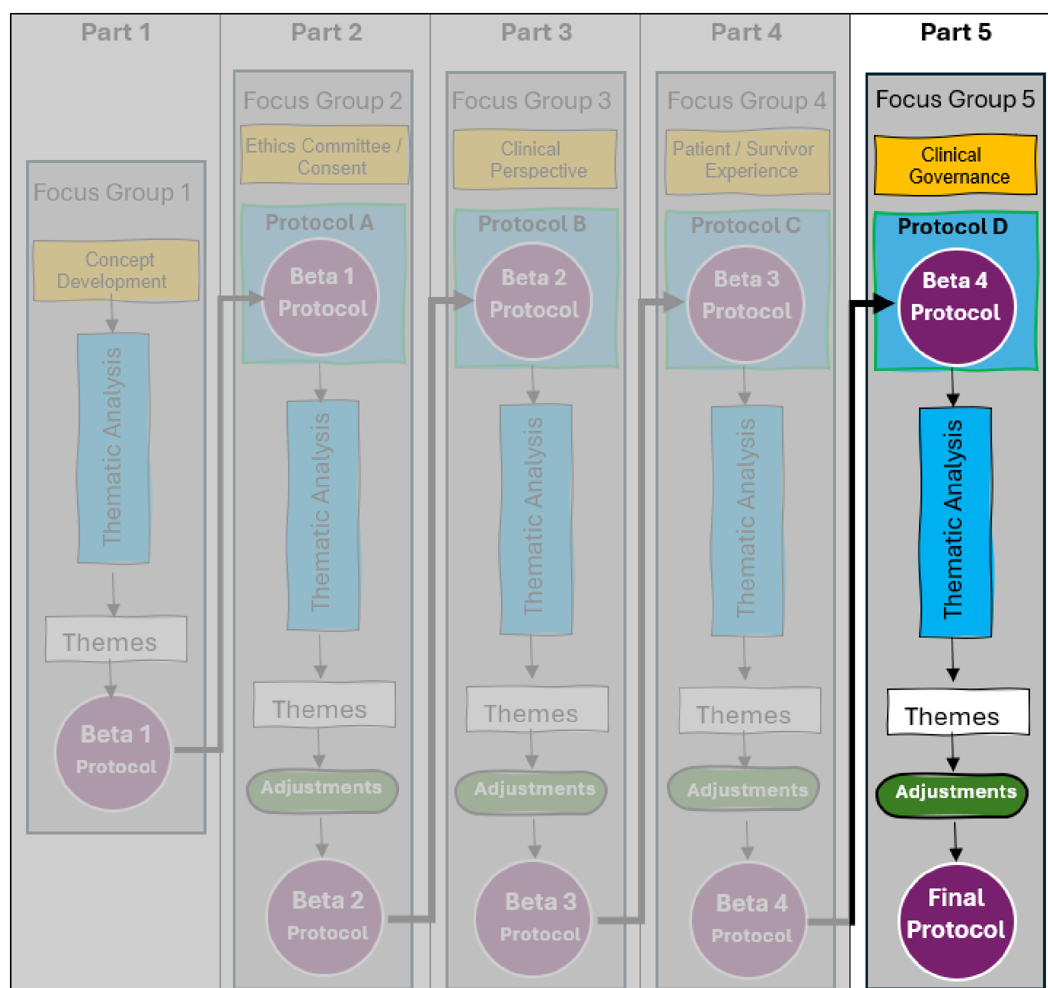


Figure 12: Part 5 – Clinical governance

5.6.1 Study participants

In the fifth stage of the study, the participants represented the senior leaders and managers from each of the departments within the Essex Cardiothoracic Centre. There were five medical staff, all with significant experience, ranging from 27 to 36 years. The Nursing team were an equally experienced group of staff, ranging from 17 years for the Theatre Manager and 22 years for the Surgical Ward Manager having the least at 17 and 22 years respectively to the Matron of Critical Care having 27 years. The Allied and Scientific team had a balanced distribution of experience levels ranging from 15 to 31 years. The General Manager have the highest level of experience at 40 years. The Finance Manager and Quality and Patient Safety team leader had 30 and 33 years of experience respectively. Table 15 provides the profile of the Clinical Governance participants.

Table 10 Clinical governance participants

Discipline	Professional Background	Age	Experience
Medical	Chair Clinical Governance	61	36
	Clinical Director	56	31
	Lead Cardiothoracic Surgeon	61	36
	Lead Consultant Anaesthetist	61	36
	Lead Consultant Cardiologist	52	27
Nursing	Cathlab Manager 2	49	28
	Cardiology Ward Manager	49	28
	Matron of Critical Care	48	27
	Outpatients Manager	58	37
	Private Suite Manager	43	22
	Surgical Ward Manager	38	17
	Theatre Manager	46	22
Allied / Scientific	Cardiac Physiologist	49	28
	Electrophysiology Manager	52	31
	Lead Perfusionist	47	23
	Lead Pharmacist	38	15
Other	Finance Manager	51	30
	General Manager	63	40
	Quality and Patient Safety team leader	54	33

5.6.2 Themes from clinical governance participants

As shown in Figure 13, analysis of the clinical governance participants of the THAW protocol produced five themes, 13 categories and 28 codes.

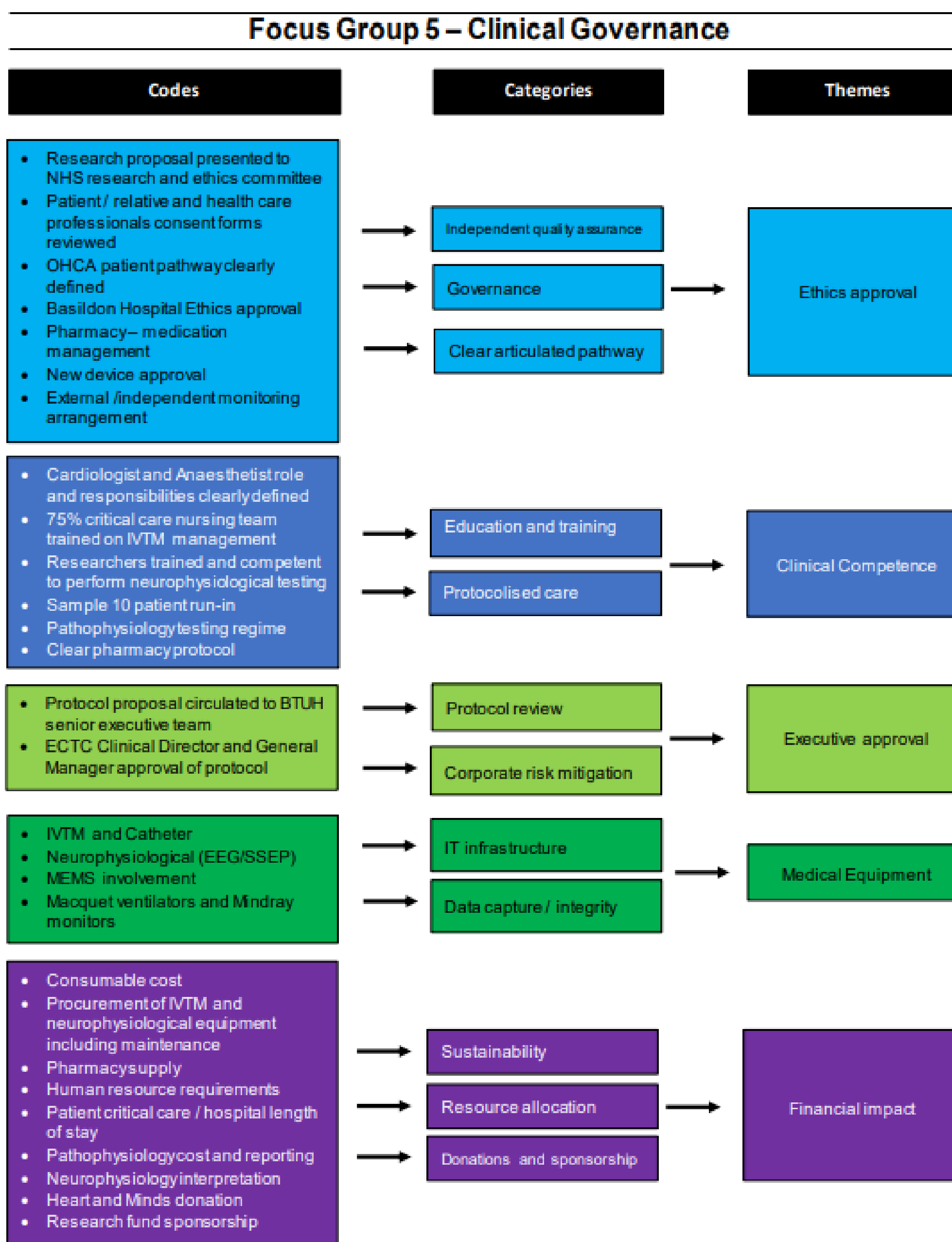


Figure 13: Thematic analysis of the clinical governance group

Theme 1 – Ethics approval

Independent quality assurance

An external research monitor was appointed due to a greater than minimal risk to patient safety. The external monitor provided expert advice during the protocol development phase. They were responsible for observing recruitment, enrolment and the consent process. They were also responsible for reviewing safety monitoring and overseeing data collection. The external monitor performed a site visit before starting the trial to assess the team's

preparedness, in terms of documentation and that the roles and responsibilities of the clinical research team had been clearly defined and understood by the team members. It was the responsibility of the external monitor to sign off the site as ready before the site could begin recruitment. Patient recruitment was estimated to take a minimum of 43 weeks to recruit 50 patients, therefore seven monitor visits were scheduled. There were two external monitor visits scheduled for the first month. These were to occur at two-week intervals. It was anticipated that two patients would have been recruited within the first two weeks for the first monitor visit and a total of five patients by the time of the second monitor visit. The remaining five monitor visits were scheduled bi-monthly.

> *Can you confirm you have an external monitor and what is the frequency of their visits?*
>
> Clinical Director

Governance

Within the NHS, there is a three-step process that must be undertaken before a clinical trial involving human subjects can proceed. This includes the protocol submission and approval by the NHS research and ethics committee, registering the research with clinical trials and finally, sign off by the local research and development department, where the intended research is going to be undertaken.

> *Thank you for providing us the NHS research and ethics committee approval of the protocol, have you received confirmation from the Director of Research and Development at Basildon Hospital?*
>
> Chair Clinical Governance

The Medicines and Healthcare products Regulatory Agency (MHRA) is responsible for ensuring that medicines and medical devices work and are acceptably safe. Whilst the IVTM catheters are CE marked, which indicates the manufacturer meets the European safety requirements, however any new product introduced to the hospital must obtain local governance approval before use. Assurance was provided to the governance group as the catheter had previously been used in the COOLAMI trial.

> *Does the IVTM catheter require approval as a new device?*
>
> Clinical Director

Clear articulated pathway

Due to the unpredictable nature of out-of-hospital cardiac arrests, admissions would occur at any time. However, neurological electrophysiology departments don't typically provide a 24 hour, seven-day week service, therefore the decision was made to train two researchers to perform EEG and SSEP. Over the course of three months, intensive training was provided to the two researchers by an expert neurological electrophysiologist on recording high quality intermittent 10-20 EEG and performing two-channel SSEP. The quality of the recordings was corroborated by a Consultant Neurologist with expertise in EEG and SSEP interpretation and recording.

Because admission times were unpredictable the two researchers were alternately rostered to cover each 24-hour period. The schedule for taking serial EEG and SSEP was on admission to critical care then at six hours, 12 hours, 24 hours, 48 hours and at 72 hours. These would be formally reported at a core laboratory at Addenbrookes hospital by the Consultant Neurologist with expertise in neurological electrophysiology.

> *With respect to the EEG and SSEP are you able to confirm who will be responsible for performing these tests, how have you ensured competency and who will be interpreting the recordings?*

Lead Consultant Anaesthetist

> *Given the 24/7 nature of out-of-hospital cardiac arrest admissions, can you provide more detail on the decision-making process that led to training the two researchers in EEG and SSEP and how their alternating schedule ensures continuous coverage?*

and

> *Also, how does the timing of the serial EEG and SSEP recordings align with the reporting process at Addenbrookes hospital?*

Lead Consultant Anaesthetist

Theme 2 – Clinical competence

Education and training

The training schedule for the IVTM catheter and Thermogard XP Temperature Management System Console was planned for approximately 100 critical care nursing and medical staff. This was intended to be a phased approach, initially the product representatives were scheduled to provide super-user training on the console to the four-person educator team and

six-person critical care outreach team. As super-users the educators and critical care outreach team would then be responsible for cascading the training to the remainder of the critical care nursing and medical staff. The training was purposefully delayed until the last two weeks of September 2018, as the beginning of October was the date when it was decided to move from surface cooling across to IVTM as standard care. By delaying the training until just before the launch date ensured the critical care team had current knowledge and experience in IVTM and console management. With education and critical care outreach staff working across all shifts, seven days a week, it was expected that at least 75 percent of the critical care staff would have received training within this two-week window.

With regards to the IVTM catheter insertion, the decision was made that this should occur in the cardiac catheter lab. As the IVTM catheter needed to be inserted in the femoral vein, it was decided the interventional cardiologist would be best placed to perform this procedure, as they would accessing either the femoral or radial artery for the PPCI. The training schedule for this was planned to coincide with the ten run-in patients when launching IVTM management as standard care from surface cooling.

Protocolised care

To ensure that all the team were competent in IVTM management, including catheter insertion, coil priming, sterile connection of set to catheter and console management, simulation in the cardiac catheter lab was scheduled for the cardiology, anaesthetic and critical care teams. This was considered an important step to appreciate the logistics of working together as a multidisciplinary team in a sterile theatre environment whilst performing angiography. This would also provide the team with an opportunity to identify correct placement of equipment and to sequence the entire procedure.

> *As with all new equipment, we would require 75% of staff trained before the equipment can be put into circulation. Do you have a training schedule and what is your anticipated time frame for reaching this target?*

Lead Perfusionist

Theme 3 – Executive approval

Protocol review

For the purposes of the clinical governance group giving final sign off, they required clear description of what constituted the early waking interventions. These were separated into two

distinct categories, testing and waking. The first category of testing would commence on admission to the critical care. The testing interventions is a series of non-invasive tests which are additional to standard care. They are performed on admission then repeated at six hours, 12 hours, 24, 48 and 72 hours. There are three components to the interventions, which include neurological assessment, neurophysiology and neuro biomarkers. The first component is the neurological assessment which incorporates the use of the Full Outline of UnResponsiveness (FOUR) sore, this tests brainstem reflexes. The second component is neurophysiology, which includes a 10, 20 configuration, 20 minute EEG recording and a two-channel SSEP. The third component is drawing blood samples for neuro biomarkers Neuron Specific Enolase (NSE) and S100b.

The second category is the early waking intervention. At 12 hours there is an assessment of cardiovascular, respiratory, neurological and metabolic patient parameters, against set criteria to determine whether the patient is clinically stable to be considered for early waking. If the patient meets the pre-determined criteria an attempt will be made to wake the patient – the 'early waking intervention'. The early waking intervention consists of an anti-shivering regime, which is applying a Bair Hugger™, administration of Buspirone and weight adjusted bolus dose of Meperidine. Concurrently stopping neuromuscular blockers and titrating sedation off.

> *The protocol clearly defines the OHCA pathway from admission to discharge. What is the actual intervention period?*
>
> Lead Consultant Anaesthetist

The administration of Buspirone and Meperidine are components of the counter-shivering regime, see Appendix Four. A clinical assessment of the patient is performed at 12 hours, stable parameters against a set criteria would need to be achieved before being confirmed by a member of the anaesthetic team. The anaesthetist would then prescribe a bolus dose of Buspirone and a weight adjusted bolus dose of Meperidine (as per THAW protocol) for the critical care nurse to administer. Following the early waking assessment, the patient will be continuously monitored for shivering against a set criteria ranked zero was the equivalent of no shivering to three which is the equivalent of severe shivering. The lowest threshold of one or mild shivering would constitute the requirement for additional bolus dose of Meperidine. A maximum of two additional bolus doses of Meperidine at 15-minute intervals before commencing a Meperidine infusion at 45 minutes from first dose being administered.

Has there been education and training with the critical care staff around the administration of Buspirone and Meperidine?

Matron of Critical Care

Corporate risk mitigation

All adverse and serious adverse events was recorded on the CRF detailing the event. There are four categories that will rank the impact of the event. The first is the severity of the event and this will be ranked from zero which is the equivalent of a mild patient impact, one constituted a moderate patient impact to two constituted a serious patient impact. The second category describes the action taken at the time of the event, this was ranked zero which meant that no action was taken, one indicated the trial interventions were temporarily interrupted and two that the patient was permanently withdrawn. The third category is outcome for the patient, this was ranked from zero which meant the issue had resolved, one indicated the issue had resolved with sequelae, to two which indicated the issue had not resolved. The fourth category was the relationship of the event to the study, this was ranked from zero which meant there was definite relationship between the event to the study, one indicated that there was probably a relationship between the event to the study, two that there was possibly a relationship between the event to the study, three indicated that is was unlikely the event was related to the study, four indicated the event was not related and five the event was not assessable. The principal investigator would be responsible for reviewing all adverse events and assessing the seriousness, causality, severity and outcome of the event. Serious adverse events will be escalated to the chief investigator within 24 hours of the event occurring. Noting that 50 percent of OHCA survivors don't survive until discharge, all deaths that occur within the 72-hour intervention period will be reported as an adverse event.

How will you be reporting adverse events?

Chair Clinical Governance

Although sign off or approval of research by the hospitals executive team would normally be implied through normal clinical governance channels, this was original research that involved multiple departments, had a patient safety element as well as significant financial implications. Therefore, it was considered necessary to obtain explicit executive team approval.

Have the hospital Executive team been informed and given approval?

Consultant Anaesthetist 1

Theme 4 – Medical equipment

IT infrastructure

Data were required to be collected from multiple sources. This included the prehospital information from the ambulance service which would provide detail of the cardiac arrest. On admission to hospital, past medical history would be required to identify any exclusion criteria for TH. All interventions performed in the cardiac catheter lab would be recorded by the cardiologist in the medical notes with procedural detail recorded by the physiologist on Tomcat™ (cardiology software). The hourly clinical observations recorded by the critical care team, were taken from the Mindray™ monitors. This included 27 data points in relation to cardiovascular, respiratory, neurological as well as renal parameters, which would be recorded for 96 hours. For the same period, critical care staff would record hourly mechanical ventilation data, this would also be captured and downloadable from the Maquet Servo® ventilator. Every two hours, 11 arterial blood gases parameters would be recorded from the Cobas® blood gas analyser. There was a total of 31 different blood tests to be performed every six hours (minimally) by the critical care staff, which would include electrolytes, liver and bone function, full blood count and clotting, as well as any drug levels for dosage adjustment purposes. All blood test results would be downloadable from the Lorenzo™ digital platform. In addition, two neuro biomarkers will be sent to a core lab offsite for analysis and reporting. These will be sent in batches and the results will be made available at the end of the trial. IVTM and temperature data would be captured and downloadable from the Thermogard XP Temperature Management System Console®. With respect to EEG and SSEP these will be recorded by two competent researchers in EEG and SSEP using the Cadwell™ neurological diagnostic equipment. The recordings will be sent for formal reporting to a core lab for interpretation of nine parameters repeated seven times over 96 hours.

> *Considering the vast array of data sources, from prehospital details and medical history to various observations, interventions and test results recorded in multiple systems and equipment, can you help to elucidate how we are ensuring the accurate collection, integration and management of all these critical data points?*

Quality and Patient Safety Team Leader

> *How are the EEG and SSEP recordings handled and what steps are in place to ensure the integrity and reliability of the data sent for formal reporting?*

General Manager

Data capture and integrity

The case report form (CRF) will be populated by the researchers from a combination of the medical records, critical care charts, downloadable data from medical devices and digital platforms. Results from neuro biomarkers and physiology tests sent to core labs will be made available at the end of the trial period.

> *Who will be responsible for data collection?*
>
> Matron of Critical Care

The critical care staff initially trained as super-users, which includes the outreach team who work across all areas within the ECTC will be responsible for training the 12 dedicated cardiology high dependency unit staff, who will be responsible for caring for any patient that is transferred from critical care whilst continuing to be treated with IVTM.

> *What is the education and training schedule for staff outside of the critical care unit on how to manage an awake patient who continues to be cooled?*
>
> Cardiology Ward Manager

Theme 5 – Financial impact

Sustainability

The consumables required were for neurophysiology and neuro-biomarker testing as well as the counter shivering strategies were interventions not considered standard care. This includes electrodes, adhesive and removal paste for performing EEG and SSEP, a maximum of seven sets per patient. Medications were limited to those specifically used for early waking and counter-shivering strategies which included Buspirone and Meperidine. Buspirone would only be used once and only for patients who met the early waking criteria. Meperidine would only given to patients who met the early waking criteria, initially given as a bolus dose and then administered as a continuous infusion, which was titrated to affect. There were two sample bottles required for the neuro biomarkers. These were taken seven times over the 72 hours.

> *Have you got a detailed consumable cost?*
>
> Finance Manager

Resource allocation

The critical care staff initially trained on IVTM as super-users, which includes the outreach team who work across all areas within the ECTC will be responsible for training the 12

dedicated cardiology high dependency unit staff, who will be responsible for caring for any patient that is transferred from critical care whilst continuing to be treated with IVTM. This will include counter-shivering strategies.

> *How the critical care staff, especially the super-users and outreach team, will train the cardiology high dependency unit staff on IVTM and managing counter-shivering strategies when a patient is transferred from critical care?*

Matron of Critical Care

The OHCA pathway is aligned with the NHS PPCI pathway. This is to ensure that only patients with a presumed cardiac cause for the cardiac arrest will be accepted for admission. The other reason for the development of the pathway was to avoid secondary referral, to enable the ambulance service to refer directly rather than transport to a local hospital, for the patient to be assessed by the medical team, therefore delaying treatment. The pathway also describes repatriation of the patient back to their local hospital following cardiac intervention, this would be once they are normothermic, having be treated with IVTM.

> *Can you clarify how the OHCA pathway ensures that we are only admitting patients requiring PPCI?*

and

> *Also, what is the process of repatriating patients back to their local hospitals?*

Lead Cardiothoracic Surgeon

Buspirone is available in 10 milligram tablets, therefore six tablets would be required as a once only bolus dose per patient, which is a maximum of 10 boxes. The maximum dose of Meperidine that would be administered over 60 hours is the equivalent of 1000 milligrams which is two boxes per patient. Whilst Buspirone is not a controlled drug this should be stored with the controlled drugs for safety and stock management. Meperidine is managed as a controlled drug. Due to controlled drug cupboard storage constraints, a minimum stock level for the equivalent of two patients.

