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

NHMRC
Australian Government
National Health and Medical Research Council

anzic
research centre

Aus-ROC
Australian Resuscitation Outcomes Consortium

HRB
Health Research Board

Irish Critical Care Clinical Trials Network

ANZICS
TAME Steering Committee

- Dr Glenn Eastwood, CPI
- Prof Rinaldo Bellomo
- Prof Alistair Nichol
- A/Prof Niklas Nielsen
- Prof Stephen Bernard
- A/Prof Carol Hodgson
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- Ms Bridget Ady
- Dr Kate Ainscough
- Ms Vanessa Singh
- Mr Tony Trapani
- Dr Ciara Fahey

CPI E: glenn.eastwood@austin.org.au
The ripple effect of acute neurological injury following cardiac arrest: a reflection
Glenn M Eastwood

TO THE EDITOR: Recently, I found myself at the bedside of a young man in the intensive care unit. I saw a lot of myself in him. We are both husbands. We both are fathers of two young children, a boy and a girl. However, when he was admitted to the ICU at 7 pm the previous night, I was at home with my family. It was now the next morning.

He was admitted to the ICU after an out-of-hospital cardiac arrest. His heart had stopped beating for about 17 minutes. The progress notes described a familiar course of events: sudden collapse, bystander cardiopulmonary resuscitation, airway management, defibrillation and coronary angiography. However, recurring in my mind were thoughts of what now, what next; thoughts likely to be shared by his wife and family.

Cardiac arrest itself heralds the onset of cellular injury in the heart and brain. After the return of spontaneous circulation, the pathophysiological onslaught of ischaemia-reperfusion injury is set in motion. Initial therapeutic interventions are applied to restore haemodynamic and physiological normality and stability. However, to a large extent, successful restoration of cardiac function does not determine hospital discharge destination or the ensuing quality of life. Typically, episodes of hypoxia-ischaemia result in acute neurological injury and such injury has the most profound effects on immediate, short-term and long-term quality-of-life outcomes. Notably, cardiac arrest survivors exhibit dramatic fluctuations in mood, a loss of executive cognitive function, and often a lack of the ability to socialise independently.

To date, the application of therapeutic hypothermia after cardiac arrest has not afforded the neurological protection or mortality benefits hoped for. Furthermore, despite our best efforts, over the past decade the Australian and New Zealand ICU mortality rate for cardiac arrest patients has essentially remained unchanged, at 46% in 2003 and 48% in 2012. Therefore, in the pursuit of evidence to improve neurological and quality-of-life outcomes, we are obligated to continue to critically appraise our current interventions and to seek novel therapeutic interventions for cardiac arrest patients admitted to our ICUs.

Over the following 6 days, I went to work, I played with my children and I enjoyed family time. He did not. He remained in the ICU with an admission prolonged by agitated delirium. Today, he is convalescing on the ward. He appears calm and is somewhat circumspect but does not recall the past 6 days. I suspect that although he is conscious, and I do. While our paths may never again cross, the ripple effect of our brief interactions will be long-lasting.

Glenn M Eastwood, ICU Research Manager
1 Department of Intensive Care, Austin Health, Melbourne, VIC, Australia.
2 School of Nursing and Midwifery, Faculty of Health, Deakin University, Melbourne, VIC, Australia.

glenn.eastwood@austin.org.au

Cerebral impact

• Cerebral hypoperfusion and cerebral hypoxia continue after ROSC.

Blue = low-perfusion
Death in ICU

![Graph showing delays between ICU admission and death (days)]
Response & resuscitation

CARDIAC ARREST SYSTEM

SETTING

AMBULANCE DELIVERED CARE

Early recognition and call for help
Early CPR
Post-resuscitation care

HOSPITAL CARE

Early defibrillation

OBJECTIVE

INITIAL SURVIVAL

LONG TERM SURVIVAL
Post resuscitation
Improving cardiac arrest outcomes
Cardiac arrest research

Cardiac Arrest

X → ED → ICU → Hospital → 30 d → 6 mth → Years+

Pre-hospital → Hospital → Post-hospital
Cardiac arrest research

Cardiac Arrest

X → ED → ICU → Hospital → 30 d → 6 mth → Years+

Pre-hospital →
Cardiac arrest research

Cardiac Arrest

X → ED → ICU → Hospital → 30 d → 6 mth → Years+

Pre-hospital →

GoodSAM
Cardiac arrest research

Cardiac Arrest

X → ED → ICU → Hospital → 30 d → 6 mth → Years+

Pre-hospital →

GoodSAM

Your nearest AED is located at

ICU, Emergency Department (ED), Hospital, 30 days (30 d), 6 months (6 mth), Years+ (Years).
Cardiac arrest research

