SUPPLEMENT 1 – POLAR TRIAL PROTOCOL, STATISTICAL ANALYSIS PLAN, AND DATA SAFETY MONITORING COMMITTEE STOPPING RULES AND REPORTS

Supplement to:


Contents:

1. ORIGINAL PROTOCOL, PUBLISHED PROTOCOL, FINAL PROTOCOL, AND SUMMARY OF AMENDMENTS
2. PUBLISHED STATISTICAL ANALYSIS PLAN (SAP), SAP UPDATE INCLUDING SUMMARY OF AMENDMENTS, AND SAP UPDATE CORRECTION
3. DATA SAFETY MONITORING COMMITTEE STOPPING RULES AND REPORTS
The POLAR-RCT

The Prophylactic hypOthermia trial to Lessen trAumatic bRain injury-Randomised Controlled Trial

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THIS STUDY IS ENDORSED BY THE AUSTRALIA AND NEW ZEALAND INTENSIVE CARE SOCIETY CLINICAL TRIALS GROUP (ANZICS CTG).
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1. MANAGEMENT COMMITTEE AUTHORISATION PAGE

The management committee members have read the attached protocol and authorize it as the official protocol for the study entitled *The prophylactic hypothermia trial to lessen traumatic brain injury – randomised controlled trial. (POLAR RCT)*. The signed original is held on file at the Centre.
This page is intentionally left blank – please refer to page 5.
2. INVESTIGATOR PROTOCOL AGREEMENT SIGNATURE PAGE

I have received and read the *The prophylactic hypothermia trial to lessen traumatic brain injury – randomised controlled trial. (POLAR RCT)* study protocol and agree to conduct the study in accordance with:

- The attached protocol (subject to amendments);
- In accordance with the NHMRC National Statement on Ethical Conduct in Human Research (2007); and
- The Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) annotated with Therapeutic Goods Administration comments.

Name of Participating Site: _________________________________

Signature of Investigator: __________________________ Date: __________

Printed Name: _______________________________
## 3. STUDY ADMINISTRATION STRUCTURE

### 3.1 Coordinating Centre & Data Management Centre

Australian and New Zealand Intensive Care Research Centre (ANZIC-RC) and Department of Epidemiology and Preventive Medicine (DEPM)

#### 3.1.1 Responsibilities

- overall management of the study including assistance with HREC 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 research coordinators and POLAR study team
- protocol training of ambulance paramedics
- preparation and arrangement of investigator payments
- study set-up
- randomisation
- 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

#### 3.1.2 Staff

- **Prof. Jamie Cooper**  Principal Investigator, ANZIC-RC
- **Ms Siouxzy Morrison**  Acting Executive Officer, ANZIC-RC
- **Dr Alistair Nichol**  Senior lecturer, ANZIC-RC
- **Prof Andrew Forbes**  Head Biostatistics Unit, DEPM, Monash University
- **A/Prof. Chris Reid**  Head, Monash Centre of Cardiovascular Research and Education in Therapeutics (CCRET)  Monash University
- **Ms Lynne Murray**  Research Fellow, ANZIC-RC
- **Ms Philippa Loane**  Case report form (CRF) coordinator, CCRET, Monash University

#### 3.1.3 Meetings:

As required

### 3.2 Management Committee

#### 3.2.1 Responsibilities

Overseeing all aspects of the study management including

- liaison with coordinating centre staff
- liaison with steering committee
- liaison with ANZICS CTG
- liaison with ambulance services
3.2.2 **Members**

- A/Professor Stephen Bernard  
  Medical Advisor, Ambulance Victoria
- Professor Jamie Cooper  
  Principal investigator ANZIC-RC
- Professor Peter Cameron  
  Head of Emergency Trauma Research Group, DEPM, Monash University
- A/Professor Andrew Forbes  
  Head Biostatistics Unit, DEPM, Monash University
- Dr. Colin Macarthur  
  Director Critical Care Medicine, Auckland City Hospital
- Ms. Lynne Murray  
  Research Fellow, ANZIC-RC
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  Staff Specialist, Intensive Care Unit, Mater Hospital
- Professor Jeffrey Rosenfeld  
  Neurosurgeon, The Alfred
- Dr. Tony Smith  
  Medical Advisor, St John Northern Region NZ Ambulance Service
- Mr. Tony Walker  
  Ambulance Victoria
- Dr. Steve Webb  
  Intensive Care Consultant, Royal Perth Hospital

3.3 **Steering Committee**

3.3.1 **Responsibilities**

- Approval of full protocol
- Approval of data collection tools and methods
- Oversight and advisory role
- Data analysis, collaboration and approval of study publications

3.3.2 **Members**

- Management committee (as above)
- State/Country Ambulance Service representative
- Associate investigators*

*Local representatives to be appointed once sites confirmed (1 Intensive Care, 1 Neurosurgeon, 1 Emergency Dept, 1 Research Coordinator per site)
3.4 Contact Details

3.4.1 Chief investigator

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### 4. ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>Adverse event</td>
</tr>
<tr>
<td>ANZ</td>
<td>Australia and New Zealand</td>
</tr>
<tr>
<td>ANZRC</td>
<td>Australian and New Zealand Intensive Care Research Centre</td>
</tr>
<tr>
<td>ANZICS</td>
<td>Australian and New Zealand Intensive Care Society</td>
</tr>
<tr>
<td>ARC</td>
<td>Australian Research Council</td>
</tr>
<tr>
<td>ARR</td>
<td>Absolute relative risk</td>
</tr>
<tr>
<td>ATBIS</td>
<td>Australasian Traumatic Brain Injury Study</td>
</tr>
<tr>
<td>BTF</td>
<td>Brain trauma foundation</td>
</tr>
<tr>
<td>CCM</td>
<td>Critical Care Medicine</td>
</tr>
<tr>
<td>CCRET</td>
<td>Centre of Cardiovascular Research and Education in Therapeutics</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CPP</td>
<td>Cerebral Perfusion Pressure</td>
</tr>
<tr>
<td>CRF</td>
<td>Case report form</td>
</tr>
<tr>
<td>CSF</td>
<td>Cerebrospinal fluid</td>
</tr>
<tr>
<td>CTG</td>
<td>Clinical Trials Group</td>
</tr>
<tr>
<td>CVP</td>
<td>Central venous pressure</td>
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<tr>
<td>DEPM</td>
<td>Department of Epidemiology and Preventive Medicine</td>
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<tr>
<td>DSMC</td>
<td>Data Safety Monitoring Committee</td>
</tr>
<tr>
<td>ED</td>
<td>Emergency Department</td>
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<tr>
<td>ETT</td>
<td>Endotracheal tube</td>
</tr>
<tr>
<td>HDEC</td>
<td>Human Disability Ethics Committee</td>
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<tr>
<td>HREC</td>
<td>Human Research Ethics Committee</td>
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<tr>
<td>HTS</td>
<td>Hypertonic saline</td>
</tr>
<tr>
<td>ICP</td>
<td>Intracranial Pressure</td>
</tr>
<tr>
<td>ICU</td>
<td>Intensive Care Unit</td>
</tr>
<tr>
<td>IMV</td>
<td>Invasive mechanical ventilation</td>
</tr>
<tr>
<td>IV</td>
<td>Intravenous</td>
</tr>
<tr>
<td>NEJM</td>
<td>New England Journal of Medicine</td>
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<tr>
<td>NHMRC</td>
<td>National Health and Medical Research Council</td>
</tr>
<tr>
<td>NNT</td>
<td>Number needed to treat</td>
</tr>
<tr>
<td>NOK</td>
<td>Next of kin</td>
</tr>
<tr>
<td>QOL</td>
<td>Quality of life</td>
</tr>
<tr>
<td>NS</td>
<td>National statement</td>
</tr>
<tr>
<td>RGC</td>
<td>Research Governance Committee</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomised controlled trial</td>
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<tr>
<td>RRI</td>
<td>Relative risk increase</td>
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<tr>
<td>RRR</td>
<td>Relative risk reduction</td>
</tr>
<tr>
<td>RSI</td>
<td>Rapid sequence intubation</td>
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<tr>
<td>SAE</td>
<td>Serious adverse event</td>
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<tr>
<td>SF</td>
<td>Short form</td>
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<tr>
<td>TBI</td>
<td>Traumatic brain injury</td>
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5. LAY DESCRIPTION

Traumatic brain injury (TBI) is a leading cause of death and long term disability, particularly in young adults. Studies from Australia have shown that approximately half of those with severe traumatic brain injury will be severely disabled or dead 6 months post injury. Given the young age of many patients with severe TBI and the long term prevalence of major disability, the economic and more importantly the social cost to the community is very high.

Pre-hospital and hospital management of patients with severe brain injury focuses on prevention of further injury due primarily to lack of oxygen. This includes optimising sedation & ventilation, maintaining the fluid balance and draining Cerebrospinal Fluid (CSF) & performing surgery where appropriate. In recent years there has been a research focus on specific pharmacologic interventions however to date there has been no treatment that has been associated with improvement of neurological outcomes.

One treatment that does show promise is the application of hypothermia (cooling). This treatment is commonly used in Australia to decrease brain injury in patients with brain injury following out-of-hospital cardiac arrest. Cooling is thought to protect the brain using a number of mechanisms. There have been a number of animal studies that have looked at how cooling is protective and also some clinical research that suggests some benefit. However at the current time there is insufficient evidence to provide enough proof that cooling should be used routinely for patients with brain injury and like all treatments there can be some risks and side effects.

The POLAR trial has been developed to investigate whether early cooling of patients with severe traumatic brain injury is associated with better outcomes. It is a randomised controlled trial, which is a type of trial that provides the highest quality of evidence.

Unconscious patients will be assessed by the ambulance service and if found to be suitable for the trial they will receive cooling by an infusion of chilled salty fluid (Intervention group) or they will be treated in the normal manner (Control group). Allocation to the two groups occurs randomly like flipping a coin. On arrival to hospital cooled patients will be checked to make sure it is safe to continue cooling and if so they will be cooled by temperature control pads placed on the skin. Control group patients will also have the pads applied. The cooled group will have the temperature set to 33°C and the control group to 37°C. The temperature pads will stay in place for up to 7 days. Data will be collected during the pre-hospital stage and the hospital admission. The patient's recovery will be measured at 6 months post the injury.
6. SYNOPSIS

6.1 Background
Traumatic brain injury (TBI) is a devastating condition which affects close to 1,000 people each year in Australia, causes extensive disability and suffering, and costs the country close to 1 billion dollars per year. There is a clear scientific rationale for the use of early prophylactic hypothermia as a treatment following TBI, including laboratory studies, positive clinical trials and meta-analyses. A single multi-centre clinical trial by Clifton et al found no improvement in outcomes in patients treated with prophylactic hypothermia.¹ This trial had important methodological limitations. These limitations, together with new evidence in current meta-analyses have led to prophylactic hypothermia for the first time being suggested as a possible therapy in international guidelines, but not as a “standard of care”. Meta-analyses should be hypothesis generating and should not alone lead to practice change. Therefore, few clinicians are likely to implement prophylactic hypothermia based on the lingering questions of efficacy, logistics, and potentially increased cost. A large, multi-centre randomised controlled trial in Australia with the capacity to demonstrate clinical benefit is urgently required.

