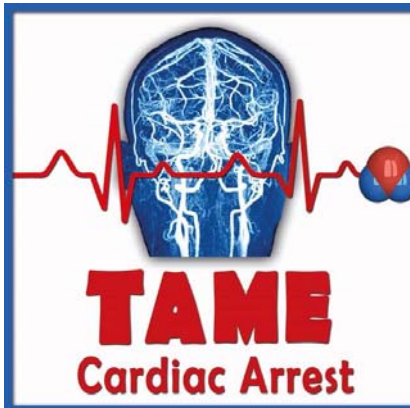




TAME Cardiac Arrest Trial

Targeted Therapeutic Mild Hypercapnia
After Resuscitated Cardiac Arrest:
A Phase III Multi-Centre
Randomised Controlled Trial

Clinical Trial Identifier:	ANZ Clinical Trials Registry Number: ACTRN12617000036314p Clinicaltrials.gov: NCT03114033
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Coordinating Centre:	Australian and New Zealand Intensive Care Research Centre (ANZIC-RC) School of Public Health and Preventive Medicine, Monash University 553 St Kilda Road Melbourne, Victoria, 3004 AUSTRALIA T: +61 3 9903 0343 F: +61 3 9903 0071 E: anzicrc@monash.edu
Endorsement:	This study is endorsed by the Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS-CTG) and the Irish Critical Care – Clinical Trials Group (ICC-CTG).

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1. SYNOPSIS

Title	Targeted therapeutic mild hypercapnia after resuscitated cardiac arrest: A phase III multi-centre randomised controlled trial
Short title	The TAME Cardiac Arrest Trial
Objective	To determine whether targeted therapeutic mild hypercapnia (TTMH) improves neurological outcome at 6 months compared to standard care (targeted normocapnia (TN)) as assessed by the Glasgow Outcome Scale Extended (GOSE) method.
Design	Phase III, multi-centre, randomised, parallel-group, controlled trial
Outcomes	<i>Primary outcome</i> The primary outcome measure for this study is the proportion of patients with a favourable neurological outcome at 6 months as assessed using the GOSE. A GOSE outcome is deemed favourable if a patient scores ≥ 5. <i>Secondary outcomes</i> 1. Mortality at ICU discharge, hospital discharge and at 6 months after randomisation 2. Functional recovery assessed using the modified Rankin scale (a scale from 0 to 6, with a score of ≤ 3 indicating favourable neurological function) at 6 months after randomisation 3. Cognitive functional recovery assessed using the Montreal Cognitive Assessment (MoCA-blind); Informant Questionnaire on Cognitive Decline (IQCODE); Symbol Digit Modalities Test (SDMT) and 30-second chair test at 6 months after randomisation 4. Quality of life assessed by the five domains of Mobility, Self-care, Usual Activity, Pain/discomfort, and Anxiety/Depression of the EQ-5D-5L scale at 6 months after randomisation 5. Safety as determined as the proportion of pre-defined adverse events occurring between groups as reported by treating clinicians 6. Health economic evaluation to determine differences in groups in hospitalisation and where patient level data linkage is possible evaluate hospital use and determine pharmaceutical and primary care service utilisation at 6 months after randomisation
Intervention	Each fully eligible patient and enrolled participant will be randomised to either to receive the TTMH protocol or TN protocol for a period of 24 hours.

	<i>TTMH protocol</i> Patients allocated to the TTMH protocol will be sedated to achieve moderate to deep sedation (a target RASS of –4). ABG and ETCO₂ levels will be measured at baseline and then used to guide respiratory rate adjustments of minute ventilation to remain within the target PaCO₂ range of 50-55 mmHg for 24 hours following randomisation. ABGs will be repeated every 4 hours for 24 hours following randomisation or if ETCO₂ values change >5 mmHg. <i>TN protocol</i> Patients allocated to the standard care (TN) protocol will be managed according to current practice and in accordance with ILCOR guidelines which recommend maintaining normocapnia in these patients. They will be sedated to achieve moderate to deep sedation (a target RASS of –4). ABGs and ETCO₂ levels will be measured at baseline and then used to guide respiratory rate adjustments of minute ventilation to remain within the target PaCO₂ range of 35-45 mmHg for 24 hours following randomisation. ABGs will be repeated every 4 hours for 24 hours following randomisation or if ETCO₂ values change >5 mmHg.
Sample size	1,700 patients
Population	Adult resuscitated out-of-hospital cardiac arrest patients
Eligibility criteria	<i>Inclusion</i> 1. Adult (age ≥18 years or older) 2. Out-of-hospital cardiac arrest of a presumed cardiac or unknown cause 3. Sustained ROSC – defined as 20 minutes with signs of circulation without the need for chest compressions 4. Unconscious (FOUR-score motor response of <4, not able to obey verbal commands after sustained ROSC) 5. Eligible for intensive care without restrictions or limitations 6. Within <180 minutes of ROSC <i>Exclusion</i> 1. Unwitnessed cardiac arrest with an initial rhythm of asystole 2. Temperature on admission <30°C 3. On ECMO prior to ROSC 4. Obvious or suspected pregnancy 5. Intracranial bleeding 6. Severe chronic obstructive pulmonary disorder (COPD) with long-term home oxygen therapy
Study duration	Follow up to death, refused/revoked consent or 6-months post randomisation, whichever is the latest. Recruitment is expected to take 5 years commencing in 2017.

2. STUDY ADMINISTRATION STRUCTURE

2.1 *Coordinating Centre and Data Management Centre in Australia*

Australian and New Zealand Intensive Care Research Centre (ANZIC-RC)
School of Public Health and Preventive Medicine, Monash University
553 St Kilda Road, Melbourne, Victoria, 3004 AUSTRALIA
T: +61 3 9903 0343 F: +61 3 9903 0071 E: anzicrc@monash.edu

Responsibilities

- Overall management of the trial including assistance with human research ethics committee applications
- Management of study budget and liaison with funding bodies
- Protocol and case report form (CRF) design and production
- Database design and management
- Protocol training of investigators, research coordinators and the TAME Cardiac Arrest trial team
- Preparation and arrangement of site payments
- Trial set-up
- Randomisation schedule
- Coordination of data entry and feedback of data enquiries
- Monitoring and close-out site visits
- Organisation of investigator meetings
- Serious adverse event notification
- Data analysis and collaboration on publications

2.2 Coordinating Centre in Europe

The HRB Irish Critical Care- Clinical Trials Network (ICC-CRN)
University College Dublin- Clinical Research Centre
St Vincent's University Hospital, Elm Park, Dublin 4, Ireland.
T: +353 1 7165823 E: tame_cardiacarrest@ucd.ie
W: <http://www.iccctn.org>

Responsibilities are to assist the ANZIC-RC in Europe to

- Assist with human research ethics committee applications in Europe
- Management of Irish study budget and liaison with Irish funding bodies
- Protocol training of investigators, research coordinators and the TAME Cardiac Arrest trial team in Europe
- Preparation and arrangement of site payments
- Coordination of data entry and feedback of data enquiries
- Monitoring and close-out site visits
- Organisation of investigator meetings
- Serious adverse event notification
- Data analysis and collaboration on publications

2.2 ***Management Committee***

Responsibilities

Overseeing all aspects of the study management including:

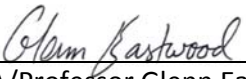
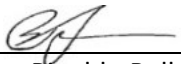
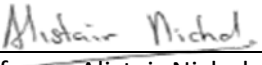
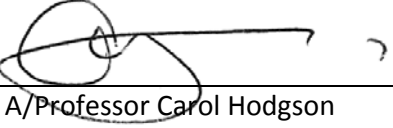
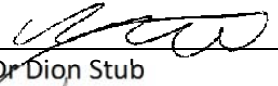
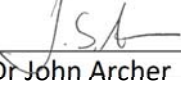
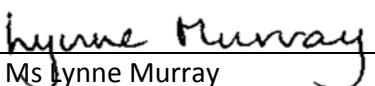
- Liaison with coordinating centre staff and trial management centre staff
- Liaison with ANZICS-CTG and/or the ICC-CTG
- Overseeing funding applications
- Overseeing disbursement and administration of funds
- Ensuring fiscal responsibilities are maintained
- Development and approval of final protocol and trial materials
- Development and approval of data collection tools and methods
- General trial management issues

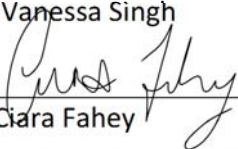
Members

Dr Glenn Eastwood, Department of Intensive Care, Austin Hospital, VIC
Professor Rinaldo Bellomo, Department of Intensive Care, Austin Hospital, VIC
Professor Alistair Nichol, Department of Intensive Care, Alfred Hospital, VIC
A/Professor Niklas Nielsen, Department of Intensive Care, Helsingborg Hospital, Sweden
Prof Stephen Bernard, Victorian Ambulance Service, Melbourne, VIC
A/Professor Carol Hodgson, ANZIC-RC, Alfred Hospital, VIC
A/Prof Rachael Parke, Cardiovascular & Intensive Care Unit, Auckland City Hospital, Auckland, NZ
Dr Shay McGuinness, Cardiovascular & Intensive Care Unit, Auckland City Hospital, Auckland, NZ
Dr Dion Stub, Cardiology Department, Alfred Hospital, VIC
Dr John Archer, Neurology Department, Austin Hospital, VIC
Dr Markus Skrifvars, Department of Intensive Care, Helsinki University Hospital, Helsinki, Finland
Prof Fabio Taccone, Department of Intensive Care, Erasme Hospital, Brussels, Belgium
Mr Tony Trapani, ANZIC-RC
Ms Bridget Ady, ANZIC-RC
Ms Vanessa Singh, ANZIC-RC
Dr Kate Ainscough, The HRB Irish Critical Care – Clinical Trials Network (ICC-CTN)
Dr Ciara Fahey, The HRB Irish Critical Care- Clinical Trials Network (ICC-CTN)

3. MANAGEMENT COMMITTEE AUTHORISATION PAGE

We the management committee have read the attached protocol and authorise it as the official protocol for the study entitled: Targeted therapeutic mild hypercapnia after resuscitated cardiac arrest: A phase III multi-centre randomised controlled trial.