> *Are you able to identify what stock levels you require of both and where these will be stored and who will be responsible for ordering top ups?*

Lead pharmacist

Donations and sponsorship

For the purposes of maintaining financial integrity, as well as safety, the clinical governance team required full disclosure of who was sponsoring or donating the neurophysiology equipment and consumables as well as biomarker storage, testing and transport. To consider whether accepting the sponsorship or donations would harm the organisations reputation was also discussed. To ensure that any sponsorship or donations were aligned with the organisation's values.

Over the past decade, Hearts and Minds had been involved in multiple fundraising events for the Essex CTC to enable the purchase of new equipment. For Hearts and Minds, this had been there largest fundraising event to purchase the EEG and SSEP machine, but had unanimously agreed to support, following a vote taken by its members.

> *Have you identified core lab for testing blood samples, transport and cost?*

Lead Consultant Cardiologist

> *Could you please provide us with detailed information about who is providing the funding for the neurophysiology equipment, consumables and other related expenses? We also need to understand how we have ensured that accepting this support won't negatively affect our organization's reputation and that it aligns with our core values.*

Chair Clinical Governance

The Research and Development department, at Basildon and Thurrock University Hospital, Foundation Trust, had a research fund that was open to applicants from researchers who were seeking financial support. Through a contestable process, an application was submitted to Research and Development for money to purchase the consumables for the EEG and SSEP machine as well as all of the equipment required for the neuro-biomarker samples, including the cost of storage, processing and transport. The application was considered favourably, which covered all THAW protocol intervention consumable costs, including all associated costs for neuro-biomarker testing.

> *Are you able to clarify how we will be funding the EEG and SSEP consumables, as well as the neuro-biomarker testing and from which department will it came from?"*

Finance Manager

5.7 Summary, findings phase I

The iterative process of the THAW protocol development involved a multidisciplinary approach. The protocol evolved through a five-stage process, involving extensive collaboration and input from various groups. The research group constituted academics and clinicians, who considered and critically evaluated contemporary literature, policy and procedure, as well as evidence-based practice. With a strong emphasis on establishing a robust protocol that could withstand empirical testing and practical implementation. The research group ensured that the protocol was scientifically valid and patient centred. Furthermore, innovative methods were used for data collection as well as facilitating the integration of complex clinical interventions within the protocol. The ethics committee played a pivotal role in validating the THAW protocol, specifically on the principles of research integrity and ethical conduct. The constructive feedback pivoted around the consent process as well as providing clear and concise information to patients, family and clinicians. Therefore, prioritising patient safety and enhancing the ethical robustness of the THAW protocol. Clinical experts were engaged for their knowledge and experience, which provided invaluable insights into the practical aspects of implementing the THAW protocol, highlighting potential limitations and suggesting strategies for seamless integration into the existing PPCI clinical pathway ensuring its clinical relevance and feasibility. Survivors and their families were active contributors in the development of the THAW protocol. Providing a unique and invaluable perspective, their narratives and lived experiences highlighting the impact of patient access, information and support, which inevitably is impacted when performing complex neurophysiology testing, during the THAW protocol interventions period. The clinical governance team provided the final comprehensive review of the THAW protocol, in terms of examining its alignment with organisational values, ethical standards and clinical best practices. Their endorsement was a significant milestone, a consensus that the THAW protocol reflected an integration of scientific inquiry, ethical responsibility and clinical expertise. The key themes are summarised in Table 11.

Table 11: Themes related to the five stages in the development of the THAW protocol

Part ONE Themes relating to the development of an early waking and neurological prognostication protocol	Part TWO Themes relating to the ethical considerations of an early waking and neurological prognostication protocol	Part THREE Themes relating to the clinical components of an early waking and neurological prognostication protocol	Part FOUR Themes relating to the patient experience of an early waking and neurological prognostication protocol	Part FIVE Themes relating to the clinical governance of an early waking and neurological prognostication protocol
Evidenced based medicine --- Patient interventions --- Define routine care --- Staff --- Resources	Consent --- Risk / benefit ratio --- Do no harm	Patient pathway --- Patient safety --- Family participation --- Pharmacology --- Temperature management	Funding stream --- Patient benefit --- Improve relative experience --- Improve outcomes	Ethics approval --- Clinical competence --- Executive approval --- Medical equipment --- Financial impact

Chapter 6: Protocol implementation

The secret of your success is determined by your daily agenda.

Roger Moore

The following chapter has been published through the following:

- Watson et al. (2019) Publication of provisional feasibility findings:

  Watson, N., Damian, M., Potter, M., Harding, J., Polderman, K., Karamasis, G., Davies, J., & Keeble, T. (2019). Increasing cardiac arrest survivor access to advanced neuromonitoring and neuroprognostication, as recommended in international guidelines: A pilot study. *Resuscitation, 137*, 213-214.

- Watson et al. (2022) Publication of THAW protocol:

  Watson, N., Karamasis, G., Stathogiannis, K., Potter, M., Damian, M., Cook, C., Pottinger, R., Clesham, G., Gamma, R., Aggarwal, R., Sayer, J., Robinson, N., Jagathesan, R., Kabir, A., Tang, K., Kelly, P., Maccaroni, M., Kadayam, R., Nalgirkar, R., Namjoshi, G., Urovi, S., Pai, A., Waghmare, K., Caruso, V., Polderman, K., Noc, M., Davies, J. R., & Keeble, T. R. (2022). Feasibility of early waking cardiac arrest patients whilst receiving therapeutic hypothermia: The therapeutic hypothermia and early waking (THAW) trial. *Resuscitation, 171*, 114-120.

6.1 Introduction, protocol implementation

The previous Chapter 5 focused on the development of the Therapeutic Hypothermia and eArly Waking (THAW) protocol, with the final iteration (Watson et al., 2019) being approved by the clinical governance group (Figure 14). Chapter 6 chapter will discuss the results of the THAW protocol implementation (Watson et al., 2022).

For the Out Of Hospital Cardia Arrest (OHCA) survivor there is a delicate balance between life and death, which often hinges on the critical care delivered within the first 24 hours following admission. Approximately 50 percent of individuals who are resuscitated and admitted to the hospital following an OHCA will unfortunately not survive, predominantly due to neurological injury that continues to be the leading cause of both mortality and long-term morbidity in this patient population (Cronberg et al., 2020; Dragancea et al., 2013). It is in this uncertain context that Targeted Temperature Management (TTM) emerges as a therapeutic intervention. Formerly referred to as Mild Therapeutic Hypothermia (MTH), TTM is a nuanced medical strategy designed to mitigate the sequelae of cerebral injury by reducing the patient's core body temperature during the critical recovery phase post OHCA.

Navigating the prognostic landscape for patients undergoing TTM is complex. A multimodal approach, encompassing electrophysiological examinations, biomarker evaluations, clinical examinations, and advanced neuroimaging, is considered paramount in determining a patient's prognosis that is both accurate and reliable (Cronberg et al., 2020; J. Nolan et al., 2015; J Nolan et al., 2015; Oddo et al., 2008). Current clinical pathways underscore the importance of promptly identifying individuals with an anticipated unfavourable outcome, with an unintended consequence of directing less attention toward those with potentially positive early outcomes.

Consensus guidelines advocate for the application of TTM for a duration of 24 hours, followed by a gradual re-warming process of 0.25° Celsius per hour, until the patient reaches normothermia. During this rewarming phase, the discontinuation of sedative and Neuromuscular Blocking (NMB) agents is advised, thereby facilitating an assessment of neurological function that is not affected by pharmacological influences (Nolan et al., 2022). Recent advances have introduced the possibility of administering TTM to conscious patients via an endovascular device; a method proven to be both feasible and safe, particularly in those recovering from myocardial infarctions and cerebrovascular accidents, when accompanied by

appropriate counter-shivering strategies (Erlinge et al., 2014; Guluma et al., 2006; Perman et al., 2014).

The aims of this study were to explore the potential of early awakening after 12 hours post-ICU admission, during TTM at 33° Celsius sustained over a 24-hour period, coupled with the prevention of hyperthermia for an extended 72 hours. This investigation was driven by the hypothesis that such an approach could not only facilitate more timely neuroprognostication but also contribute to a reduction in the duration of ICU stay for OHCA patients. This chapter presents the findings of the THAW protocol implementation, and its impact on patient outcomes in the critical care setting. The final iteration of the THAW protocol is presented in the following flowchart detailing the clinical pathway for OHCA patients admitted to the Essex Cardiothoracic Centre. The flowchart outlines the sequence and timing of interventions, monitoring and decision points for the first 72 hours, see Figure 14.

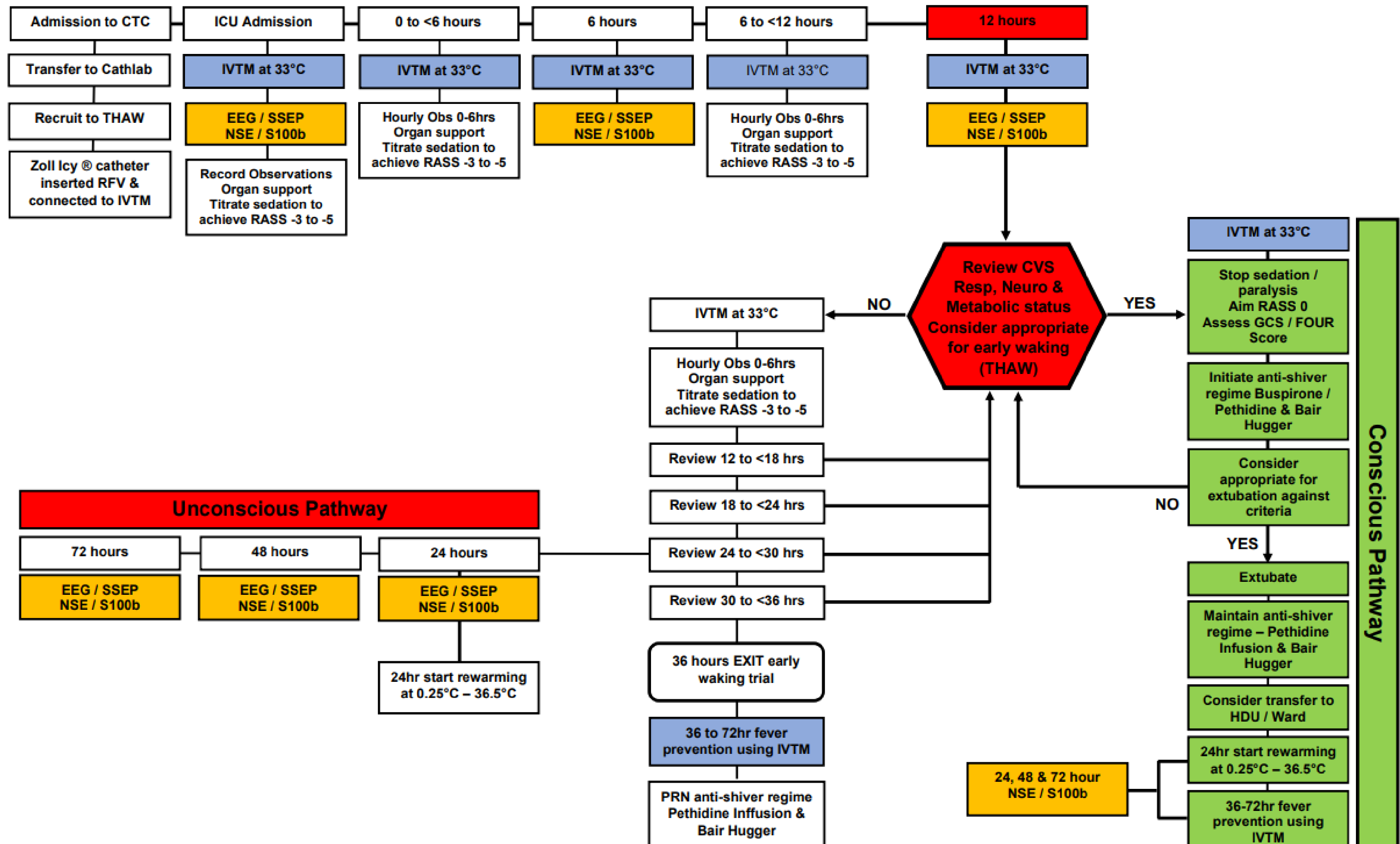


Figure 14 **Final approved THAW protocol intervention flow chart**

6.2 Study design

The research study is described as a single-centre, prospective, non-randomised design, used to assess the safety and feasibility of implementing an early waking protocol for OHCA survivors whilst being treated with TTM set to 33° Celsius. This was conducted at the Essex Cardiothoracic Centre, Basildon and Thurrock University Hospital between February 2017 and January 2018. There were 50 adult patients who met the specified inclusion criteria and were deemed suitable to evaluate the safety and feasibility of implementing the THAW protocol interventions. Eligible participants were adults over 18 years who had been resuscitated following OHCA who would be treated with TTM as part of their routine post-resuscitation care management. Patients were excluded if they suffered from non-cardiac causes of arrest, had a pre-existing 'do not resuscitate' order, terminal illnesses, pregnancy, blood clotting disorders, reliance on oxygen, a height under 1.5 meters, allergies to Buspirone or meperidine, had an inferior vena cava filter (which would prevent the insertion of a cooling catheter), or unresolved substance abuse issues. The research received ethical clearance from the local Institutional Review Board at Basildon and Thurrock University Hospitals NHS Foundation Trust's Research and Development Department and the UK, NHS Health Research Authority (reference 15/EE/0173 and NCT03065946).

The THAW protocol interventions were carried out in the ICU at the Essex Cardiothoracic Centre. As all recruited patients were unconscious, they were not able to give consent therefore the relative were consulted and given an information sheet (Appendix A) on whether they considered the patient would be in agreement to participate in the study and to complete a personal consultee declaration form (Appendix B). Once the patient regained consciousness and were able to understand, they were given trial participation information (Appendix C) and were asked for their consent (Appendix D). In the event no relatives were present, two independent doctors, not involved in the study, were provided with a trial information sheet (Appendix E) and asked to be the nominated consultee and complete a declaration form (Appendix F).

6.3 The protocol interventions

6.3.1 Targeted Temperature Management

The detailed protocol of the study has been previously published and is described in the previous chapter. As a designated Cardiothoracic Centre, OHCA patients with a presumed cardiac cause were admitted directly to the cardiac catheter laboratory where they were initially assessed for coronary intervention and appropriateness for TTM to be delivered using an endovascular catheter. Suitable patients had an ICY® catheter (Zoll Medical Corp, Chelmsford, MA, USA) inserted into the femoral vein, and Intravenous Temperature Management (IVTM) was initiated in the cardiac catheter lab, immediately before or after coronary angiography and if required, revascularisation. The core temperature was taken from a bladder probe which was continuously monitored using an indwelling urinary catheter with an incorporated temperature probe. The target temperature was set to 33 °C using the Thermogard XPTM temperature management system (Zoll Medical Corp, Chelmsford, MA, USA) for 24 hours. Patients were then slowly re-warmed at a rate of 0.25° Celsius per hour until they reached 36.5° Celsius and prevention of hyperthermia was maintained for 72 hours. Early extubation was considered any patient extubated less than 36 hours. Suitable patients could be discharged to the ward, from the ICU while receiving TTM.

6.3.2 Counter-shivering regimen

Patients were given a sedative regimen of propofol and fentanyl, which were adjusted to maintain a sedation level from minus three (indicating moderate sedation) to minus five (meaning the patient was deeply sedated and unarousable), according to the Richmond Agitation-Sedation Scale (RASS) Score. To prevent shivering, intermittent doses of a Neuromuscular Blocking (NMB) agent, either Rocuronium or Atracurium, were used when necessary. The use of an NMB was determined by observable shivering in the patient or an involuntary rise in core temperature exceeding 0.3° Celsius. Dexmedetomidine was not used for any patient because it was not available during the time of the study.

A strict counter-shivering regime (Figure. 15) was initiated for every patient who was eligible for early waking had a hot air warming blanket, with the temperature set up to a maximum of 42° Celsius. Additionally, for those patients who were considered appropriate for early waking, sedatives, and NMB were discontinued, and these patients received an initial dose of Buspirone 60 milligrams through a nasogastric tube, along with 0.5 to 1.0 milligram per kilogram of Meperidine, which was given intravenously over a 15-minute period. Following the loading dose, up to three additional doses of Meperidine, ranging from 10 to 50 milligrams, based on

the patient's ideal body weight and responsiveness were administered intravenously at 15-minute intervals. Furthermore, a continuous intravenous infusion of Meperidine at a rate of 5 to 25 milligrams per hour, which was adjusted as necessary to ensure the patient's comfort and prevent shivering while undergoing therapeutic temperature management at 33° Celsius.

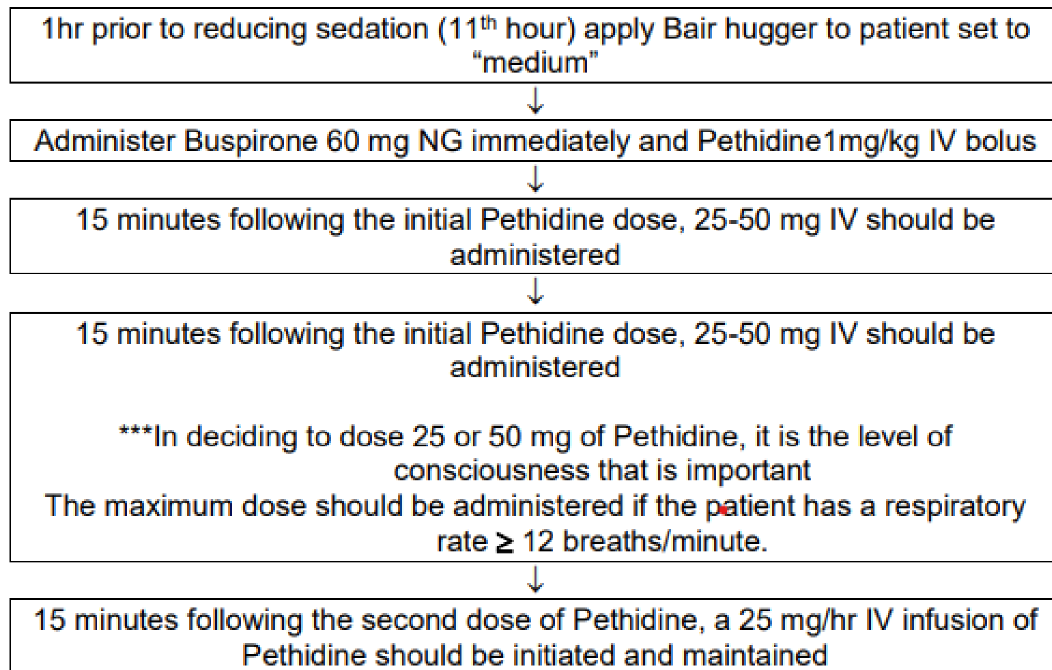


Figure 15 Counter shivering regimen

Determination of shivering: The following measures can be employed to determine if the shivering protocol is adequately controlling the patient: If the patient's level of consciousness is such, ask the patient if they are feeling cold. Look for muscle twitching on the ECG (it will make the baseline look jagged). Look for visible muscle twitching, particularly in the neck region. Look for piloerection (goosebumps).

6.3.3 Early waking assessment

Patients were evaluated against an early waking criteria (Figure 15) after 11 hours from admission to the ICU, to decide if they were clinically suitable to be considered for early waking. This assessment comprised of a comprehensive examination of the cardiovascular and respiratory physiological recorded parameters, an evaluation of the patient's neurological status, as well as metabolic functionality. If these parameters were all within the predetermined limits, sedation was decreased to attain a Richmond Agitation-Sedation Scale (RASS) of minus 3 or lower. To evaluate the patients' neurological function and determine if they were ready for extubation, a combination of the Glasgow Coma Scale (GCS) and the Full Outline of UnResponsiveness (FOUR) score was used. Those patients determined to be neurologically appropriate for extubation required a GCS of at least eight and a FOUR score of 13 or above.

6.3.4 Neurological biomarkers and neurophysiology

Utilising a prompt sheet (Appendix 7) serum biomarkers and neurophysiology tests were performed when the patient was admitted to the ICU, then at six hours, 12 hours, and 24 hours, then at 48 hours and 72 hours if the patient remained unconscious, which was considered the end of the protocol interventions. Serum biomarkers, Neuron-Specific Enolase (NSE) and S100b were initially sent to the on-site laboratory for safe storage, then transported in batches to an offsite core laboratory for processing and the results were reported and made available for post hoc analysis.

Serial EEGs and two-channel SSEPs were performed at the time intervals as indicated. A 10-20 EEG configuration (Figure 16) were recorded over 20 minutes at each of these time points up to 72 hours if the patient was woken and extubated recording of EEGs was discontinued as no longer required. The international 10-20 or "double banana" configuration refers to the EEG electrode placement on the patient's scalp based on specific skull measurements. The 10-20 configuration is designed to ensure consistency across different patients, with "10" and "20" denoting the percentages of distances between adjacent electrodes. This is calculated by measuring the distance between the nasion or the indent at the top of the nose, where it joins the forehead, to the inion, which is the most prominent point of the skull at the back of the head, as well as the measured distance between the two preauricular points located in front of each ear. By dividing the longitudinal and transverse measurements into 10 and 20 percent intervals, identifies the position of where each electrode was placed. Letters are used to indicate the underlying brain region (F for frontal, C for central, P for parietal, O for occipital, and T for temporal). Even numbers indicate the right side of the brain and odd numbers indicate the left, with z indicating the midline position.