6.2 Design
Prospective randomised controlled multi-centre trial of early and sustained prophylactic hypothermia in 512 patients with severe TBI

6.3 Aim
The primary aim of the study is to determine whether early and sustained prophylactic hypothermia, compared to standard Australian ‘normothermic’ care, is associated with an increased proportion of favourable neurological outcomes six months after severe TBI. The null hypothesis is that there is no difference in the proportions of favourable neurological outcomes between patients assigned to either prophylactic hypothermia or standard normothermic care.

6.4 Inclusion Criteria
- Non–penetrating severe TBI (i.e. Glasgow Coma Scale (GCS) ≤ 8)
- Estimated age ≥ 15 and < 60 years of age
- Injury estimated to have occurred within 2 hours of paramedic arrival.
- The patient is intubated

6.5 Exclusion Criteria
- Pre-intubation airway reflexes are absent
- Pre-intubation Systolic BP <100mmHg
- Pre-intubation heart rate > 120bpm
- Pre-intubation GCS=3 + un-reactive pupils
- Penetrating neck/torso injury
- Obvious pregnancy
- Receiving hospital is not a study site.
- Medi-alert bracelet for Warfarin treatment or if known

6.6 Methods
Eligible patients will be randomised by attending paramedics at the scene. Prophylactic hypothermia will be induced by exposure and by infusing 2 litres intravenous ice-cold (4°C) 0.9% sodium chloride to a temperature of 35°C during transport. In the emergency department the patient will be assessed to exclude significant bleeding and, once excluded, surface cooling pads will be used to reach the target...
temperature of 33°C, and the patient will be then maintained at this temperature for a further 72 hours. Patients allocated to standard Australian 'normothermic' care will be maintained at 36.5-37°C.

6.7 Primary outcome measure

- The proportion of favourable neurological outcomes (Glasgow Outcome Score Extended: GOSE 5 to 8) at six months following injury.

6.8 Secondary outcome measure

- Probability of an equal or greater GOSE level at 6 months compared to the probability of a lesser GOSE: using the proportional odds model.
- Six month neurological outcomes assessed by the "sliding dichotomy" method
- Quality of life assessments (QOL) –
  - EQ5D
  - AQOL8.
- Proportion of favourable neurological outcomes in survivors at six months following injury
- Mortality (all cause) at
  - six months
  - hospital discharge.
  - ICU discharge
- Incidence of potential adverse events, specifically
  - Incidence of bleeding
  - Incidence of infection.

6.9 Benefits

If prophylactic hypothermia is found to improve neurological outcomes, given the high disability rate, at least 200 patients per year will have significantly improved neurological outcomes in Australia/New Zealand by the widespread application of prophylactic hypothermia. If standard 'normothermic' care is shown to be equivalent, or even superior to prophylactic hypothermia, patients will be able to continue to receive less invasive and less expensive care and the features of Australian/New Zealand standard care can be used to inform practice worldwide.
7. BACKGROUND & RATIONALE

7.1 Clinical & biological rationale

Traumatic brain injury (TBI) is a leading cause of death and long term disability, particularly in young adults. In a recent analysis of an international database of 2664 patients with severe TBI, mortality was 28%. Of great societal importance, many of the patients who survived had permanent neurological disability. At 6-months, only 52% of these patients had favourable neurological outcomes (good recovery or moderate disability) and were able to live independently and 48% had unfavourable neurological outcomes (dead, vegetative state or severe disability). Given the young age of many patients with severe TBI and the long term prevalence of major disability, the economic and social cost to the community is very high.

Australian Perspective

The ANZICS-CTG identified TBI as a key research area where interventional trials might improve survival and functional outcomes and has conducted key preliminary studies. The prospective Australasian Traumatic Brain Injury Study (ATBIS) was undertaken over a 6-month period during 2001 to determine the prevalence, management strategies and outcomes of TBI patients admitted to intensive care units (ICUs) in Australia and New Zealand (ANZ). There were 363 patients with severe TBI (defined initial Glasgow Coma Score (GCS) ≤ 8) recruited from 16 centres. The twelve-month mortality in patients with severe TBI was 35.1% and the rate of favourable neurological outcomes at 12 months was 48.5%. The ANZICS-CTG then conducted a detailed analysis of the TBI patients in the SAFE study (saline vs. albumin fluid evaluation). The 318 patients with severe TBI had a 32% mortality rate and 46% had favourable neurological outcomes at 24 months. Finally, an interim analysis (n=150) of a pre-hospital trial evaluating paramedic rapid sequence intubation in severe TBI (Rapid Sequence Induction (RSI) trial, ACTRN12605000177651), found a mortality rate of 35% and 59% favourable neurological outcomes at 6 months (personal communication, CI-B).

Clearly, these findings confirm that, despite a well resourced and integrated health system, severe TBI in Australia continues to carry a high rate of mortality and long term disability. The mean lifetime medical and rehabilitation cost of each TBI survivor with severe disability in Australia currently exceeds $3 million. The lifetime cost of caring for the 150 Australian victims of TBI who survive with significant disability each year amounts to nearly a billion dollars. Even a small increase in the number of TBI patients who have favourable rather than unfavourable neurological outcomes, would yield major human and economic savings.

Prophylactic hypothermia: a treatment for severe TBI

Current management of TBI is supportive and focuses on prevention and treatment of cerebral hypoxia using sedation, intravenous fluids, monitoring and manipulation of oxygen, intra-cranial pressure (ICP) and cerebral perfusion pressure (CPP). Despite decades of research investigating novel pharmacological therapies for patients with TBI, clinical trials of novel therapies to date have not demonstrated substantial improvements in outcomes. However, the recent landmark paper in the New England Journal of Medicine (NEJM) reported that the choice of fluid therapy after primary brain injury may possibly influence long term neurological outcomes by decreasing secondary brain injury. This paper restored optimism that it is feasible to decrease secondary brain injury and improve long term outcomes.

Currently, a therapy with great potential to reduce neurological damage and improve outcome after severe TBI is the application of early prophylactic hypothermia. This therapy involves the rapid reduction of core body temperature after injury to 33°C, to attenuate brain injury. This treatment is commonly used in Australia to decrease brain injury in patients with severe neurological injury following out-of-hospital cardiac arrest.

There is extensive scientific rationale supporting early prophylactic hypothermia as a treatment following TBI including extensive laboratory data, supportive clinical trials and meta-analyses.

Laboratory studies of hypothermia in TBI

Many experimental studies have confirmed that moderate hypothermia confers protection against ischaemic and non-ischaemic brain hypoxia. Many post-traumatic adverse events that occur in the injured brain at a cellular and molecular level are highly temperature-sensitive and are a good target for induced hypothermia. Hypothermia has demonstrated powerful neuroprotective effects in experimental models and influences multiple biochemical cascades that are set in motion after TBI (secondary brain injury). These mechanisms are multifactorial and include: reduction in brain...
metabolic rate, positive effects on cerebral blood flow, blockade of excitotoxic mechanisms, calcium antagonism, decrease in oedema, modulation of the inflammatory response and modulation of apoptosis\(^\text{14}\). Furthermore, experimental models also suggest that a ‘therapeutic window’ exists where the induction of hypothermia soon after the primary TBI may provide optimal neurological protection leading to improved outcomes\(^\text{15-18}\).

**Clinical studies of hypothermia in TBI**

Over the past two decades, clinical trials of prophylactic hypothermia in TBI have been conducted and supported a likely benefit\(^\text{13}\). These include single centre trials\(^\text{19-23}\) and a single multi-centre trial\(^\text{1}\). Furthermore, a meta-analysis of the highest quality clinical trials of hypothermia in severe TBI was conducted in 2007\(^\text{24}\) by the Brain Trauma Foundation (BTF), the recognised international medical body which promulgates evidence-based guidelines for the management of TBI. This meta-analysis reported a significant increase in long term favourable neurological outcomes (Relative Risk (RR)\(1.46, p=0.006, \text{figure 1}\)) with no significant decrease in mortality (RR 0.76, 95% confidence interval (CI) 0.05 to 1.05, \(p=0.18\)) in patients treated with prophylactic hypothermia compared to normothermia.

Figure 1 \(^9\)

The only published multi-centre hypothermia trial (Clifton, 2001\(^\text{1}\)) reported no improvement in outcomes in patients treated with prophylactic hypothermia. This trial was well conducted but had key methodological limitations.

First, there was an average delay of 8.4 hours in attaining the target temperature \(^1\). This delay was largely due to inferior cooling technology and this may have confounded detection of a protective effect. The subgroup of patients in this trial who were initially hypothermic and then randomised to hypothermia had a significant long-term neurological advantage compared to normothermia\(^1,25\).

Future trials should induce hypothermia as early as possible and ideally at the location of the traumatic event. There is considerable Australian and international experience with paramedic-initiated early hypothermia for cardiac arrest, and this experience can be applied to severe TBI patients\(^26,27\).

Second, in severe TBI the generalised swelling of brain tissue frequently persists for over 48 hours. It is therefore likely that therapeutic levels of hypothermia lasting for only 48 hours (in the Clifton trial \(^1\)) were insufficient. This assertion is supported by the BTF meta-analysis finding that trials of prophylactic hypothermia longer than 48 hours were associated with significantly reduced mortality (RR 0.51; 95% CI 0.34, 0.78\(^9\)). Therapeutic levels of hypothermia should be induced in excess of 48 hours, which has been well tolerated in patients with severe TBI\(^28\).

Third, the Clifton trial withdrew hypothermia on a time based trigger rather than according to a physiological trigger \(^1\). Rewarming of patients despite increases in intracranial pressure is not considered optimal clinical practice \(^29\). Hypothermia should be withdrawn using a physiological trigger (i.e. ICP) and over a prolonged period to avoid uncontrolled intracranial hypertension\(^29\).

Fourth, the Clifton trial induced and maintained hypothermia using cooling blankets and bags of ice. This practice is associated with difficulty achieving a constant patient temperature and problems targeting gradual re-warming. The recent development of electronically controlled surface (skin) cooling pads through which cold water is channelled has revolutionised the controlled induction, maintenance and ultimate emergence from hypothermia.

Finally, the lack of a ‘run in’ period, lack of protocolised brain specific care, the inclusion of low-enrolment centres and the large inter-centre variance in the Clifton trial\(^1\) may have further confounded the detection of a protective effect. Interestingly, when the problematic Clifton trial was excluded from the BTF meta-analysis, a pooled estimate demonstrated a significant reduction of mortality (RR 0.64; 95%CI 0.46 to 0.89\(^9\)).
Potential adverse effects and complications of hypothermia

Despite a temperature of 33ºC being the ideal balance of therapeutic effect and potential adverse side-effects, it is important to consider the potential complications, specifically coagulopathy and infection. Hypothermia may prolong clotting times and alter platelet function and this could lead to increased blood loss. However, this may not significantly increase bleeding in the context of severe TBI. Future trials of prophylactic hypothermia should include a strategy to minimise potential risks of bleeding. For example, induction of mild hypothermia (minimum temperature 35ºC) in the field to optimise brain protection, while limiting the risk of coagulopathy prior to a robust assessment of bleeding in the Emergency Department (ED). Meta-analyses reported increased pneumonia in patients cooled for prolonged periods. While it has previously been demonstrated in a small study that this increased rate of infection did not increase mortality, any future trial should incorporate optimal standard of care measures to reduce infectious complications.