Chief Investigator	 A/Professor Glenn Eastwood	Date	<u>29/5/2017</u>
Management Committee	 Professor Rinaldo Bellomo	Date	<u>29/5/2017</u>
Management Committee	 Professor Alistair Nichol	Date	<u>29/5/2017</u>
Management Committee	 A/Professor Niklas Nielsen	Date	<u>29/5/2017</u>
Management Committee	 Professor Stephen Bernard	Date	<u>29/5/2017</u>
Management Committee	 A/Professor Carol Hodgson	Date	<u>29/5/2017</u>
Management Committee	 Dr Rachael Parke	Date	<u>29/5/2017</u>
Management Committee	 Dr Shay McGuinness	Date	<u>29/5/2017</u>
Management Committee	 Dr Dion Stub	Date	<u>29/5/2017</u>
Management Committee	 Dr John Archer	Date	<u>29/5/2017</u>
Management Committee	 Ms Lynne Murray	Date	<u>29/5/2017</u>
Management Committee	 Ms Bridget Ady	Date	<u>29/5/2017</u>

Management Committee		Date	<u>29/5/2017</u>
	Ms Vanessa Singh		
Management Committee		Date	<u>29/5/2017</u>
	Dr Clara Fahey		

3.1 **Steering committee**

Dr Glenn Eastwood, Department of Intensive Care, Austin Hospital, VIC
 Professor Rinaldo Bellomo, Department of Intensive Care, Austin Hospital, VIC
 Professor Alistair Nichol, Alfred Hospital, VIC
 A/Professor Carol Hodgson, ANZIC-RC, Alfred Hospital, VIC
 A/Prof Rachael Parke, CVICU, Auckland City Hospital, NZ
 Dr Dion Stub, Cardiology Department, Alfred Hospital, VIC
 Ms Bridget Ady, ANZIC-RC, VIC
 Ms Vanessa Singh, ANZIC-RC, VIC
 Dr Kate Ainscough, The HRB Irish Critical Care- Clinical Research Network (ICC-CRN)

3.2 **Project Managers**

	Project Manager/s
	Ms Bridget Ady / Ms Vanessa Singh ANZIC-RC Monash University 553 St Kilda Road Melbourne, Victoria, 3004 AUSTRALIA T: +61 (0)3 9903 0035 / 9903 0263 F: +61 (0)3 9903 0071 E: bridget.ady@monash.edu vanessa.singh@monash.edu Dr Kate Ainscough The HRB Irish Critical Care- Clinical Trials Network (ICC-CTN) University College Dublin- Clinical Research Centre St Vincent's University Hospital, Elm Park, Dublin 4, IRELAND T: +353 1 7165823 E: kate.ainscough@ucd.ie tame_cardiacarrest@ucd.ie

4. LAY DESCRIPTION

Cardiac arrest is a common and dramatic event with major human and financial consequences. It is well understood that cardiac arrest leads to brain injury from lack of blood flow to the brain. However, what is not widely appreciated is that, even after the heart has been restarted, poor blood flow to the brain continues and can cause more brain injury. This continued poor blood flow has been repeatedly shown to happen by many complex technologies (positron emission tomography, brain vessel ultrasound, jugular bulb oxygen saturation and cerebral oximetry).

A likely reason for this continued poor brain blood flow after the heart has been restarted is the loss of the normal ability of brain blood vessel to adjust blood flow to meet the needs of the brain, a function called “autoregulation”. Such impaired brain vessel auto-regulation may make even a normal blood carbon dioxide tension (PaCO_2) (the major factor that normally controls brain blood flow) unable to achieve and maintain best brain blood flow and best brain oxygen levels. However, an increased PaCO_2 (hypercapnia) can still increase brain blood flow in these patients. In this way, arterial carbon dioxide can be increased above normal levels to hopefully deliver best brain blood flow in patients admitted to the intensive care unit after a cardiac arrest.

The TAME Cardiac Arrest Trial is a definitive trial in cardiac arrest patients whose heart has been restarted and who are on a breathing machine in the intensive care unit. This trial will determine whether increasing carbon dioxide to above normal levels [so-called targeted therapeutic mild hypercapnia (TTMH)] during the first 24 hours on a breathing machine in the intensive care unit improves brain recovery at 6 months compared to current standard care.

Supported by strong preliminary studies, significant improvements in patient outcomes are achievable with this simple and cost free therapy. Recruiting 1,700 patients, from multiple sites in many countries, this will be the largest trial ever conducted involving cardiac arrest patients admitted to the ICU. If the TAME Cardiac Arrest Trial confirms that TTMH is effective, its findings will improve the lives of many and transform clinical practice.

5. GLOSSARY OF ABBREVIATIONS AND TERMS

AE	Adverse event
AI	Associate Investigator
ANZICS	Australian and New Zealand Intensive Care Society
ANZICS-CTG	Australian and New Zealand Intensive Care Society Clinical Trials Group
ANZIC-RC	Australian and New Zealand Intensive Care Research Centre
Aus-ROC	Australian Resuscitation Outcome Consortium
CA	Cardiac Arrest
CI	Chief Investigator – responsible for the overall conduct of the study; Confidence Interval
CRF, eCRF	Case Report Form, electronic Case Report Form
CRRT	Continuous Renal Replacement Therapy
DSMC	Data and Safety Monitoring Committee
ECMO	Extracorporeal membrane oxygenation
GCP	Good Clinical Practice
GOSE	Glasgow Outcome Scale Extended
HRC	Health Research Council (NZ)
HREC	Human Research Ethics Committee
ICC-CTG	Irish Critical care – Clinical Trials Group
ICU	Intensive Care Unit
ILCOR	International Liaison Committee on Resuscitation
IQCODE	Informant Questionnaire on Cognitive Decline
IWRS	Interactive Web based Randomisation System
OHCA	Out-of-hospital Cardiac Arrest
mRS	Modified Rankin Scale
NHMRC	National Health and Medical Research Council (Aus)
NIRS	Near Infrared Spectroscopy
NSE	Neuron Specific Enolase
PaCO ₂	Arterial carbon dioxide tension
RSN	Patient Study Number: The unique code number to identify each patient in the study
PI	Principal Investigator – responsible for the study at a participating site
RCT	Randomised Controlled Trial
RASS	Richmond Agitation Scale Score
ROSC	Return Of Spontaneous Circulation
SAE	Serious Adverse Event
SDM	Substituted Decision Maker
SDMT	Symbol Digit Modalities Test
SctO ₂	Cerebral tissue oxygen saturation
SSEP	Somatosensory Evoked Potential
SUSAR	Suspected Unexpected Serious Adverse Reaction
TN	Targeted Normocapnia
TTMH	Targeted Therapeutic Mild Hypercapnia

6. ADMINISTRATIVE INFORMATION

6.1 *Funding*

This study is funded by a Project Grant from the Australian National Health and Medical Research Council (NHMRC) – Project Grant ID APP1119855; and, a Definitive Interventions and Feasibility Awards 2017 (Project Grant ID DIFA-2017-036) by the Irish Health Research Board (HRB).

6.2 *Trial Registration*

This protocol has been registered on the following registries:

1. Australian New Zealand Clinical Trials Registry, Number: ACTRN12617000036314p
2. Clinicaltrials.gov, NCT03114033

7. BACKGROUND AND SIGNIFICANCE

7.1 *Cardiac arrest is a major public health problem*

Cardiac arrest is a common and catastrophic event. Out-of-hospital cardiac arrest has an estimated incidence of approximately 1 per 1,000 persons per year (approximately 25,000 individuals in Australia each year), with Australian mortality rates varying between 87 to 94%.¹ In keeping with such estimates, in 2013-2014, Ambulance Victoria attended 5,581 out-of-hospital cardiac arrest events in adults.² Of these, 48% received an attempt at resuscitation by paramedics with 39% achieving successful return of spontaneous circulation (ROSC) and reaching a hospital.² Once admitted to an Intensive Care Unit (ICU), however, survival is still unacceptably low at approximately 40% and has remained unchanged over the last decade, as shown in the Australian New Zealand Intensive Care Society – Adult Patient Database (ANZICS-APD) for >16,000 cardiac arrest patients from 2003 to 2013.^{3,4} Of key relevance to the TAME Cardiac Arrest trial, for those patients admitted to the ICU, devastating neurological injury leading to withdrawal of life support or clinically important neurological impairment are the most common outcomes following cardiac arrest.^{3,5} Accordingly, while the initial problem is cardiac in nature, after ICU admission, the dominant reason for such dismal outcomes is neurological injury. Thus, a better neurological outcome is the logical and dominant therapeutic goal in a population where more than half are of working age.⁴

The disabling effects of cardiac arrest persist for many years and the human and financial costs of supporting survivors are substantial.^{6,7} For *each* resuscitated cardiac arrest patient admitted to ICU who survives to hospital discharge, admission costs alone exceed \$120,000.⁷ Moreover, the estimated ongoing community-based costs for *each* patient with moderate cerebral injury is AUD\$34,000/year.⁸ Accordingly, for the thousands of people admitted to ICU alive after a cardiac arrest, given the devastating neurological impact and the financial costs associated with it, novel treatment strategies are urgently needed to attenuate neurological injury; improve patient-centred outcomes, and yield major cost savings.

7.2 ***Cardiac arrest, neurological injury and cerebral perfusion in preventing neurological injury***

The fundamental concept in resuscitated cardiac arrest patients is that neurological injury occurs during the early post-resuscitation period and is responsible for the majority of deaths. Of these deaths, most occur following withdrawal of life support from day three onwards because of devastating neurological injury.⁵ Perhaps even more important, in cardiac arrest survivors, there is often significant neurological injury that imposes disabling immediate and long-term consequences on patients, their families and the broader community. Thus, prevention of neurological injury is a key priority in the ICU management of resuscitated cardiac arrest patients.