Cardiac Arrest

Pre-hospital →

X → ED → ICU → Hospital → 30 d → 6 mth → Years+

GoodSAM
Cardiac arrest research

Cardiac Arrest

X → ED → ICU → Hospital → 30 d → 6 mth → Years'

Pre-hospital →

GoodSAM

Your nearest AED is located at

Fire Station Car Park

HICA Paramedic
A Randomized Trial of Epinephrine in Out-of-Hospital Cardiac Arrest


Table 1. Characteristics of the Patients at Baseline.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Epinephrine (N=4913)</th>
<th>Placebo (N=3999)</th>
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</thead>
<tbody>
<tr>
<td>Mean age ±SD — yr</td>
<td>69 ±16.6</td>
<td>69 ±16.4</td>
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<tr>
<td>Sex — no. (%) [9]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>2689 (55.0)</td>
<td>2584 (64.6)</td>
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<tr>
<td>Female</td>
<td>1224 (25.0)</td>
<td>1415 (35.4)</td>
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<tr>
<td>Initial cardiac rhythm — no. [9]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shockable</td>
<td>779 (15.2)</td>
<td>748 (18.7)</td>
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<tr>
<td>Ventricular fibrillation</td>
<td>716 (14.5)</td>
<td>684 (17.1)</td>
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<tr>
<td>Pulseless ventricular tachycardia</td>
<td>25 (0.5)</td>
<td>20 (0.5)</td>
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<tr>
<td>Not otherwise identified with AED</td>
<td>20 (0.4)</td>
<td>44 (1.1)</td>
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<tr>
<td>Nonshockable</td>
<td>3143 (63.8)</td>
<td>3181 (79.5)</td>
</tr>
<tr>
<td>Asystole</td>
<td>2135 (43.2)</td>
<td>2194 (54.9)</td>
</tr>
<tr>
<td>Pulseless electrical activity</td>
<td>955 (19.3)</td>
<td>937 (23.4)</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>70 (1.4)</td>
<td>16 (0.4)</td>
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<tr>
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<td>1 (&lt;0.1)</td>
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<tr>
<td>Medical cause</td>
<td>3656 (91.1)</td>
<td>3691 (92.3)</td>
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</table>

DOI: 10.1056/NEJMoa1806842
A Randomized Trial of Epinephrine in Out-of-Hospital Cardiac Arrest


Table 1. Characteristics of the Patients at Baseline.

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<th>Characteristic</th>
<th>Epinephrine (N=4813)</th>
<th>Placebo (N=3999)</th>
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<tr>
<td>Mean age ±SD — yr</td>
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<td>69 ±16.4</td>
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<tr>
<td>Sex — no. [%]</td>
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<td></td>
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<tr>
<td>Male</td>
<td>2609 (54.0)</td>
<td>2584 (64.6)</td>
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<tr>
<td>Female</td>
<td>1204 (25.0)</td>
<td>1415 (35.4)</td>
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<tr>
<td>Initial cardiac rhythm — no. [%]</td>
<td></td>
<td></td>
</tr>
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<tr>
<td>Not otherwise identified with AED</td>
<td>29 (0.6)</td>
<td>44 (1.1)</td>
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<tr>
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<td>3181 (79.5)</td>
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<tr>
<td>Asystole</td>
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<tr>
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<td>39 (0.8)</td>
<td>34 (0.8)</td>
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<td>2 (&lt;0.1)</td>
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<tr>
<td>Not identified</td>
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<td>69 (1.7)</td>
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<td>Cause of cardiac arrest — no. [%]</td>
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<tr>
<td>Medical cause</td>
<td>3456 (31.1)</td>
<td>3691 (32.3)</td>
</tr>
</tbody>
</table>

Score on Modified Rankin Scale

- Placebo Group:
  - 0: 15, 1: 10, 2: 29, 3: 20, 4: 8, 5: 8, 6: 3904

- Epinephrine Group:
  - 0: 12, 1: 17, 2: 23, 3: 35, 4: 12, 5: 27, 6: 3881

Figure 2. Survival with a Favorable Neurologic Outcome at Hospital Discharge.