The requirement for a multi-centre phase III trial of prophylactic hypothermia in severe TBI

Methodological shortcomings of the multi-centre trial, together with limited evidence in recent meta-analyses has led to prophylactic hypothermia for the first time being suggested as a possible therapy in the international BTF guidelines, but not a “standard of care”. Meta-analyses are best considered as hypothesis generating and should never form the basis for changes in clinical practice. Therefore, despite this recommendation, few if any clinicians are likely to implement prophylactic hypothermia owing to lingering concerns of efficacy, logistics, and increased costs. A large, multi-centre randomised controlled trial with the capacity to demonstrate benefit is required.

Currently, 2 multi-centre phase III trials of prophylactic hypothermia in severe TBI are underway (USA; NCT00178711, Japan; NCT00134472). However, there are a number of reasons why an Australian multi-centre phase III trial of prophylactic hypothermia in severe TBI is urgently required. First, these trials may not succeed, being underpowered to detect a plausible improvement in patient-centred outcomes, by repeating previous methodological concerns such as insufficient duration of hypothermia, time based triggers for rewarming and the lack of a national hospital / ICU research network. Second, there are substantial differences in organisational and training structures of pre-hospital care and transport, emergency departments and ICUs between Australia and other countries. Finally, the standard of emergency and ICU care in Australia is high. The ATBIS survey found that Australian TBI patients are more likely than European patients to receive invasive monitoring. Therefore, if prophylactic hypothermia was shown to be beneficial in a setting where care levels are high, it would likely change practice not only in Australia but also internationally.

7.2 Significance

If prophylactic hypothermia is found to improve neurological outcomes, given the high disability rate, at least 200 patients per year will have significantly improved neurological outcomes in Australia/New Zealand by the widespread application of prophylactic hypothermia. If standard ‘normothermic’ care is shown to be equivalent, or even superior to prophylactic hypothermia, patients will be able to continue to receive less invasive and less expensive care and the features of Australian/New Zealand standard care can be used to inform practice worldwide.

8. OBJECTIVES

8.1 Aim

The primary aim of the study is to determine whether early and sustained prophylactic hypothermia, compared to standard Australian ‘normothermic’ care, is associated with an increased proportion of favourable neurological outcomes six months after severe TBI. The null hypothesis is that there is no difference in the proportions of favourable neurological outcomes between patients assigned to either prophylactic hypothermia or standard normothermic care.

8.2 Hypothesis

In patients with severe TBI, early and sustained hypothermia, compared to standard normothermic management, increases favourable neurological outcomes six months after injury.
9. STUDY OUTCOME MEASURES

9.1 Primary outcome
- The proportion of favourable neurological outcomes (Glasgow Outcome Score Extended: GOSE 5 to 8) at six months following injury

9.2 Secondary outcome
- Probability of an equal or greater GOSE level at 6 months compared to the probability of a lesser GOSE level, using a proportional odds model
- Six month neurological outcomes assessed by the “sliding dichotomy” method
- Quality of life assessments (QOL)
  - EQ5D
  - AQOL8
- Proportion of favourable (GOSE 5-8) neurological outcomes in survivors at six months following injury
- Mortality (all cause) at
  - six months
  - hospital discharge.
  - ICU discharge
- Incidence of potential adverse events, specifically
  - Incidence of bleeding
  - Incidence of infection.

10. OVERALL STUDY DESIGN

10.1 Study population
The study population will consist of trauma patients treated by the ambulance service in the field.

10.2 Inclusion Criteria
- Non–penetrating severe TBI (i.e. Glasgow Coma Scale (GCS) ≤ 8)
- Estimated age ≥ 15 and < 60 years of age
- Injury estimated to have occurred within 2 hours of paramedic arrival.
- The patient is intubated

10.3 Exclusion Criteria
- Pre-intubation airway reflexes are absent
- Pre-intubation Systolic BP <100mmHg
- Pre-intubation heart rate > 120bpm
- Pre-intubation GCS=3 + un-reactive pupils
- Penetrating neck/torso injury
- Obvious pregnancy
- Receiving hospital is not a study site.
- Medi-alert bracelet for Warfarin treatment or if known
10.4 Co-enrolment

Co-enrolment of participants in other randomised controlled trials will not be permitted.

11. PARTICIPATING STUDY SITES

- Alfred Hospital, Melbourne, Australia
- Royal Melbourne Hospital, Melbourne, Australia
- Princess Alexandra Hospital, Brisbane, Australia
- Royal Brisbane Hospital, Brisbane, Australia
- Royal Perth Hospital, Brisbane, Australia
- Nepean Hospital, Sydney, Australia
- St George Hospital, Sydney, Australia

12. STUDY PROCEDURES

12.1 Assessment of patient for study suitability

Patients will be assessed by the ambulance paramedic. If they fulfil the inclusion criteria and have no exclusion criteria they will be randomised by opening the next opaque envelope in the randomisation series. The randomisation series of envelopes will be kept in each participating ambulance. The envelopes will contain 2 sticky labels which designate the study number and treatment allocation. A small number of details will be completed on the 2 labels (Patient's initials, Date of birth, Date and time of randomisation). One label will be placed on the patient's endotracheal tube (ETT) and the other label will be placed in the patient's hospital medical record on hospital arrival. The ambulance paramedics will also document the randomisation of the patient on the ambulance case report form.

12.2 Standard care (normothermia group) Pre-Hospital

Patient's randomised to the standard care arm, will be transferred to the nearest participating centre with no exposure and no cold fluids during transport. If the patients temperature is <36.5°C the patient will be transported covered by blankets in a heated vehicle.

12.3 Study intervention Induction of hypothermia

The prophylactic hypothermia protocol will be commenced at the scene. Hypothermia will be induced pre-hospital by exposure and infusing intravenously (IV) up to 2000ml of ice-cold (4°C) 0.9% sodium chloride (similar to the RICH26 and other27 trials) to achieve a target temperature of 35°C during transport. If the patients temperature is <35°C the patient will not receive cold fluid however they will be transported to hospital uncovered.

12.4 Patient review on ED arrival

On arrival in the emergency department the patient will be assessed for significant bleeding specifically:

- Significant injury to abdominal organ or Positive FAST scan or Positive CT Free Fluid
- Pelvic fracture requiring External Fixation + Angiography + surgery & pelvic packing
- Significant retroperitoneal haematoma on CT
- Chest drain in situ with > 300mls drained on insertion or > 100mls in the first hour post insertion.
- Transfusion of >2 units packed red blood cells associated with > 2 long bone lower limb fractures
12.5 **Temperature control**

Temperature control of all patients will be achieved using a temperature control console & surface temperature control pads which facilitate thermal transfer. The pads will be applied by nursing staff to approximately 40% of the surface body area. Temperature control will be initiated in the ED after the patient has been reviewed.

12.6 **Standard care (normothermia/control group)**

In line with current Australian practice, patients will be warmed to normothermia at the treating clinician’s discretion. When normothermia has been achieved the pads will be applied to maintain a temperature of 36.5°C – 37°C. The pads will remain in situ up to a maximum of 7 days or until the patient is discharged if prior to 7days.

12.7 **Study intervention (hypothermia group)**

If significant bleeding is excluded following review on arrival in the ED, temperature control pads will be applied with a target temperature of 33°C. This temperature will be maintained for a further 72 hours. Patients randomised in the field to the hypothermia group with haemodynamic instability presumed secondary to bleeding will have the cooling protocol with held or withdrawn depending on the clinical circumstances. Patients in whom bleeding is clearly controlled (i.e. correction of surgically isolated lesion), will later resume the hypothermic protocol. Patients who have the cooling protocol withdrawn due to significant bleeding will follow the standard care for the control group.

12.8 **Application of temperature control**

The intention of the trial is to apply the surface temperature control pads as soon as possible however there may be delays due to urgent surgery or other procedures.

12.9 **Witholding hypothermia**

If a patient allocated to hypothermia develops clinically significant bleeding at any time, they will be rewarmed (to 36.5°C -37°C). Patients in whom any such bleeding is controlled may resume the hypothermic protocol (to 33°C) within 60 hours of the initial injury. Patients with bleeding controlled but requiring surgery will have hypothermia withheld and will be rewarmed to 36.5°C - 37°C. They will be reviewed for significant bleeding following the surgery and will resume the hypothermia protocol as soon as possible if there are no bleeding concerns.

12.10 **Withdrawal of hypothermia:**

Patients with

- Significant injury to abdominal organ or Positive FAST scan or Positive CT Free Fluid
- Pelvic fracture requiring External Fixation + Angiography + surgery & pelvic packing
- Significant retroperitoneal haematoma on CT
- Chest drain in situ with > 300mls drained on insertion or > 100mls in the first hour post insertion.
- Transfusion of >2 units packed red blood cells associated with > 2 long bone lower limb fractures
- Positive β HCG
- Normal CT Brain scan & patient localising after decreased sedation

Will be withdrawn from the hypothermia protocol and will follow the standard care control group protocol.

12.11 **Rewarming protocol**

After 72 hours, the hypothermic patient will be assessed for suitability for controlled, active, gradual rewarming (0.25°C per hour) to 37°C. If the ICP is normal (<20mmHg) re-warming will be commenced. However, if there is a spontaneous sustained rise in ICP (>20mmHg for > 5mins) during
the re-warming period, the patient will be re-cooled (33°C) and assessed daily for suitability for re-warming. The planned maximum period of hypothermia will be 7 days. Once a patient has completed the re-warming protocol and reached 37°C, they will be maintained to normothermia using the surface cooling pads up to a maximum of 7 days or until the patient is discharged if prior to 7 days.

12.12 TBI management & ICU management

Patients enrolled in both the hypothermia and normothermia groups will be managed according to current international evidence based guidelines. This protocolised care (as previously used by ANZICS CTG TBI network in DECRA and HTS trials) includes a stepped regimen for both the management of increased intra-cranial pressure (ICP) (>20mmHg) and severely lowered cerebral perfusion pressure (CPP) (<60mmHg), and targets for fluid management.

ICU management guidelines to ensure optimal standard of care and reduction of infectious complications have been developed.

See Appendix D.

12.13 CT Brain scans

For data collection purposes only the admission CT Brain scan will be assessed by a Neurosurgeon blinded to the treatment group using the Marshall Grading system. Deidentified CT brain scans will be forwarded to the coordinating centre for assessment.

12.14 Blinding

To ensure appropriate treatment, participants must be monitored closely and investigation results known to the treating clinical staff. As patient safety is paramount, and a key patient vital sign (temperature) is due to the treatment itself, it is not possible to blind clinical staff as to the patient’s treatment allocation. Bias will be minimised by concealed treatment allocation prior to randomisation, by protocolising treatment in both groups, by applying surface temperature control pads to all patients (both normothermia and hypothermia groups) and by assessment of the primary outcome by blinded and trained research staff (SAFE, SAFE-TBI, TBI, HTS, and ATBIS). The primary outcome measure is robust and subject to minimal ascertainment bias.