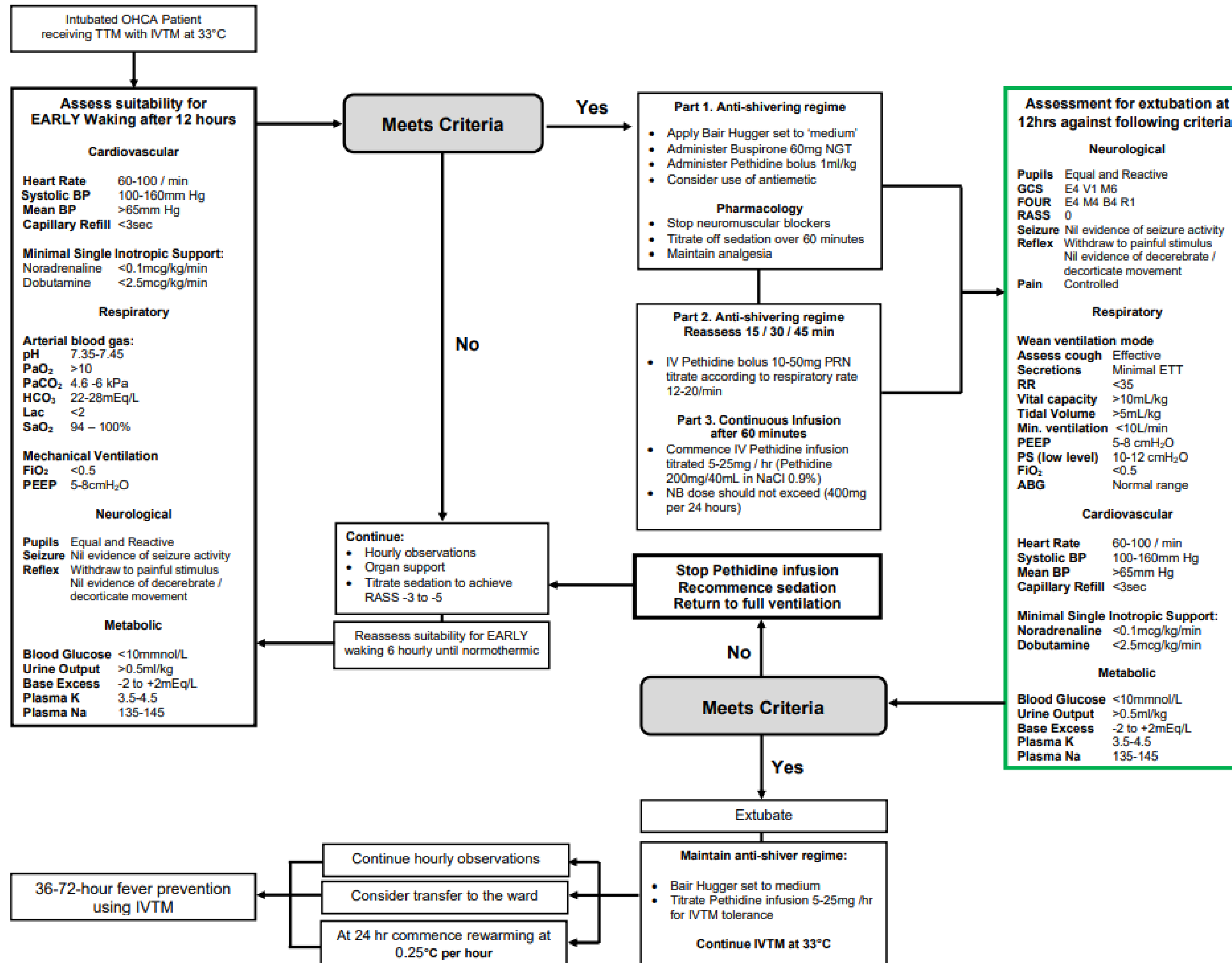


Figure 16 Early waking assessment criteria

While recording the EEG various stimulus activities were employed, each with a distinct purpose in evaluating the patient's neurological status. The specific stimulus activities were marked on the EEG recording. By marking the exact stimulus activities on an EEG recording at the precise moment they were conducted would allow for accurate correlation between the applied stimulus and the brain's electrical response, ensuring that any changes in the EEG trace can be directly attributed to the stimulus and assessing neurological status. While the EEG captures all brain activity, including both spontaneous and stimulus-induced activities, marking the stimulus would differentiate between responses specifically elicited by the stimulus from the brain's natural activity, therefore ensuring accurate interpretation. At least 30 seconds was given between each stimulus to ensure brief and subtle responses were able to be noted correctly. This was also considered important for tracking delayed responses.

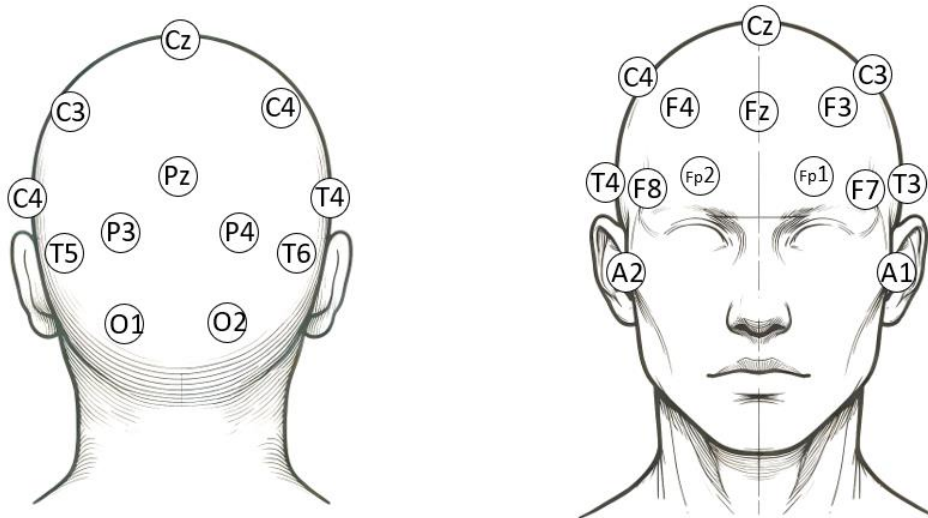


Figure 17: 10-20 EEG configuration

During the EEG recording, four types of stimuli were employed on both the left and right sides of the patient, including auditory, nociceptive, corneal, and tactile stimuli. The auditory stimuli involved clapping and calling the patient's name near each ear to assess the level of consciousness and auditory processing capabilities. Nociceptive stimuli involved applying pressure to the patient's nail beds, aiming to evaluate the brain's response to pain and to gauge the depth of unconsciousness and overall brain function. The corneal swab test was performed by gently touching the cornea with a gauze swab in each eye to elicit the corneal reflex, marked by involuntary blinking, also a measure of brainstem function. The final stimulus technique was a gentle tactile stimuli, involving stroking the patient's arms and legs,

to check for any cerebral response to soft touch, providing insights into the patient's sensory processing capabilities. Any observed response was marked on the EEG recording.

The two channel Somatosensory Evoked Potential (SSEP) refers to one channel being dedicated to determining cortical response such as N20, and the second for peripheral response, specifically that of the brachial plexus or Erb's point. Dual channelling allows clinicians to pinpoint where along the pathway potential disruptions or abnormalities may be occurring. If an abnormality is detected at Erb's point but not at the cortical level, it suggests an issue in the peripheral nerves or the brachial plexus. Conversely, normal responses at Erb's point with abnormalities in the cortical response could indicate problems within the central nervous system, possibly in the spinal cord or brain. By employing this two-channel approach, the diagnostic accuracy and precision of SSEP monitoring is significantly enhanced, facilitating more accurate localisation of neurological issues. N20 refers to the "N" meaning negative, and the "20" indicates milliseconds. The N20 measures the integrity of the peripheral sensory nerves through the spinal cord an up to the primary somatosensory cortex in the brain, which includes the peripheral nerves from the thumb, index and middle fingers to the cervical spine, brainstem and thalamus, to the parietal cerebral cortex of the brain. The cathode (negative electrode) was positioned over the medial nerve at the wrist and the anode (positive electrode) was placed two centimetres proximal. These electrodes deliver an electrical impulse lasting about 0.1 to 0.5 milliseconds at a frequency ranging from two to 15 milliamps per second, starting at the lowest setting and increased incrementally depending on patient responsiveness. A visible twitch of the thumb or fingers would indicate correct placement of the stimulating electrodes. The recording electrodes were placed on the scalp to capture the evoked responses. The primary recording electrode was located over the contralateral primary somatosensory cortex, approximately two centimetres posterior to the C3 or C4 position (Fig. 18) based on the 10-20 EEG system. This placement corresponds to the opposite side of the stimulated limb. Additionally, a reference electrode was placed at the Fz position, and a ground electrode was attached to the forehead.

For consistency and reliability, the SSEP was repeated three times (Fig. 18) at each time point indicated, for up to 72hours, unless the patient was successfully woken and extubated, at which point SSEP was discontinued as it was no longer necessary. The electrical stimulation of the median nerve and the monitoring of evoked responses through either the C3 or C4 the scalp electrodes were amplified and displayed, with the critical N20 waveform, being the primary focus for analysis.

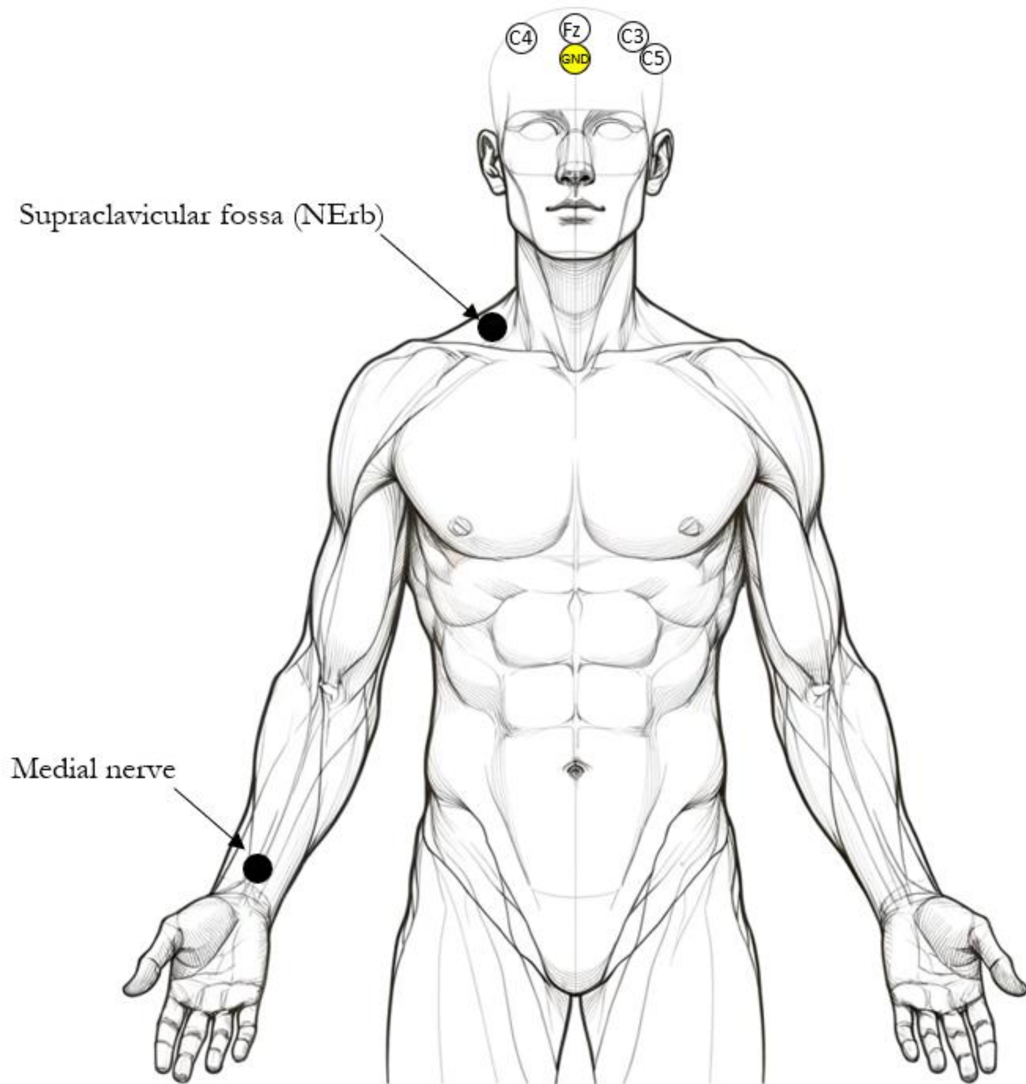


Figure 18 SSEP electrode position

The following Figure 19 is an example of a bilateral SSEP recording, with the left and right panels corresponding with the patients left and right side. Overlay of sequential recordings in each of the panels, differentiated by line colour variations. The overlay of the recordings is useful to demonstrate consistency to the operator taking the recording.

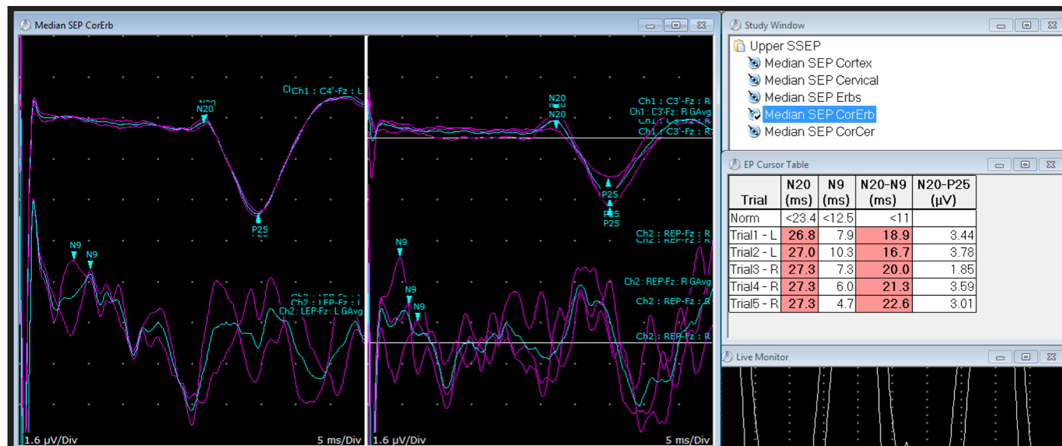


Figure 19: SSEP consecutive recording at 12 hours patient 20

The EEG and SSEP recordings were sent to a Consultant Neurophysiologist off-site for interpretation and reporting, with the results being made available for post hoc analysis only. A standardised template (Appendix 8) was used to ensure consistency in analysis and reporting, which was considered paramount to enable reliable comparisons across patients. Not disclosing the results of the EEG and SSEP to the clinical team was intentional, to maintain objectivity, especially in the context of the safety and feasibility imperatives of the early waking THAW protocol. Therefore, to prevent bias or influence in treatment decision making. This approach also allowed the clinical team to focus on the broader range of clinical indicators and physiological parameters, without being influenced by EEG and SSEP test results.

6.4 Results, protocol implementation

6.4.1 Baseline characteristics

The demographics and clinical characteristics of the study cohort participants is shown in Table 15. Figure 9 illustrates the flow of patients through the research. A total of 50 patients were enrolled in the study, four patients (8%) were excluded from the final cohort as they died within 12 hours of admission to the ICU (Fig. 20). Median age of the final cohort was 65.8 ± 11.5 years and 82 percent (n=41) were male. Median time to achieve ROSC was 29 ± 24.1 minutes, 88 percent of patients (n = 44) presented with a shockable rhythm and 68 percent of patients (n=34) received bystander cardiopulmonary resuscitation.

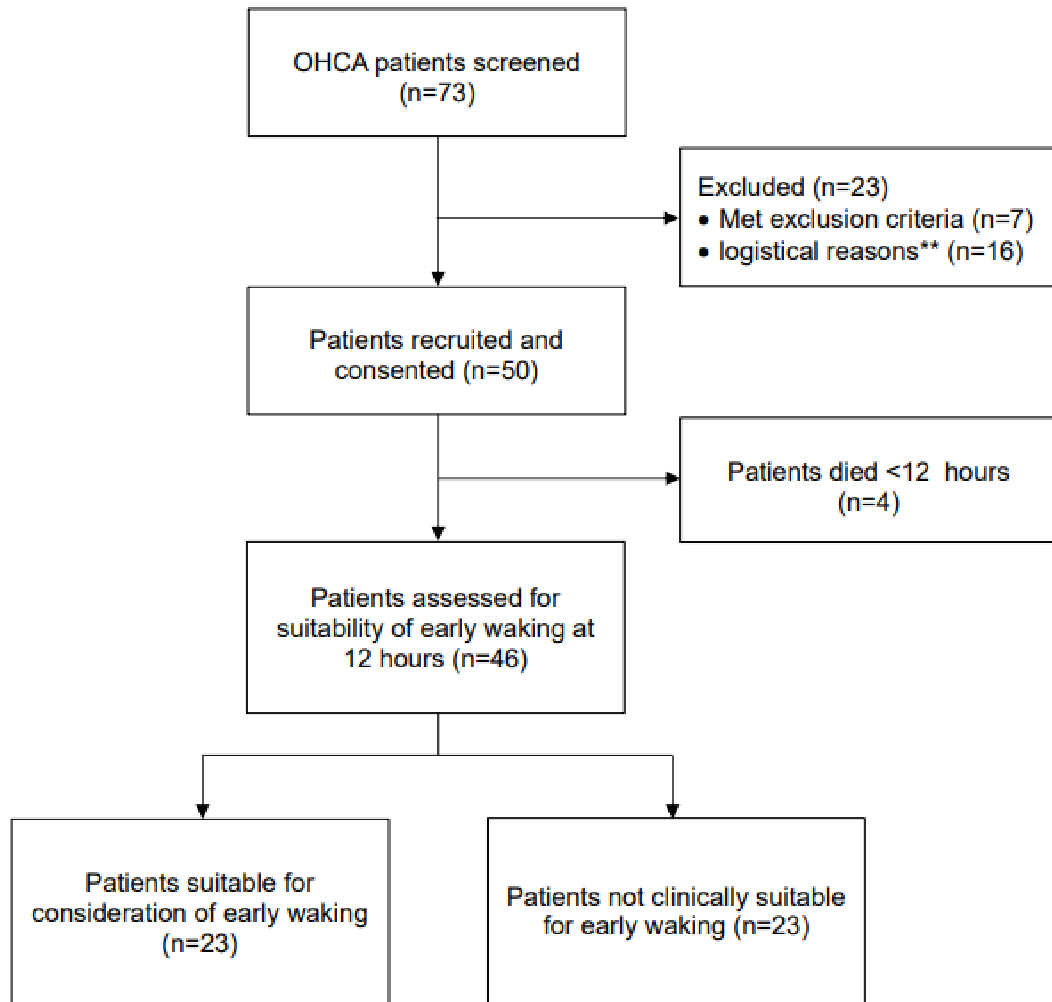


Figure 20: THAW study flowchart

** 16 patients not recruited due to logistical reasons which included IVTM not available (n=4) Research team not available to recruit patient and perform interventions (n=12)

Table 12: Baseline characteristics of OHCA survivors

Demographic data	Mean	Early	Late
Age	65.5 ± 11.5	66.2 ± 7.9	65.5 ± 13.8
Weight	91.5 ± 24.9	92.5 ± 28.8	90.9 ± 22.5
BMI	28.1 ± 4.3	27.6 ± 3.6	28.7 ± 4.8
Sex - Male (%)	82	82	82
Race (%)			
White British	90	87	93
Black British	1 (2)	1 (4.3)	0
Asian	3 (6)	2 (8.7)	1 (3.7)
European	1 (2)	0	1 (3.7)
Comorbidity			
AF	2 (4)	2 (8.7)	0
Asthma	6 (12)	2 (8.7)	4 (14.8)
COPD	5 (10)	1 (4.3)	4 (14.8)
Coronary Artery Disease	13 (26)	3 (13)	10 (37)
CKD	5 (10)	3 (13)	2 (7.4)
Diabetes	8 (16)	1 (4.3)	7 (25.9)
Hypertension	22 (44)	9 (39.1)	13 (48.1)
Peripheral Vascular Disease	5 (10)	0	5 (18.5)
Previous Stroke / TIA	0	0	0
Current Smoker	11 (22)	4 (17.4)	7 (25.9)
Cardiac Arrest			
Bystander CPR (%)	34 (68)	16 (69.6)	19 (70.4)
Total downtime	29.4 ± 24.1	17.3 ± 10.6	39.1 ± 27.5
VF / pulseless VT	44 (88)	23 (100)	21 (77.8)
PEA	2 (4)	0	2 (7.4)
Asystole	4 (8)	0	4 (14.8)
Temperature			
at 12hr	33.27 ± 0.43	33.25 ± 0.35	33.31 ± 0.55
at 24h	33.56 ± 0.75	33.65 ± 0.60	33.43 ± 0.70
at 36h	35.81 ± 0.77	36.18 ± 0.49	35.76 ± 0.61
at extubation		34.24 ± 1.28	

Abbreviations: **COPD =** Chronic Obstructive Pulmonary Disease; **TIA** = Transient Ischemic Attack; **CPR** = Cardiopulmonary Resuscitation; **VT** = Ventricular Tachycardia; **VF** = Ventricular Fibrillation; **PEA** = Pulseless Electrical Activity

Note: All values are n (%), unless stated otherwise. Downtime refers to no flow time plus CPR time

6.4.2 Early waking

All surviving patients (n=46) were assessed after 11 hours from admission to the ICU, to determine their suitability for early waking. Almost half (46%, n=23) of patients fulfilled the early waking assessment criteria (Figure 21). Out of these, 12 patients (24%) were extubated early averaging 21.4 hours of mechanical ventilation, with eight patients (16%) being extubated less than 24 hours and four patients (8%) less than 36 hours. Furthermore, an additional four patients (8%) were extubated less than 72 hours. All patients who were extubated early continued to be treated with TTM for the remainder of the maintenance phase of TTM, at an average core body temperature of 34.2° Celsius. However, TTM had to be stopped prematurely in four patients (8%). This was at the end of the re-warming phase for one patient due to dislodging the IVTM catheter during an episode of agitation. TTM was electively terminated during the fever prevention phase in the remaining three patients, at the request of the treating clinician, to enable the patient to mobilise and receive physiotherapy. There were seven patients (14%) who were discharged from ICU and transferred to the cardiology high dependency unit within the first 72 hours of their admission. Four of these patients had an IVTM catheter in situ and continued to receive TTM for the remainder of the fever prevention phase.