It is well understood and obvious that cardiac arrest leads to immediate brain ischemia and that resuscitation leads to reperfusion injury with acute neuronal damage.⁹ However, what is not widely appreciated is that a state of sustained cerebral hypoperfusion develops and persists even after successful immediate resuscitation, return of spontaneous circulation, and admission to the ICU.¹⁰⁻¹³ In this regard, several studies confirm such persistent cerebral vasoconstriction and cerebral hypoperfusion after resuscitated cardiac arrest. Investigations using technologies like positron emission tomography,¹⁴ middle cerebral artery blood flow assessment via Doppler ultrasound,¹⁵ jugular bulb oxygen saturation¹⁶ and cerebral oximetry,¹⁷ all consistently show sustained hypoperfusion and cerebral hypoxia. For example, observational studies measuring cerebral tissue oxygen saturation (SctO₂) by near infrared spectroscopy in patients receiving post-resuscitation care have demonstrated persistent cerebral under-oxygenation and a statistically significant association between such lower SctO₂ values and higher mortality rates.¹⁰ A likely pathophysiological mechanism responsible for such sustained early hypoperfusion relates to impaired cerebrovascular auto-regulation.^{12,13} Such impaired auto-regulation may, in turn, make even a normal arterial carbon dioxide tension (PaCO₂) (the major physiological regulator of cerebral blood flow) insufficient to achieve and maintain adequate cerebral perfusion and, consequently, cerebral oxygenation. However, PaCO₂ is a modifiable variable and therefore a potential therapeutic target for the maintenance of cerebral perfusion and oxygenation in resuscitated cardiac arrest patients.⁴

7.3 ***Carbon dioxide and cardiac arrest***

The brain is particularly susceptible to damage following return of spontaneous circulation with reperfusion injury and inflammation both of which may contribute to subsequently increased vascular resistance and sustained hypoperfusion. PaCO₂ is the major determinant of cerebral blood flow in man.^{18,19} An increase in PaCO₂ (hypercapnia) markedly increases cerebral blood flow under normal physiological conditions.⁹ The rapid vasodilatory effect of hypercapnia appears related to changes in arterial pH and cerebral vascular resistance.^{12,20} In addition, elevated PaCO₂ levels are known to have anti-convulsive, anti-inflammatory and anti-oxidant properties, which may attenuate the inflammatory component of reperfusion injury.^{21,22} Conversely, hypocapnia is known to increase neuronal excitability, increase cerebral oxygen consumption, reduce cerebral blood flow and, thereby, potentially worsen reperfusion injury.

In order to understand the effects of elevated PaCO_2 in resuscitated cardiac arrest patients, we conducted a large, multicentre, retrospective observational study. In this study, we evaluated the association of early PaCO_2 values (first 24 hours) with clinical outcomes in 16,542 cardiac arrest patients admitted to 125 Australia and New Zealand ICUs between 2000 and 2011.⁴ In these patients, in keeping with International Liaison Committee on Resuscitation (ILCOR) recommendations, targeting normocapnia is the dominant practice.²³ Our study confirmed that this approach is the standard of care with the greatest proportion of patients achieving such targets. In this population and of relevance to our hypothesis, we found that the occurrence of hypocapnia ($\text{PaCO}_2 < 35$ mmHg) carried a higher mortality rate and a lower likelihood of discharge home for survivors compared with normocapnia (PaCO_2 35-45 mmHg). In contrast, hypercapnia ($\text{PaCO}_2 > 45$ mmHg) was not associated with increased mortality but was independently associated with a 16% increase in the likelihood that a cardiac arrest survivor would be discharged home, thus suggesting both safety and potential neurological benefit. While 'discharged home' does not represent a full assessment of neurological recovery, it is a robust patient-centred endpoint likely to be free from bias and indicative of improved neurological outcome compared with patients discharged to rehabilitation or a nursing facility.

Other observational studies involving adult resuscitated cardiac arrest patients admitted to ICU indicate that hypercapnia is independently associated with improved neurological outcomes among survivors, while hypocapnia is associated with worse neurological outcomes, thus providing further evidence of the likely safety and possible benefit of hypercapnia.^{24,25} For example, to study the independent relationship between PaCO_2 levels in ICU and neurological outcome as assessed by the cerebral performance category (CPC) method, Finnish investigators studied 409 resuscitated cardiac arrest patients admitted to ICU and followed them to 12 months.²⁵ They found, again, that hypercapnia was independently associated with improved neurological outcome, with a 5% increase in the odds of good neurological outcome for every 1 mmHg increase in PaCO_2 above 45 mmHg. Thus, targeting mild hypercapnia and avoiding hypocapnia may be of major importance to cerebral protection and recovery among resuscitated cardiac arrest patients admitted to ICU. However, until recently, there was no direct evidence on the effect of targeted hypercapnia on cerebral oxygenation in resuscitated cardiac arrest patients to provide the additional biological rationale for its therapeutic application.

7.4 ***Mild hypercapnia and cerebral oxygenation***

To address the impact of targeted mild hypercapnia on cerebral oxygenation, we²⁶ performed a prospective double crossover physiological clinical study. We enrolled resuscitated cardiac arrest patients within 36 hours of their cardiac arrest and compared the effect of targeting mild hypercapnia (PaCO_2 50-55 mmHg) to standard care (TN) (PaCO_2 35-45 mmHg) on regional cerebral tissue oxygen saturation (SctO_2) assessed by near infrared spectroscopy. We studied adult resuscitated cardiac arrest patients, with a median time to ROSC of 28 minutes, at a median of 26 hours 30 minutes after cardiac arrest.²⁶ During standard care, at a median PaCO_2 of 37 mmHg, the median near infrared spectroscopy derived right and left frontal lobe SctO_2 was low with a significant proportion of values clearly below normal. However, during targeted mild hypercapnia, at a median PaCO_2 of 52 mmHg, the median SctO_2 increased to normal or just above normal (**Figure 1**). Such increases were substantial in magnitude and

reliably occurred in every patient every time and were not associated with any adverse events.

These findings provide further evidence for the potential role of targeting mild hypercapnia to safely improve cerebral oxygenation, present evidence to justify its study as a means to improve outcomes in resuscitated cardiac arrest patients and have led to a recently completed phase II randomised controlled trial.

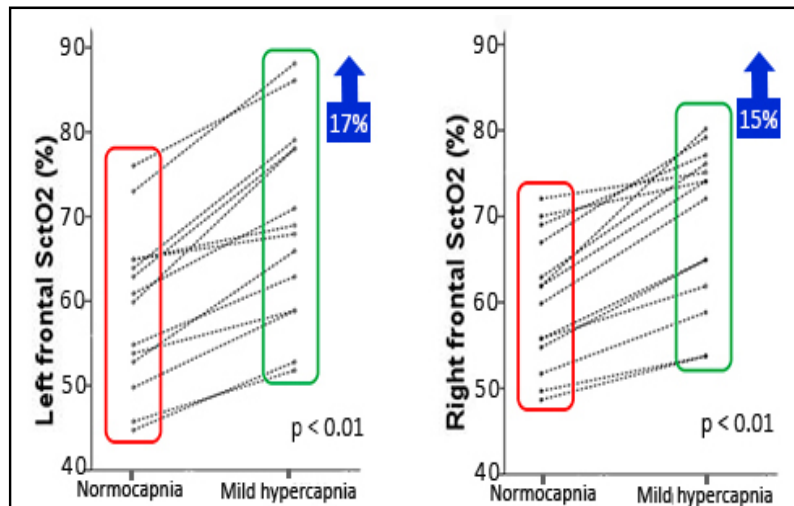


Figure 1: Changes in SctO2 values induced by mild hypercapnia.

7.5 *Phase II multi-centre randomised controlled trial of targeted therapeutic mild hypercapnia*

The proposed pivotal trial follows our completion in late 2015 of a randomised, controlled, parallel group, multicentre, phase II trial.²⁷ The aim of this phase II trial was to determine the preliminary biological efficacy, feasibility, safety of delivering TTMH to resuscitated cardiac arrest patients compared to standard care (TN) for the 24 hours following ICU admission. This study allocated patients to either TTMH (PaCO₂ 50-55 mmHg) or standard care (TN) (PaCO₂ 35-45 mmHg). These targets were deliberately established to avoid episodes of hypocapnia in both arms. In order to achieve a target of 50 patients with full assessment of serum neuron specific enolase levels (baseline, 24 hour, 48 hour and 72 hour), we randomised 86 patients from four ICUs in Australia and New Zealand. Neuron specific enolase is a biomarker of neuronal injury that is released into the bloodstream after injury. Similar to troponin for myocardial infarction, lower concentrations of neuron specific enolase over the first 72 hours following cardiac arrest indicate decreased neuronal injury and are associated with improved neurological outcome.²⁸

For the overall cohort, the median age was 61 years and 79% of patients were male. Of these, 67 (81%) had an out-of-hospital cardiac arrest and 20% an in-hospital cardiac arrest. Their median time from cardiac arrest onset to return of spontaneous circulation was 17 minutes and ventricular fibrillation or ventricular tachycardia was the initial monitored rhythm for 59 (71%) patients. These values are typical of patients admitted to ICU after a cardiac arrest in developed countries. Without differences in ventilation, temperature, or sedation management, we found TTMH significantly attenuated neuron specific enolase release compared with standard care (TN) (**Figure 2**), with an identical pattern for out-of-hospital cardiac arrest patients, thus providing a robust signal of biological efficacy for TTMH.

Moreover, we confirmed that blinding and allocation concealment could be achieved and that patients randomised to TTMH were typically either in the hypercapnic or mild hypercapnic range. Similarly, those allocated to standard care (TN) were typically in the normocapnic range, thus successfully establishing treatment separation between the two groups and protocol adherence (**Figure 3**).