12.15 Contamination

Contamination will be minimised by:

- Standardising and protocolising patient management in both groups by paramedics and emergency department staff
- Managing patients with clearly distinct temperature goals.

Induced hypothermia will not be delivered as a brain specific therapy in the normothermia group.

12.16 Study run-in phase

A study run-in phase will be conducted at each site. This will involve enrolling 2 patients to the hypothermia arm group. The study run in phase will allow the co-ordinating site to check and refine the protocol paying particular attention to inclusion/exclusion criteria, pre-hospital cooling, safety assessment on hospital admission, administration of the cooling and rewarming protocol.

12.17 Randomisation

Randomisation will be performed by the paramedics using a previously used and effective closed envelope system including block randomisation (RSI and RICH trials). Treatment allocation will be stratified by ambulance (HTS, RSI and RICH trials) and since specific paramedic crews feed specific hospitals, POLAR will therefore also be stratified by centre. Eligible patients will be randomised to normothermia (standard care) or prophylactic hypothermia. After the initiation of treatment, patients will be rapidly transported to the participating centre.
12.18 Table of events
See Appendix A

13. ETHICS

13.1 Guiding principles

This study will be performed in accordance with the ethical principles of the Declaration of Helsinki (June 1964 and amended 1975, 1983, 1989, 1996, 2000, 2008 and Note of Clarification 2002 and 2004), ICH GCP Notes for Guidance on Good Clinical Practice (CPMP/ICH/135/95) annotated with Therapeutic Goods Administration comments and NHMRC National Statement on Ethical Conduct in Research Involving Humans (March 2007).

13.2 Ethical issues of the study

The two ethical considerations in this study are:

- Emergency research & consent
- The risk/benefit ratio of the study treatment.

Emergency research and consent

Some research must necessarily be performed on patients in emergency (definition is unexpected) situations when they are unable to provide consent, as with all other categories of patients. The principle of justice requires this to be the case. This study constitutes emergency research. Principle 29 of the Declaration of Helsinki acknowledges that some clinical research will involve patients who are physically incapable of giving consent “Research on individuals from whom it is not physically possible to obtain consent, including proxy or advance consent, should be done only if the physical or mental condition that prevents obtaining informed consent is a necessary characteristic of the research population”

To be eligible for recruitment in this study patients will be unconscious (GCS<8) and consequently will be unable to consent to participation. The study intervention must be instigated as soon as possible by the paramedics in the field; thus consent cannot be sought from the participant’s next of kin (NOK)/person responsible. The National Statement (NS) on Ethical Conduct in Research Involving Humans (March 2007) acknowledges in section 4.4 that research involving patients who are heavily dependent on medical care in emergency circumstances, such as the patients in this study, may proceed when the participants ability to give consent is non existent. This requires approval from the appropriate ethical body to waiver consent (section 7.3).

Risk /benefit ratio of study treatment

As discussed previously in section 3.5 current literature supports a likely benefit from the use of prophylactic hypothermia in severe TBI. These include single centre trials and a single multi-centre trial. Furthermore, a meta-analysis of the highest quality clinical trials of hypothermia in severe TBI was conducted in 2007 by the Brain Trauma Foundation (BTF), the recognised international medical body which promulgates evidence-based guidelines for the management of TBI. This meta-analysis reported a significant increase in long term favourable neurological outcomes (RR 1.46, p=0.006, figure 1) with no significant decrease in mortality (RR 0.76, 95% CI 0.05 to 1.05, p=0.18) in patients treated with prophylactic hypothermia compared to normothermia. The only published multi-centre hypothermia trial in adults reported no improvement in outcomes in patients treated with prophylactic hypothermia. This trial was well conducted but had key methodological limitations discussed previously in section 3.5.

As with most treatment interventions there are some potential associated risks. Patients with severe TBI are at increased risk for ventilator associated pneumonia and it is thought that the risk increases with hypothermia. The risk of VAP and other infections will be minimised by utilising guidelines for optimal standard of care to reduce infectious complications.

Coagulopathy can also occur with cooling although to date none of the large clinical trials in patients with TBI has reported significantly increased risk of bleeding associated with hypothermia. However to minimise potential risks of bleeding induction of mild hypothermia (minimum temperature 35oC) in the field will be utilised to optimise brain protection, while limiting the risk of coagulopathy prior to a robust assessment of bleeding in the ED. Once admitted to hospital the participant will be reviewed to ensure that there is no significant bleeding and that it is safe to continue to receive the study intervention. Patients randomised in the field to the hypothermia group with haemodynamic instability...
presumed secondary to bleeding will be rewarmed until bleeding is controlled. Patients in whom bleeding is clearly controlled (i.e. correction of surgically isolated lesion), will later resume the hypothermic protocol.

Low electrolyte levels may develop in the induction phase of cooling due to increased renal excretion and intracellular shift. Electrolytes are measured regularly as part of standard intensive care and abnormalities can be treated accordingly. Potassium levels may rise during the rewarming phase as potassium that was excreted into the cell in the induction phase is released. Controlled slow rewarming will give the kidneys time to excrete the excess potassium. Hypovolemia can occur due to “cold diuresis” during the induction phase. Haemodynamic parameters will be monitored carefully and if instability develops a fluid challenge test would be warranted.

Cardiac arrhythmias have been linked to cooling however there is no hypothermia induced risk for severe arrhythmias unless core temperature decreases to <30°C. Bradycardia may occur when the temperature drops below 35.5°C. The bradycardia generally does not require treatment however stimulation of the heart rate can be achieved with pharmacological measures if required. Temperature will be tightly controlled at 33°C. Patients will have constant cardiac monitoring as part of standard intensive care.

Hypothermia can simultaneously decrease insulin sensitivity & reduce insulin secretion by pancreatic islet cells. Patients treated with hypothermia will be at a higher than average risk for developing hyperglycaemia. Patients have blood glucose tests performed regularly and control of hyperglycaemia form a part of regular intensive care.

There is an increased risk of feeding intolerance in patients with traumatic brain injury. The risk may increase with hypothermia as cooling may impair bowel function and aggravate gastric emptying. Feeding rates and tolerance will need to be carefully monitored and appropriate measures instituted if feeding intolerance develops.

### 13.3 Ethics committee approval

In Australia, this protocol will be submitted to a Human Research and Ethics Committee constituted according to the NHMRC National Statement on Ethical Conduct in Research Involving Humans (March 2007) for each institution. In New Zealand, this protocol will be submitted to the appropriate Health and Disability Ethics Committee, accredited by the Health Research Council and constituted in accordance with the Operational Standard for Ethics Committees March 2002. Ethical clearance from the appropriate legal body will be required from any participating sites in other countries. Approval will also be sought using the appropriate legislative requirements for each state and country. Approval of the protocol, plans for obtaining consent, and related documents will be obtained prior to the start of the study at each site.

It is the investigator’s responsibility to ensure that all conditions for approval of the study are met and that amendments to the protocol or serious adverse events are also reported to the HREC (or equivalent) as required by that committee.

### 13.4 Confidentiality of patient data

Patients will be randomised pre-hospital and will receive a study number. The ambulance paramedics will complete a randomisation form including name, address & date of birth which will be forwarded to the Research Coordinator at each site. These details are required to notify the Research Coordinator that the patient is a participant in the trial. The Research Coordinator will compile an enrolment log using the details forwarded by the ambulance service. Subsequent data will be identified by the study number. The enrolment log and study data will be kept separately. Follow up details of the patient and their family will be collected including name, address and contact telephone numbers. The contact details will be forwarded to the co-ordinating centre. The co-ordinating site will perform the follow up assessments to ensure consistency and accuracy. All data collected in the follow up assessment will be identified by the study code. The follow up contact details and study data will be kept separately. Study data will be entered into a password protected database managed by the CCRET (Monash University). 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 site.

### 13.5 Informed consent

Unconscious patients with severe head injury will not be able to provide informed consent. This trial will therefore use a deferral of consent, in accordance with section 4.4 of the NS. This approach has
proven successful for 5 previous NHMRC funded randomised trials (including TBI and pre-hospital trials) - (SAFE\(^6\), RSI\(^7\), RICH\(^26\), out of hospital cardiac arrest\(^20\) and HTS\(^5\) trials).

As soon as is reasonably possible and appropriate the patient's NOK/person responsible will be informed of the patient's inclusion in the research and will be informed of the option to withdraw from the patient from it without any reduction in quality of care (NS 4.4.14). If the NOK/person responsible chooses to withdraw their consent for continued participation they will be asked for permission to use the data collected up to that time.

Patients who recover sufficiently to understand the explanation of the study will be asked to consent to continue in the study or be offered the chance to withdraw. If the patient chooses to withdraw from the study, they will be asked for permission to use their data up to the time of withdrawal (as per 4.4.14).

All interaction between research staff and participants and their relatives will take into consideration the stress or emotional factors associated with critical illness and ensure that the dependency of potential participants and their relatives on medical personnel providing treatment does not compromise the freedom of decision making to participate (as per 4.4.11).

### 14. DATA MANAGEMENT

#### 14.1 Data collection methods

All data will be collected by trained staff at each study site using a paper source document developed by the coordinating centre. Data will then be entered into a website designed by the CCRET. Data queries will be automatically generated via the website.

Randomised patients will be followed up to death or six months post-randomisation. Data collection will be restricted primarily to those variables necessary to define clinical patient characteristics including: baseline demographics, primary diagnoses, physiological parameters, diagnostic interventions, therapeutic interventions and documentation of deaths and other serious adverse events.

Patients and/or their legal surrogates will be asked to provide 3 possible points of contact (home and close family contact details) to the research staff prior to discharge. For patients discharged alive from ICU, follow-up will be restricted to information concerning duration of hospital stay and vital status at hospital discharge and six months. Full protocol data will be collected in all patients including those excluded at any stage. In addition, patients who are alive at 6 months after randomization will be interviewed by a single, trained and blinded assessor. This blinded assessor will use a standardized structured telephone questionnaire\(^41\) to measure the eight-grade GOSE\(^42\), and a QOL assessment EQ5D\(^32\) & AQOL8\(^44\). Neurological outcomes will then be defined as favourable (GOSE 5 to 8; moderate disability and good recovery) or unfavourable (GOSE 1 to 4; death and severe disability). Patients allocated to the prophylactic hypothermia group in whom hypothermia is subsequently withdrawn for any reason (i.e. bleeding) will be followed up, according to the study follow-up schedule and analysed on an intention-to-treat principle.