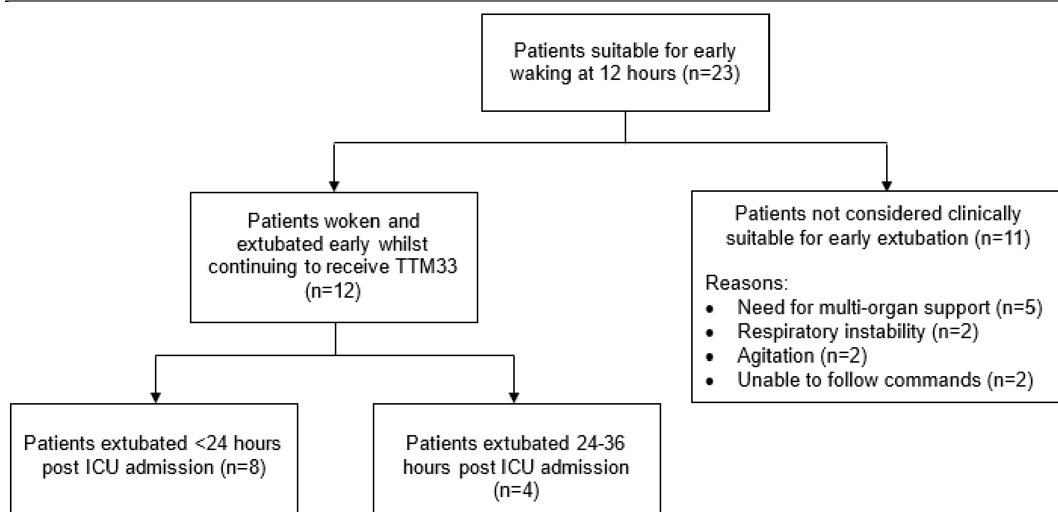


Figure 21: Patients eligible for early waking

Note : All 12 patients were extubated within 36 hours from ICU admission

In this study, early extubation was successful in 12 patients, with five patients (10%) being discharged from the ICU in less than 48 hours following admission. All surviving patients (n=28) were discharged from the ICU showed good recovery as indicated by their Cerebral Performance Category (CPC) and modified Rankin Scale (mRS) scores. Additionally, three

patients who needed ongoing critical care were repatriated to their local hospitals and eventually left the ICU in a stable condition. The in-hospital mortality rate was 50 percent (n=25). Of the patients who were initially discharged from the ICU, three subsequently died: one patient was awaiting cardiac surgery, another due to complications from necrotising fasciitis related to a Bartholin abscess, and the third patient died from issues arising after cardiac surgery. The mean hospital length of stay was 24.1 days, with a variation of 20.6 days.

6.5 Summary, protocol implementation

In the implementation of the early waking THAW protocol the emphasis was on positive prognostication, and the identification of OHCA patients suitable for early waking based on rigorous physiological parameters and standard neurological assessments such as the Glasgow Coma Scale (GCS) and the Full Outline of UnResponsiveness (FOUR) score. This was done while patients continued to be treatment with TTM at 33° Celsius, integrated with a strict counter-shivering strategy. While the protocol interventions included the use of neuro biomarkers and neurophysiological assessments, the results of these diagnostic tests were intentionally not used to inform clinical decision-making but reserved for post hoc analysis.

The THAW protocol enabled the early and successful waking and extubation of 12 patients, effectively reducing the duration of mechanical ventilation and ICU Length Of Stay (LOS), without any adverse events. It was anticipated that 50 percent of OHCA would not survive, predominantly due to neurological injuries, highlighting the severity and complexities associated with OHCA. Additionally, 14 percent of patients could be stepped down from ICU within 72 hours, continuing their TTM treatment in the cardiology High Dependency Unit (HDU).

The implementation of the early waking THAW protocol suggests that there are potential benefits of early neurological assessments to positively prognosticate and reduce mechanical ventilation. The combined application of IVTM with a counter shivering strategy was shown to be both safe and effective in waking unconscious OHCA patients and doesn't need to be a barrier to performing comprehensive neurological assessments, including EEG and SSEP. Chapter seven discusses the findings of the research presented in Chapter five and six and will elaborate on the use of incorporating the early waking THAW protocol into critical care practice.

Chapter 7: Discussion

In the middle of difficulty lies opportunity

Albert Einstein, 1940s

7.1 Introduction, discussion

The conception and development of the THAW protocol, as well as its actual implementation, strongly featured hypothesis testing, and understanding of the various and complex factors affecting early waking of unconscious survivors of Out-of-Hospital-Cardiac Arrest (OHCA). Despite multiple challenges, the THAW protocol continuously evolved and was refined to be both holistic and adaptable. The transition to the implementation phase marked a critical shift from theory to practice, involving testing, refinements, and feedback incorporation to ensure efficacy, scalability, and adaptability in a cardiothoracic critical care environment. This discussion provides a thorough overview of the THAW protocol's evolution, highlighting its strengths, limitations, and contributions to the early waking of unconscious survivors of OHCA patients for the purpose of performing a neurological assessment. It highlights the protocol's impact on critical care research and practice, offering insights into the dynamic process of medical research, specifically protocol development with a distinct focus on positive neurological outcomes for unconscious survivors of OHCA.

This chapter discusses the findings presented in Chapters five and six against the background of the literature review in Chapter two and consists of three sections. The first addresses the research questions while the second explores areas of interest emerging from the study. The final section presents reflections on the study, discusses the study's limitations, conclusions, and implications for clinical practice, in particular critical care.

Part 1: The study research questions

The current investigation was guided by three research questions throughout the various stages. Whilst these questions correspond to different phases of the research, they overlap significantly, contributing to the study's complexity. In this initial section of this Discussion chapter, the findings will be presented by addressing each of the research questions. This approach sets the stage for a deeper examination of the study's foundational concepts. The development of the THAW protocol is specifically aimed at answering these three pivotal research questions:

1. To what extent, can early neurological assessments and accurate prognostication contribute to reducing ventilation time in OHCA patients?

2. What is the safety and efficacy of utilising Intravenous Temperature Management (IVTM) combined with counter shivering strategies in waking unconscious OHCA patients for neurological assessments?

3. How can physiological assessments be utilised to determine the suitability of waking unconscious OHCA patients early, to perform a neurological assessment?

7.3 Research questions

7.3.1 To what extent can early neurological assessments and accurate prognostication contribute to reducing ventilation time in OHCA patients?

Early neurological assessment and accurate prognostication plays a crucial role in managing OHCA patients, which in turn potentially reduces the need for prolonged ventilation. Identification of patients who are showing favourable neurological signs, enables the critical care team to provide a more patient centred approach to care delivery. Early recognition also allows the clinical team to make informed decisions about critical care support interventions, specifically the necessity and duration of mechanical ventilation. Conversely, identification of patients with a poor prognosis, early assessment facilitates discussions about the appropriateness of continued life sustaining care, potentially avoiding prolonged and unnecessary critical care support. Consequently, this not only optimises critical care resources, like mechanical ventilation and ICU beds, but also minimises the risks associated with prolonged ventilation, such as Ventilator Associated Pneumonia (VAP). More importantly,

for patients with a positive prognosis, reducing mechanical ventilation time could potentially expedite the initiation of rehabilitation and recovery.

Four patients died within the first 12 hours following admission to ICU. Therefore, 46 patients were assessed from a physiological perspective, against the THAW protocol pre-determined criteria to identify which patients were considered clinically stable to be woken early. While 23 patients did not fulfil the criteria, 23 patients did meet the early waking criteria. However, after titrating sedation to achieve a Richmond Agitation Sedation Scale of zero and discontinuing the administration of neuromuscular blockers, 11 patients had deleterious changes to their physiological parameters therefore were not considered appropriate to progress for early waking. The remaining 12 patients demonstrated positive neurological signs, including a Glasgow Coma Scale (GCS) above eight and a Full Outline of UnResponsiveness (FOUR) score above 13, they also remained clinically stable and were continuously reassessed against the established THAW protocol criteria, therefore were progressed to state of preparedness for extubation. For the 12 patients who were woken early, GCS and the FOUR score were successfully used to determine whether the patients were neurologically appropriate to be considered for early waking.

In a recent study by Cardi et al. (2022), the efficacy of the FOUR score and GCS in predicting favourable neurological outcomes after OHCA was considered they reported that motor function recovery is more closely linked to survival than brainstem reflexes, that FOUR-Motor (M), FOUR-Brainstem (B) and GCS scores can predict survival (Cardi et al., 2022). Similarly, Lee et al. (2023) reports that GCS-Motor (M) scores were found to be considerably higher in patients with good neurological outcome compared to those with poor outcomes (Lee et al., 2023). Furthermore, when combining GCS-M with NSE levels, Lee et al. (2023) showed a high specificity of greater than 70 percent and sensitivity of greater than 98 percent for predicting good neurological outcomes (Lee et al., 2023). Incorporating the FOUR score of 13 or above into the THAW protocol, alongside a GCS score of eight or above to assess a patient's readiness for early waking and preparation for possible extubation was considered to provide a more nuanced understanding of a patient's neurological status, rather than just relying on GCS alone. The FOUR score, which evaluates eye response, motor response, brainstem reflexes, and respiration, was shown to complement the GCS by offering additional insights, particularly in patients with deeper levels of unconsciousness.

When a patient achieved a GCS score of eight or above and a FOUR score of 13 or above, this indicated the patient had a level of consciousness and neurological function that would

suggest they could protect their airway effectively, as well as being capable of breathing independently and maintaining adequate oxygenation and ventilation, both considered essential milestones before extubating a patient. Additionally, these scores indicate the patient had the ability to follow commands and communicate, enabling patients to express discomfort or any other issues effectively. However, it is important to acknowledge that the decision to extubate was multifactorial, which incorporated a comprehensive physiological assessment, and was not solely based on GCS and FOUR scores.

Eight patients were successfully extubated within the first 24 hours from admission, the earliest being at 12 hours, which was during the maintenance phase of the TTM when the core target temperature was at 33° Celsius. The remaining four patients were extubated between 24 and 36 hours which was during the rewarming phase of TTM. The successful extubation of 12 patients within 36 hours of admission, challenges traditional standard practice of sedating patients for a minimum of 36 hours before considering reducing or discontinuing sedation, suggesting the feasibility of identifying appropriate, clinically stable OHCA patients earlier for the purpose of performing a neurological assessment, which has the potential for reducing mechanical ventilation time.

To establish the reliability and validity of incorporating neurophysiology and neuro biomarkers as possible diagnostic tools that could be used to determine a positive prognosis in OHCA patients, the THAW protocol included these during the 72-hour intervention phase. The neurophysiology tests included EEG and SSEP, and the neuro biomarkers were NSE and S100b. Both the neurophysiology and neuro biomarkers were taken on ICU admission and at subsequent intervals (6, 12, 24, 48 and 72 hours), if the patient remained unconscious. A study by Fenter et al. (2023), considered the predictive value of a benign EEG in identifying patients with favourable neurological outcomes (Fenter et al., 2023). By redefining the concept of a benign EEG, which does not include criteria such as amplitude, anterior-posterior amplitude gradient, and allows for discontinuity of the background, Fenter et al. (2023) was able to demonstrate this improved its sensitivity in identifying patients with favourable outcomes (Fenter et al., 2023). In addition, Wimmer et al. (2023) describes the positive predictive value of SSEP for predicting good neurological outcomes in OHCA patients with a high sensitivity of 86 to 100 percent, with a low false positive rate, particularly when used in combination with pupillary light reflex, EEG, NSE and computed tomography (Wimmer et al., 2023).

NSE levels are considered a significant indicator in determining positive neurological outcomes in patients following OHCA (Lee et al., 2023; Moseby-Knappe et al., 2021; Sandroni,

D'Arrigo, et al., 2022). Lee et al. (2023) found that NSE levels, measured 24 hours after ROSC, showed the highest prognostic performance as a single test (Lee et al., 2023). Patients with NSE levels less than or equal to 32.1 nanograms per millilitre were strongly associated with a good neurological outcome, particularly when used in combination with the GCS-M score (Lee et al., 2023). S100b is considered to have a limited yet significant role in predicting good neurological outcomes following OHCA (Moseby-Knappe et al., 2021). In patients with a S100b peak value of less than 105 nanograms per litre at 24 hours, Moseby-Knappe et al. (2021) found that these patients are likely to have a good neurological outcome in 76 to 82.2 percent of patients (Moseby-Knappe et al., 2021).

In the context of a safety and feasibility of waking unconscious OHCA patients early for the purpose of performing a neurological assessment, the decision was made not to use neurophysiology and neuro biomarker test results for directing patient treatment, but only to be used for post hoc analysis. This was imperative to ensure that the primary objective of the study, to assess the safety and feasibility of early waking for neurological evaluation, was not confounded by these variables. This separation was to ensure that any improvements or deterioration in a patient's condition could be directly attributed to the early waking intervention, rather than neurophysiological or biomarker test results. Not to include neurophysiological and biomarker test results to inform real-time adjustments, the study avoids potential ethical dilemmas that might arise from acting on preliminary or non-definitive data. Incorporating neurophysiology and neuro biomarker test results into the post hoc analysis enables a thorough assessment of how these factors correlate with patient outcomes. Furthermore, it ensures that the primary focus remains on evaluating whether early waking for neurological assessment, is safe and feasible, as well as setting the stage for future research that could emerge from the post hoc analysis of the data. This approach enhances the validity and reliability of the study's findings, ensuring that they are reflective of the early waking interventions being tested without the influence of other variables.

7.3.2 What is the safety and efficacy of utilising Intravenous Temperature Management (IVTM) combined with counter shivering strategies in waking unconscious OHCA patients for neurological assessments?

Utilising Intravenous Temperature Management (IVTM) in conjunction with counter-shivering strategies for waking unconscious patients after OHCA involves balancing safety and efficacy. IVTM, is an invasive procedure which requires the sterile insertion of a large catheter into the femoral vein. The circulating fluid through the IVTM catheter ranges from 4 to 42° Celsius, which automatically adjusts in response to the bio feedback from the

temperature probe at the distal end of the indwelling urinary catheter. Therefore, in the awake patient, counter-shivering measures must be employed, not only for patient comfort but to prevent significant variations in the patient's core body temperature, which would potentially undermine the efficacy of TTM.

IVTM is currently the only TTM method that can be used in conscious or awake patients (De Georgia et al., 2004; Simon R. Dixon et al., 2002; Erlinge et al., 2014; Gotberg et al., 2010; Islam, Hampton-Till, MohdNazri, et al., 2015; Lyden et al., 2014; Noc et al., 2017). All other TTM methods are placed over the surface of the patient therefore prevent the use of hot air warming blankets as a counter-shivering strategy and would be counterintuitive. Furthermore, patients treated with surface cooling, often necessitates the extensive use of sedatives and neuromuscular blockers to manage shivering (Bartlett et al., 2020). Reliance on medications like midazolam, fentanyl, and potentially propofol, along with neuromuscular blockers such as rocuronium or atracurium, all of which obscure accurate neurological assessments (Bartlett et al., 2020).

While IVTM has been trialled in conscious patients who have suffered from myocardial infarction it has been limited in its application for only short periods, of up to six hours (S. R. Dixon et al., 2002; Erlinge et al., 2014; Gotberg et al., 2010; Islam, Hampton-Till, Watson, et al., 2015; Noc et al., 2017). However, Lyden et al. (2016) successfully demonstrated IVTM was safe and feasible to be used in conscious patients, who suffered from acute ischemic stroke, being treated for 36 hours at 35.5° Celsius, including a 12 hour re-warming phase (Lyden et al., 2016). In both the cardiac and acute stroke studies, IVTM with counter-shivering strategies, such as pharmacological agents and external warming devices were integral to maintaining patient comfort as well as maintaining the desired target temperature. The same principles employed in the aforementioned trials were applied as part of the THAW protocol interventions. In Chapter five, the clinical expert group recommended the development of a counter shivering strategy that clearly defined not only the counter shivering interventions but also the timing and dosage of these interventions. The THAW protocol incorporated sedation targets using the Richmond Agitation Sedation Scale (RASS) score, as well as a shivering detection tool, to guide pharmacological dosing. The timing of pharmacological adjuncts included the administration of a nasogastric bolus of buspirone and weight adjusted intravenous administration of meperidine after 12 hours, which was initially given as a bolus dose followed by a continuous infusion. The use of meperidine as a continuous infusion and counter shivering strategy was used in the acute stroke study but was limited to thirty six hours (Lyden et al., 2016). Meperidine continues to be used as a counter shivering strategy, however

due to its potential side effects and requirement for close observation, other medications such as dexamethasone and ibuprofen are considered viable alternatives (Akhavanakbari et al., 2023; Destaw et al., 2020). As discussed in Chapter five, during the clinical governance review, the pharmacist identified the maximum dosage of 600 milligrams per 24 hours or 25 milligrams per hour was agreed, which was consistent with the British National Formulary (BNF) Guidance.

This research reported on the 12 patients who were woken early and extubated with a mean mechanical ventilation time of 21.4 hours, while continuing to be treated with TTM using IVTM and counter shivering strategies as previously described. The mean core temperature for this cohort was 33.3° Celsius at 12 hours and 34.2° Celsius when extubated. However, TTM had to be stopped prematurely for four patients. One patient became agitated and dislodged the IVTM catheter, therefore IVTM was removed for safety reasons. For the remaining three patients, TTM was electively terminated and the IVTM catheter was removed at the request of the treating clinician to facilitate patient mobilisation and physiotherapy.

Ongoing TTM did not prevent patients being discharged from ICU, seven patients were able to be stepped down to the cardiology, High Dependency Unit (HDU) within the first 72 hours, with three patients being transferred less than 36 hours, during the rewarming phase of TTM. The efficacy of the THAW protocol highlights that a significant proportion of patients were able to be extubated early, whilst continuing to be treated with TTM post-extubation. In terms of safety, the premature termination of TTM in a small percentage of patients highlights some challenges. The dislodging of the IVTM catheter indicates a need for careful monitoring and management, especially with agitated patients. The elective termination of TTM to prioritise physiotherapy, was an intentional clinical decision based on what was determined to be a higher a clinical priority.

Overall, these findings suggest that IVTM combined with counter-shivering strategies can be both safe and effective in the context of early waking to perform a comprehensive neurological assessment in unconscious OHCA patients but an emphasis on the need for careful patient monitoring and individualised decision-making based on each patient's clinical presentation.

7.3.3 How can physiological assessments be utilised to determine the suitability of waking unconscious OHCA patients for early neurological assessments?

Physiological assessments play a pivotal role in determining the suitability of waking unconscious patients who have experienced OHCA to enable a comprehensive neurological assessment. These assessments involve a comprehensive evaluation of the patient's physiological parameters, neurological status, and overall physical condition.

The THAW protocol describes the physiological assessment, which incorporates target parameters that need to be met to ensure the patient is considered clinically stable and appropriate for early waking. The neurological assessments, include evaluating pupil reactions, checking for seizure activity, as well as assessing the patient's response to pain. This provides an understanding of the patient's level of consciousness or the potential of a neurological injury. A GCS score greater than 8 combined with a FOUR score greater than 14 collectively signifies the patient had regained a level of consciousness, therefore suggesting the patient could protect their own airway and reducing the aspiration risk. It also indicates improved cognitive functioning necessary for effective response in early neurological assessments. A FOUR score evaluates brainstem reflexes and eye responses, areas not fully covered by the GCS. Therefore, a FOUR score of above 14 indicates a low likelihood of neurological injury.

Determining respiratory readiness for early waking involved assessing several key parameters, each underpinned by scientific reasoning. Shifting to a ventilation weaning mode signified the patient's increasing ability to breathe independently. An effective cough was considered essential not only for clearing airway secretions but also for reducing the risk of aspiration and respiratory complications post-extubation (Kutchak et al., 2015). Minimal secretions in the Endotracheal Tube (ET) indicated effective airway management. A controlled respiratory rate below 35 breaths per minute reflected a stable respiratory function and the absence of respiratory distress (Muzette et al., 2022). As Tejerina et al. (2021) suggest, adequate lung capacity is represented by a vital capacity greater than 10 millilitres per kilogram and a tidal volume above five millilitres per kilogram, ensuring effective gas exchange and the patient's ability to take deep breaths and cough effectively (Tejerina et al., 2021). A minute ventilation rate below ten litres per minute suggested efficient breathing without overexertion. Maintaining a Positive End-Expiratory Pressure (PEEP) between five to eight centimetres of water was important for keeping the lungs open effectively without excessive pressure, preventing lung collapse while avoiding lung overdistension, and is reported to improve aeration and reduce adverse events following extubation (Prabhakaran et al., 2023). As Taran

et al. (2023) found that patients requiring a PEEP above eight centimetres of water would suggest an underlying lung pathology and would be unlikely to manage with the respiratory workload if extubated (Taran et al., 2023). Lower levels of Pressure Support (PS) between 10 to 12 centimetres of water indicates the patient's capacity to breathe with minimal assistance (Ouellette et al., 2017). A Fraction of Inspired Oxygen (FiO2) requirement below 0.5 or 50 percent oxygen suggested the patient was likely to require minimal supplemental oxygen following extubation. Finally, normal Arterial Blood Gas (ABG) values were considered crucial in evaluating respiratory and metabolic function, assessing the patient's respiratory efficiency and acid-base balance (Keyal et al., 2020). Collectively, these parameters provided a comprehensive assessment of the patient’s respiratory system, ensuring they had the patient had the capability to function independently and maintain effective gas exchange and airway clearance post-extubation.

In determining cardiovascular readiness for extubation, key parameters were included in the THAW protocol. A heart rate between 60 to 100 beats per minute would normally indicate a stable cardiac rate, however as Polderman (2009) suggests, a heart rate of 30 to 40 beats per minute is common in patients treated with TTM and would not necessarily require intervention unless the patient had associated hypotension (K. H. Polderman, 2009). Thomsen et al. (2016) and Inoue et al. (2018) suggest that bradycardia during TTM, particularly during the rewarming phase is associated with favourable neurological outcomes (Inoue et al., 2018). When considering a blood pressure target, a systolic blood pressure is less important for clinicians than Mean Arterial Pressure (MAP), which reflects the average arterial pressure during one cardiac cycle (Torrini et al., 2021). Grand et al. (2019) recommend a MAP greater than 80 millimetres of mercury, not only to maintain adequate cerebral perfusion but also renal function (Grand et al., 2019). This approach is also supported by Sekhon et al. (2019) and Janiczek et al. (2019) (Janiczek et al., 2016; Sekhon et al., 2019). The capillary refill time of less than three seconds is considered a quick and practical way to assess peripheral perfusion and circulatory status. A prompt capillary refill of less than three seconds indicates good blood flow and is a positive sign of cardiovascular stability. These parameters provided a comprehensive view of the patient's cardiovascular function, ensuring that they are hemodynamically stable and are more likely to tolerate extubation.

Determining metabolic readiness for extubation involved assessing several parameters that directly reflect patient homeostasis and end organ perfusion. A stable blood glucose level below 10 millimoles per litre, is imperative, as hypoglycaemia or hyperglycaemia can adversely affect both neurological function and overall physiological stability, potentially impacting the

ability to successfully wake patients and extubation outcomes (Pescatore et al., 2021). According to Daviaud et al. (2014), preventing hypoglycaemia and reducing fluctuations in blood sugar levels are associated with better neurological outcomes (Daviaud et al., 2014). Fluctuations in blood sugar levels have been associated with higher mortality rates and unfavourable outcomes (Cueni-Villoz et al., 2011). However, for patients experiencing Post-Cardiac Arrest Syndrome (PCAS), the ideal blood sugar range is still unclear.