Importantly, patients allocated to either group both avoided episodes of hypocapnia or severe hypercapnia and no clinical adverse events, sudden neurological deterioration, or clinical signs of raised intracranial pressure were reported, supporting the safety of TTMH.

Most importantly at 6 months, overall, 23 (59%) TTMH patients had improved neurological outcomes compared with 18 (46%) standard care (TN) patients. In addition, hospital mortality occurred in 11 (26%) TTMH patients compared with 15 (37%) standard care (TN) patients ($p = 0.31$). Thus, TTMH was associated with a beneficial biological effect (attenuated neuron specific enolase release) and a pattern of improved neurological and clinical outcomes.

This effect was even stronger when only patients with out-of-hospital cardiac arrest (80% of the cohort) were assessed as hospital mortality occurred in 8 (29%) TTMH patients compared with 13 (61%) standard care (TN) patients. In addition, 20 (65%) TTMH patients had improved neurological outcomes compared with 16 (50%) standard care (TN) patients ($p=0.16$). When looked at separately, TTMH treated, out-of-hospital cardiac arrest patients had a very similar pattern of improved neurological outcomes (56% vs 44%), supporting the notion that this intervention may affect neurological recovery irrespective of location of cardiac arrest. Moreover, for this trial alone, which used a cost-free intervention, the estimated average hospital care saving derived from the additional patients who achieved improved neurological outcome after surviving to hospital discharge was AUD\$200,000.

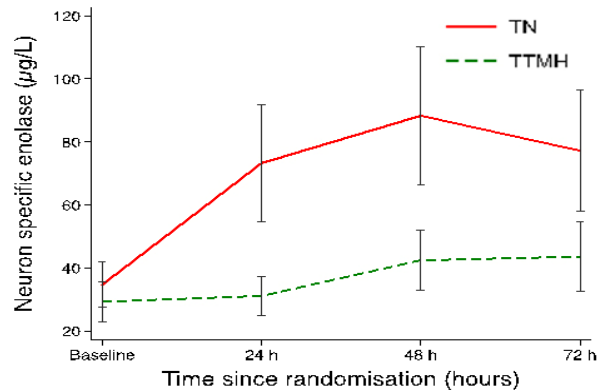


Figure 2: Baseline, 24 hour, 48 hour, and 72 hour mean (SE) neuron specific enolase concentrations for patients allocated to targeted therapeutic mild hypercapnia (TTMH) and standard care (TN). Values are reported as mean (SE).

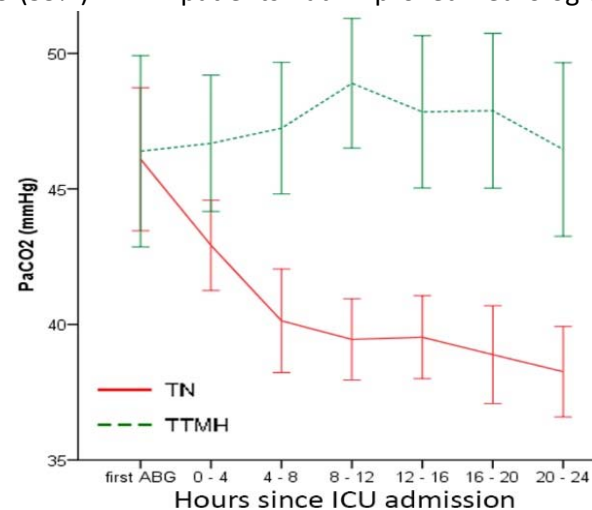


Figure 3: Time course of mean (SD) arterial carbon dioxide tension (PaCO₂) for patients allocated to TTMH and standard care (TN) over the first 24 hours following admission to ICU.

The proposed therapeutic CO₂ target was simple, easy to aim for, with no signs of harm and cost free. Together with our large epidemiological study, double crossover physiological study and phase II trial, there is now epidemiological, biological, physiological, and supportive clinical data suggesting that TTMH can deliver significant outcome improvements in resuscitated cardiac arrest patients admitted to ICU. In their aggregate, these findings strengthen the need to perform a larger phase III trial to address the question of whether targeting mild therapeutic hypercapnia improves patient-centred outcomes in resuscitated cardiac arrest patients admitted to the ICU. Thus, a larger definitive phase III trial is needed now and is uniquely possible here in Australia and New Zealand.

7.6 *TAME Cardiac Arrest Trial significance and knowledge translation*

If this trial demonstrates significantly improved functional outcomes using this TTMH in resuscitated cardiac arrest patients admitted to the ICU, such a finding will rapidly change practice worldwide and positively impact countless cardiac arrest survivors world-wide. Based on conservative estimates from our Phase II trial, in this Phase III trial, we expect to move 35 (8%) patients from 'unfavourable' to 'favourable' neurological outcome. Thus, this trial alone would save AUD\$2.5 million in estimated hospital care costs for such enrolled patients. Such impact would then translate into approximately \$20 million/year in acute care savings and AUD\$11.1 million/year for continuing community-based care in Australia thereafter. Significantly, knowledge of major societal gains will ensure the immediate uptake of this cost-free intervention. The translation of the results into practice nationally and internationally will be facilitated by the investigating team's executive roles within ambulance services, high profile roles within the ANZ ICU clinical trials community and on bodies that influence resuscitation practice, such as the Australian Resuscitation Council, European Resuscitation Congress, and ILCOR. Finally, using the National ANZ ICU database, such uptake will be measurable and centres failing to rapidly adhere to the new protocol identified for detailed follow-up.

7.7 *Study hypothesis*

The hypothesis being evaluated is that, in resuscitated cardiac arrest patients admitted to the ICU, TTMH improves neurological outcome at 6 months as assessed by the Glasgow Outcomes Scale Extended (GOSE) method (Appendix A).

8. STUDY OBJECTIVES

8.1 *Primary objective*

The primary objective of this study is to determine whether targeted therapeutic mild hypercapnia (TTMH) improves neurological outcome at 6 months compared to standard care (targeted normocapnia) (TN).

9. STUDY DESIGN

This is a phase III multi-centre, randomised, parallel-group, controlled trial in resuscitated cardiac arrest patients who are admitted to the intensive care unit.

10. STUDY OUTCOMES

10.1 *Primary outcome*

The primary outcome measure for this study is the proportion of patients with a favourable neurological outcome at 6 months as assessed using the GOSE as previously applied to this population.²⁹ The GOSE uses an 8-level scale from death (1) to upper good recovery (8) and can be administered by proxy or direct patient interview.³⁰ A GOSE outcome is deemed to be favourable if a patient scores ≥ 5 .³⁰

10.2 *Secondary outcomes*

- (i) Mortality at ICU and hospital discharge and at 6 months after randomisation.
- (ii) Functional recovery as measured by the proportion of patients with a favourable functional outcome at 6 months after randomisation as assessed using the modified Rankin scale (mRS)(Appendix B) (a scale from 0 to 6, with a score of ≤ 3 indicating favourable neurological function).^{31,32 32}
- (iii) Cognitive functional recovery assessed at 6 months after randomisation using the Montreal Cognitive Assessment (MoCA-blind).³³⁻³⁵ The MoCA assesses several cognitive domains, including Visuospatial/Executive, Naming, Memory, Attention, Language, Abstraction, Delayed Recall and Orientation (to time and place); Informant Questionnaire on Cognitive Decline (IQCODE); Symbol Digit Modalities Test (SDMT) and 30-second chair test.
- (iv) Quality of life at 6 months after randomisation assessed by the five domains of Mobility, Self-care, Usual Activity, Pain/discomfort, and Anxiety/Depression of the EQ-5D-5L scale.^{36,37} (Landmark quality of life measures are standard measures in large-scale ICU trials and are key secondary end points.^{35,38} These outcome measures for cardiac arrest clinical trials are routinely used and are recommended by international consensus statements.²³
- (v) Safety as determined as the proportion of adverse events occurring between groups as reported by treating clinicians.
- (vi) A health economic assessment will be performed to evaluate differences in costs for hospital length of stay and destination at discharge for patients allocated to TTMH and standard care (TN) for the index cardiac arrest hospital admission. In jurisdictions where patient level data linkage can be obtained (e.g. New South Wales (Aust.) state based hospital registry), we will continue to track patients to look at long-term hospital use and determine pharmaceutical and primary care service utilisation by linking to Medicare and Pharmaceutical Benefits Scheme data after obtaining patient consent.³⁹

10.3 ***Exploratory tertiary outcomes***

- (i) Mortality outcome at 30 days and 2 years* after randomisation.
- (ii) Functional recovery assessed at 30 days using the mRS, and 2 years* assessed using the GOSE and mRS;
- (iii) Quality of life at 6 months and 2 years* after randomisation assessed by the EQ-5D-5L scale.

* 2 years pending funding

11. **STUDY POPULATION**

Patients admitted to the intensive care unit are eligible for recruitment provided all of the inclusion criteria are met:

11.1 ***Inclusion criteria***

1. Adult (age ≥ 18 years or older)
2. Out-of-hospital cardiac arrest of a presumed cardiac or unknown cause
3. Sustained ROSC – defined as 20 minutes with signs of circulation without the need for chest compressions
4. Unconscious (FOUR-score motor response of <4 , not able to obey verbal commands after sustained ROSC) (Appendix C)
5. Eligible for intensive care without restrictions or limitations
6. Within <180 minutes of ROSC

Patients are excluded from the study if one or more of the following exclusion criteria are present:

11.2 ***Exclusion criteria***

1. Unwitnessed cardiac arrest with an initial rhythm of asystole
2. Temperature on admission $<30^{\circ}\text{C}$
3. On ECMO prior to ROSC
4. Obvious or suspected pregnancy
5. Intracranial bleeding
6. Severe chronic obstructive pulmonary disorder (COPD) with long-term home oxygen therapy

12. **RANDOMISATION AND STUDY INTERVENTION**

12.1 ***Care and screening prior to randomisation***

Pre-hospital and pre-ICU based care will be performed in accordance with national, state/territory best practice guidelines and existing local protocols. On arrival to the hospital, clinicians will evaluate the patient's arterial blood gases (ABG) and assess the patient for

eligibility. Fully eligible patients will be randomised and allocated to either the TTMH or standard care (TN) protocol.