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A Randomized Trial of Epinephrine in Out-of-Hospital Cardiac Arrest


<table>
<thead>
<tr>
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<td>Sex — no. (%)</td>
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<td></td>
</tr>
<tr>
<td>Not identified</td>
<td>93 (2.3)</td>
<td>69 (1.7)</td>
</tr>
<tr>
<td>Missing data</td>
<td>3634 (91.1)</td>
<td>3695 (93.3)</td>
</tr>
</tbody>
</table>

Figure 2. Survival with a Favorable Neurologic Outcome at Hospital Discharge.

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Cardiac Arrest research

Cardiac Arrest

X → ED → ICU → Hospital → 30 d → 6 mth → Years+

Hospital
Cardiac arrest research

Cardiac Arrest

X → ED → ICU → Hospital → 30 d → 6 mth → Years

Hospital
Cardiac arrest research

Cardiac Arrest

X ➔ ED ➔ ICU ➔ Hospital ➔ 30 d ➔ 6 mth ➔ Years^
Cardiac arrest research

Cardiac Arrest

X → ED → ICU → Hospital → 30 d → 6 mth → Years+

Hospital

Neuroprotective drugs after cardiac arrest

- Epo: Positive experimental results, encouraging preliminary clinical results, negative phase III RCT
- Exenatide: Positive experimental results, encouraging preliminary clinical results, negative phase III RCT
- Ciclosporin: Positive experimental results, encouraging preliminary clinical results, negative phase III RCT
- Xenon: Positive experimental results, positive phase III results, phase III required

Fig. 4 Neuroprotective drugs recently investigated for the treatment of post-cardiac arrest syndrome.
Cardiac arrest research

Cardiac Arrest

X → ED → ICU → Hospital → 30 d → 6 mth → Years+

Hospital

Neuroprotective drugs after cardiac arrest

- **Epo**
  - Positive preclinical results
  - Encouraging preliminary clinical results
  - Negative phase III RCT
  - Carrió A et al. JACC 2016

- **Exenatide**
  - Positive preclinical results
  - Encouraging preliminary clinical results
  - Negative phase III RCT

- **Ciclosporin**
  - Positive preclinical results
  - Encouraging preliminary clinical results
  - Negative phase III RCT
  - Arpaia L et al. JAMA Cardiology 2016

- **Xenon**
  - Positive preclinical results
  - Positive phase I trials
  - Phase III required
  - On the way

Fig. 4 Neuroprotective drugs recently investigated for the treatment of post-cardiac arrest syndrome.
MILD THERAPEUTIC HYPOTHERMIA TO IMPROVE THE NEUROLOGIC OUTCOME AFTER CARDIAC ARREST

THE HYPOTHERMIA AFTER CARDIAC ARREST STUDY GROUP*

Figure 1: Brainstem Temperature in the Normothermia and Hypothermia Groups. The bars indicate the 25th percentile in the normothermia group and the 75th percentile in the hypothermia group. The target temperature in the hypothermia group was 32°C to 34°C, and the duration of cooling was 24 hours. Only patients with recorded temperatures were included in the analysis.
MILD THERAPEUTIC HYPOTHERMIA TO IMPROVE THE NEUROLOGIC OUTCOME AFTER CARDIAC ARREST

THE HYPOTERMIA AFTER CARDIAC ARREST STUDY GROUP

Figure 1: Bispectral Temperatures in the Normothermia and Hypothermia Groups. The bars indicate the 75th percentile in the normothermia group and the 25th percentile in the hypothermia group. The target temperature in the hypothermia group was 32°C to 34°C, and the duration of cooling was 24 hours. Only patients with recorded temperatures were included in the analysis.

Figure 2. Cumulative Survival in the Normothermia and Hypothermia Groups. Censored data are indicated by tick marks.
Temperature targets in 2013

Targeted Temperature Management
at 33°C versus 36°C after Cardiac Arrest

Figure 1. Body Temperature during the intervention period.
Temperature targets in 2013

Targeted Temperature Management at 33°C versus 36°C after Cardiac Arrest

Figure 1. Body Temperature during the Intervention Period.

Figure 2. Probability of Survival through the End of the Trial.