Adequate urine output, defined as more than 0.5 millilitres per kilogram, was considered not only a key indicator of renal health and effective circulation, but imperative for fluid and electrolyte balance and an indicator of overall metabolic stability (Frutos-Vivar et al., 2006; Koeze et al., 2017). Furthermore, renal function is pivotal in regulating acid-base balance, by excreting hydrogen ions and reabsorbing bicarbonate to neutralise excess acid. The acid base balance is measured by the base excess range, between negative two to positive two milliequivalents per litre. This indicates a balanced acid-base status, therefore cellular function and metabolic processes are being effectively maintained. Shirvani et al. (2021) study highlights the association between acid-base disturbances and the development of delirium, these finding suggest this has the potential to affect patient recovery and extubation outcomes (Shirvani et al., 2022).

For the purposes of early waking and possible extubation, both plasma sodium and potassium were considered critical in achieving normal concentrations. However, maintaining plasma potassium levels slightly lower than normal, between 3.5 to 4.0 milliequivalents per litre is recommended, due to the risk of rebound hyperkalaemia during the rewarming phase of TTM (Madden et al., 2017). When considering sodium levels, Shida et al. (2022) study suggests that dysnatremias are associated with a decreased probability of favourable neurological outcomes in OHCA patients (Shida et al., 2022). Therefore, ensuring plasma sodium levels were within 135 to 145 milliequivalent per litre is important not only for maintaining fluid balance and neurological function, but also in relation to blood pressure control, blood volume, and osmotic equilibrium. Collectively, these parameters provided a comprehensive assessment of the patient's metabolic status, ensuring that they were in a stable state, would indicate the patient was clinically stable and potentially suitable for early waking and successful extubation. Utilising physiological assessments was pivotal in deciding the suitability of early waking unconscious OHCA patients for early neurological assessment. Sedation was titrated to achieve a Richmond Agitation-Sedation Scale (RASS) score of minus three, a level of sedation that would enable a neurological assessment to be performed. However, based on the THAW early waking assessment criteria, 11 patients were deemed inappropriate for progressing to

early waking. This decision was due to various patient-specific factors including: five patients required multiorgan support, two exhibited respiratory instability, two were agitated, and two could not follow commands. For the remaining patients not considered for early waking, outcomes varied, with six patients surviving after an mean mechanical ventilation time of 11.1 days, while the other 17 died, with an mean ICU stay of 5.9 days. This patient-centred approach emphasises the importance of decisions being made based on a comprehensive understanding of each patient's unique physiological state.

Part 2: To wake or not to wake

The previous section considered the safety and feasibility of implementing the THAW protocol to enable early neurological assessment of the unconscious OHCA patient, with an emphasis on identifying clinically stable patients that could be woken early and potentially extubated. This study indicates that performing advanced neurological assessments, including GCS and FOUR scores, alongside physiological stability are crucial in determining a patient's readiness for early waking and successful extubation. This section focuses discussion on areas of interest emerging from the development of the THAW protocol, through to the implementation phase.

7.4 A collaborative approach in the development of a clinical protocol

There are various definitions that distinguish what constitutes a clinical protocol, from guidelines and checklists. Protocols provide specific, step-by-step instructions for clinical practice, offering precise guidance for particular scenarios. In contrast, guidelines offer more general recommendations or principles without explicit, actionable steps, providing opportunities for individual clinical judgment. Whereas checklists, serve as tools to ensure all necessary steps or components are completed or reviewed, often supporting the implementation of protocols and guidelines but not offering detailed guidance themselves. Fesler and Brower (2005) describe a clinical protocol as a set of explicit, algorithmic rules designed to direct clinical management or research, while guidelines provide broader principles or suggestions without specific directions for clinical decision making (Fessler & Brower, 2005). Chang et al. (2012) describe checklists as useful tools to facilitate the implementation of protocols or guidelines (Chang et al., 2012). Morris (2003) defines protocols as providing a broader perspective on the role of protocols in reducing clinical variability and enhancing individualised care, compared with Fessler's (2005) definition, which is more focused on the operational or methodological aspects of protocols in guiding specific clinical interventions (Fessler & Brower, 2005; Morris, 2003).

Barrow and Gasquoine (2018) suggest the benefit of multidisciplinary involvement in the development of clinical protocols, provides a number of benefits including the standardisation of practices, therefore enhancing efficiency and patient care (Barrow & Gasquoine, 2018). Furthermore, Baumgarten et al. (2023) found that when protocols are developed collaboratively, incorporating insights from a variety of healthcare professionals, they tend to

be more thorough, comprehensible, and practically applicable, promoting teamwork, shared accountability, and improving the quality of patient care (Baumgarten et al., 2023). In the development of the THAW protocol there was an emphasis on a collaborative and multidisciplinary approach that perhaps contrasts with conventional approaches to protocol development, which often rely on a limited number of clinical experts (Watson et al., 2018). Incorporating an extensive range of stakeholders, including healthcare professionals from various disciplines, researchers, ethicists, patients, and their families, as well as the hospitals leadership and clinical governance group, all contributed to the development of the THAW protocol. This inclusive strategy ensured that the protocol not only benefited from a wealth of perspectives, but enhanced its relevance and applicability, but ultimately, was patient centred.

O'Hara and Canfield (2024) describe the importance of integrating patients, families and caregivers as partners in healthcare for enhancing patient safety (O'Hara & Canfield, 2024). They suggest, that due to the complexity of healthcare systems, that institutional needs are sometimes prioritised over patient centred care, advocating for a more inclusive, collaborative approach to healthcare, where patient and family engagement is central to designing safer, more effective and patient centred care (O'Hara & Canfield, 2024). The intentional inclusion of patients and their families during the development of the THAW protocol, provided invaluable insights, specifically around communication, quality of life, and likelihood of recovery following OHCA, ensuring the THAW protocol aligned with the actual needs and experiences of patients and their families. Furthermore, DeBronkart (2018) champions patient empowerment and active engagement, suggesting that a partnership model where healthcare providers, patients and their families co-create health care strategies, will not only enhance a more personalised approach to care delivery, but ultimately result in greater patient satisfaction (deBronkart, 2018).

7.5 Developing a focus on positive prognostication

International resuscitation guidelines place significant emphasis on identifying patients with a poor neurological prognosis following OHCA to guide clinical decision making, specifically for the purpose of determining whether to continue or the withdrawal of life-sustaining treatment (Australian and New Zealand Committee on Resuscitation, 2016a; Lavonas et al., 2020; Nolan et al., 2021). Whilst these guidelines recommend using a multimodal approach, including neuroimaging, electrophysiological studies, and biochemical markers, the emphasis has been on identifying patients likely to have an unfavourable outcome. However, there has

been a noticeable gap in utilising this same multimodal approach for early identification of OHCA patients who are likely to have a positive neurological prognosis.

One of the most significant issues preventing clinicians from performing early neurological assessment in OHCA patients is the influence of sedatives and neuromuscular blocking medications (Ceric et al., 2023; Helbok et al., 2012; Weant et al., 2010). Therefore, reducing sedation within the first 36 hours following admission to ICU has previously been considered prohibitive, due to the administration of these medications, necessary for patient comfort and tolerance of TTM. However, a number of studies have demonstrated that conscious patients can tolerate TTM, only when delivered using an IVTM device and in conjunction with counter shivering strategies (De Georgia et al., 2004; Simon R. Dixon et al., 2002; Erlinge et al., 2014; Gotberg et al., 2010; Islam, Hampton-Till, MohdNazri, et al., 2015; Lyden et al., 2014; Noc et al., 2017), negating the need for sedatives and neuromuscular blocking medications. The findings of this study demonstrated that 50 percent of unconscious OHCA patients, admitted to ICU were considered clinically stable after 12 hours and appropriate for sedation to be reduced to achieve a RASS score of minus three or lower, with concurrent deployment of the same counter shivering strategies used in aforementioned studies. Furthermore, the use of the counter shivering strategy enabled a comprehensive neurological assessment to be performed, whilst maintaining patient comfort and tolerance of TTM. As described in international resuscitation guidelines, a multimodal approach, including electrophysiology studies EEG and SSEP, the drawing of blood samples for neuro biochemical testing, as well as GCS and FOUR scoring was able to be successfully performed after 12 hours following admission. Of the 23 patients considered appropriate for early waking, 52 percent achieved a GCS score of eight or above and combined with a FOUR score of 13 or above and remained clinically stable, enabling them to progress to early extubation within the first 36 hours of ICU admission (Watson et al., 2022).

The benefit of focusing on early and positive prognostication in unconscious survivors of OHCA, potentially offers a transformative approach to OHCA management in ICU. In this study, early and accurate prognostication using the THAW protocol enabled clinical decision-making that resulted in early extubation and discharge from ICU. It also enabled the clinical team to provide families with early patient progress reports that would have otherwise not been possible.

7.6 Training and simulation

Simulation and training played a pivotal role in preparing the multidisciplinary and interprofessional teams from the Coronary Care Unit (CCU), ICU and cardiac catheter laboratory (cardiac cathlab), in the management of OHCA patients and implementation of the THAW protocol. The management of an OHCA patient involves significant coordination among multidisciplinary and interprofessional teams, under time-critical conditions (Islam, Hampton-Till, MohdNazri, et al., 2015). The complexity of orchestrating such specialised teams; each with their distinct roles and expertise, emphasises the challenge of delivering prompt and effective care. Simulation training was vital in this context, offering a platform for these diverse teams to enhance their skills and confidence in a risk-free environment. By replicating the high-pressure scenarios, simulation helped improve interdepartmental communication, team efficiency, and coordination. Supported by Kennedy-Metz et al. (2022) findings, that simulation enables interprofessional teams to enhance their skills and confidence, thereby contributing to patient safety and team efficiency (Kennedy-Metz et al., 2022). Steinemann's et al. (2011) study, which evaluated the impact of simulation based teamwork training in the context of trauma resuscitation, similar to the time critical nature of OHCA management, describe simulation as having a significant impact on reducing overall resuscitation times as well as improving completion of tasks (Steinemann et al., 2011).

Within the context of the National Institute for Health and Care Excellence (NICE) Clinical Guideline (CG167) (superseded by clinical guideline 185 [2020]), which recommend that patients presenting with an acute ST Elevation Myocardial Infarction (STEMI) that a Primary Percutaneous Coronary Intervention (PPCI) should be performed within 120 minutes (NICE, 2020), commonly known as the door to balloon time. The complexity of achieving this time critical intervention in the unconscious and intubated OHCA patient presented several challenges for the multidisciplinary teams involved in their care. Following notification from the ambulance service, the ICU and cardiac cathlab teams would be alerted by the CCU staff. On arrival to the Essex Cardiothoracic Centre, the patient would need to be handed over by the ambulance service. The patient would then be triaged by the Consultant Cardiologist and if indicated transferred to the cardiac cathlab for urgent PPCI. The ICU team, which consisted of an anaesthetist, Operating Department Practitioner (ODP) and Critical Care Registered Nurse (CCRN) would be responsible for the patient's airway, TTM and cardiovascular management. The cardiac cathlab team, which consisted of the interventional cardiologist, registrar, radiographer, nurses and cardiac physiologist would be responsible for performing

the PPCI procedure (Figure 23). Following the procedure, the patient would be transferred to the ICU where post cardiac arrest care would be managed.

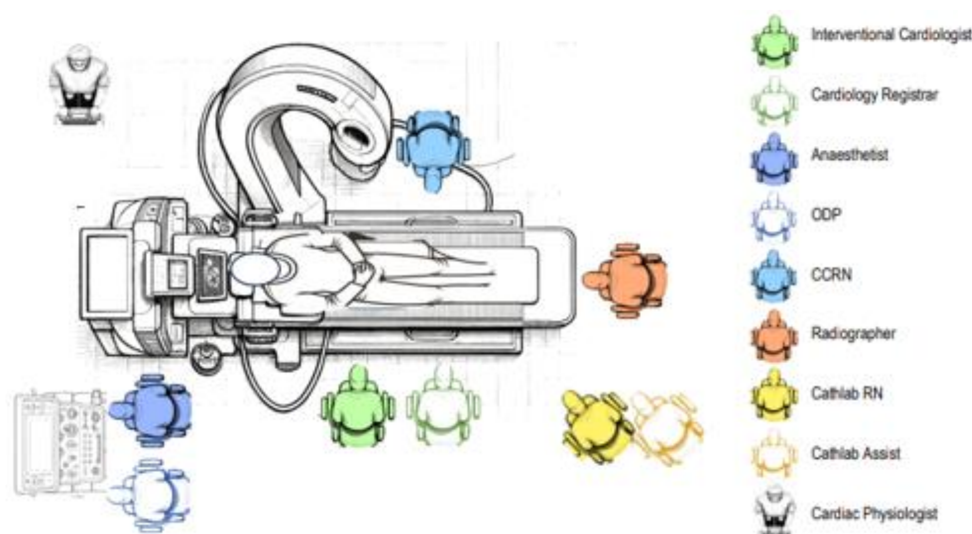


Figure 22 The multidisciplinary team

According to Villemure et al. (2016), in situ simulation is useful to identify the internal system gaps, in terms of interdisciplinary and interdepartmental communication, as well as the management and distribution of resources within different hospital units (Villemure et al., 2016). Furthermore, simulation-based training has been highlighted as a safe and effective way of preparing healthcare professionals without exposing them to real patient risks (Alinier & Platt, 2014). It was identified through simulation, that admitting OHCA patients to either ICU or cardiology HDU, prior to transferring the patient to cathlab, contributed to significant delays in terms of meeting CG185 as well as initiating TTM. Therefore, all OHCA admissions were admitted directly to the cardiac cathlab. This not only reduced the need for secondary handovers but also prioritised PPCI as per NICE CG185, as well as enabling the IVTM catheter to be inserted so TTM could be commenced. As described by Lassche and Wilson (2016), simulation goes beyond education and competency testing but addresses system factors, including resource allocation as well as the physical environment, resulting in broader healthcare system improvements (Lassche & Wilson, 2016).

The utilisation of simulation was also fundamental for skill acquisition, improvement, and competency assessment, in the context of initiating TTM by ICU staff. Through repetitive simulation scenarios, ICU staff practiced the setting up for the insertion of the IVTM catheter, by the interventional cardiologist, under sterile conditions in the cathlab. This included priming the Thermogard XPTM temperature management console (Zoll Medical Corp, Chelmsford, MA, USA), to ensure staff were adept at managing the technical aspects of

initiating TTM. Beyond the cathlab, simulation and training were extended to include the transfer of the patient to the ICU. An approach supported by Boling and Hardin-Perce (2016) who suggest that the utilisation of high-fidelity simulation is fundamental for skill acquisition, improvement and competency assessment in the context of critical care training (Boling & Hardin-Pierce, 2016). Furthermore, Brunette and Thibodeau-Jarry (2017) highlight that simulation-based learning provides a safe environment for ICU staff to practice and refine skills to achieve competency of various technical skills (Brunette & Thibodeau-Jarry, 2017).

Simulation and training were instrumental in preparing the multidisciplinary and interprofessional teams from CCU, ICU and cardiac cathlab in managing OHCA patients and implementing the THAW protocol. Given the time-sensitive nature of STEMI patients requiring PPCI within 120-minutes, as well as early initiation of TTM. Simulation was invaluable in identifying and addressing multiple challenges, importantly with enhancing and improving skills acquisition, facilitating competency assessments, as well as promoting confidence among healthcare professionals. Simulation was also key in optimising team communication and multidisciplinary teamwork (Rosen et al., 2018), specifically around improving procedural and patient flow efficiency. Additionally, it enabled the identification of systemic gaps, particularly in interdepartmental interactions and resource utilisation, thereby streamlining handovers and prioritising urgent medical interventions such as PPCI and initiation of TTM. By replicating the complexities of real-life scenarios in a controlled environment such as simulation, not only improved teamwork and technical proficiency, but also contributed to overall healthcare system improvements, enhancing patient safety and care quality. Figure 23. illustrates the multifaceted benefits of simulation in preparing healthcare teams for high-stakes clinical situations.

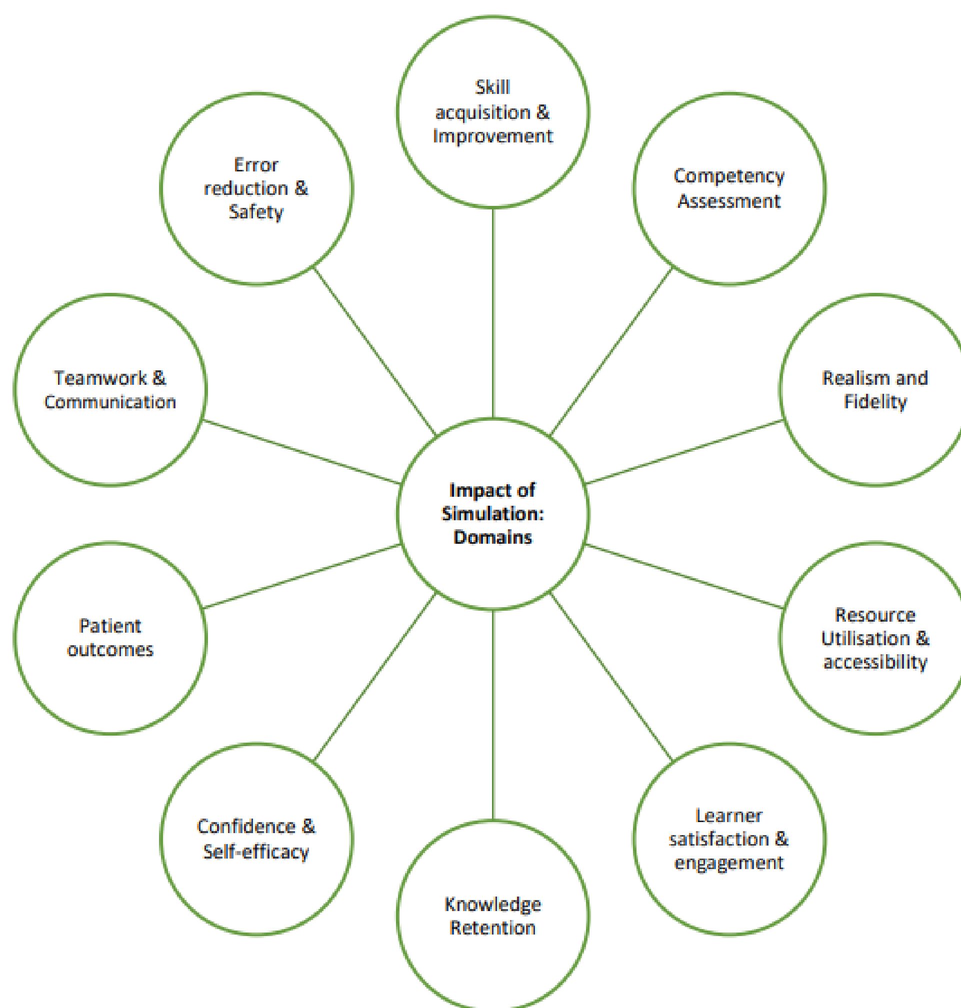


Figure 23 Impact of simulation in the management of OHCA patients

7.7 IVTM as standard Care

As Deye et al. (2016) discusses, there has recently been a movement away from incorporating TTM at 33° Celsius as standard care for unconscious OHCA survivors (Deye et al., 2016). This was primarily attributed to the 2013 TTM trial (N. Nielsen et al., 2013). Whilst a significant number of respondents from Deye's et al. (2016) survey, reported modifying their target temperature toward a milder temperature, the majority of respondents remained committed to some form of temperature management (Deye et al., 2016). Regarding the delivery method of TTM, Vaity et al. (2015) highlighted that IVTM is more precise at temperature control than surface cooling, however it did require staff to have advanced technical skills to operate and manage the device (Vaity et al., 2015). More recent evidence from a systematic review and meta-analysis by Bartlett et al. (2020) reveals that IVTM has been associated with a greater chance of achieving a good neurological outcome compared to

surface cooling with approximately 53 percent of centres reported to be using IVTM (Bartlett et al., 2020).

The Essex Cardiothoracic Centre had previously used surface cooling for delivery of TTM for unconscious OHCA survivors. However, its application was ad-hoc depending on clinician preference. Through the THAW concept development phase, based on available evidence and best practice, the decision was to introduce IVTM as standard care for all unconscious OHCA patients, unless contraindicated. Furthermore, IVTM is the only TTM modality which enables patients to be conscious with appropriate counter shivering strategies.

7.8 Incorporation of advanced diagnostics:

A recent study by Jorge-Perez et al. (2023) suggests there has certainly been improved compliance with the European Resuscitation Council – European Society of Intensive Care Medicine (ERC-ESICM) guidelines (Sandroni, Nolan, et al., 2022a), in relation to the application of advanced neurological diagnostic tests in OHCA patients (Jorge-Perez et al., 2023). However, Jorge-Perez et al. (2023) found there remains a notable variation in the application of advanced neurological diagnostics such as CT, MRI, NSE, EEG and SSEP across different European regions and hospitals (Jorge-Perez et al., 2023). That MRI, NSE and SSEP remain underutilised in less than 50 percent of respondents, whereas CT and EEG were better utilised in 79 and 73 percent of respondents, respectively. However, Rush et al. (2017) found that EEG was only performed in two percent of OHCA patients in the United States (Rush et al., 2017), despite a multimodal approach being recommended in the resuscitation guidelines by the American Heart Association (AHA) (C. Callaway et al., 2015; Panchal et al., 2020).

The underutilisation of incorporating advanced diagnostics such as EEG, SSEP and neuro-biomarkers, can in part be explained due to accessibility. Suen et al. (2023) found that only 27.3 percent of hospitals in the United States have neuro electrophysiology capability (Suen et al., 2023). However, the cost for neuro electrophysiology capability is considered significant, which not only includes equipment costs for hardware, software and consumables, but the costs for specialists to perform neurophysiology tests, as well as the cost for clinical expertise to interpret and report the tests (Crepeau et al., 2014; Hoedemaekers et al., 2023).

Prior to the implementation of the THAW protocol, two senior ICU staff were trained in performing EEGs and SSEPs. This was achieved with four months of dedicated training to

demonstrate competence in lead placement, recording of the EEGs and SSEPs, including the identification and elimination of artefact. This process was supervised and signed off by a qualified neuro electrophysiology technician. This enabled 24-hour, seven-day cover for EEG and SSEP to be performed on all OHCA patients recruited into the study. While there was no neuro electrophysiologist on-site, instead the electronic EEG and SSEP recordings were sent to a consultant off-site for interpretation and reporting. This study demonstrated that serial, good quality EEGs and SSEPs could be performed within the first 72 hours of admission (Watson et al., 2019). Furthermore, the findings of this study indicate that neurophysiology tests, specifically EEG and SSEP, can be achieved in hospitals that are not considered neuro electrophysiology capable with limited investment and training.