12.2 **Randomisation**

Randomisation will be achieved using a minimization algorithm via a password-protected encrypted web based interface incorporating a computer-generated code with permuted blocks. Randomisation will be stratified according to:

- Participating site
and, where applicable:
- Co-enrolment with the EXACT trial (ClinicalTrials.gov - NCT03138005)
- Co-enrolment with the TTM-2 trial (ClinicalTrials.gov - NCT029008303)

Following successful randomisation, each patient will be assigned a unique 'patient study number' and their study intervention allocation will be identified.

12.3 **Study intervention**

Fully eligible patients enrolled into this trial will be allocated to the TTMH protocol or the Standard Care (TN) protocol. Each protocol is described below:

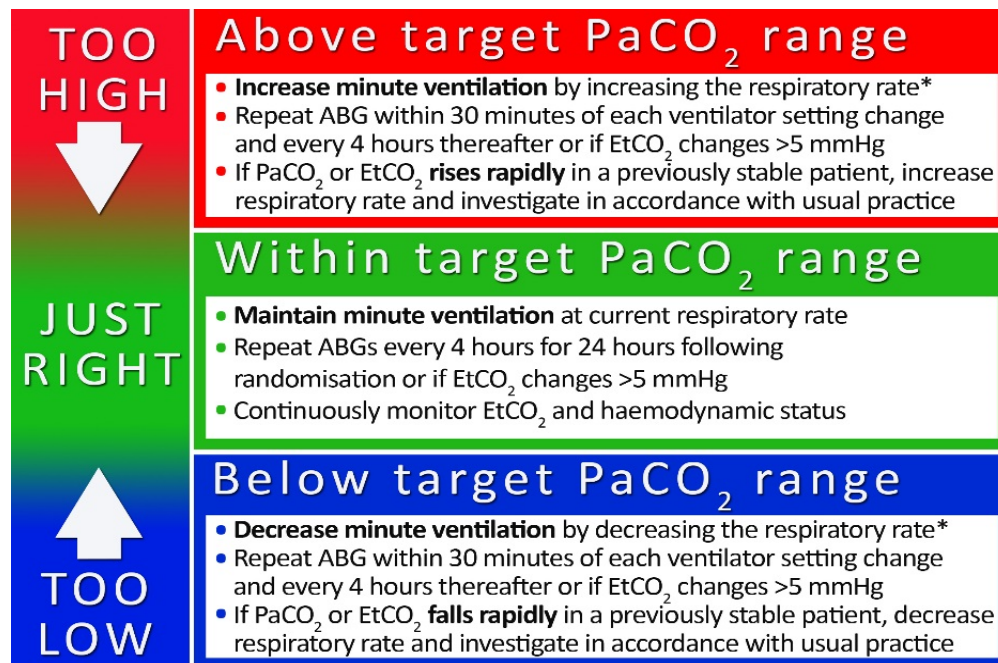
TTMH protocol

Patients allocated to the TTMH protocol will be sedated to achieve deep sedation (a target Richmond Agitation Scale Score (RASS) of -4). ABGs and end-tidal carbon dioxide levels (ETCO₂) will be measured at baseline and then used to guide respiratory rate adjustments of minute ventilation to remain within the target PaCO₂ range of 50-55 mmHg for 24 hours following randomisation. ABGs will be repeated every 4 hours for 24 hours following randomisation or if ETCO₂ values change >5 mmHg (**Figure 4**).

In the event of initial severe metabolic acidosis (pH <7.1 and base excess <-6 mmol/L) the initiation of the TTMH protocol will occur when the acidosis has been corrected. Time to resolve the initial severe metabolic acidosis will be included in the 24-hour intervention period. Additionally, if sedation is insufficient to achieve the target PaCO₂ range of 50-55 mmHg then short-term paralysis is recommended.

Standard Care (TN) protocol

Patients allocated to the standard care (TN) protocol will be managed according to current practice in Australia and New Zealand⁴ and internationally according to ILCOR guidelines which recommend maintaining normocapnia in these patients.²³ They will be sedated to achieve moderate to deep sedation (a target RASS of -4). ABG and ETCO₂ levels will be measured at baseline and then used to guide respiratory rate adjustments of minute ventilation to remain within the target PaCO₂ range of 35-45 mmHg for 24 hours following randomisation. ABGs will be repeated every 4 hours for 24 hours following randomisation or if ETCO₂ values change >5 mmHg (**Figure 4**).



*If an arterial blood gas demonstrates that the PaCO₂ is not within the target range, minute ventilation should be altered initially by a respiratory rate change. Secondary interventions to alter PaCO₂ include the use of sedative agents, muscle relaxants and paralysis as clinically indicated.

Figure 4: Flow chart for the ventilator management of resuscitated cardiac arrest patients allocated to either targeted therapeutic mild hypercapnia or standard care (targeted normocapnia) for the first 24 hours following randomisation.

Importantly, ventilation management for all patients will be guided by ABG data assessed after adjustment to 37°C (alpha-stat)(standard care)⁴⁰ and, to ensure safety, the treating ICU physician can modify patient management, including the use of sedative agents, muscle relaxants and paralysis, as clinically indicated throughout the 24-hour intervention period.

After the 24-hour intervention period, for patients allocated to TTMH, it is recommended that restoration of normocapnia occur slowly over the subsequent 4-hours (study time period 24-28 hours) facilitated by the use of ABG samples and ETCO₂ levels to guide respiratory rate adjustments.

Notably, all other standard hospital practices for the management of resuscitated CA patients will be in accordance with existing best practical protocols and ILCOR recommendations for blood pressure control and targeted temperature management.²³ The decision to discharge the patient from the ICU will be on an individual basis by the patient's treating ICU physician.

12.4 *Care and management after discharge from the ICU*

All post-ICU patient management will be at the discretion of the patient's ward-based treating physicians.

12.5 ***Prognostication***

Evaluating an intervention that cannot be blinded to the treating clinicians, the TAME Cardiac Arrest trial will employ a conservative and strict protocol for neurological prognostication and related decisions regarding limitations in level-of-care to mitigate potential bias.

Prognostication will be performed on all participants still in the ICU at 96 hours after randomisation. The prognostication will be based on the ERC and European Society for Intensive Care Medicine recommendations^{41,42} and performed at approximately 96 hours after randomisation, but may be delayed due to practical reasons (such as weekend or national holiday). The physician performing the prognostication will be a neurologist, intensivist or other specialist experienced in neuroprognostication after cardiac arrest and who has not been involved in patient care. The prognosticator will be blinded for group allocation, but not for relevant clinical data. Prognostication and the potential decision to withdraw active intensive care are closely related but will be considered separate entities.

The result of the prognostication will be categorised as “YES” or “NO”, based on the answer to the question “Does this patient fulfil the TAME Cardiac Arrest trial criteria for a likely poor neurological outcome?”. This assessment will be recorded in the case report form and will be communicated to the treating clinician.

Any decision to withdraw active life support will be made by the treating physicians, together with the patient’s relatives or legal surrogates, as required by local legislation. In making this decision the treating physician may use the information from the prognostication. The blinded external physician will not make any recommendation on withdrawal of life supporting therapies (WLST). Efforts will be made to sufficiently delay prognostication to ensure that any lingering effects of sedative agents will not affect the assessment.

Prognostication will be based on two mandatory, and four optional modalities as outlined below.

Clinical examination - *mandatory*

A clinical examination including assessment of brainstem reflexes and described using the FOUR-score will be performed daily on all patients. An exception to the FOUR-score is that myoclonus will be considered separately in this trial. Absent or extensor motor response to pain (FOUR-score motor response 0-1) at 96h or later in a patient who is considered unaffected by sedative agents, is a prerequisite to consider the neurologic prognosis poor. The bilateral absence of pupillary and corneal reflexes at 96h after CA or later, is a finding indicative of a poor prognosis.

The daily clinical examination by the ICU staff should also include an assessment of status myoclonus (continue and generalised myoclonus persisting for at least 30 minutes) A prospectively documented early status myoclonus (within 48 hours) is indicative of a poor prognosis.

Information from daily examinations including evaluation of status myoclonus should be available to the blinded physician performing the evaluation

Electroencephalogram - *mandatory*

An electroencephalogram (EEG) performed between 48 hours and 96 hours after randomisation will be performed on all participants who survive, and remain unconscious to this point, in line with standard clinical practice. If it is not possible to perform an EEG study in the specified time frame due to practical reasons (such as weekend or national holiday), the EEG should be performed as soon as possible after 96 hours.

An EEG with a highly malignant pattern, and without reactivity to sound and pain is indicative of a poor prognosis.

Brain CT - *optional*

If a brain-CT shows signs of global ischaemic injury, such as: generalised oedema with reduced grey/white matter differentiation and sulcal effacement, this is indicative of a poor prognosis. A CT should be considered in patients who remain unconscious to exclude other pathologies such as intracranial haemorrhage or infarction.

Brain MRI - *optional*

A brain MRI at 3-5 days may be incorporated into prognostication if it has been performed. Signs of global, diffuse, or bilateral multifocal ischaemic lesions is indicative of a poor prognosis.

Neuron specific enolase - *optional*

High levels of NSE are indicative of a poor prognosis. NSE-sampling will not be mandatory, but may be used by sites with experience. If serial samples are available, and these are consistently higher than locally established levels associated with a poor outcome, this may be seen as indicative of a poor outcome. Samples with haemolysis should be disregarded.

Somatosensory Evoked Potential - *optional*

Absent Somatosensory Evoked Potential (SSEP) N20-responses bilaterally may be seen as indicative of a poor prognosis, if SSEP is performed more than 48 hours after randomisation.