Shown are Kaplan–Meier estimates of the probability of survival for patients assigned to a target temperature of either 33°C or 36°C and the number of patients at risk at each time point. The P value was calculated by means of Cox regression, with the effect of the intervention adjusted for the stratification variable of study site.
Targeted Temperature Management at 33°C versus 36°C after Cardiac Arrest

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Cardiac arrest research

Cardiac Arrest

X → ED → ICU → Hospital → 30 d → 6 mth → Years+

Post-hospital
Cardiac arrest research

Cardiac Arrest

X → ED → ICU → Hospital → 30 d → 6 mth → Years\(^+\)

Post-hospital
Cardiac arrest research

Cardiac Arrest

X → ED → ICU → Hospital → 30 d → 6 mth → Years

Post-hospital
Cardiac arrest research

Cardiac Arrest

X → ED → ICU → Hospital → 30 d → 6 mth → Years+

Post-hospital
Cardiac arrest research

Cardiac Arrest

X → ED → ICU → Hospital → 30 d → 6 mth → Years⁺

Post-hospital
Outcomes across ANZ for OHCA

![Graph showing mortality rates for hospital and ICU from 2003 to 2012.](image)

<table>
<thead>
<tr>
<th>Year</th>
<th>Hospital Deaths</th>
<th>ICU Deaths</th>
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<tbody>
<tr>
<td>2003</td>
<td>665</td>
<td>489</td>
</tr>
<tr>
<td>2004</td>
<td>752</td>
<td>592</td>
</tr>
<tr>
<td>2005</td>
<td>852</td>
<td>676</td>
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<td>2006</td>
<td>802</td>
<td>644</td>
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<td>2007</td>
<td>863</td>
<td>711</td>
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<td>2008</td>
<td>905</td>
<td>733</td>
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<td>2009</td>
<td>947</td>
<td>774</td>
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<td>2010</td>
<td>1041</td>
<td>888</td>
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<td>2011</td>
<td>1017</td>
<td>851</td>
</tr>
<tr>
<td>2012</td>
<td>1019</td>
<td>872</td>
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</table>

**Figure 1.** Hospital and ICU Mortality, 2003–2012.

Shown are hospital and ICU mortality among patients with cardiac arrest who were admitted to ICUs in Australia and New Zealand between 2003 and 2012. Error bars indicate 95% confidence intervals. Data are from the Australian and New Zealand Intensive Care Society Adult Patient Database.
• **Arterial carbon dioxide** ($\text{PaCO}_2$) is the major physiological controller of cerebral blood flow.
The new approach ... VENTILATION

• **Targeting mild hypercapnia** may be sufficient to improve cerebral perfusion, and consequently, cerebral oxygenation.

• **PaCO\textsubscript{2}** is a highly monitored clinical parameter in the intensive care setting, particularly so for ventilated patients.

• **PaCO\textsubscript{2}** is a modifiable component of patient care.
Research Program

• Compared with normocapnia, hypocapnia associated with worse outcomes and hypercapnia associated with a greater likelihood of discharge home among survivors.

Observational cohort study

Phase II pilot study

• Determined preliminary biological, efficacy, feasibility and safety of delivering mild hypercapnia compared to normocapnia

Prospective double crossover study

• Demonstrated the relationship between mild hypercapnia and cerebral oxygenation: every time CO₂ went up cerebral oxygenation went up!

Phase III multinational RCT
Management overview

TAME Steering Committee

Irish Critical Care Clinical Trials Network

PM E: kate.ainscough@ucd.ie

PM E: bridget.ady@monash.edu
Sample & eligibility

1700 adult resuscitated OHCA patients

**Inclusion criteria**

1. **Adult** (age 18 years or older)
2. **OHCA** of a presumed cardiac or unknown cause
3. Sustained ROSC (≥20 mins. without chest compressions)
4. Unconscious (not obeying verbal command)
5. Eligible for ICU admission without restriction
6. Within 3 **hours from ROSC**
Sample & eligibility

1700 adult resuscitated OHCA patients

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3. Sustained ROSC (≥20 mins. without chest compressions)
4. Unconscious (not obeying verbal command)
5. Eligible for ICU admission without restriction
6. Within 3 **hours from ROSC**

**Exclusion criteria**

1. Unwitnessed CA with an initial rhythm of asystole
2. Temperature on admission <30°C
3. On ECMO prior to ROSC
4. Obvious or suspected pregnancy
5. **Suspected or confirmed intracranial bleeding**
6. **Severe COPD with long-term home oxygen therapy**
1700 adult resuscitated OHCA patients

Patient flow

Cardiac arrest → Target PaCO₂ as per treating clinician (while ventilated)

Intervention → 6 mth GOSE

admission/Randomisation

X → O → O → // → // → Star

Pre-ICU → ICU → Hospital → Out of hospital
1700 adult resuscitated OHCA patients

Intervention

Cardiac arrest → X → Pre-ICU → ICU → Hospital → Out of hospital

admission/ Randomisation → Intervention → Target PaCO₂ as per treating clinician (while ventilated)