Part 3 Limitations, implications and conclusion

7.9 Introduction

Several key insights, alongside certain limitations have arisen through the development and implementation of the THAW protocol. As a single-centre, safety and feasibility study, using a non-randomised design, the THAW protocol has limited generalisability. The protocol emphasises early patient waking, integrating TTM with novel counter-shivering techniques. Developed through multidisciplinary collaboration, including the perspectives of patients and family, its clinical relevance and patient-centred approach, demands precise implementation, as well as significant resource investment. There are also challenges with long-term outcome analysis and technology requirements. Future research includes the study scope and long-term effects for patients.

7.10 Limitations

7.10.1 Research design

The research is based on a single-centre, prospective, non-randomised design, which may limit the generalisability of its findings to other settings such as non-cardiac arrest centres. The robustness of these findings is also influenced by the number of participants (n=50) and the selection criteria; a limited sample size and specific inclusion and exclusion criteria, which may not accurately represent the broader population affected by cardiac arrest. Ethical considerations are particularly significant in the implementation of the THAW protocol, as participants involved were unconscious patients who are unable to consent at the time of the early waking interventions. The process described in this study involved obtaining a declaration of no objection from the patients relative or independent doctors, which could introduce biases or ethical complexities.

The THAW protocol demanded precise and controlled conditions for implementing TTM and early waking assessments. Any deviation or lack of uniformity in these conditions could have impacted the results. Moreover, the study emphasises the importance of integrating multiple assessment methods for prognostication, but the complexity and nuanced nature of these methods may challenge their applicability in different clinical settings. Another crucial aspect of the THAW protocol is the focus on immediate and short-term outcomes, while the understanding of long-term impacts of these interventions on patient recovery and quality of life remains a gap.

7.10.2 Data collection and analysis

In an attempt to minimise bias and variation in collecting data, the numbers of participants in each of the focus groups were oversampled. During the development of the THAW protocol the participant composition, included the concept development group, ethics committee, clinical experts, family and patient representatives as well hospital management. The dynamics within each group, particularly dominant voices, or senior clinicians may have influenced participant's responses. Furthermore, the inclusion of patients and families adds invaluable insights, yet their subjective experiences may not universally represent all stakeholders.

In the development phase of the THAW protocol, data analysis was conducted using a general inductive approach, where the researcher played a central role in identifying significant data points and determining the methods for analysis, coding, and categorisation. Although steps were taken to ensure consistency in coding, it's important to note that the interpretation of the data ultimately reflects the researcher's perspective.

7.10.3 Sample bias

The design of this study might also contain inherent biases, such as selection bias or confirmation bias, which could have influenced the results. The implementation of advanced neurological monitoring and TTM treatment protocols required specific technologies and resources, which might not be universally available. These limitations are essential to consider when interpreting the study results and their potential application in clinical practice or further research.

7.10.4 The researcher

The characteristics of the researcher, including age, gender, profession, and nonverbal cues like facial expressions, could have influenced the responses during the focus group sessions. Furthermore, the researcher's presence and certain unavoidable attributes may have shaped the participants' responses and behaviour, potentially impacting the study's results. Additionally, the varying levels of familiarity between the participants and the researcher might have further influenced the responses, although the exact impact on the study's findings remains uncertain.

7.10.5 The useability of the THAW protocol

Thematic analysis of the data from the five focus groups led the researcher to decide which data were considered important and how the data were analysed, coded and categorised. These

decisions affected the construction of the THAW protocol and may therefore influence the usability and generalisability of the THAW protocol.

7.11 Conclusions

The THAW protocol, aimed to redefine the management and care of unconscious OHCA patients, representing a comprehensive and multidisciplinary effort in post-resuscitation treatment and research. Fundamentally the THAW protocol focused on early waking of OHCA patients and positive prognostication, incorporating TTM at 33° Celsius, incorporating concurrent counter-shivering strategies. This safety and feasibility study successfully demonstrated the possibility of early waking and extubation of 12 patients, reducing the duration of mechanical ventilation and ICU stay without any significant adverse events.

This nuanced approach to the development of a clinical protocol, was a collaborative effort involving academics, clinicians, ethicists, patient and family members. It was rigorously tested for empirical validity and practical implementation, ensuring scientific rigor with a particular emphasis of the THAW protocol being patient centred. Ethics played a pivotal role in maintaining research integrity, ensuring an appropriate risk benefit ratio was carefully considered during the development and implementation of the THAW protocol. Including multiple disciplines in the development of the THAW protocol, provided critical insights into the existing OHCA pathway, which lead to process mapping the patient journey and generating a robust patient flow pathway for unconscious OHCA survivors. This was considered imperative, to protect the critical care bed capacity as well as potential impact on the cardiothoracic surgical programme. Additionally, survivors and their families provided unique perspectives and experiences, in terms of patient access and support during the first 24 hours following admission to ICU as well as communication when performing complex neurophysiology testing. The clinical governance team's comprehensive review of the protocol ensured its alignment with organisational values, ethical standards as well as current evidence and best practice. This holistic approach in the development of a clinical protocol and implementation of the THAW protocol, emphasised patient-centred care, clinical feasibility, and ethical considerations in advancing post-resuscitation care and management.

7.12 Practice implications

Study findings and literature have introduced several innovative practices and areas for future research in the critical care management of OHCA survivors. Key practice implications

include identifying physiologically stable OHCA patients for early waking to perform a comprehensive neurological assessment, providing critical insights into the patients' neurological function and prognosis while continuing TTM. The use of IVTM alongside counter-shivering strategies offers a more precise method for temperature control, potentially replacing traditional surface cooling methods and importantly allows patients to be awake. The integration of IVTM with counter-shivering strategies into clinical practice would be considered transformative. However, there would need to be comprehensive training and education for the healthcare team to safely implement. Furthermore, the cost implications for purchase of equipment and consumables would also need to be taken into consideration. It would also be prudent to consider this for high-volume cardiac arrest centres, ensuring that resource investment would be realised, including staff training and maintaining proficiency.

The implementation of this protocol could potentially reduce the patient's mechanical ventilation time and ICU length of stay, therefore impacting on ICU resource utilisation. This is important with limited critical care bed capacity, to ensure elective surgical programmes can continue, as well as ensuring emergency bed capacity is available to support tertiary services and local population demands. For the patient, a shorter mechanical ventilation time and ICU length of stay has the potential to reduce the risks of VAP as well delirium. Furthermore, an expedited recovery has been associated with improving a patient's quality of life and return to normality. For the family, knowing the prognosis earlier can alleviate the emotional stress and anxiety associated after the traumatic event of cardiac arrest. It also reduces the logistical burden related to prolonged hospital stays, which include travel, accommodation and potential loss of income.

The THAW protocol emphasises the importance of comprehensive neurological assessments, integrating neuro biomarkers, EEG and SSEP monitoring into standard care. This approach could have significant implications for hospitals or cardiac arrest centres that lack neuro electrophysiology capabilities. Such hospitals would need to implement significant changes, including acquiring specialised equipment and developing the infrastructure required to support advanced neurological monitoring. This includes not only the procurement of consumables but also the education and training of staff. It is essential for staff to become proficient in performing electrophysiology testing and interpreting the results, ensuring seamless integration into standard care and safe, informed decision-making. This protocol demands a multidisciplinary approach, necessitating collaboration among healthcare professionals across various specialties to effectively implement these advanced practices.

7.13 Future research

Research related to the THAW protocol opens several avenues for further investigation that could significantly advance the care and outcomes of cardiac arrest survivors. One critical area is the study of long-term outcomes and quality of life, focusing on the neurological and physical aftermath for patients who have undergone the THAW protocol, including assessments of their quality of life and functional status over time. Expanding the study's scope to include multiple centres and diverse patient populations is also crucial to validate the findings and assess the protocol's effectiveness in different healthcare settings.

For future research, there is a need to investigate the long-term neurological and physical outcomes of patients who underwent the THAW protocol, including quality of life and functional status. Expanding the study to multiple centres and diverse populations would help in assessing its generalisability. Comparative studies with standard care or emerging treatments are essential to determine the protocol's efficacy and safety. Further research is also needed in the role and effectiveness of neurological assessments in early prognostication, the psychological and emotional impact on families and patients, and the optimisation of the THAW protocol in terms of timing, duration, and methods.

Comparative studies play a vital role, particularly randomised controlled trials that compare the THAW protocol with standard care or other emerging treatments for cardiac arrest survivors, aiming to robustly determine its efficacy and safety. Further research into the role and effectiveness of various neurophysiological assessments, such as EEG and SSEP, in early prognostication for cardiac arrest survivors, is essential to refine these methods.

The psychological and emotional impact of early waking and prognostication methods on families and patients, including strategies to support them through the process. Optimising the THAW protocol involves investigating the ideal timing, duration, and methods of temperature management and neurophysiological monitoring to achieve the best outcomes. The economic evaluation is another key aspect, analysing the cost-effectiveness of the THAW protocol, taking into account factors like ICU length of stay, resource utilisation, and long-term care needs. Lastly, exploring the underlying biological and neurological mechanisms through examination of the neuro biomarkers and electrophysiology tests performed on patients enrolled in the study. Together, these areas of research represent a rich field for exploration, offering the potential for substantial advancements in medical care for cardiac arrest survivors.

Appendices

This section includes the following appendices:

Appendix A:	Full Outline of UnResponsiveness (FOUR) Score
Appendix B:	Richmond Agitation Sedation Scale
Appendix C:	Extubation criteria
Appendix D:	Anti-shiver regimen
Appendix E:	Ethics approval
Appendix F:	CRF
Appendix G:	Personal consultee information sheet
Appendix H:	Personal consultee declaration form
Appendix I:	Patient information sheet
Appendix J:	Patient consent form
Appendix K:	Nominated consultee information sheet
Appendix L:	Nominated consultee declaration form
Appendix M:	Prompt sheet for neurophysiology and biomarkers
Appendix N:	Neurophysiology interpretation sheet

Appendix A: Full Outline of UnResponsiveness (FOUR) Score

Response	Score
Eye response	
Eyelids open or opened, tracking, or blinking to command	4
Eyelids open but not tracking	3
Eyelids closed but open to loud voice	2
Eyelids closed but open to pain	1
Eyelids remain closed with pain	0
Motor response	
Thumbs-up, fist, or peace sign	4
Localizing to pain	3
Flexion response to pain	2
Extension response to pain	1
No response to pain or generalized myoclonus status	0
Brainstem reflexes	
Pupil and corneal reflexes present	4
One pupil wide and fixed	3
Pupil or corneal reflexes absent	2
Pupil and corneal reflexes absent	1
Absent pupil, corneal, and cough reflex	0
Respiration pattern	
Not intubated, regular breathing pattern	4
Not intubated, Cheyne-Stokes breathing pattern	3
Not intubated, irregular breathing	2
Breathes above ventilatory rate	1
Breathes at ventilator rate or apnea	0

Appendix B: Richmond Agitation Sedation Scale

Score	Term	Description	
+4	Combative	Overly combative, violent, immediate danger to staff	
+3	Very Agitated	Pulls or removes tube(s) or catheter(s); aggressive	
+2	Agitated	Frequent non-purposeful movement, fights ventilator	
+1	Restless	Anxious but movements not aggressive vigorous	
0	Alert and calm		
-1	Drowsy	Not fully alert, but has sustained awakening (eye-opening/ eye contact) to voice (> 10 secs)	Verbal Stimulation
-2	Light sedation	Briefly awakens with eye contact to voice (<10 sec)	
-3	Moderate sedation	Movement or eye opening to voice (but no eye contact)	
-4	Deep sedation	No response to voice, but movement or eye opening to physical stimulation	Physical Stimulation
-5	Unarousable	No response to voice or physical stimulation	

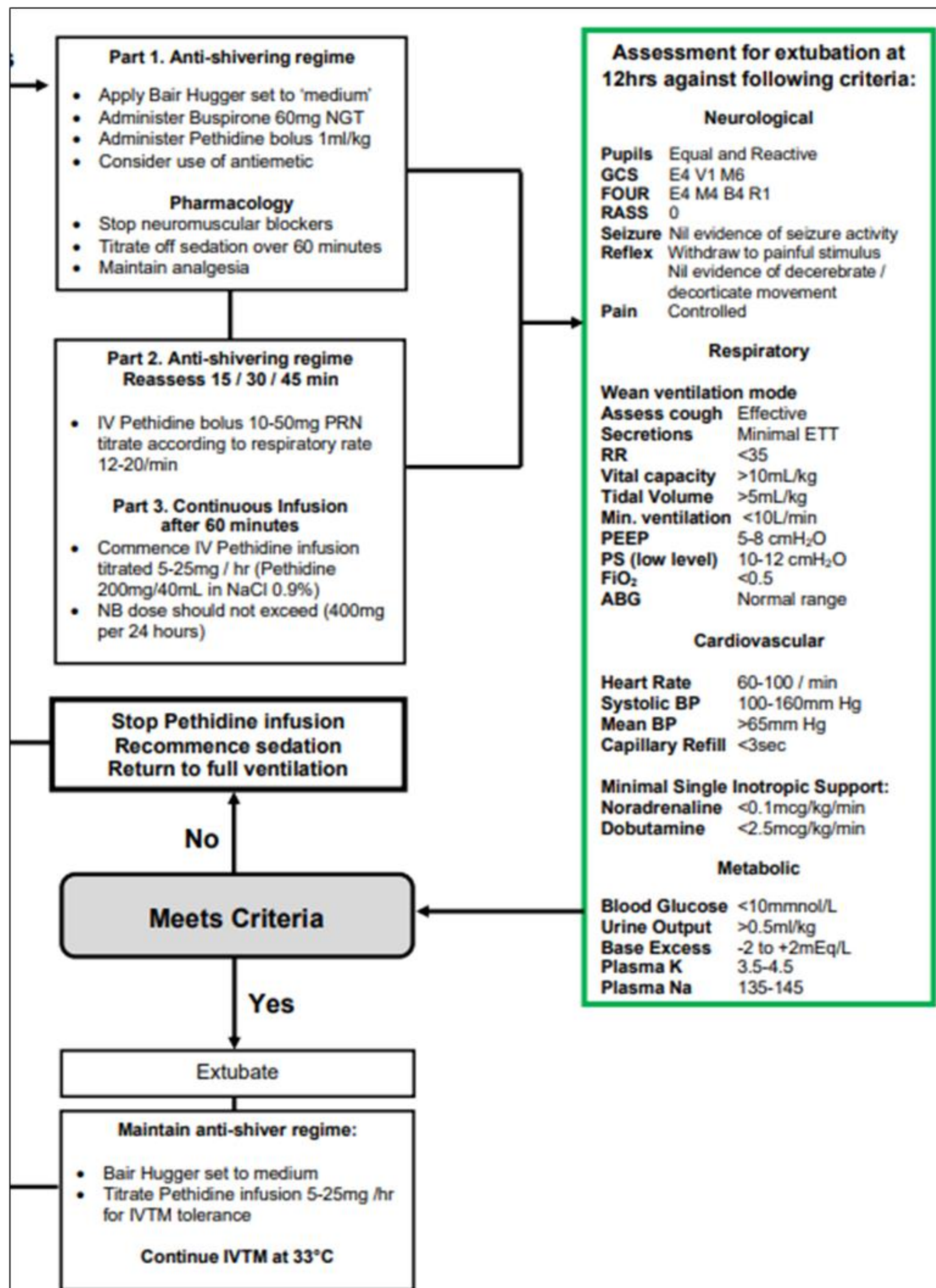
Procedure for RASS Assessment

Observe patient
- Patient is alert, restless, or agitated **(score 0 to +4)**

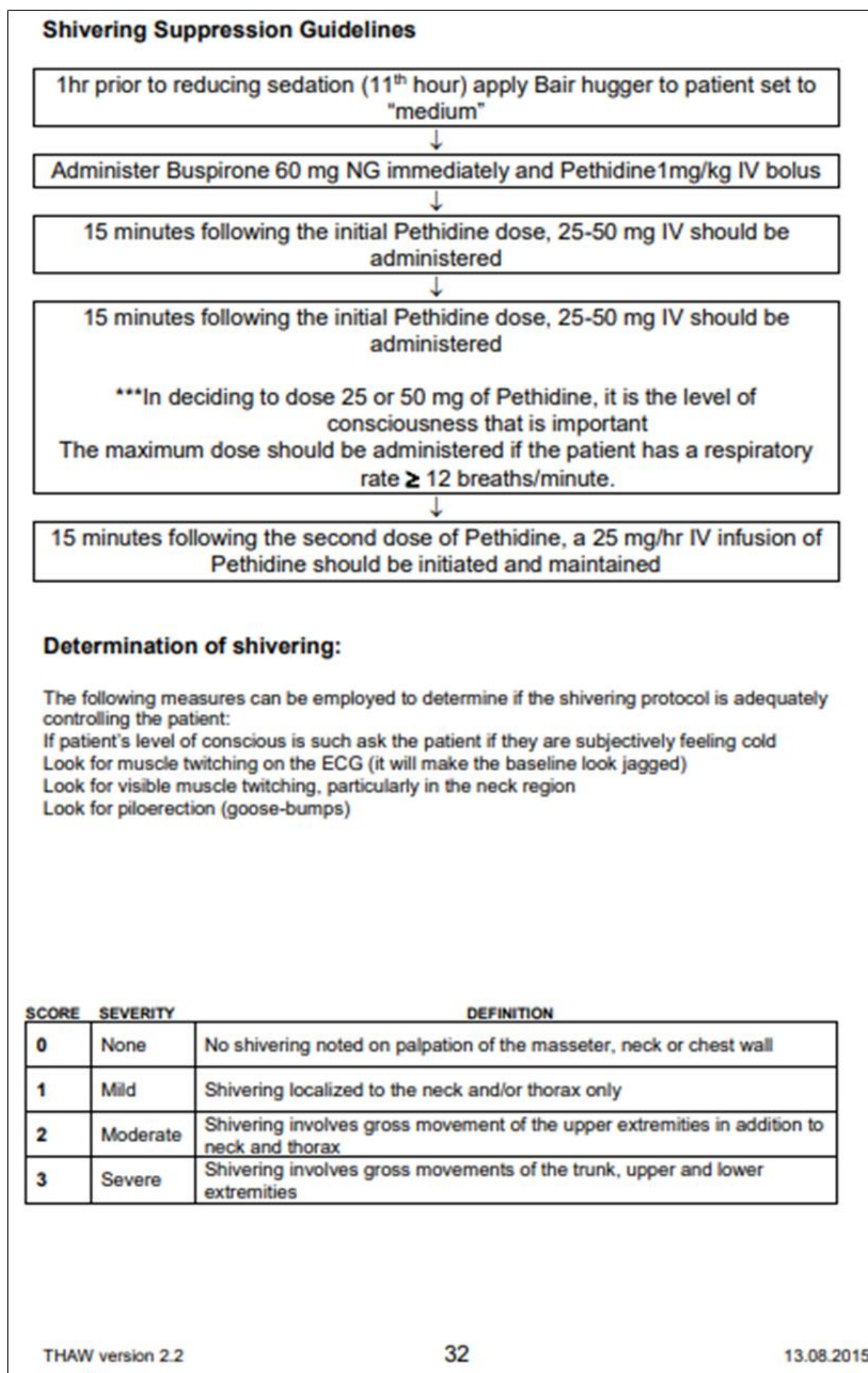
If not alert, state patient's name and say to open eyes and look at speaker
- Patient awakens with sustained eye opening and eye contact **(score -1)**
- Patient awakens with eye opening and eye contact, but not sustained **(score -2)**
- Patient has any movement in response to voice but no eye contact. **(score -3)**

When no response to verbal stimulation, physically stimulate patient by shaking shoulder and/or rubbing sternum.
- Patient has any movement to physical stimulation. **(score -4)**
- f. Patient has no response to any stimulation. **(score -5)**

Appendix C: Extubation criteria



Appendix D: Anti-shiver regimen



Shivering Suppression Guidelines

1hr prior to reducing sedation (11th hour) apply Bair hugger to patient set to "medium"

↓

Administer Buspirone 60 mg NG immediately and Pethidine1mg/kg IV bolus

↓

15 minutes following the initial Pethidine dose, 25-50 mg IV should be administered

↓

15 minutes following the initial Pethidine dose, 25-50 mg IV should be administered

***In deciding to dose 25 or 50 mg of Pethidine, it is the level of consciousness that is important
The maximum dose should be administered if the patient has a respiratory rate ≥ 12 breaths/minute.

↓

15 minutes following the second dose of Pethidine, a 25 mg/hr IV infusion of Pethidine should be initiated and maintained

Determination of shivering:

The following measures can be employed to determine if the shivering protocol is adequately controlling the patient:
If patient's level of conscious is such ask the patient if they are subjectively feeling cold
Look for muscle twitching on the ECG (it will make the baseline look jagged)
Look for visible muscle twitching, particularly in the neck region
Look for piloerection (goose-bumps)

SCORE	SEVERITY	DEFINITION
0	None	No shivering noted on palpation of the masseter, neck or chest wall
1	Mild	Shivering localized to the neck and/or thorax only
2	Moderate	Shivering involves gross movement of the upper extremities in addition to neck and thorax
3	Severe	Shivering involves gross movements of the trunk, upper and lower extremities

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Appendix E: Ethics approval

30 June 2015

Dr Thomas Keeble
Consultant Cardiologist
Basildon and Thurrock University FT Hospital
Nethermayne
SS16 5NL

Dear Dr Keeble,

Study Title:	**Therapeutic Hypothermia and eArly Waking (THAW)**
REC reference:	**15/EE/0173**
IRAS project ID:	**162893**

The Research Ethics Committee reviewed the above application at the meeting held on 12 June 2015. Thank you to yourself and Noel Watson for attending to discuss the application.

Provisional opinion

The Committee is unable to give an ethical opinion on the basis of the information and documentation received so far. Before confirming its opinion, the Committee requests that you provide the further information set out below.

Authority to consider your response and to confirm the Committee's final opinion has been delegated to the Chair and other members of the committee.

Further information or clarification required

1) There is to be clear information and clear separation as to what is part of standard care and what is part of research. The revised protocol, participant information sheets/ consultee information sheets and consent/declaration documents should include this clarity. Information on what will happen to the participants biomarker samples and what information will be kept relating to these should be detailed in the protocol and information sheets. Consent/declaration should include a clear statement of understanding about biomarker work. Please clarify on the PIS that early waking and use of shivering protocol has not been used in this group of participants before and that participants could be sedated again if it is needed.