#### 14.2 Data variables collected

**Pre-hospital**

- Patient identifier(s)
- Baseline demographics
- Incident details
- Concurrent medical conditions and co-morbidities
- Inclusion and exclusion criteria
- Pre-hospital vital signs, Glasgow coma scale & temperature
- Date & timing of cooling intervention
- Type and volume of fluid therapy
- Brain injury management interventions

**Hospital admission**
• Vital signs, Glasgow coma scale
• Date & time of surface temperature control pads application
• Haematological and biochemical parameters
• Hourly temperature
• Type and volume of fluid therapy including blood
• Bleeding incidents
• Brain injury management interventions
• CT Brain scan (Marshall score (ref))
• Injury description

**Intensive Care Admission**

• Vital signs, Glasgow coma scale
• Haematological and biochemical parameters
• Hourly temperature
• Type and volume of fluid therapy including blood
• Brain injury management interventions
• Feeding; type and volume
• Feeding tolerance
• Clinical Pulmonary Infection Score
• Infection surveillance
• Bleeding incidents

**Hospital discharge**

• Length of mechanical ventilation
• Length of stay
• Discharge destination
• Vital status at ICU and hospital discharge
• Treatment limitations/withdrawal

**Other data**

• Outcome data:
  o 6 month GOSE
  o EQ5D
  o AQoL8

### 14.3 Data management

Data management will be performed by the CCRET. Streamlined data collection instruments and procedures will be developed using experience from our previous TBI trials (HTS\(^{11}\), RSI\(^{7}\), ATBIS\(^{4}\), SAFE-TBI\(^{5}\)).

### 14.4 Monitoring

Prior to study commencement, a start up-meeting will be held for study staff. During the study, the project manager will make at least one monitoring visit to each site during the recruitment period. The purpose of these visits is to ensure the study is conducted according to the protocol, all applicable guidelines and regulations, and to perform source data verification.
A monitoring report will be prepared following each visit and reviewed by the management committee. A copy of the report will be sent to the principal investigator and study coordinator at the site and will be filed in the site investigator file.

Medical records, any other relevant source documents and the site investigator files must be made available to the monitor for these monitoring visits during the course of the study and at the completion of the study as needed.

**Aims of monitoring visits:**

- Check the accuracy of the data base by performing source data verification of the CRF against the original source documents.
- Check for protocol violations or deviations and report these to the chief investigator as necessary.
- Review secondary outcome data available for each patient.
- Confirm the consent procedures approved by the site's HREC have been followed and view each original signed consent form.
- Check data security and access.
- Review all serious adverse events (SAEs) and follow up all reported SAEs.
- Review investigator site files for completeness and accuracy.
- Assist the study staff with any queries or problems they may have in relation to the study.

15. **STATISTICAL CONSIDERATIONS**

15.1 **Sample size calculation**

**Sample size and power calculations (primary analysis)**

The recent prospective studies (RSI7, SAFE-TBI5 and ATBIS3) found a weighted mean rate of current favourable neurological outcomes of 50% in Australian patients with severe TBI.

A beneficial effect of prophylactic hypothermia in severe TBI of 30% relative risk increase (RRI) from 50% to 65% (15% absolute risk increase (ARI)) in favourable neurological outcome at 6 months following injury would be a clinically relevant and important effect. Based on these figures, a study of fixed size with full compliance and follow-up would require 364 patients (182 in each of two treatment arms) to have an 80% two-sided power to detect a 15% ARI (from 50% to 65%) in favourable neurological outcome at 6 months following injury. This is a plausible and conservative estimate, based on:

- A recent meta-analysis1 in severe traumatic brain injury comparing prophylactic hypothermia to normothermia which demonstrated a 46% improvement of favourable outcomes (Relative Risk (RR) of 1.46, 95% (CI) 1.12 - 1.92, p=0.006).
- A finding of a 50% increase (p=0.02) in favourable outcomes in a sub-group of patients with severe traumatic brain injury <45 years of age who were hypothermic on arrival and subsequently randomised to hypothermia versus normothermia1,9.

A 30% RRI in favourable neurological outcomes is approximately two-thirds of the RRI demonstrated elsewhere 11. If prophylactic hypothermia was proven to be beneficial, such a difference in neurological outcomes would be highly clinically significant (NNT=7) and would lead to a widespread change in management of severe TBI patients in Australia and internationally.

To ensure availability of the required number of evaluable patients, this sample size will be inflated to account for losses to follow-up, withdrawal of hypothermia, and interim data analysis. Allowing an overall proportion of 5% loss to long term follow up (previous CTG studies and HTS4 of 1%), expands the sample size to 384 patients. Furthermore, based on pilot data (ATBIS11), allowance for a 12% rate of withdrawal of hypothermic intervention for patients randomised to hypothermia (8% bleeding, 2% withdrawal of surrogate / physician consent (previous pre-hospital trials (HTS)45 <1%), and an estimated 2% rate of inappropriate paramedics enrolment (i.e. cardiovascular accident not TBI) increases the sample size to 496 patients. In addition the trivial 0.3% sample size inflation factor associated with use of one interim Haybittle-Peto analysis adds a requirement for two more subjects. The trial recruitment target is 498 subjects. Including the ‘run in’ phase of two patients per site, the overall trial recruitment target is 512 subjects in total.
Power with proportional odds model (secondary analysis)

Assuming a proportional odds cumulative logit model applied to the eight-level GOSE outcome category vector, a reference improvement with therapy of ln(OR) = 0.62, and a one-sided linear rank test that the two multinomial populations had equal probabilities versus the alternative that the treatment population was stochastically larger than the control, this study of 182 evaluable subjects in each of two treatment groups would have a one-sided power of 96% to detect this magnitude of reference improvement as statistically significant with type I error (alpha) = 0.05

15.2 Statistical and analytical plan

Independent statisticians at Monash University will perform an intention-to-treat analysis. Baseline and outcome variables will be compared using Students t-test and Chi-squared test as appropriate. The favourable – unfavourable neurological outcome dichotomy at six months, quality of life assessment, proportion of favourable outcomes in survivors and mortality proportions will also be compared between treatment groups using the stratified Mantel-Haenszel test, and with logistic regression models adjusting for relevant covariates. Time-to-event analyses will be undertaken using non-parametric Kaplan-Meier and semi-parametric Cox proportional hazards regression methods. In addition to the above analyses of binary outcome variables, two further secondary analytic approaches will be applied to generate secondary outcomes. First, a proportional odds cumulative logit model, adjusting for relevant covariates, will be applied to the eight-level vector of 6-month GOSE. Second, the tertiles-of-risk sliding dichotomy approach to the analysis of outcome from severe TBI will be reported. The latter involves a dichotomisation of the 6-month GOSE for unfavourable versus favourable outcome differentiated according to each subject’s baseline prognostic risk

15.3 Interim analysis

One planned interim safety analysis will be performed by the independent data and safety monitoring committee (DSMC) at 50% patient enrolment, using a Haybittle-Peto rule applied to mortality data between treatment groups and the conventional 3-standard deviation threshold of a standardised statistic (|Z_k|≥ 3) calculated from a normal approximation to the discrete binomial difference in mortality proportions. Assuming no early stopping, such a single interim Haybittle-Peto analysis will not, in practice, require adjustment (for repeated significance testing) to the conventional statistical significance level (p<0.05) to be applied at the final analyses of the completed trial.

16. SAFETY

16.1 Data Safety Management Committee

An independent data safety monitoring committee (DSMC), comprising experts in clinical trials, biostatistics, emergency medicine and intensive care will be established. The committee will be charged with monitoring total mortality and serious adverse events and performing the interim analysis

16.2 Adverse events

Adverse events (AEs) are defined as any untoward medical occurrence in a patient or clinical investigation subject administered an investigational intervention and which does not necessarily have to have a causal relationship with this treatment (adapted from the Note for Guidance on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (CPMP/ICH/377/95 July 2000).

It is recognised that the patient population with severe traumatic brain injury will experience a number of common aberrations in laboratory values, signs and symptoms due to the severity of the underlying injury and the impact of standard therapies. These will not necessarily constitute an adverse event unless they require significant intervention or are considered to be of concern in the investigator’s clinical judgement.

In all cases, the condition or disease underlying the symptom, sign or laboratory value should be reported e.g. renal failure rather than hyperkalaemia, and agitation rather than self-extubation.
16.3 Serious adverse events

Serious Adverse Events (SAE) are defined in accordance with the Note for Guidance on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (CPMP/ICH/377/95) (July 2000) as any untoward medical occurrence that:

- Results in death
- Is life-threatening
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event which may require intervention to prevent one of the previously listed outcomes.

In this study all SAEs will be reported regardless of suspected causality.

16.4 Reporting

Separate case report forms will be developed to record adverse events and serious adverse events. SAEs which occur from the time of commencement of study treatment to 7 days post cessation of study treatment will be reported to the coordinating centre (ANZIC-RC) by faxing the supplied SAE form. SAEs should be reported to the ANZIC-RC within 24 hours of study staff becoming aware of the event.

Minimum information to report will include:

- patient initials and study number
- nature of the event
- commencement and cessation of the event
- an investigator’s opinion of the relationship between study involvement and the event (unrelated, possibly, probably or definitely related).
- whether treatment was required for the event and what treatment was administered.

Fax number
+ 61 3 9903 0071

Telephone Numbers
ANZIC RC: + 61 3 9903 0513
ANZIC RC: +61 419 155 983

Chief Investigator:
Prof DJ Cooper + 61 3 90762838 / +61 419 770 051

SAEs must be reported on the fax form but may also be discussed with the ANZIC RC staff or chief investigator if necessary.

Coordinating centre staff will be responsible for following-up SAEs to ensure all details are available. It is the responsibility of each site to inform their HREC of all SAEs which occur at their site, in accordance with local requirements.

17. FUNDING

The POLAR study is funded by a project grant from the National Health and Medical Research Council (NHMRC) (Project grant no. 545901). The ANZIC-RC will supply infrastructure and administrative support.
18. AUTHORSHIP & PUBLICATION

The study will be conducted in the name of the POLAR RCT investigators, the ANZIC RC, and the ANZICS CTG. The central project coordination and data management will be provided by the ANZIC-RC at Monash University, Melbourne. The principal publication from the study will be in the name of the POLAR RCT Investigators with full credit assigned to all collaborating investigators, research coordinators and institutions. Where an individuals’ name is required for publication it will be that of the writing committee, with the chair of the writing committee listed first and subsequent authors listed alphabetically.
# 19. RESEARCH TIMELINES

<table>
<thead>
<tr>
<th>Time frame indicators</th>
<th>Milestone</th>
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<tbody>
<tr>
<td>January 2008</td>
<td>Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS CTG) endorsement obtained</td>
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<tr>
<td>March 2008</td>
<td>NHMRC funding application submitted</td>
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<tr>
<td>October 2008</td>
<td>NHMRC funding application approved</td>
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<tr>
<td>January 2009</td>
<td>Commence study organisation</td>
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<tr>
<td>April 2009</td>
<td>Protocol finalised</td>
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<tr>
<td>April 2009</td>
<td>The Alfred HREC submission</td>
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<tr>
<td>April 2009</td>
<td>Participating sites finalised</td>
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<tr>
<td>June 2009</td>
<td>Monash University HREC submission</td>
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<td>Participating sites HREC submission</td>
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<tr>
<td>September 2009</td>
<td>Ambulance Research Governance Committee approval</td>
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<tr>
<td>November 2009</td>
<td>Study start up meeting</td>
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<tr>
<td>November 2009</td>
<td>Ambulance paramedic training completed</td>
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<tr>
<td>January 2009</td>
<td>Run-in phase commenced at each site</td>
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<tr>
<td>February 2009</td>
<td>Main phase of study commenced</td>
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<tr>
<td>April 2011</td>
<td>50% recruitment completed</td>
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<tr>
<td>November 2011</td>
<td>6 mth follow up of 50% recruitment completed</td>
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<tr>
<td>December 2011</td>
<td>Interim analysis</td>
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<tr>
<td>July 2012</td>
<td>Patient recruitment completed</td>
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<td>January 2013</td>
<td>6mth follow up of 100% recruitment completed</td>
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<td>February 2013</td>
<td>Query resolution and data cleaning completed</td>
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<td>March 2013</td>
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<td>May 2013</td>
<td>Complete data analysis</td>
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<tr>
<td>July 2013</td>
<td>Submission of initial manuscript</td>
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# APPENDIX A: TABLE OF EVENTS