12.6 TAME Cardiac Arrest trial criteria for a likely poor neurological outcome

The following criteria, evaluated at 96 hours after randomisation or later, need to be fulfilled to establish a likely poor neurological outcome.

- Absent or extensor motor response to pain
 - AND at least two of the following:
- Bilaterally absent pupillary and corneal reflexes

- Bilaterally absent SSEP N20-responses
- Diffuse anoxic brain injury on computed tomography (CT) or magnetic resonance imaging (MRI)
- Documented status myoclonus within 48 hours or randomisation
- High levels of serum NSE
- An EEG with a highly malignant pattern and without any observed reactivity to sound or pain. Patterns that are considered highly malignant are:
 1. Suppressed background (amplitude <10mV, 100% of the recording) without discharges
 2. Suppressed background with superimposed continuous periodic discharges
 3. Burst-suppression (periods of suppression with amplitude <10mV constituting 50% of the recording) without discharges.
 4. Burst-suppression with superimposed discharges

Note. Participants with suspected ongoing status myoclonus at the time of assessment should still be assessed for a response to pain. An increase in the frequency or amplitude of myoclonic jerks when a painful stimuli is applied should not be considered as a motor response. If the participant localises to pain, the prognosis should not be stated as "likely poor neurological outcome", as this state may be compatible with a diagnosis of Lance-Adams syndrome.

12.7 *Withdrawal of life supporting therapies*

All participants in the trial will be actively treated until 96 hours after randomisation. There will be two exemptions from this rule.

- Participants in whom further treatment is considered unethical due to irreversible organ failure, a documented medical comorbidity, or other reasons.
- Participants in whom brain death is established, however this will be defined as death and not WLST.

The assumption of a poor neurological prognosis alone will not be considered sufficient to employ withdrawal of active intensive care prior to 96 hours after randomisation. After prognostication has been performed, WLST due to a presumed poor prognosis will be allowed if the TAME Cardiac Arrest criteria for a likely poor neurological outcome are fulfilled and all effects of sedation on consciousness are ruled out.

Participants who have an unclear prognosis at 96 hours after randomisation should be re-examined daily and WLST may be considered if neurological function does not improve and, metabolic and pharmacological reasons for prolonged coma are ruled out. If a decision of WLST is made, the time point and the main reasons for withdrawing life-supporting therapies will be recorded. However, supporting therapy may also be continued regardless of the neurological assessment of prognosis, at the discretion of the treating physician.

Brain death

Participants in whom brain death due to cerebral herniation is established will be documented as dead when a conclusive assessment has been made. If death is due to brain death this will be documented.

13. STUDY ASSESSMENTS

13.1 *Assessment summary*

Study participants who survive to hospital discharge will be followed-up to death, 30 days, 6 months and 2 years post-randomisation. At each post-randomisation follow-up a single trained blinded assessor will contact the participant (or a nominated carer) in person (face-to-face), via video-link or telephone and collect information on vital status, quality of life and functional recovery.

Data collected by site research staff and entered directly into an electronic record form will include baseline patient demographics (age, sex, weight); ICU admission diagnosis, CA characteristics (time of event, time to ROSC, initial rhythm, need for defibrillation) and severity of illness score (e.g. Acute Physiological and Chronic Health Evaluation III score or Sequential Organ Failure Assessment Score), and chronic co-morbidities (including chronic respiratory conditions). Information during the first 24 hours will include complete invasive haemodynamic data and ventilation parameters as well as the need for inotrope/vasopressor medications and the type and amount of sedatives used. Data quality and protocol standardisation will be optimised by arranging a start-up meeting and by providing an early monitoring visit and regular feedback to each centre via phone, the trial web-site, and a monthly newsletter. A complete procedures manual will be produced. All study personnel will have 24-hour access to the study coordinating centre to resolve any questions that might arise. Data transfer and storage will follow the requirements of the approving Human Research Ethics Committee (HREC) and site research governance officers.

There is a standard description of all units of measurement in the eCRF. If a trial site uses different units of measurement and this might be a potential source of error, the site investigator should contact the coordinating team to have the data capture module modified. Data not obtainable will be documented as missing and measures to obtain data should not delay intervention or concomitant treatment.

The software for the web-based form will be provided by Spinnaker Software, Wellington, New Zealand. Data from the web-based forms will be migrated to a trial database, which will be handled by the coordinating team.

13.2 *Data collection*

Baseline data

This data will be obtained from emergency medical services/ambulance personal or hospital records.

Pre-randomisation characteristics

- Inclusion and exclusion criteria
- Age
- Sex
- Time and date of ROSC
- Type of temperature management system planned (intravascular or surface cooling)

Pre-hospital data

- Scene of arrest (home, work, public place, nursing facility, other)
- Witnessed arrest (Y/N)
- Bystander CPR (Y/N)
- Bystander defibrillation performed (Y/N)
- First monitored rhythm at arrival of EMS (asystole, PEA, VF, non-perfusing VT, ROSC after bystander defibrillation, unknown (shockable or unshockable))
- Use of active compression-decompression device (None, Yes (LUCAS, Autopulse, manual))
- Number of defibrillations (if applicable)
- Date and time of cardiac arrest
- Time from emergency call
- Estimated time from arrest to advanced life support
- Pre-hospital airway (no, intubated, supra-glottic airway device)
- Amount of Adrenaline (mg)

Background data

- Height
- Weight
- Pre-arrest neurological data (Frailty score)
- Previous
 - percutaneous coronary intervention? (yes/no)
 - coronary artery bypass grafting? (yes/no)
 - implantable cardioverter defibrillator (ICD)? (yes/no)
 - atrial fibrillation or flutter? (yes/no)
 - hypertension with pharmacologic treatment? (yes/no)
- Charlson comorbidity index (Appendix D)

Data on hospital admission

- First recorded tympanic temperature (bilateral, highest value)
- FOUR-score (Appendix C)
- STEMI - New ST-segment elevation ≥ 1 mm in ≥ 2 contiguous ECG leads
- ECG suspicious for acute ischaemia (No, ST-segment depressions [yes/no], T-wave inversions [yes/no], Acute LBBB [yes/no])
- ECG rhythm (sinus / atrial fibrillation or flutter / other)

- Prophylactic antibiotics prescribed [Yes/No/Treatment warranted]
- Shock after admission, BP<90mmHg for at least 30 minutes or the need for supportive measure to maintain a systolic $\geq$ 90mmHg and end-organ hypoperfusion (cool extremities, or urine output of less than 30ml/hr, and a HR >60 beats per minute)

In the ICU

Data during the intervention

- Hourly temperature (bladder)
- Mean arterial pressure, heart rate
- Use of invasive haemodynamic monitoring (No, Thermodilution catheter, Pulmonary artery catheter)
- Cumulative dose of sedatives

Additional temperature measurements

- Between 41 and 48 h after randomisation temperature will be recorded hourly
- Between 49 and 72 h after randomisation temperature will be recorded every four hours

Daily during the ICU stay

- FOUR-score, eye response, motor response, brainstem score, respiratory score
- Need for mechanical circulatory assistance
- Highest body temperature
- Highest level of shivering (BSAS)
- Adverse events
- If trial intervention has discontinued, time of discontinuation and specified reason
- If active intensive care is withdrawn, specify reason
- If dead, specify presumed cause of death, cardiac, cerebral, other

Neurology

- Results of clinical neurological examination
- Results and time of SSEP, MRI, CT, NSE and EEG
- The stated prognosis from the blinded examiner, dichotomised as poor outcome likely (Y/N, based on the definition in the trial protocol) and which criteria are fulfilled

At ICU discharge

- Time and results of coronary angiography
- Time of PCI/open-heart surgery, if performed
- Discharge facility (coronary care unit/general ward/other ICU/dead)
- Results of microbial cultures for patients with sepsis

At hospital discharge

- Discharged to: nursing home/rehabilitation unit/other hospital/home/dead
If dead, presumed cause of death: cardiac/cerebral/multiorgan failure/other
- Probable cause of cardiac arrest
- Organ donation? (No / Donation after cardiac death / Donation after confirmed brain death)

30 days after randomisation

- If the patient is deceased, date of death, presumed cause of death: cardiac/cerebral/other
- mRS assessment

6 months after randomisation

- Survival status obtained from hospital or civil registries
- GOSE and mRS assessment
- Cognitive function tested with MoCA, IQCODE, SDMT, 30-second chair stand test, and health-related quality of life tested with: EQ5D-5L
- Cardiovascular risk factors (Physical activity, HbA1c, cholesterol, blood pressure)

2 years after randomisation (subject to funding)

- Repeat evaluation of GOSE, mRS, EQ5D-5L, cognitive tests, participation in society and cardiovascular risk factors, including physical activity

Planned investigations

Most investigations and interventions are performed at the discretion of the treating physician. However, an EEG performed between 48 hours and 96 hours after randomisation is included in the protocol, since this may be considered standard practice. Reasons for omission will be collected.

Laboratory testing

Laboratory testing will be performed as soon as possible after ROSC and continuously during the ICU-period. All blood gases will be analysed using the alpha-stat method.

- Earliest available blood gas after ROSC: FiO₂, PaO₂, PaCO₂, BE, pH, lactate, glucose.
- Blood gas every four hours during the intervention (FiO₂, PaO₂, PaCO₂, BE, pH, lactate, glucose and insulin dose)
- On admission to ICU (Lowest Thrombocytes, Lowest PaO₂, highest creatinine, highest bilirubin, HbA1c)
- Daily in the ICU (highest creatinine)

Biobank

There is an optional biobank of the TAME Cardiac Arrest trial.

The TAME Participant Information Sheet will include a paragraph describing the optional biobank component and a tick box on the TAME Consent Form will indicate the participant's willingness or not to participate in the biobank.