2) The correct information sheets and consent forms to be used in the correct context. The consultee forms need to be separated by nominated consultee or personal consultee, and what it means to be that type of consultee should be explained.

Appendix F: CRF

Page 1

Date	
Patient Identification number	
Study Number	

On Admission Assessment

	Exclusion Criteria
	Do not attempt to Resuscitate orders
	Known Terminal Illness (eg Malignancy in End stages)
	Known or Obvious Pregnancy
	Known Coagulation disorder (except those induced by medication)
	Known oxygen dependency
	The patient has a height of <1.5 metres (4 feet 11 inches)
	The patient has a known sensitivity to Busiprone Hydrochloride or Pethidine
	Patient has a known history of severe hepatic or renal impairment, untreated hypothyroidism, Addison's disease, benign prostatic hypertrophy, or urethral stricture that in the opinion of the treating consultant would be incompatible with pethidine administration
	The patient has an inferior Vena Cava (IVC) filter in place
	The patient has a known, unresolved history of drug use or alcohol dependency, or lacks the ability to comprehend or follow instructions
	Cardiac arrest caused by: trauma, head injury, haemorrhage, drug overdose, cerebrovascular accident, drowning, electric shock or hanging

	Inclusion Criteria
	≥18 years old
	Receiving MTH as part of post-cardiac arrest care
	Post Cardiac arrest with ROSC

Eligibility for the study		Date	Time
	NOK identified		
	Relative Information Sheet given		
	Consent Obtained		
	Consent Declined		

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	Past Medical History (please tick):		
	Coronary Artery Disease		
	Recent Alcohol/Drug intake (give detail)		
	Radiotherapy		
	Chemotherapy		
	Home Ventilation		
	Metastatic Disease		
	Lymphoma		
	HIV/Aids		
	Hepatic Encephalopathy		
	Chronic Renal Replacement Therapy		
	Steroid Treatment (≥ 0.3mg/kg/day)		
	Seizure activity		
	TIA		
	Stroke		
	Carotid Artery Disease		
	Cardiac Family history		
	Peripheral Vascular Disease		
	Smoker		
	Ex Smoker (date quit)		
	Known Valvular Disease		
	Known AF		
	Diabetes:	Insulin	
	Tablet	Diet	

Cathlab Admission	
Time of entry to Cath Lab	
Direct admission from Ambulance Service	
Time of return of Spontaneous circulation:	

Ventilation	
Self Ventilated	
NIV	
ETT	
Time initiated	
Has the Patient been Defibrialted?	
Number of times	
Time of defibrillation(s)	
Is patient CVS Stable	
Does the pt require Inotropes/ Vasopressor:	
Time initiated:	
Other interventions	

Coronary intervention?		
	Start	
	End time	
Type of Intervention performed:		
	Angio	
	Angioplasy	
Patient Condition at End of Procedure:		
	ROSC	
	Deceased	
Neurological State		
	GCS Score:	
	FOUR Score:	
	Time	
Pupil Reactivity		
	Left	
	Right	

Appendix G: Personal consultee information sheet

The Essex
Cardiothoracic Centre

The Essex Cardiothoracic Centre
Nethermayne
Basildon
Essex
SS16 5NL

PERSONAL CONSULTEE INFORMATION SHEET

THAW – a study into Therapeutic Hypothermia and eArly Waking with patients that have suffered a cardiac arrest.

We are providing you with this information because your relative / close friend has recently been admitted to hospital after having a cardiac arrest (heart stopped). Following initial treatment by the ambulance service they were brought to the Essex Cardiothoracic Centre for further tests and treatment.

Due to your relative / close friend being unconscious they are unable to decide for them self whether or not they should take part in a study we are conducting, therefore we are asking you as their personal consultee.

The personal consultee must be a family member, or close friend of the patient. Who is able to act in accordance with any relevant previous statement or wishes made by the patient. You must feel able to take on the role of personal consultee, as you are being asked to advise on whether your relative / close friend would agree to participate in the study.

Before you decide we would like you to understand why the research is being done and what it would involve for your relative / close friend. One of our team will go through the information sheet with you and answer any questions you have, which will take about 10 minutes. You may also like to talk to others about the study.

What is the purpose of the study?

To assess whether it is feasible to wake unconscious survivors of cardiac arrest early using a rigorous early waking protocol. This will include performing complex neurological assessments and tests to identify patients who can be safely woken early whilst continuing to receive therapeutic hypothermia.

Over recent years, a lot of research has been performed that has shown that strict temperature management following cardiac arrest can improve the chances of survival. Cooling a patient to 32-34°C is now standard care in our Trust, to ensure the brain can be protected from the very damaging and often fatal effects caused by the lack of blood and oxygen.

It is important to start the cooling process quickly and to get the patient to a target temperature between 32-34°C as soon as possible. Intravascular cooling will be used as this allows patients to be conscious whilst still being cooled. An intravascular catheter (tube) is inserted into the femoral (leg) vein, and connected to a cooling machine, which allows the medical team to cool the blood to a set temperature for 24 hours.

Conventionally patients are usually given powerful sedative medications to keep them asleep and paralysing medications to stop them from shivering whilst they are being cooled. However, these medications prevent the intensive care medical team from assessing the patient's brain function and/or potentially treating any brain injury. For the purposes of this study, sedative and paralysing medications are reduced after 12 hours, which enables us to perform a neurological (brain) assessment. If at anytime the patient demonstrates adverse signs these medications are immediately restarted.

Our experience with intravascular cooling in awake patients has taught us to prevent patients

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from feeling cold we cover their body with a warm air blanket and give specific medication to prevent shivering, whilst continuing to provide the benefits of therapeutic hypothermia. The purpose of this study is to determine whether the combination of intravascular cooling combined with surface warming and anti-shivering medications allows unconscious cardiac arrest survivors to be woken early so we can assess their neurological function.

Patients involved in the study will have specific brain monitoring to ensure only suitable patients are woken early. The intensive care team will monitor the electrical activity of the brain (EEG) for abnormal waveforms, and perform a procedure called nerve stimulation (SSEP) to check brain function. Following a full examination and blood tests, an assessment of the patient's brain function a decision is made to wake the patient or continue with sedation if the patient is not suitable for being woken early.

When the brain is injured specific chemicals (NSE and S100-B) are released into the bloodstream, which can indicate the severity of damage to the brain. Testing for these chemicals requires blood samples to be sent to a specialised laboratory. Patients involved in the study will have a series of blood samples taken which will be sent for analysis to detect these chemicals. As these blood tests are currently not routine, results wont be available for at least six weeks, which is unlikely to be during the patient's hospital stay therefore will not influence care or treatment. The results of these blood tests will be collated and analysed at the end of the study. The neurological outcome and blood results will be compared to establish whether there is any correlation.

This research study aims to find out if it is possible to wake patients early whilst they are being cooled and whether patients have a quicker recovery following cardiac arrest, which is being undertaken as part of the co-investigators PhD research.

Why has your relative / close friend been invited and what is the purpose of the study?

All patients who suffer cardiac arrest and come to the Essex Cardiothoracic Centre have been automatically invited into this study. As part of our standard care, patients like your relative / close friend are cooled using an intravascular temperature management (IVTM) system. To ensure patients are kept sedated (asleep), only as long as absolutely necessary, we are trying to assess whether using complex monitoring and assessment tools we can safely wake patient's early whilst they continue to receive IVTM and whether they have a quicker recovery.

Does your relative / close friend have to take part?

It is up to you to decide whether your relative / close friend should join the study. We will describe the study and go through this information sheet. If you agree for your relative / close friend to take part, we will then ask you to sign the personal consultee form. You are free to withdraw at any time, without giving a reason. This would not affect the standard of care your relative / close friend will receive.

When your relative / close friend had their cardiac arrest, they very quickly became unconscious. Therefore, it was not possible to ask them if they wanted to take part before the treatment started. All patients coming to the Essex Cardiothoracic Centre are automatically invited into this study. We are asking you as the patient's relative/close friend (personal consultee) whether you consider the patient would agree to participate in the study. At this point, we are asking whether you consider your relative/close friend would agree to participate in the THAW study. Once the patient sufficiently recovers they will be asked for consent.

What will happen to your relative / close friend if they continue to take part?

They have already received treatment for their cardiac arrest. A research nurse or doctor will come and see you and ask if you would like to discuss the study before making your decision.

The THAW study will involve the intensive care team reducing sedation early to assess neurological function, which will include EEG and SSEP monitoring. Patients who wake up appropriately will be extubated (removed from the breathing machine) and patient's who show adverse signs will be re-sedated. A series of specific neurological biomarkers (blood tests) will also be taken, however these are sent off-site and the results are unlikely to be available until after the patient has been discharged. The blood results will not affect the care or management of your relative/close friend.

Before your relative/close friend is discharged from hospital they will be offered to attend an outpatient follow-up clinic, provided to all long-term critical care patients. For the specific purpose of this study, information gathered at the follow-up clinic will be collected and analysed to assess how they have recovered from the cardiac arrest. It will also enable us to ascertain whether it is feasible to wake patients early whilst being cooled and whether this approach has increased survival rates, or improved neurological recovery when compared to conventional management.

What are the possible risks and benefits of taking part?

Any benefit or risk to your relative / close friend from taking part is likely to occur when the intensive care doctors and nurses attempt to wake them. A full assessment will be made against strict criteria to determine their appropriateness to be woken early. If they do not meet the criteria they will be put back to sleep and reassessed later.

Our procedures for handling, processing, storage and destruction of medical data is compliant with the Data Protection Act 1998. All staff have a duty of confidentiality and will comply with the NHS Code of Practice (2003) on Confidentiality.

What if something goes wrong?

It is extremely unlikely that anything will go wrong as a result of taking part in this study, because treatment for their cardiac arrest has already finished. However, if you feel that your relative / close friend has been harmed during their treatment, or have any concerns, questions or complaints, then please discuss these with Dr Thomas Keeble (Chief Investigator), Noel Watson (Co-investigator), Critical Care Outreach Lead or the patient liaison office (PALS).

In the event that something does go wrong and your relative / close friend is harmed during the research and this is due to someone's negligence then they may have grounds for legal action for compensation against Basildon and Thurrock NHS Foundation Trust, but they may have to pay their legal costs. The normal National Health Service complaints mechanisms will still be available to them (if appropriate). There are no specific indemnity arrangements for payment of compensation in the event of non-negligent harm.

Will your relative / close friend's participation in the study be kept confidential?

Any information that is collected about your relative / close friend during the course of the study will be anonymised and kept strictly confidential and will only be seen by authorised staff involved in the study and people from regulatory authorities who ensure that studies such as this are carried out correctly. All of them will have a duty of confidentiality to you as a research participant.

All personal information and data collected is subject to the Data Protection Act and Caldicott Principles. Further information and reading material can be gained from the research team on request.

Information that is used in the study will include relevant parts of their medical care records from the ambulance service and the Essex Cardiothoracic Centre. All data will be kept within the Essex Cardiothoracic Centre and will be kept secure at all times to ensure that no accidental disclosure of personal information will occur.

Because we need to contact your relative / close friend during the period after they leave hospital, we will need to keep records of their name and address and other contact details. Any information about them will be used only for this study and will not be given to anyone else. They have the right to see their personal health information related to the research study. When any information from the study is published in medical journals it will contain no personal information and it will not be possible to identify any individual.

The data from this study will be kept for at least ten years after its conclusion and may be used in other research studies. If it is used in this way all personal identifiers will be removed and it will not be possible to identify any individual.

What will happen if I don't want my relative / close friend carry on with the study?

You are free to withdraw them from the study at any time if you wish. If you withdraw, we will not collect any more information about their health, but the information about their cardiac arrest and treatment up to the point of their withdrawal will still be included in the analysis of the study. Withdrawal from the study will not in any way adversely affect the medical treatment that they receive at the Essex Cardiothoracic Centre or any other NHS Trust.

What will happen to the results of the research study?

The study is expected to take up to 18 months to be fully recruited (50 patients required). The study results will not be available until 2016 at the earliest. The results will be analysed and published in a medical journal. If you would like a copy of the published results, please contact the study Co-Investigator (contact details below)

Who is organising and funding the study?

THAW is being organised by a small group of clinicians who are researching better treatments for patients suffering from cardiac arrest. Leading the study is Mr Noel Watson (Intensive Care Unit) and Dr Thomas Keeble (Consultant Cardiologist), both of whom work the Essex Cardiothoracic Centre. The study is funded internally.

Who has reviewed the study?

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee, to protect your safety, rights, wellbeing and dignity. This study has been reviewed and approved by an independent ethics committee.

Contact Details

Chief Investigator: Dr Thomas Keeble
Consultant Cardiologist
Essex Cardiothoracic Centre, Basildon and Thurrock University Hospitals NHS Trust
Nethermayne, Basildon, Essex SS16 5NL
Email: Thomas.keeble@btuh.nhs.uk

Co-Investigator: Mr Noel Watson
Critical Care Outreach Lead
Essex Cardiothoracic Centre, Basildon and Thurrock University Hospitals NHS Trust
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Patient Advice and Liaison Service (PALS)
Basildon and Thurrock University Hospitals NHS Trust
Nethermayne, Basildon, Essex SS16 5NL
Tel: 0845 155 3111 ext. 4440

Appendix H: Personal Consultee declaration form

The Essex
Cardiothoracic Centre

The Essex Cardiothoracic Centre
Nethermayne
Basildon
Essex
SS16 5NL

Centre Number:	
Study Number	
Patient Identification Number for this trial:	

PERSONAL CONSULTEE DECLARATION FORM

Title of Project:	Therapeutic Hypothermia And early Waking (THAW)
Name of Researcher:	Mr Noel Watson

Please Initial Box

1. I (name of personal consultee).. confirm that I have been consulted about (name of potential participants)……... participation in the above study. I have been provided with an information sheet dated 10 August 2015 version 2.1 and have had the opportunity to ask questions about the study and understand what is involved. ☐
2. In my opinion he / she would have no objection to taking part in the above study. ☐
3. I understand that I can request he / she is withdrawn from the study at any time, without giving any reason and without his / her care or legal rights being affected. ☐
4. I understand that relevant sections of his / her care records and data collected during the study, including the follow-up clinic, may be looked at by responsible individuals from the Essex Cardiothoracic Centre or from regulatory authorities, where it is relevant to their taking part in this research. ☐
5. I understand that specific neurological bio-markers (blood samples) have been collected during the study and will be analysed off-site in a specialist laboratory. I give permission for responsible individuals from regulatory authorities or from the Essex Cardiothoracic Centre to have access to these results. ☐

Name of Consultee: Relationship to participant:	Date	Signature
Person undertaking consultation (if different from researcher) Name:	Date	Signature
Researcher	Date	Signature

When completed 1 (original) to be kept in the site file, a copy to be kept in the patients care record and a copy for the Personal Consultee.

THAWRCF V2.0 19 July 2015 19.07.2015

Appendix I: Patient information sheet

The Essex
Cardiothoracic Centre

The Essex Cardiothoracic Centre
Nethermayne
Basildon
Essex
SS16 5NL

PATIENT INFORMATION SHEET

THAW – a study into **T**herapeutic **H**ypothermia and e**A**rly **W**aking with patients that have suffered a cardiac arrest.

We are providing you with this information because you were recently admitted to hospital after having a cardiac arrest (your heart stopped). Following initial treatment by the ambulance service you were brought to the Essex Cardiothoracic Centre for further tests and treatment.

When you became ill (unconscious), you were unable to decide for yourself whether or not you should take part in a study we are conducting, therefore we asked a relative / close friend on your behalf. Now you are recovering, we want to ask if you wish to continue in the study.

Before you decide we would like you to understand why the research is being done and what it would involve for you. One of our team will go through the information sheet with you and answer any questions you have, this should take about 10 minutes. You may also like to talk to others about the study.

At the time of your admission to the hospital, you were enrolled into this study. This information sheet explains about the study and what it means for you.

What is the purpose of the study?

To assess whether it is feasible to wake unconscious survivors of cardiac arrest early using a rigorous early waking protocol. This will include performing complex neurological assessments and tests to identify patients who can be safely woken early whilst continuing to receive therapeutic hypothermia.

Over recent years, a lot of research has been performed that has shown that strict temperature management following cardiac arrest can improve the chances of survival. Cooling a patient to 32-34°C is now standard care to ensure the brain can be protected from the very damaging and often fatal effects caused by the lack of blood and oxygen.

It is important to start the cooling process quickly and to get the patient to a target temperature between 32-34°C as soon as possible. There are two main methods of delivering therapeutic hypothermia i.e. surface or intravascular. However, for the purpose of this study only the intravascular cooling method will be used as this allows patients to be conscious whilst still being cooled. An intravascular catheter (tube) is inserted into the femoral (leg) vein, and connected to a cooling machine, which allows the medical team to cool the blood to a set temperature for 24 hours.

Conventionally patients are usually given powerful sedative medications to keep them asleep and paralysing medications to stop them from shivering whilst they are being cooled. However, these medications prevent the intensive care medical team from assessing the patient's brain function and/or potentially treating any brain injury. For the purposes of this study, sedative and paralysing medications are reduced after 12 hours instead of the usual 24 hours, which enables us to perform an early neurological (brain) assessment. If at anytime the patient demonstrates adverse signs these medications are immediately restarted.

Our experience with intravascular cooling in awake patients has taught us to prevent patients from feeling cold we cover their body with a warm air blanket and give specific medication to prevent shivering, whilst continuing to provide the benefits of therapeutic hypothermia. The purpose of this study is to determine whether the combination of intravascular cooling combined with surface warming and anti-shivering medications allows unconscious cardiac arrest survivors to be woken early so we can assess their neurological function.

Patients involved in the study will have specific brain monitoring to ensure only suitable patients are woken early. The intensive care team will monitor the electrical activity of the brain (EEG) for abnormal waveforms, and perform a procedure called nerve stimulation (SSEP) to check brain function. Following a full examination and assessment of the patient's brain function a decision is made to wake the patient or continue with sedation if the patient is not suitable for being woken early.

When the brain is injured specific chemicals (NSE and S100-B) are released into the bloodstream, which can indicate the severity of damage to the brain. Testing for these chemicals requires blood samples to be sent to a specialised laboratory. Patients involved in the study will have a series of blood samples taken which will be sent for analysis to detect these chemicals. As these blood tests are currently not routine, results wont be available for at least six weeks, which is unlikely to be during the patient's hospital stay therefore will not influence care or treatment. The results of these blood tests will be collated and analysed at the end of the study. It is only at this point that neurological outcome and blood results will be compared to establish whether there is any correlation.

This research study aims to find out if it is possible to wake patients early whilst they are being cooled and whether patients have a quicker recovery following cardiac arrest, which is being undertaken as part of the co-investigators PhD research.

Why have I been invited and what is the purpose of the study?

When you had your cardiac arrest, the ambulance service provided your initial treatment and brought you to the Essex Cardiothoracic Centre. All patients who suffer cardiac arrest and come to the Essex Cardiothoracic Centre have been included in this study. As part of our standard care, patients like yourself are cooled using an intravascular temperature management (IVTM) system. To ensure patients are kept sedated (asleep) only as long as absolutely necessary, we are trying to assess whether using complex monitoring and assessment tools we can safely wake patient's early whilst continuing to receive IVTM and whether they have a quicker recovery.

Do I have to take part?

It is up to you to decide to join the study. We will describe the study and go through this information sheet. If you agree to take part, we will then ask you to sign a consent form. You are free to withdraw at any time, without giving a reason. This would not affect the standard of care you receive.

When you had your cardiac arrest, you very quickly became unconscious. Therefore, it was not possible to ask you if you wanted to take part before the treatment started. All patients coming to the Essex Cardiothoracic Centre are automatically included in the study. Initially we asked your relative/close friend (personal consultee) whether you would agree to participating in this study. Where they were not immediately identifiable/available a healthcare professional (not involved in this research study) was identified as your nominated consultee. Now that you have sufficiently recovered, it is your decision whether or not to participate in this study.

At this point we are asking for your consent to continue participating in the study, which will involve you receiving standard in-hospital care (no extra investigations or blood

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tests). As part of standard care before you're discharged from hospital you will be invited to attend a critical care follow-up clinic. This will provide you with psychological support and referral to any specialist services you might require.

What will happen to me if I continue to take part?

You have already received treatment for your cardiac arrest, so no further treatment will be involved. A research nurse or doctor will come and see you to ask if you would like to discuss the study before making your decision.

There aren't any further tests required for this study. You will receive a letter to attend an outpatient follow-up clinic, which is provided to all long-term critical care patients. For the specific purpose of this study, information that is gathered at the follow-up clinic will be collected and analysed to assess how you have recovered from the cardiac arrest. It will also enable us to ascertain whether it is feasible to wake patients early whilst being cooled and whether this approach has increased survival rates, or improved neurological recovery when compared to conventional management.

What are the possible risks and benefits of taking part?

Any benefit or risk to you from taking part in the study will already have occurred.

What if something goes wrong?

It is extremely unlikely that anything will go wrong as a result of taking part in this study, because treatment for your cardiac arrest has already finished. However, if you feel that you have been harmed during your treatment, or have any concerns, questions or complaints, then please discuss these with Dr Thomas Keeble (Chief Investigator), Noel Watson (Co-investigator) Critical Care Outreach Lead or the patient liaison office (PALS).

In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against Basildon and Thurrock NHS Foundation Trust, but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you (if appropriate).

Will my participation in the study be kept confidential?

Any information that is collected about you during the course of the study will be anonymised and kept strictly confidential and will only be seen by authorised staff involved in the study and people from regulatory authorities who ensure that studies such as this are carried out correctly. All of them will have a duty of confidentiality to you as a research participant.

All personal information and data collected is subject to the Data Protection Act and Caldicott Principles. Further information and reading material can be gained from the research team on request.

Information that is used in the study will include relevant parts of your medical care records from the ambulance service and the Essex Cardiothoracic Centre. All data will be kept within the Essex Cardiothoracic Centre and will be kept secure at all times to ensure that no accidental disclosure of personal information will occur.

Any information about you will be used only for this study and will not be given to anyone else. You have the right to see your personal health information related to the research study. When any information from the study is published in medical journals it will contain no personal information and it will not be possible to identify any individual.

The data from this study will be kept for at least ten years after its conclusion and may be used in other research studies. If it is used in this way all personal identifiers will be removed and it will not be possible to identify any individual.

What will happen if I don't want to carry on with the study?

You are free to withdraw from the study at any time if you wish. If you withdraw, we will not collect any more information about your health, but the information about your cardiac arrest and treatment up to the point of your withdrawal will still be included in the analysis of the study. Withdrawal from the study will not in any way adversely affect the medical treatment that you will receive from the Essex Cardiothoracic Centre or any other NHS Trust.

What will happen to the results of the research study?