<table>
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<tr>
<th>Event Description</th>
<th>Pre-hospital</th>
<th>ED Admission</th>
<th>ICU Admission</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4-6</th>
<th>Day 7</th>
<th>Day 8-14</th>
<th>Hospital Discharge</th>
<th>Follow Up 6 months</th>
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<tbody>
<tr>
<td>1) Inclusion &amp; Exclusion Criteria</td>
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<td>2) Randomisation</td>
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<td>4) Systolic BP</td>
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<td>5) RR(pre-intubation)</td>
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<td>6) Temperature</td>
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<td>7) Initiation of cooling protocol</td>
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<td>10) Continuation of cooling protocol – temperature control device</td>
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<td>Pre-hospital</td>
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<td>21) GOSE by independent blinded assessor</td>
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(#ab) Rewarming will be dependent on ICP control
21. **APPENDIX B: PRE-HOSPITAL STUDY PROCESS**

Assess patient for study suitability

**Inclusion Criteria**

- Non-penetrating severe TBI (i.e. Glasgow Coma Scale (GCS) ≤ 8)
- Estimated age ≥ 15 and < 60 years of age
- Injury estimated to have occurred within 2 hours of paramedic arrival.
- The patient is intubated

**Exclusion Criteria**

- Pre-intubation airway reflexes are absent
- Pre-intubation Systolic BP <100mmHg
- Pre-intubation heart rate > 120bpm
- Pre-intubation GCS=3 + un-reactive pupils
- Penetrating neck/torso injury
- Obvious pregnancy
- Receiving hospital is not a study site.
- Medi-alert bracelet for Warfarin treatment or if known

*If no exclusion criteria proceed to RANDOMISATION*

Select the randomisation envelope in numerical order.

Document study parameters.

Hypothermia:
If patient temp > 35°C administer chilled 0.9% NaCl IV 100mls/min & keep exposed
If patient temp <35°C no cold fluid, keep exposed

Normothermia:
Standard care
Aim for temperature 36.5-37°C
22. APPENDIX C: EMERGENCY DEPARTMENT STUDY PROCESS

Primary survey following usual protocol

NORMOTHERMIC GROUP:
- Apply surface temperature control pads
- Connect to temperature control module
- Commence temperature control to target temperature 36.5°C - 37°C
- Follow brain injury guidelines

HYPOTHERMIC GROUP
The patient will be assessed for significant bleeding specifically:
- Significant injury to abdominal organ or Positive FAST scan or Positive CT Free Fluid
- Pelvic fracture requiring External Fixation + Angiography
- Retroperitoneal haematoma on CT
- Chest drain in situ with > 300mls drained in ??? time limit
- Transfusion of >2 units packed red blood cells associated with > 2 long bone lower limb fractures

IF NONE OF THE ABOVE PRESENT CONTINUE WITH COOLING PROTOCOL:
- Apply surface temperature control pads
- Connect to temperature control module
- Commence temperature control to target temperature 33°C

WITHHOLD COOLING PROTOCOL IF
- Patient has clinically significant bleeding.
- Rewarm & correct coagulopathy if present.
- Perform any interventions to control bleeding.
- Follow cooling protocol when bleeding controlled

WITHDRAW PATIENT FROM COOLING PROTOCOL IF THE FOLLOWING IS PRESENT
- Significant injury to abdominal organ or Positive FAST scan or Positive CT Free Fluid
- Pelvic fracture requiring External Fixation + Angiography + surgery & pelvic packing
- Significant retroperitoneal haematoma on CT
- Chest drain in situ with > 300mls drained on insertion or > 100mls in the first hour post insertion.
- Transfusion of >2 units packed red blood cells associated with > 2 long bone lower limb fractures
- Positive β HCG
- Normal CT Brain scan & patient localising after decreased sedation
23. APPENDIX D: SEVERE TBI & ICU MANAGEMENT GUIDELINE

LINES/FLUIDS
- Arterial line and CVP
- iv Fluid to CVP 5-10
- 0.9% saline, blood & FFP as indicated.
- Albumin containing solutions & colloids should be avoided.

VENTILATION/OXYGENATION
- $S_aO_2 > 95\%$;
- $P_aO_2 > 90$ mHg;
- $P_aCO_2$ 35-40 mmHg
- Ventilator settings may require adjustment during the induction phase of hypothermia due to decrease in metabolic rate.
- Hb 90-100 gm/L

PATIENT POSITION
- Nurse 30 degrees head up, flexed at waist
- Lay patient flat if known spinal cord injury or if vasopressors (Noradrenaline/Adrenaline 10mcg/min) are being administered
- Elevate the head of the bed if ICP rises more than MAP rises.
- Avoid venous obstruction of neck (check ETT, Tracheostomy, Cervical Collar)

SEDATION
- Morphine 2-20 mg/hr,
- Midazolam 1-20 mg/hr
- ± Propofol 20-200mg/hr

GLYCAEMIC CONTROL
- Maintain BSL 6-8 mmol/L
- Insulin resistance maybe associated with hypothermia

SERUM SODIUM
- Serum Na 140-150 mmol/L

MEAN ARTERIAL PRESSURE (MAP)
- Noradrenaline infusion to MAP > 80 mmHg until ICP inserted

ICP MONITORING
- Monitor ICP - EVD preferred, Codman parenchymal catheter acceptable (see Appendix E ICP control)

EVD DRAINAGE
- EVD Intermittent drainage if ICP>20 mmHg prn (drain for 5 min and monitor for 10 min)
CPP CONTROL

- Target CPP >60mmHg if ICP ≥ 15mmHg
- If ICP ≤ 15mmHg, target MAP
- If CPP <60mmHg, intervene to decrease ICP (See Appendix E)
- Ensure intravascular volume adequate, consider fluid boluses 0.9% saline if not adequate
- Increase or commence a vasopressor to increase MAP.
- Noradrenaline up to 10mcg/min
- Adrenaline can be added if Noradrenaline >10mcg/min
- if Noradrenaline >10mcg/min consider insertion of pulmonary artery catheter (adjust dose vasopressor to achieve reasonable Cardiac Index), or performance of echocardiogram
- Avoid cardiotoxic doses of vasopressors (combined dose of Noradrenaline/Adrenaline > 30-40 mcg/min)
- If high dose vasopressor consider Hydrocortisone (200mg bolus followed by 10mg/hr or 50mg qid) after taking baseline cortisol.
- Avoid Vasopressin as it can increase the risk of water retention and cerebral oedema

SEIZURE PROPHYLAXIS

- Commence phenytoin on admission: usual dose - bolus 15-20mg/kg followed by 300-400mg/daily
- Check phenytoin levels after 3-4 days
- Cease phenytoin after 7 days if seizure free.

VENOUS THROMBO-EMBOLISM PROPHYLAXIS

- Calf compressors & TED stockings should be used in all patients.
- Timing and type of further VTE prophylaxis determined after 2nd CT brain scan & discussion with Neurosurgeon
- Generally Enoxaparin 40mg subcutaneously
- If unable to administer VTE prophylaxis and calf compressors/TEDS cannot be placed twice weekly ultrasounds should be performed
- An IVC filter may be considered if enoxaparin contra-indicated and there is 1. Spinal cord injury, 2. Major pelvic fracture 3. Known venous thrombo-embolism

STRESS ULCER PROPHYLAXIS

- Ranitidine used as 1st line drug unless the patient is known to have been on a proton pump inhibitor.
- Initially Ranitidine 50mg IV tds
- Change to 150mg enterally bd when enteral nutrition is being tolerated.
- Commence a proton pump inhibitor if active gastrointestinal bleeding occurs.

NUTRITIONAL SUPPORT

- Aim for commencement of enteral nutrition within 24 hrs
- Be aware that hypothermia is associated with impaired bowel function & may aggravate gastric emptying problems
- Follow standard care for gastric intolerance

VENTILATOR CARE

- Use new ventilator circuit for each patient
- Change if ventilator circuit becomes soiled
- Use heat and moisture exchangers for airway humidification (if no contraindications)
- Use a new closed endotracheal suction system for each patient and change as clinically indicated
- Use semi-recumbent positioning in patients without contraindications
24. **APPENDIX E: ICP CONTROL**

ICP >20mmHg

- Optimise sedation
  - ICP still >20

- Consider 7.5% HTS (50-100mls) or mannitol (0.5-1.0 gm/kg)
  - ICP still >20

- Increase frequency and length of EVD venting
  - ICP still >20

- Consider repeat CT scan? Surgical intervention required

- Neuromuscular blockade (bolus rather than infusion)
  - ICP still >20

- Bolus thiopentone 4mg/kg
  - ICP still >20

- Thiopentone infusion 100mg/hr
  - ICP still >20

- Increase thiopentone infusion to burst suppression using EEG
25. **APPENDIX F: GLASGOW OUTCOME SCALE**

**POLAR STUDY**

<table>
<thead>
<tr>
<th>Study Number</th>
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Ax DATE ___/___/___

The questions can be answered by the patient or close relative, friend or by rehabilitation/nursing staff if appropriate

**RESPONDENT:**

Patient alone ☐

Relative or friend or carer alone ☐

Patient and relative, friend or carer together ☐

Patient lost to follow up ☐

**The injured person is:**

Out of hospital ☐

In hospital, rehabilitation centre or residential care ☐

**What is the most important factor in recovery?**

Effects of head injury ☐

Effects of illness or injury to another part of the body ☐

A mixture of these ☐

Please answer by ticking one box ☐, which best answers the question.
1. Is the injured person able to obey simple commands, or say any words?