6 mth GOSE
**Intervention**

1700 adult resuscitated OHCA patients

**PaCO₂ target**
- 35 – 45 mmHg or 50 – 55 mmHg
- 4.4 – 6.0 kPa (TN)
- 6.6 – 7.3 kPa (TTMH)

for 24 h after randomization during mechanical ventilation

**6 mth GOSE**
1700 adult resuscitated OHCA patients

Intervention

Cardiac arrest → X → O → O → // → // → 6 mth GOSE → Out of hospital

admission/ Randomisation

Intervention

Target PaCO₂ as per treating clinician (while ventilated)

Pre-ICU → ICU → Hospital
Outcomes & assessments

Outcomes

• Primary
  • Favourable GOSE at 6 months in survivors

• Secondary
  • Mortality
  • Functional / Neurological
  • QOL
  • Safety & $$

Patient
Outcomes & assessments

Outcomes

- **Primary**
  - Favourable GOSE at 6 months in survivors

- **Secondary**
  - Mortality
  - Functional / Neurological
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  - Safety & $$

<table>
<thead>
<tr>
<th>Patient</th>
<th>Outcomes</th>
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<tr>
<td>8</td>
<td>Upper Good Recovery</td>
</tr>
<tr>
<td>7</td>
<td>Lower Good Recovery</td>
</tr>
<tr>
<td>6</td>
<td>Upper Moderate Disability</td>
</tr>
<tr>
<td>5</td>
<td>Lower Moderate Disability</td>
</tr>
<tr>
<td>4</td>
<td>Upper Severe Disability</td>
</tr>
<tr>
<td>3</td>
<td>Lower Severe Disability</td>
</tr>
<tr>
<td>2</td>
<td>Vegetative State</td>
</tr>
<tr>
<td>1</td>
<td>Dead</td>
</tr>
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Outcomes & assessments

### Outcomes

**Primary**
- Favourable GOSE at 6 months in survivors

**Secondary**
- Mortality
- Functional / Neurological
- QOL
- Safety & $$

### Favourable GOSE at 6 months in survivors

<table>
<thead>
<tr>
<th>Outcome</th>
<th>GOSE Score</th>
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<td>Lower Severe Disability</td>
<td>3</td>
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<tr>
<td>Vegetative State</td>
<td>2</td>
</tr>
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<td>Dead</td>
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Outcomes & assessments

• Primary
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<th>Outcome Level</th>
<th>Description</th>
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<tr>
<td>4</td>
<td>Upper Severe Disability</td>
</tr>
<tr>
<td>3</td>
<td>Lower Severe Disability</td>
</tr>
<tr>
<td>2</td>
<td>Vegetative State</td>
</tr>
<tr>
<td>1</td>
<td>Dead</td>
</tr>
</tbody>
</table>

Favourable

Unfavourable
Outcomes & assessments

### Outcomes

- **Primary**
  - Favourable GOSE at 6 months in survivors
- **Secondary**
  - Mortality
  - Functional / Neurological
  - QOL
  - Safety & $$$

### Neurological assessment

- **Daily (0-7 days)**
  - 4-score (eye, motor, brainstem)
  - Seizures, shivering
- **@ 96 h neuro-prognostication**
  - Mandatory
    - Clinical assessment
    - EEG
  - Optional
    - CT, MRI, NSE, SSEPs
Biobank & co-enrolment

- Baseline, 24, 48 & 72 h
- Neurological biomarkers
- Cardiac injury
- Inflammatory
Biobank & co-enrolment

**Biobank**
- Baseline, 24, 48 & 72 h
- Neurological biomarkers
- Cardiac injury
- Inflammatory

**Co-enrolment**
- Observational studies
  - Likely ‘yes’, please let us know.
- Interventional studies
  - Likely YES - just be mindful of intervention and/or POM impact

**Patient**
Randomisation, data collection & support

Web-based randomisation & data collection

- **Online randomisation**
  - Via web + easy
  - Can occur in ED/ICU

- **Electronic CRF**
  - CA characteristics
  - Intervention period
  - Hospital outcomes
  - Primary outcome
  - Long-term follow-up

Data
Randomisation, data collection & support

Web-based randomisation & data collection

- Online randomisation
  - Via web + easy
  - Can occur in ED/ICU

- Electronic CRF
  - CA characteristics
  - Intervention period
  - Hospital outcomes
  - Primary outcome
  - Long-term follow-up

Data

Coordination & support

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Study update

24 / 1700 & climbing

13 active sites from 4 countries

TAME TIP:
Engage with ED & Educate ICU !!