Participants who consent to be a part the biobank will have blood tissue samples (approximately 6 ml or 1 teaspoon at each time-point) drawn from an existing drip line at randomisation (baseline), 24 hours, 48 hours, and 72 hours after cardiac arrest. Drawn blood samples will be re-identified, coded and labelled at the site level. All blood tissue samples will initially be stored locally prior to being batch transported to, and stored at the Integrated Biobank of Luxembourg (IBBL), Luxembourg. Blood samples may be analysed for routine clinical laboratory measurements (e.g. creatinine) and prognostic biomarkers, including markers of neuronal injury (e.g. neuron specific enolase), cardiac injury (troponin), inflammation (e.g. C-reactive protein, procalcitonin, B-type natriuretic peptide) and mitochondrial content. No analysis of nuclear DNA will be performed within the scope of the trial. Analyses will use available software tools as well as bespoke programming that allows versatility and exploration of new approaches.

Following analysis, all remaining biological samples will be destroyed according to the biobank policy or if the patient withdraws consent for their sample(s) to be included in the biobank analysis. Other than the sample collection and analysis there will be no extra data collection above that already specified for the TAME Cardiac Arrest dataset. No measurements will take place before the end of the trial, and no results from the biobank will be published in the initial manuscript.

Detailed instructions regarding sample collection, sample processing, sample storage and shipment are provided in the study procedures manual.

14. CO-ENROLMENT

14.1 *Co-enrolment statement*

Study participants may be included in any observational trial which does not affect protocol adherence in the TAME Cardiac Arrest trial. Approval for co-enrolment in other trials will be granted by the management committee on a case-by-case basis.

14.2 *Co-enrolment in the EXACT trial*

Reduction of oxygen after cardiac arrest (EXACT)(NCT03138005) is a phase III multi-centre, randomised, controlled trial to determine whether reducing oxygen administration to target a normal level as soon as possible following successful resuscitation from out-of-hospital cardiac arrest, compared to current practice of maintaining 100% oxygen, improves outcome to hospital discharge. Co-enrolment in this trial will be allowed for sites participating in the EXACT trial. However, the option to participate in only the TAME Cardiac

Arrest trial will be retained for sites that are not willing, or able to co-enrol. We consider co-enrolment in EXACT and TAME Cardiac Arrest as an effective utilisation of research resources.

14.3 ***Co-enrolment in the TTM-2 clinical trial***

Targeted Hypothermia versus Targeted Normothermia after Out-of-hospital cardiac Arrest. A Randomised Clinical Trial (TTM-2 Trial (NCT02908308) is a international, multicentre, parallel group, non-commercial, randomized, superiority trial in which a target temperature of 33°C after cardiac arrest will be compared to normothermia with early treatment of fever ($\geq 37^\circ\text{C}$). Co-enrolment in this trial will be allowed for sites participating in the TTM-2 trial. However, the option to participate in only the TAME trial will be retained for sites that are not willing, or able to co-enrol. We consider co-enrolment in TTM-2 trial and TAME Cardiac Arrest as an effective utilisation of research resources.

15. **SAFETY MONITORING AND REPORTING**

It is recognised that the patient population in the ICU will experience a number of aberrations in laboratory values, signs and symptoms due to the severity of the underlying disease and the impact of standard critical medicine therapies. These will not necessarily constitute an adverse event or serious adverse event unless they are considered to be related to study treatment or a concern in the principal investigator's clinical judgement.

In this study, report of adverse events will be restricted to events that are considered to be related to the study intervention (possibly, probably or definitely).

15.1 ***Adverse events***

An adverse event (AE) is any untoward medical occurrence in a clinical trial subject. Untoward medical occurrences are expected in all patients who are resuscitated from cardiac arrest and treated in intensive care. This critically ill group of patients will per definition experience be monitored and treated for untoward medical occurrences, and this is considered standard care. To strike a balance between over-reporting, and maximise the probability of finding any true and important differences only the following will be considered adverse events: .

Specific adverse events:

- Pneumonia (defined as purulent tracheal secretions, a radiographic infiltrate and a decreased P/F ration ($\text{PaO}_2/\text{FiO}_2 < 32 \text{ kPa}$ or $< 240 \text{ mmHg}$))
- Bleeding (defined as moderate (treatment requiring blood transfusion) or severe (substantial haemodynamic compromise requiring treatment) according to the GUSTO* criteria)
- Arrhythmia resulting in haemodynamic compromise
- Cooling device related skin complication

The definition and reporting of serious adverse events is listed below.

*GUSTO investigators. An international randomized trial comparing four thrombolytic strategies for acute

myocardial infarction. *N Engl J Med*, 1993 329(10):673-82

15.2 ***Serious adverse events***

A serious adverse event (SAE) is defined as any adverse event that:

- Results in death
- Is life threatening
- Requires hospitalization or prolongation of current hospitalization
- Results in persistent or significant disability or incapacity

Death is an expected outcome among survivors of cardiac arrest. Approximately 45% of patients will not survive to 6 months, therefore death will not be considered a serious adverse event. Standard care of cardiac arrest patients includes a host of complications that fit the definition of an SAE. Complications potentially attributable to mild hypercapnia primarily include raised intracranial hypertension, arrhythmias and seizures. Despite this, none of these were reported in the phase II trial. To strike a balance between over-reporting, and maximise the probability of finding any true and important differences only the following will be considered serious adverse events:

Specific serious adverse events

- Suspected or confirmed raised intracranial hypertension necessitating normocapnia
- Arrhythmias necessitating normocapnia
- Suspected or confirmed seizures necessitating normocapnia

Other serious adverse events

- Unexpected serious adverse events

15.3 ***Reporting SUSARs***

Any Suspected Unexpected Serious Adverse Reaction (SUSAR) is a medical occurrence that is both serious and unexpected in a clinical subject.

The minimum information to report will include:

- Patient initials and study number
- Nature of the event
- Commencement and cessation of the event
- The principal or co-investigator's opinion of the relationship between the study intervention and the event (not related, possibly related and probably related)
- Whether treatment was required for the event and what treatment was administered.

The coordinating centre staff will be responsible for following-up all SUSARs to ensure all details are available. The coordinating centre is also responsible for alerting other participating sites of the report of a SUSAR as required. It is the responsibility of each principal investigator to inform the local or lead HREC of all SUSAR events which occur at their hospital, in accordance with local requirements. Copies of any reporting and correspondence to and from the local HREC or RGO should also be sent to the coordinating centre.

15.4 *Independent Data and Safety Monitoring Committee*

A DSMC, independent from the coordinating centre and investigators, will perform an ongoing review of predefined safety parameters, study outcomes and overall study conduct. The DSMC will be comprised of experts in clinical trials, biostatistics and intensive care medicine. The DSMC will review all unblinded adverse reactions at predetermined intervals during the study or as deemed appropriate by the DSMC. Full details of the DSMC procedures and processes can be found in the DSMC charter.

15.5 *Study termination*

The study may be terminated at any time at the request of the study management committee, or a regulatory authority, with proper and timely notification of all parties concerned. The local or lead HREC will be informed promptly and the coordinating centre or the investigator will supply reason(s) for the termination or suspension. Otherwise, the study is considered terminated upon completion of all patient treatments and evaluations.

16. CONSENT AND ETHICAL CONSIDERATIONS

16.1 *Ethical conduct of the study*

This study will be performed in accordance with all relevant ethical and regulatory approvals and guidelines laid down by the National Health and Medical Research Council of Australia, the Declaration of Helsinki, its subsequent amendments, and the ICH-GCP guidelines on the ethical conduct of research.

16.2 *Human research ethics committee review*

The protocol for this project will be reviewed by a lead human research ethics committee (HREC). In jurisdictions where single ethical review of multicentre trials is in place, one principal investigator (known as the coordinating investigator) will take responsibility for applying to a lead HREC on behalf of investigators covered by that committee. Each principal investigator will then be responsible for applying for local research governance approval at each participating site. Documentation of the approval of the protocol and the consent documents will be provided to the coordinating centre before the study may begin at any investigative centre.

The coordinating centre will assist with this process by preparing a standard application form (in Australia, the National Ethics Application Form [NEAF] or HREA [equivalent]; in New Zealand, the National Application Form) and template consent documents. In European sites and those outside Europe a standard application form will be submitted at all participating sites. The content and format of the standard information statements and consent forms will be adapted if necessary to comply with local HREC guidelines and requirements. During the trial, any amendment or modification to the study protocol or consent documents will be notified to the HREC by the principal investigator and only implemented on receipt of HREC

approval, unless the change is necessary to eliminate an immediate hazard to patients, in which case the HREC will be informed as soon as possible. The principal investigator will also be responsible for submitting progress reports, adverse event reports, and any other required documentation to the HREC in accordance with their guidelines. Copies of all HREC and research governance officer correspondence will be provided to the coordinating centre together with a copy of the approved consent documents. Copies of the same documents will also be kept with the study investigator files.

16.3 *Informed consent procedures*

Since all patients in the study are unconscious and the study must commence immediately after ICU admission, it is not possible to obtain informed consent prior to enrolment. The ethical issues associated with non-consent randomisation of unconscious patients have been previously considered by Human Research Ethics Committees in each of the participating states. The approach of consent to continue patient/next-of-kin information provision has been accepted by the Australian and New Zealand Ethics Committees in the previous phase II trial cited above. This approach meets the recommendations of the NHMRC guidelines for the conduct of research in this patient group and was used very successfully in the Phase II trial.

16.4 *Confidentiality and privacy*

All patient data pertaining to the study will be stored in a computer database maintaining confidentiality in accordance with local legislation on privacy and use of health data.

To enable follow-up assessment, patient contact details including name, address and telephone numbers will be collected by the site and sent via a secure file transfer process to the coordinating centre of each country. For Australian sites the outcome assessor is located at the Australian co-ordinating centre. For New Zealand sites the outcome assessors will be located at the New Zealand co-ordinating centre. For all other sites these details will be sent to the local/regional coordinating centre or to the lead coordinating centre and performed in accordance with local legislation on privacy and use of health data.