Yes ☐ No ☐ (2-Vegetative State)

2. Before the injury was the injured person able to look after themselves at home?

Yes ☐ No ☐

3. As a result of the injury does the injured person now need some one to help look after them at home? For a no answer they should be able to look after themselves at home (safely) for 24 hrs if necessary. They should not require prompting or reminding and should be capable of being left alone overnight. (Please tick ☐ one box)

- Do not need frequent help or supervision in the home ☐
- Need some help in the home, but can look after themselves for at least 8 hours if necessary ☐ (4-Upper SD)
- Could not look after themselves for 8 hours during the day ☐ (3-Lower SD)
- Need help in the home, but not because of the injury ☐

4. Before the injury was the injured person able to buy things at shops without help?

Yes ☐ No ☐

5. As a result of the injury does the injured person now need help to buy things at shops? (Please tick ☐ one box)

- Do not need help to shop ☐
- Can plan what to buy, take care of money themselves, behave appropriately in public

- Need help to get to the shops but once there can do own shopping ☐
- Need help to shop ☐ (4-Upper SD)
- Need help to shop but not because of the injury ☐

Before the injury was the injured person able to travel without help

Yes ☐ No ☐
6. As a result of the injury does the injured person now need help to travel? Either driving a car, catching public transport or catching a taxi

(Please tick ☐ one box)

Do not need help to travel ☐

Need help to travel ☐ (4- Upper SD)

Need help to travel but not because of the injury ☐

7. Employment before the injury: (please tick ☐ one box)

Working ☐ Looking for work ☐

Looking after family ☐ Studying as a student ☐

Retired ☐ None of these ☐

8. As a result of the injury has there been a change in the injured persons ability to work? (Or to study; or to look after your family) (Please tick ☐ one box)

Still do the same work ☐

Still work, but at a reduced level (eg: change from full time to part time or change in level of responsibility) ☐ (6- Upper MD)

Am unable to work, or only able to work in sheltered workshop ☐ (5- Lower MD)

Ability to work has changed but not because of the injury ☐

9. 10. Before the injury did the injured person take part in social and leisure activities outside home (at least once a week)

Examples include going out with or visiting friends, going to the cinema or live performances, attending sporting events or participating in sporting events, attending religious ceremonies or services

Yes ☐ No ☐

10. As a result of the injury has there been a change in the ability of the injured person to take part in social or leisure activities outside the home?

(Please tick ☐ one box)

Take part about as often as before ☐

Take part a bit less but at least half as often ☐ (7 - Lower GR)
11. Before the injury did the injured person have any problems getting on with friends & family?

Yes ☐ No ☐

12. As a result of the injury does the injured person have any emotional or behavioural problems which cause difficulties in relationships with friends or family?

Examples include quick temper, irritability, mood swings, depression, anxiety, insensitivity to others, rigid thinking, unreasonable or childish behaviour (please tick ☐ one box)

- Things are still much the same ☐
- There are occasional problems (less than one a week) ☐ (7 – Lower GR)
- There are frequent problems (once a week or more) ☐ (6– Upper MD)
- There are constant problems (problems every day) ☐ (5– Lower MD)
- There are problems for some other reason, not because of the injury ☐

13. Are there currently any other problems resulting from the injury?

Problems sometimes reported after head injury: headaches, dizziness or balance problems, tiredness or sleeping disturbances, sensitivity to noise or light, slower speed of thinking, trouble with memory, concentration problems (please tick ☐ one box)

- No current problems ☐
- Some problems, ☐ (7 – Lower GR)
- Some problems for other reasons, not because of the head Injury ☐

14. Before the injury were similar problems present?

(Please tick ☐ one box)
No problems or they were minor problems

Similar problems before

Comments? (add extra page if required)
### GLASGOW OUTCOME SCALE – EXTENDED

(TICK APPROPRIATE SCORE)

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### GLASGOW OUTCOME SCORE

(TICK APPROPRIATE SCORE)

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<tr>
<td>SEVERE DISABILITY (SD)</td>
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<td>MODERATE DISABILITY (MD)</td>
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<tr>
<td>GOOD RECOVERY (GR)</td>
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</table>

**PATIENT LOST TO FOLLOW UP**

(TICK IF APPROPRIATE)
26. APPENDIX G: ASSESSMENT OF QUALITY OF LIFE (AQOL-8)

Instructions: Please circle the alternative that best describes you during the last week

1. When doing household tasks (E.g. preparing foods, gardening, using the video recorder, telephone or washing the car):
   A. I need no help at all
   B. Occasionally I need some help with household tasks
   C. I need help with more difficult tasks
   D. I need daily help with most or all household tasks

2. Thinking about how easily I can get around home or the community:
   A. I get around home and community by myself without any difficulty
   B. I find it difficult to get around my home or the community by myself
   C. I cannot get around the community by myself, but I can get around my home with some difficulty.
   D. I cannot get around the community or my home by myself

3. Thinking about my relationship with other people:
   A. I have plenty of friends, and am never lonely
   B. Although I have friends I am occasionally lonely
   C. I have some friends, but am often lonely for company
   D. I am socially isolated and feel lonely

4. Thinking about my health and my relationship with my family:
   A. My role in the family is unaffected by my health.
   B. There are some parts of my family role I cannot carry out.
   C. There are many parts of my family role I cannot carry out.
   D. I cannot carry out any part of my family role.

5. Thinking about my hearing, including using my hearing aid if needed:
   A. I hear normally
   B. I have some difficulty hearing or I do not hear clearly. E.g I ask people to speak up, or turn up the TV or radio
   C. I have difficulty hearing things clearly. E.g. Often I do not understand what is said. I usually do not take part in conversations because I cannot hear what is said.
   D. I hear very little indeed. E.g I cannot fully understand loud voices speaking directly to me.
6. When I communicate with others: (For example: by talking, listening, writing or signing)
   A. I have no trouble speaking to them or understanding what they are saying.
   B. I have some difficulty being understood by people who do not know me. I have no trouble understanding what others are saying to me.
   C. I am only understood by people who know me well. I have great trouble understanding what others are saying to me.
   D. I cannot adequately communicate with others.

7. Thinking about how I generally feel:
   A. I do not feel anxious, worried or depressed.
   B. I am slightly anxious, worried or depressed.
   C. I feel moderately anxious, worried or depressed.
   D. I am extremely anxious, worried or depressed.

8. How much pain or discomfort do I experience:
   A. None at all.
   B. I have moderate pain.
   C. I suffer from severe pain.
   D. I suffer unbearable pain.
27. **APPENDIX H: EURO QUALITY OF LIFE - (EQ5D)**

*Instructions: Please circle the alternative that best describes you during the last week*

**Mobility**
- A. I need no help at all
- B. Occasionally I need some help with household tasks
- C. I need help with more difficult tasks
- D. I need daily help with most or all household tasks

**Personal care**
- A. I have no problems with personal care
- B. I have some problems washing or dressing myself
- C. I am unable to wash or dress myself

**Usual activities (e.g. work, study, housework, family or leisure activities)**
- A. I have no problems with performing my usual activities
- B. I have some problems with performing my usual activities
- C. I am unable to perform my usual activities.

**Pain/Discomfort**
- A. I have no pain or discomfort
- B. I have moderate pain or discomfort
- C. I have extreme pain or discomfort

**Anxiety/Depression**
- A. I am not anxious or depressed
- B. I am moderately anxious or depressed
- C. I am extremely anxious or depressed
EURO QUALITY OF LIFE - (EQ5D)

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today
28 REFERENCES

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Published Protocol – POLAR Trial


PMID: 26017126

The POLAR-RCT

The Prophylactic hypOthermia trial to Lessen trAumatic bRain injury-Randomised Controlled Trial

(NCT 00987688 & ACTRN12609000764235)

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Ms Lynette Newby
Assoc/Professor Jeffrey Presneill
Dr Stephen Rashford
Professor Jeffrey Rosenfeld
Dr Tony Smith
Mr Michael Stephenson
Mr Tony Trapani
Assoc/Professor Tony Walker
Professor Steve Webb
Professor Gilles Capellier
Assoc/Professor Dinesh Varma
Ms Shirley Vallance

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mailto:anzicrc@monash.edu

This study is endorsed by the
Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS CTG)
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1. MANAGEMENT COMMITTEE AUTHORISATION PAGE

The management committee members have read the attached protocol and authorize it as the official protocol for the study entitled *The prophylactic hypothermia trial to lessen traumatic brain injury – randomised controlled trial. (POLAR RCT)*. The signed original is held on file at the Centre.
This page is intentionally left blank – please refer to page 8.
2. INVESTIGATOR PROTOCOL AGREEMENT SIGNATURE PAGE

I have received and read the prophylactic hypothermia trial to lessen traumatic brain injury – randomised controlled trial (POLAR RCT) study protocol and agree to conduct the study in accordance with:

- The attached protocol (subject to amendments);
- In accordance with the NHMRC National Statement on Ethical Conduct in Human Research (2007); and
- The Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) annotated with Therapeutic Goods Administration comments.

Name of Participating Site: ______________________________

Signature of Investigator: ______________________________ Date: ____________

Printed Name: ______________________________
3. STUDY ADMINISTRATION STRUCTURE

3.1. Coordinating Centre and Data Management Centre
Australian and New Zealand Intensive Care Research Centre (ANZIC-RC) and Department of Epidemiology and Preventive Medicine (DEPM) Monash University, Victoria, Australia

3.1.1. Responsibilities

- Overall management of the study including assistance with HREC 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 research coordinators and POLAR study team
- Protocol training of ambulance paramedics
- Preparation and arrangement of investigator payments
- Study set-up
- Randomisation
- 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

3.1.2. Staff

<table>
<thead>
<tr>
<th>Name</th>
<th>Position</th>
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<tbody>
<tr>
<td>Prof Jamie Cooper</td>
<td>Principal Investigator, ANZIC-RC</td>
</tr>
<tr>
<td>Ms Lynne Murray</td>
<td>Research Manager, ANZIC-RC</td>
</tr>
<tr>
<td>Prof Alistair Nichol</td>
<td>Professor, ANZIC-RC</td>
</tr>
<tr>
<td>Prof Andrew Forbes</td>
<td>Head Biostatistics Unit, DEPM, Monash University</td>
</tr>
<tr>
<td>Prof. Chris Reid</td>
<td>Head, Monash Centre of Cardiovascular Research and Education in Therapeutics (CCRET), Monash University</td>
</tr>
<tr>
<td>Mr Tony Trapani</td>
<td>Project Manager, ANZIC-RC</td>
</tr>
<tr>
<td>A/Prof Michael Bailey</td>
<td>Biostatistician, ANZIC-RC</td>
</tr>
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3.1.3. Meetings

As required.
3.2. Executive Committee

3.2.1. Responsibilities
- Day to Day study management
- Liaise with Management Committee and sites

3.2.2. Members
Professor Jamie Cooper Principal investigator ANZIC-RC
Professor Alistair Nichol Professor, ANZIC-RC
Professor Stephen Bernard Medical Advisor, Ambulance Victoria
Mr Tony Trapani Research Fellow, ANZIC-RC
Ms Lynne Murray Research Manager, ANZIC-RC

3.2.3. Meetings
- Weekly and as required

3.3. Management Committee

3.3.1. Responsibilities
Overseeing all aspects of the study management including:
- Liaison with coordinating centre staff
- Liaison with steering committee
- Liaison with ANZICS CTG
- Liaison with ambulance services
- Overseeing funding applications
- Overseeing disbursement and administration of funds
- Ensuring fiscal responsibilities are maintained
- Development and approval of final protocol and study materials
- Development and approval of data collection tools and methods
- General study management issues