The study is expected to take up to 18 months to be fully recruited (50 patients required). The study results will not be available until 2016 at the earliest. The results will be analysed and published in a medical journal. If you would like a copy of the published results, please contact the study Chief Investigator or Co-Investigator (contact details below).

Who is organising and funding the study?

THAW is being organised by a small group of clinicians who are researching better treatments for patients suffering from cardiac arrest. Leading the study is Mr Noel Watson (Intensive Care Unit) and Dr Thomas Keeble (Consultant Cardiologist), both of whom work the Essex Cardiothoracic Centre. The study is funded internally.

Who has reviewed the study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect your safety, rights, wellbeing and dignity. This study has been reviewed and approved by an independent ethics committee.

Contact Details

Chief Investigator: Dr Thomas Keeble
Consultant Cardiologist
Essex Cardiothoracic Centre, Basildon and Thurrock University Hospitals NHS Trust
Nethermayne, Basildon, Essex SS16 5NL
Email: Thomas.keeble@btuh.nhs.uk

Co-Investigator: Mr Noel Watson
Critical Care Outreach Lead
Essex Cardiothoracic Centre, Basildon and Thurrock University Hospitals NHS Trust,
Nethermayne, Basildon, Essex SS16 5NL
Tel : 0845 155 3111 ext. 4266 / 4295 dect.7326 bleep 6001
Email : noel.watson@btuh.nhs.uk

Patient Advice and Liaison Service (PALS)
Basildon and Thurrock University Hospitals NHS Trust
Nethermayne, Basildon, Essex SS16 5NL
Tel: 0845 155 3111 ext. 4440

Appendix J: Patient consent form

The Essex
Cardiothoracic Centre

The Essex Cardiothoracic Centre
Nethermayne
Basildon
Essex
SS16 5NL

Centre Number:	
Study Number	
Patient Identification Number for this trial:	

PATIENT CONSENT FORM

Title of Project:	Therapeutic Hypothermia And early Waking (THAW)
Name of Researcher:	Mr Noel Watson

Please Initial Box

1. I can confirm that I have read and understood the information sheet dated 10 August 2015 Version 2.1 for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.
2. I understand that my participation is voluntary and that I am free to withdraw at anytime without giving any reason, without my medical care or legal rights being affected.
3. I understand that relevant sections of my care records and data collected during the study, including the follow-up clinic, may be looked at by responsible individuals from regulatory authorities or from the Essex Cardiothoracic Centre where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.
4. I understand that specific neurological bio-markers (blood samples) have been collected during the study and will be analysed off-site in a specialist laboratory. I give permission for responsible individuals from regulatory authorities or from the Essex Cardiothoracic Centre to have access to these results.
5. I agree to take part in the above study.

Name of Patient:	Date	Signature
Person undertaking consultation (if different from researcher) Name:	Date	Signature
Researcher	Date	Signature

When completed 1 (original) to be kept in the site file, 1 copy kept in care record, 1 copy for patient

THAWPCF V2.0 19 July 2015 19.07.2015

Appendix K: Nominated consultee information sheet

The Essex
Cardiothoracic Centre

The Essex Cardiothoracic Centre
Nethermayne
Basildon
Essex
SS16 5NL

NOMINATED CONSULTEE INFORMATION SHEET

THAW – a study into Therapeutic Hypothermia and eArly Waking with patients that have suffered a cardiac arrest.

We are providing you with this information because a patient has recently been admitted to hospital after having a cardiac arrest (heart stopped). Following initial treatment by the ambulance service they were brought to the Essex Cardiothoracic Centre for further tests and treatment.

Due to the patient being unconscious they are unable to decide for them self whether or not they should take part in a study we are conducting. We have been unable to contact family or a close friend of the patient, therefore we are asking you as a nominated consultee.

The nominated consultee is required to perform the same role as a personal consultee i.e. family member / close friend. We are asking you to make a decision which considers the wishes and best interests of the patient who lacks capacity. As the nominated consultee it is unlikely that you will know the patient, however it is important that you consider any possible potential or perceived conflict of interest in the outcome of this study when making your decision.

Before you decide we would like you to understand why the research is being done and what it would involve for the patient. One of our team will go through the information sheet with you and answer any questions you have, which will take about 10 minutes. You may also like to talk to others about the study.

What is the purpose of the study?

To assess whether it is feasible to wake unconscious survivors of cardiac arrest early using a rigorous early waking protocol. This will include performing complex neurological assessments and tests to identify patients who can be safely woken early whilst continuing to receive therapeutic hypothermia.

Over recent years, a lot of research has been performed that has shown that strict temperature management following cardiac arrest can improve the chances of survival. Cooling a patient to 32-34°C is now standard care in our Trust, to ensure the brain can be protected from the very damaging and often fatal effects caused by the lack of blood and oxygen.

It is important to start the cooling process quickly and to get the patient to a target temperature between 32-34°C as soon as possible. Intravascular cooling will be used as this allows patients to be conscious whilst still being cooled. An intravascular catheter (tube) is inserted into the femoral (leg) vein, and connected to a cooling machine, which allows the medical team to cool the blood to a set temperature for 24 hours.

Conventionally patients are usually given powerful sedative medications to keep them asleep and paralysing medications to stop them from shivering whilst they are being cooled. However, these medications prevent the intensive care medical team from assessing the patient's brain function and/or potentially treating any brain injury. For the purposes of this study, sedative and paralysing medications are reduced after 12 hours, which enables us to perform a neurological (brain) assessment. If at anytime the patient demonstrates adverse signs these medications are immediately restarted.

THAWNCIS V1.0 10 Aug 2015 1 10.08.2015

Our experience with intravascular cooling in awake patients has taught us to prevent patients from feeling cold we cover their body with a warm air blanket and give specific medication to prevent shivering, whilst continuing to provide the benefits of therapeutic hypothermia. The purpose of this study is to determine whether the combination of intravascular cooling combined with surface warming and anti-shivering medications allows unconscious cardiac arrest survivors to be woken early so we can assess their neurological function.

Patients involved in the study will have specific brain monitoring to ensure only suitable patients are woken early. The intensive care team will monitor the electrical activity of the brain (EEG) for abnormal waveforms, and perform a procedure called nerve stimulation (SSEP) to check brain function. Following a full examination and blood tests, an assessment of the patient's brain function a decision is made to wake the patient or continue with sedation if the patient is not suitable for being woken early.

When the brain is injured specific chemicals (NSE and S100-B) are released into the bloodstream, which can indicate the severity of damage to the brain. Testing for these chemicals requires blood samples to be sent to a specialised laboratory. Patients involved in the study will have a series of blood samples taken which will be sent for analysis to detect these chemicals. As these blood tests are currently not routine, results wont be available for at least six weeks, which is unlikely to be during the patient's hospital stay therefore will not influence care or treatment. The results of these blood tests will be collated and analysed at the end of the study. The neurological outcome and blood results will be compared to establish whether there is any correlation.

This research study aims to find out if it is possible to wake patients early whilst they are being cooled and whether patients have a quicker recovery following cardiac arrest, which is being undertaken as part of the co-investigators PhD research.

Why has this patient been invited and what is the purpose of the study?

All patients who suffer cardiac arrest and come to the Essex Cardiothoracic Centre have been automatically invited into this study. As part of our standard care, patients like your relative / close friend are cooled using an intravascular temperature management (IVTM) system. To ensure patients are kept sedated (asleep), only as long as absolutely necessary, we are trying to assess whether using complex monitoring and assessment tools we can safely wake patient's early whilst they continue to receive IVTM and whether they have a quicker recovery.

Does this patient have to take part?

It is up to you to decide whether this patient should join the study. We will describe the study and go through this information sheet. If you agree for this patient to take part, we will then ask you to sign the nominated consultee form. You are free to withdraw at any time, without giving a reason. This would not affect the standard of care the patient will receive.

When the patient had their cardiac arrest, they very quickly became unconscious. Therefore, it was not possible to ask them if they wanted to take part before the treatment started. All patients coming to the Essex Cardiothoracic Centre are automatically included in the study. We are asking you as the patient's nominated consultee (not directly involved in the research study) whether you consider the patient would agree to participate in the study. At this point, we are asking whether you consider the patient would agree to participate in the THAW study. Once the patient sufficiently recovers they will be asked for consent.

What will happen to the patient if they continue to take part?

The patient has already received treatment for their cardiac arrest. A research nurse or doctor will come and see you and ask if you would like to discuss the study before making your decision.

The THAW study will involve the intensive care team reducing sedation early to assess neurological function, which will include EEG and SSEP monitoring. Patients who wake up appropriately will be extubated (removed from the breathing machine) and patient's who show adverse signs will be re-sedated. A series of specific neurological biomarkers (blood tests) will also be taken, however these are sent off-site and the results are unlikely to be available until after the patient has been discharged. The blood results will not affect the care or management of your relative/close friend.

Before the patient is discharged from hospital they will be offered to attend an outpatient follow-up clinic, provided to all long-term critical care patients. For the specific purpose of this study, information gathered at the follow-up clinic will be collected and analysed to assess how they have recovered from the cardiac arrest. It will also enable us to ascertain whether it is feasible to wake patients early whilst being cooled and whether this approach has increased survival rates, or improved neurological recovery when compared to conventional management.

What are the possible risks and benefits of taking part?

Any benefit or risk to the patient from taking part is likely to occur when the intensive care doctors and nurses attempt to wake them. A full assessment will be made against strict criteria to determine their appropriateness to be woken early. If they do not meet the criteria they will be put back to sleep and reassessed later.

Our procedures for handling, processing, storage and destruction of medical data is compliant with the Data Protection Act 1998. All staff have a duty of confidentiality and will comply with the NHS Code of Practice (2003) on Confidentiality.

What if something goes wrong?

It is extremely unlikely that anything will go wrong as a result of taking part in this study, because treatment for their cardiac arrest has already finished. However, if you feel that the patient has been harmed during their treatment, or have any concerns, questions or complaints, then please discuss these with Dr Thomas Keeble (Chief Investigator), Noel Watson (Co-investigator), Critical Care Outreach Lead or the patient liaison office (PALS).

In the event that something does go wrong and the patient is harmed during the research and this is due to someone's negligence then they may have grounds for legal action for compensation against Basildon and Thurrock NHS Foundation Trust, but they may have to pay their legal costs. The normal National Health Service complaints mechanisms will still be available to them (if appropriate). There are no specific indemnity arrangements for payment of compensation in the event of non-negligent harm.

Will the patient's participation in the study be kept confidential?

Any information that is collected about the patient during the course of the study will be anonymised and kept strictly confidential and will only be seen by authorised staff involved in the study and people from regulatory authorities who ensure that studies such as this are carried out correctly. All of them will have a duty of confidentiality to you as a research participant.

All personal information and data collected is subject to the Data Protection Act and Caldicott Principles. Further information and reading material can be gained from the research team on request.

Information that is used in the study will include relevant parts of their medical care records from the ambulance service and the Essex Cardiothoracic Centre. All data will be kept within the Essex Cardiothoracic Centre and will be kept secure at all times to ensure that no accidental disclosure of personal information will occur.

Because we need to contact the patient during the period after they leave hospital, we will need to keep records of their name and address and other contact details. Any information about them will be used only for this study and will not be given to anyone else. They have the right to see their personal health information related to the research study. When any information from the study is published in medical journals it will contain no personal information and it will not be possible to identify any individual.

The data from this study will be kept for at least ten years after its conclusion and may be used in other research studies. If it is used in this way all personal identifiers will be removed and it will not be possible to identify any individual.

What will happen if I don't want the patient carry on with the study?

You are free to withdraw them from the study at any time if you wish. If you withdraw, we will not collect any more information about their health, but the information about their cardiac arrest and treatment up to the point of their withdrawal will still be included in the analysis of the study. Withdrawal from the study will not in any way adversely affect the medical treatment that they receive at the Essex Cardiothoracic Centre or any other NHS Trust.

What will happen to the results of the research study?

The study is expected to take up to 18 months to be fully recruited (50 patients required). The study results will not be available until 2016 at the earliest. The results will be analysed and published in a medical journal. If you would like a copy of the published results, please contact the study Co-Investigator (contact details below)

Who is organising and funding the study?

THAW is being organised by a small group of clinicians who are researching better treatments for patients suffering from cardiac arrest. Leading the study is Mr Noel Watson (Intensive Care Unit) and Dr Thomas Keeble (Consultant Cardiologist), both of whom work the Essex Cardiothoracic Centre. The study is funded internally.

Who has reviewed the study?

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee, to protect your safety, rights, wellbeing and dignity. This study has been reviewed and approved by an independent ethics committee.

Contact Details

Chief Investigator: Dr Thomas Keeble
Consultant Cardiologist
Essex Cardiothoracic Centre, Basildon and Thurrock University Hospitals NHS Trust
Nethermayne, Basildon, Essex SS16 5NL
Email: Thomas.keeble@btuh.nhs.uk

Co-Investigator: Mr Noel Watson
Critical Care Outreach Lead
Essex Cardiothoracic Centre, Basildon and Thurrock University Hospitals NHS Trust
Nethermayne, Basildon, Essex SS16 5NL
Tel : 0845 155 3111 ext. 4266 / 4295 dect.7326 bleep 6001
Email : noel.watson@btuh.nhs.uk

Patient Advice and Liaison Service (PALS)
Basildon and Thurrock University Hospitals NHS Trust
Nethermayne, Basildon, Essex SS16 5NL
Tel: 0845 155 3111 ext. 4440

Appendix L: Nominated consultee declaration form

The Essex
Cardiothoracic Centre

The Essex Cardiothoracic Centre
Nethermayne
Basildon
Essex
SS16 5NL

Centre Number:	
Study Number	
Patient Identification Number for this trial:	

NOMINATED CONSULTEE DECLARATION FORM

Title of Project:	Therapeutic Hypothermia And early Waking (THAW)
Name of Researcher:	Mr Noel Watson

Please Initial Box

1. I (name of nominated consultee)... confirm that I have been consulted about (name of potential participants)……... participation in the above study. I have been provided with an information sheet dated 10 August 2015 version 1.0 and have had the opportunity to ask questions about the study and understand what is involved.

2. In my opinion he / she would have no objection to taking part in the above study.

3. I understand that I can request he / she is withdrawn from the study at any time, without giving any reason and without his / her care or legal rights being affected.

4. I understand that relevant sections of his / her care records and data collected during the study, including the follow-up clinic, may be looked at by responsible individuals from the Essex Cardiothoracic Centre or from regulatory authorities, where it is relevant to their taking part in this research.

5. I understand that specific neurological bio-markers (blood samples) will/have be/been collected during the study and will be analysed off-site in a specialist laboratory. I give permission for responsible individuals from regulatory authorities or from the Essex Cardiothoracic Centre to have access to these results

Name of Consultee: Relationship to participant:	Date	Signature
Person undertaking consultation (if different from researcher) Name:	Date	Signature
Researcher	Date	Signature

When completed 1 (original) to be kept in the site file, a copy to be kept in the patients care record and a copy for the Nominated Consultee.

THAWNCF V2.0 19 JULY 2015 19.07.2015

Appendix M: Prompt sheet

THAW Study

THAW Study Number _________ ICU Bed location ________.

EEG, SSEP and Bloods (Red top and yellow top vacutainers) need to be taken at the following times:

	Initials once all recordings complete
Time of Admission to ICU ___________(actual time)	☐
6 Hours since admission ___________(actual time)	☐
12 Hours since admission ___________(actual time)	☐
24 Hours since admission ___________(actual time)	☐
48 Hours since admission ___________(actual time)	☐
72 Hours since admission ___________(actual time)	☐

Appendix N: Neurophysiology monitoring interpretation sheet

THAW (**T**herapeutic **H**ypothermia and e**A**rly **W**aking) The Essex Cardiothoracic Centre

Neurophysiology Monitoring Interpretation Sheet

Admission:

What is your interpretation of the EEG/SSEP. Please include descriptions of waveforms, epileptiform activity and any treatment suggestions you may have

1. In your opinion, does the EEG indicate a good or poor prognosis? (Good, Poor or Cannot Say – please give any extra comments)

2. In your opinion, does the SSEP indicate a good or poor prognosis? (Good, Poor or Cannot Say – please give any extra comments)

3. In your opinion, together does the EEG/SSEP indicate a good or poor prognosis? (Good, Poor or Cannot Say – please give any extra comments)

4. In your opinion, using the data, do you think the patient is appropriate for early waking? (12 Hours after admission to the ICU whilst cooled using Intravenous Temperature management) (Yes, No or Cannot Say?)

1

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5. Are you happy with the quality of the EEG? (Yes or No– please give any comments or suggestions)

6. Are you happy with the quality of the SSEP? (Yes or No – please give any comments or suggestions)

7. Do you have any suggestions or recommendations for the patients further treatment? (Yes or No plus any comments you may have)

8. Please give any extra comments you may have

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6 Hours following Admission

1. What is your interpretation of the EEG/SSEP. Please include descriptions of waveforms, epileptiform activity, any treatment suggestions you may have and if you used any earlier recordings for comparison

2. In your opinion, does the EEG indicate a good or poor prognosis? (Good, Poor or Cannot Say – please give any extra comments)

3. In your opinion, does the SSEP indicate a good or poor prognosis? (Good, Poor or Cannot Say – please give any extra comments)

4. In your opinion, together does the EEG/SSEP indicate a good or poor prognosis? (Good, Poor or Cannot Say – please give any extra comments)

3

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5. In your opinion, using the data, do you think the patient is appropriate for early waking? (12 Hours after admission to the ICU whilst cooled using Intravenous Temperature management) (Yes, No or Cannot Say?)

6. Are you happy with the quality of the EEG? (Yes or No– please give any comments or suggestions)

7. Are you happy with the quality of the SSEP? (Yes or No – please give any comments or suggestions)

8. Do you have any suggestions or recommendations for the patients further treatment? (Yes or No plus any comments you may have)

9. Please give any extra comments you may have

4

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12 Hours following admission

6 Hours following Admission

1. What is your interpretation of the EEG/SSEP. Please include descriptions of waveforms, epileptiform activity, any treatment suggestions you may have and if you used any earlier recordings for comparison.

2. In your opinion, does the EEG indicate a good or poor prognosis? (Good, Poor or Cannot Say – please give any extra comments)

3. In your opinion, does the SSEP indicate a good or poor prognosis? (Good, Poor or Cannot Say – please give any extra comments)

4. In your opinion, together does the EEG/SSEP indicate a good or poor prognosis? (Good, Poor or Cannot Say – please give any extra comments)

5

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5. In your opinion, using the data, do you think the patient is appropriate for early waking? (12 Hours after admission to the ICU whilst cooled using Intravenous Temperature management) (Yes, No or Cannot Say?)

6. Are you happy with the quality of the EEG? (Yes or No– please give any comments or suggestions)

7. Are you happy with the quality of the SSEP? (Yes or No – please give any comments or suggestions)

8. Do you have any suggestions or recommendations for the patients further treatment? (Yes or No plus any comments you may have)

9. Please give any extra comments you may have

6

THAW (**T**herapeutic **H**ypothermia and e**A**rly **W**aking) The Essex Cardiothoracic Centre

24 Hours following admission

1. What is your interpretation of the EEG. Please include descriptions of waveforms, epileptiform activity, any treatment suggestions you may have and if you used any earlier recordings for comparison.

2. In your opinion, does the EEG indicate a good or poor prognosis? (Good, Poor or Cannot Say – please give any extra comments)

3. In your opinion, together does the EEG indicate a good or poor prognosis? (Good, Poor or Cannot Say – please give any extra comments)

4. In your opinion, using the data, do you think the patient is appropriate for early waking? (whilst cooled using Intravenous Temperature management) (Yes, No or Cannot Say?)

5. Are you happy with the quality of the EEG? (Yes or No– please give any comments or suggestions)

7

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24 Hours following admission

1. What is your interpretation of the EEG. Please include descriptions of waveforms, epileptiform activity, any treatment suggestions you may have and if you used any earlier recordings for comparison.

2. In your opinion, does the EEG indicate a good or poor prognosis? (Good, Poor or Cannot Say – please give any extra comments)

3. In your opinion, together does the EEG indicate a good or poor prognosis? (Good, Poor or Cannot Say – please give any extra comments)

4. In your opinion, using the data, do you think the patient is appropriate for early waking? (whilst cooled using Intravenous Temperature management) (Yes, No or Cannot Say?)

5. Are you happy with the quality of the EEG? (Yes or No– please give any comments or suggestions)

7

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6. Do you have any suggestions or recommendations for the patients further treatment? (Yes or No plus any comments you may have)

7. Please give any extra comments you may have

8

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48 Hours following admission

1. What is your interpretation of the EEG/SSEP. Please include descriptions of waveforms, epileptiform activity, any treatment suggestions you may have and if you used any earlier recordings for comparison

2. In your opinion, does the EEG indicate a good or poor prognosis? (Good, Poor or Cannot Say – please give any extra comments)

3. In your opinion, does the SSEP indicate a good or poor prognosis? (Good, Poor or Cannot Say – please give any extra comments)

4. In your opinion, together does the EEG/SSEP indicate a good or poor prognosis? (Good, Poor or Cannot Say – please give any extra comments)

5. In your opinion, using the data, do you think the patient is appropriate for early waking? (whilst cooled using Intravenous Temperature management) (Yes, No or Cannot Say?)

6. Are you happy with the quality of the EEG? (Yes or No– please give any comments or suggestions)

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7. Are you happy with the quality of the SSEP? (Yes or No – please give any comments or suggestions)

8. Do you have any suggestions or recommendations for the patients further treatment? (Yes or No plus any comments you may have)

9. Please give any extra comments you may have

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72 Hours Following admission

1. What is your interpretation of the EEG/SSEP. Please include descriptions of waveforms, epileptiform activity, any treatment suggestions you may have and if you used any earlier recordings for comparison

2. In your opinion, does the EEG indicate a good or poor prognosis? (Good, Poor or Cannot Say – please give any extra comments)

3. In your opinion, does the SSEP indicate a good or poor prognosis? (Good, Poor or Cannot Say – please give any extra comments)

4. In your opinion, together does the EEG/SSEP indicate a good or poor prognosis? (Good, Poor or Cannot Say – please give any extra comments)

5. In your opinion, using the data, do you think the patient is appropriate for waking? (Yes, No or Cannot Say?)

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6. Are you happy with the quality of the EEG? (Yes or No– please give any comments or suggestions)

7. Are you happy with the quality of the SSEP? (Yes or No – please give any comments or suggestions)

8. Do you have any suggestions or recommendations for the patients further treatment? (Yes or No plus any comments you may have).

9. Please give any extra comments you may have

Summary

Please give your summary of all recordings, your final prognosis plus any extra comments you may have.

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