For European sites, patient data will be protected by complying with EU legislation; the Data Protection Act 2018, the EU Data Protection Directive 95/46/EC; the EU ePrivacy Directive 2002/58/EC (as amended, and its successor); and the General Data Protection Regulation (Regulation (EU) 2016/679) ("**GDPR**") and all other applicable law, regulations and codes of conduct in any jurisdiction relating to the processing of Personal Data and privacy; including guidance and codes of practice and the European Data Protection Board or the Article 29 Working Party.

All data collected in the follow-up assessment will be identified by the study number. The follow-up contact details and study data will be kept separately. Study data will be entered into a password protected databased managed by Spinnaker, Wellington, New Zealand. No identifying data will be entered into the database. The contact details and study data will be kept in a locked office at both the study site and coordinating centre.

When archiving or processing data pertaining to the investigator and/or to the patients, the

coordinating centre will take all appropriate measures to safeguard and prevent access to this data by any unauthorised third party.

The investigator will maintain the confidentiality of all study documentation, and take measures to prevent accidental or premature destruction of these documents. The investigator will retain the study documents at least 15 years after the completion or discontinuation of the study. The investigator must notify the study management committee prior to destroying any study essential documents following the study completion or discontinuation. If the investigator's personal situation is such that archiving can no longer be ensured by him/her, the investigator shall inform the study management committee and the relevant records shall be transferred to a mutually agreed upon designee.

If any investigator retires, relocates, or otherwise withdraws from conducting a study, the responsibility for maintaining records may be transferred to the coordinating centre, or another investigator. The coordinating centre must be notified of and agree to the change. All associated documentation must also be updated.

17. STATISTICAL METHODS

17.1 *Sample size calculation*

In our phase II trial, we identified a difference in improved GOSE of 65% v 50% (15% difference) for those allocated to TTMH compared to TN. For the purpose of this study, we will assume a difference of 8% in favourable GOSE.²⁷ This is a conservative estimate at approximately 50% of that seen in our phase II trial.⁴ Moreover, this effect is essentially identical to the effect seen in our observational study of >16,000 patients linking hypercapnia with an increased rate of discharge home. Finally, this difference in outcome is 50% of that reported by Finnish investigators in a one year follow up of hundreds of patients after cardiac arrest.²⁵ Our definitive phase III trial, therefore, will require 812 patients per arm (total of 1624 patients) to achieve a 90% power to detect such a difference at an α of 0.05. This number has been rounded up to 1,700 to account for loss to follow-up. All previous ANZICS Clinical Trial Group studies have had a loss to follow rate below 5%.

17.2 *Statistical analysis plan*

All analyses will be conducted on an intention to treat basis using standard statistical methods for categorical and continuous data. Analyses will also be conducted in pre-defined subgroup pairs. A formal statistical analysis plan will be agreed upon and placed in the public domain before the study database is locked for the analysis of the primary outcome.

17.3 *Interim analysis*

An independent Data Safety Monitoring Committee will be formed to review pre-defined adverse events and to perform the first interim analysis after 50% enrolment.

18. QUALITY ASSURANCE

The study will be conducted in accordance with the ICH Guidelines for Good Clinical Practice and with all relevant local and national regulations.

18.1 *Investigator file*

A file containing essential documents as outlined in the ICH guidelines for Good Clinical Practice will be maintained at each participating site. A copy of the same documents will be held at the coordinating centre.

18.2 *Study materials*

A comprehensive guide to the data collection with definitions and rationale will be provided together with a paper version of the data collection forms. A guide to using the web based data management system is also provided in the guideline for CRF completion. All of these documents are available in PDF format for printing from the study website as required. These aim to assist the research coordinator to ensure high-quality data collection and data entry.

18.3 *Initiation*

All site personnel will receive training, explaining the protocol and procedures, use of the web-based randomisation system and electronic case report forms (eCRF). The Site 'initiation visit' will be conducted by teleconference or video conference or face-to-face meeting at the participating site. Written and electronic materials will be supplied for study staff and for the education of clinical ICU staff at each participating site.

18.4 *Monitoring during the study*

A coordinating centre appointed monitor will visit each study centre on several occasions during the recruitment phase. This will ensure that the study is conducted according to the protocol, good clinical practice guidelines and relevant regional regulatory requirements. The study monitor will review study records for source document verification, confirm valid patient consents, data quality, and the completeness of follow-up. In addition, the study may also be audited by local or national regulatory authorities. Access to source documents and other study files will be made available at all study centres for monitoring and audit purposes.

The coordinating centre team will conduct regular remote monitoring on the web-based database by applying validation and consistency rules and with regular data cleaning to ensure the integrity of the study data.

18.5 *Close out*

At completion of the study, the monitor will ensure that there are plans in place for the long-term storage of all the relevant data and source documentation (for 15 years).

19. PUBLICATIONS AND REPORT

The trial will be analysed by independent statistician(s) and the results interpreted by the management group. The analysis will be performed 6 months after inclusion of the last patient. The analysis process will be performed with the allocation code unbroken and with the trial arms only known as A and B. Two abstracts will be prepared before the allocation code is broken, with the different arms inter-changed (one assuming arm A is normocapnia, and the other assuming arm B is targeted therapeutic mild hypercapnia). All authors must approve both versions before the code is broken. The final manuscript will be submitted to a peer-reviewed international journal. Authorship will be granted using the Vancouver definitions and depending on personal involvement and fulfilment of the author's respective roles. The author list will include the management group members, national investigators and additional names. Centres recruiting >30 participants will be entitled to one name, >60 two names, >100 three names, >150 four names, >220 five names in the author list (additional names). After the author list there will be added: "and the TAME Cardiac Arrest trial group" and a reference to an appendix with all sites, site investigators and number of participants enrolled. The main publication will report the primary and secondary outcomes. In doing so, survival, functional outcome and HRQoL will be reported. Exploratory outcomes will, due to complexity of reporting be submitted to a peer-reviewed journal as a separate manuscript, as will the results from the 2-year follow-up. A detailed authorship plan will be decided upon after the first interim analysis.

20. INVESTIGATOR RESPONSIBILITIES

The trial site investigator is responsible for:

- Screening and listing eligible patients
- Performing randomisation
- Achieving arterial carbon dioxide control according to allocation group
- Ensuring that achievement of arterial carbon dioxide target is feasible within 2 hours of randomisation
- Maintaining arterial carbon dioxide targeting according to allocation group
- Collection and reporting of data according to the trial protocol and electronic case report form (eCRF)
- Obtaining written informed consent from patients whom regain consciousness
- Performing and reporting follow-up according to the trial protocol and the eCRF

The national investigator is responsible for:

- Coordination of national sites
- Representing national sites in the management group
- Reviewing reasons for potential incomplete screening and randomisation at national sites
- Ethical Review Board - application and approval
- Dissemination of protocols and updates to sites
- Proposing suitable candidates for vacant site investigator positions

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22. APPENDICES

22.1 *Appendix A – The Glasgow Outcome Scale Extended (GOSE) Score*

Following assessment select the most appropriate category score.

Dead	1
Vegetative state (VS)	2
Lower severe disability (Lower SD)	3
Upper severe disability (Upper SD)	4
Lower moderate disability (Lower MD)	5
Upper moderate disability (Upper MD)	6
Lower good recovery (Lower GR)	7
Upper good recovery (Upper GR)	8

22.2 *Appendix B – Modified Rankin Score (mRS)*

Following assessment select the most appropriate category score.

Score	Description
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderate severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Death

22.3 **Appendix C – The Four Score**

Eye response

Eyelids open and tracking, or blinking on command	4
Eyelids open but not tracking	3
Eyelids closed but open to loud voice	2
Eyelids closed but open to pain	1
Eyelids closed with pain	0

Motor response

Makes sign (thumbs-up, fist, other)	4
Localising to pain	3
Flexion response to pain	2
Extension response to pain	1
No response to pain	0
Generalised myoclonic status	0

Brainstem response

Pupil reflexes present, corneal reflexes present and cough present	4
One pupil wide and fixed, corneal reflexes present and cough present	3
Pupil reflexes absent, corneal reflexes present	2
Pupil reflexes present, corneal reflexes absent	2
Pupil reflexes absent, corneal reflexes absent, cough present	1
Pupil reflexes absent, corneal reflexes absent, cough absent	0

Breathing

Not intubated with regular breathing	4
Not intubated with Cheyne- Stokes type of breathing	3
Not intubated with irregular breathing	2
Not intubated with apnea	0
Intubated with breathing above ventilator rate	1
Intubated with breathing at ventilator rate	0

In contrast to previous trials on cardiac arrest, the TAME-Cardiac Arrest trial will not use the Glasgow Coma

Score in any reporting. There are several reasons for this:

- The FOUR-score offers a less equivocal inclusion criteria as a "fist" or "thumbs-up" response is required for a motor score of 4. This also applies to the definition of awakening which is made clearer by requiring a limb movement rather than only eye movements.
- The FOUR-score can be rated in the intubated patient

Links:

[Figure of FOUR-score from Iyer et.al \[34\]](#)

[FOUR-score calculator](#)

22.4 **Appendix D – Charlson comorbidity index**

Age _____ in years Serum albumin _____ g/dL

One point

- Myocardial infarction (history, not ECG changes only)
- Congestive heart failure
- Peripheral disease (includes aortic aneurysm ≥ 6 cm)
- Cerebrovascular disease: CVA with mild or no residua or TIA
- Dementia
- Chronic pulmonary disease
- Connective tissue disease
- Peptic ulcer disease
- Mild liver disease (without portal hypertension, includes chronic hepatitis)
- Diabetes without end-organ damage (excludes diet-controlled alone)

Two points

- Hemiplegia
- Moderate or severe renal disease
- Diabetes with end-organ damage (retinopathy, neuropathy, nephropathy, or brittle diabetes)
- Tumor without metastasis (exclude if >5 year from diagnosis)
- Leukaemia (acute or chronic)
- Lymphoma

Three points

- Moderate or severe liver disease

Six points

- Metastatic solid liver disease
- AIDS (not just HIV positive)