3.3.2. Members
Professor Stephen Bernard Medical Advisor, Ambulance Victoria
Professor Jamie Cooper Principal investigator ANZIC-RC
Professor Peter Cameron Head of Emergency Trauma Research Group, DEPM, Monash University
Professor Andrew Forbes Head Biostatistics Unit, DEPM, Monash University
Dr Colin McArthur Director Critical Care Medicine, Auckland City Hospital
Ms Lynne Murray Adjunct Senior Research Fellow, ANZIC-RC
Ms Lynette Newby Research Coordinator, DCCM, Auckland City Hospital
Professor Alistair Nichol Senior Lecturer, ANZIC-RC
A/ Professor Jeffrey Presneill Staff Specialist, Intensive Care Unit, Mater Hospital
Dr Stephen Rashford Medical Director, Queensland Ambulance Service
Professor Jeffrey Rosenfeld Neurosurgeon, The Alfred
Dr Tony Smith Medical Advisor, St John Northern Region, NZ Ambulance Service
Mr Michael Stephenson MICA Group Manager, Ambulance Victoria
Mr Tony Trapani Research Fellow, ANZIC-RC
3.4. Steering Committee

3.4.1. Responsibilities

- Oversight and advisory role
- Data analysis, collaboration and approval of study publications

3.4.2. Members

- Management committee (as above)
- State/Country Ambulance Service investigators
- Associate investigators*

*Local representatives to be appointed once sites confirmed (suggested: 1 Intensive Care Physician, 1 Neurosurgeon, 1 Emergency Dept Physician, 1 Research Coordinator per site)
3.5. Contact Details

3.5.1. Chief investigator
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### 4. ABBREVIATIONS

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<tr>
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<th>Definition</th>
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<tr>
<td>AE</td>
<td>Adverse event</td>
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<tr>
<td>AKI</td>
<td>Acute Kidney Injury</td>
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<tr>
<td>ANZ</td>
<td>Australia and New Zealand</td>
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<tr>
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<td>Australian and New Zealand Intensive Care Research Centre</td>
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<td>ANZICS</td>
<td>Australian and New Zealand Intensive Care Society</td>
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<tr>
<td>ARC</td>
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<tr>
<td>ARR</td>
<td>Absolute risk reduction</td>
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<td>ATBIS</td>
<td>Australasian Traumatic Brain Injury Study</td>
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<td>BTF</td>
<td>Brain trauma foundation</td>
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<td>CCM</td>
<td>Critical Care Medicine</td>
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<td>CCRET</td>
<td>Centre of Cardiovascular Research and Education in Therapeutics</td>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
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<tr>
<td>CPP</td>
<td>Cerebral Perfusion Pressure</td>
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<tr>
<td>CRF</td>
<td>Case report form</td>
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<tr>
<td>CSF</td>
<td>Cerebrospinal fluid</td>
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<td>Clinical Trials Group</td>
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<td>DEPM</td>
<td>Department of Epidemiology and Preventive Medicine</td>
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<tr>
<td>DSMC</td>
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</tr>
<tr>
<td>ED</td>
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<td>ETT</td>
<td>Endotracheal tube</td>
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<td>HDEC</td>
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<td>HTS</td>
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<td>IMV</td>
<td>Invasive mechanical ventilation</td>
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<td>NEJM</td>
<td>New England Journal of Medicine</td>
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<tr>
<td>NHMRC</td>
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</tr>
<tr>
<td>NNT</td>
<td>Number needed to treat</td>
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<tr>
<td>NOK</td>
<td>Next of kin</td>
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<tr>
<td>QOL</td>
<td>Quality of life</td>
</tr>
<tr>
<td>NS</td>
<td>National statement</td>
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<td>RCT</td>
<td>Randomised controlled trial</td>
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<td>RRI</td>
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<td>RRR</td>
<td>Relative risk reduction</td>
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<tr>
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<td>Rapid sequence intubation</td>
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<td>SAE</td>
<td>Serious adverse event</td>
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<tr>
<td>SF</td>
<td>Short form</td>
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<tr>
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5. LAY DESCRIPTION
Traumatic brain injury (TBI) is a leading cause of death and long term disability, particularly in young adults. Studies from Australia have shown that approximately half of those with severe traumatic brain injury will be severely disabled or dead 6 months post injury. Given the young age of many patients with severe TBI and the long term prevalence of major disability, the economic and more importantly the social cost to the community is very high.

Pre-hospital and hospital management of patients with severe brain injury focuses on prevention of additional injury due primarily to lack of oxygen and insufficient blood pressure. This includes optimising sedation and ventilation, maintaining the fluid balance and draining Cerebrospinal Fluid (CSF) and performing surgery where appropriate. In recent years there has been a research focus on specific pharmacologic interventions however to date there has been no treatment that has been associated with improvement of neurological outcomes.

One treatment that shows promise is the application of hypothermia (cooling). This treatment is commonly used in Australia to decrease brain injury in patients with brain injury following out-of-hospital cardiac arrest. Cooling is thought to protect the brain using a number of mechanisms. There have been a number of animal studies that have looked at how cooling is protective and also some clinical research that suggests some benefit. However at the current time there is insufficient evidence to provide enough proof that cooling should be used routinely for patients with brain injury and like all treatments there can be some risks and side effects.

The POLAR trial has been developed to investigate whether early cooling of patients with severe traumatic brain injury is associated with better outcomes. It is a randomised controlled trial, which is a type of trial that provides the highest quality of evidence.

Unconscious patients will be assessed by ambulance paramedics and if found to be suitable for the trial they will receive cooling by an infusion of chilled salty fluid (Intervention group) or they will be treated in the normal manner (Control group). Allocation to the two groups occurs randomly like flipping a coin. On arrival to hospital, cooled patients will be checked to make sure it is safe to continue cooling and if so they will be cooled by a vest containing cooled water. Control group patients will have their temperature maintained at 37°C using cooling vests if required for fever prevention. The cooled group will have their temperature lowered to 33°C and will be kept cool for at least 3 days. After 3 days their temperature will be slowly raised. If they have any issues with control of brain swelling they will be re-cooled to a temperature that helps maintain control of the swelling. Some patients may also be enrolled into the trial when they are admitted to hospital. All patients will have data collected during the pre-hospital stage and during the hospital admission. The patient’s recovery will be measured at 6 months post the injury.
6. SYNOPSIS

6.1. Background
Traumatic brain injury (TBI) is a devastating condition which affects close to 1,000 people each year in Australia, causes extensive disability and suffering, and costs the country close to 1 billion dollars per year. There is a clear scientific rationale for the use of early prophylactic hypothermia as a treatment following TBI, including laboratory studies, positive clinical trials and meta-analyses. A single multi-centre clinical trial by Clifton et al found no improvement in outcomes in patients treated with prophylactic hypothermia. This trial had important methodological limitations. These limitations, together with new evidence in current meta-analyses have led to prophylactic hypothermia for the first time being suggested as a possible therapy in international guidelines, but not as a “standard of care”. Meta-analyses should be hypothesis generating and should not alone lead to practice change. Therefore, few clinicians are likely to implement prophylactic hypothermia based on the lingering questions of efficacy, logistics, and potentially increased cost. A large, multi-centre randomised controlled trial in Australia and New Zealand with the capacity to demonstrate clinical benefit is urgently required.

6.2. Design
Prospective randomised controlled multi-centre trial of early and sustained prophylactic hypothermia in 500 patients with severe TBI.

6.3. Aim
The primary aim of the study is to determine whether early and sustained prophylactic hypothermia, compared to standard Australian and New Zealand ‘normothermic’ care, is associated with an increased proportion of favourable neurological outcomes six months after severe TBI. The null hypothesis is that there is no difference in the proportions of favourable neurological outcomes between patients assigned to either prophylactic hypothermia or standard normothermic care.

6.4. Patient population
Patients with severe blunt traumatic brain injury who do not have bleeding or other contraindications to cooling.

6.5. Methods
Eligible patients will be randomised in the pre-hospital setting or on admission to the Emergency Department. POLAR study trained paramedics and physicians will screen patients in the pre-hospital setting. Eligible patients will be randomised if they fulfil the inclusion criteria with no pre-hospital exclusion criteria. Those randomised to the normothermia group will follow standard care. For those randomised to the “cooling arm”, pre-hospital prophylactic hypothermia will be induced by exposure and by infusing up to 2 litres intravenous cold (4°C) 0.9% sodium chloride aiming for a core temperature of 35°C during transport. In the emergency department the “cooling arm” patients will be assessed to exclude significant bleeding and, once significant bleeding has been excluded, surface cooling vests/wraps will be applied to reach the target core temperature of 33°C. The patient will be then maintained at this temperature for a further 72 hours. Patients with significant bleeding will have cooling withheld until it is safe to decrease the temperature to the target core temperature of 33°C. Patients who have not been randomised pre-hospital will be re-screened in the ED. Eligible patients will be randomised if they fulfil the inclusion criteria with no ED exclusion criteria. Hypothermia will be induced by administration of up to 2L intravenous ice-cold (4°C) 0.9% sodium chloride followed by application of the surface cooling vests/wraps to achieve the target core temperature of 33°C. Patients allocated to standard ‘normothermic’ care will be maintained at a core temperature of 37°C ± 0.5°C.

6.6. Outcome measures
The primary outcome measure is the proportion of favourable neurological outcomes (Glasgow Outcome Score Extended: GOSE 5 to 8) at six months following injury. Secondary outcome measures include quality of life, mortality and incidence of adverse events.

7. BACKGROUND AND RATIONALE

7.1. Clinical and biological rationale
Traumatic brain injury (TBI) is a leading cause of death and long term disability, particularly in young adults. In a recent analysis of an international database of 2664 patients with severe TBI, mortality was 28%. Of great societal importance, most of the patients who survive TBI have permanent neurological disability. At 6-months, only 52% of these patients had favourable neurological outcomes (good recovery or moderate disability) and were able to live independently and 48% had unfavourable neurological outcomes (dead, vegetative state or severe disability). Given the young age of many patients with severe
TBI and the long term prevalence of major disability, the economic and social cost to the community is very high.

### 7.1.1. Australia and New Zealand Perspective

The ANZICS-CTG identified TBI as a key research area where interventional trials might improve survival and functional outcomes and has conducted key preliminary studies. The prospective Australasian Traumatic Brain Injury Study (ATBIS)\(^4\) was undertaken over a 6-month period during 2001 to determine the prevalence, management strategies and outcomes of TBI patients admitted to intensive care units (ICUs) in Australia and New Zealand (ANZ). There were 363 patients with severe TBI (defined initial Glasgow Coma Score (GCS) \(\leq 8\)) recruited from 16 centres. The twelve-month mortality in patients with severe TBI was 35.1% and the rate of favourable neurological outcomes at 12 months was 48.5%. The ANZICS-CTG then conducted a detailed analysis of the TBI patients in the SAFE study\(^6\) (saline vs. albumin fluid evaluation\(^9\)). The 318 patients with severe TBI had a 32% mortality rate and 46% had favourable neurological outcomes at 24 months. Finally, an interim analysis (n=150) of a pre-hospital trial evaluating paramedic rapid sequence intubation in severe TBI (Rapid Sequence Induction (RSI)\(^7\) trial, ACTRN12605000177651), found a mortality rate of 35% and 59% favourable neurological outcomes at 6 months (personal communication, CI-B).

Clearly, these findings confirm that, despite well-resourced and integrated health systems, severe TBI in Australia and New Zealand continues to carry a high rate of mortality and long term disability. The mean lifetime medical and rehabilitation cost of each TBI survivor with severe disability in Australia currently exceeds $3 million\(^6\). The lifetime cost of caring for the 150 Australian victims of TBI who survive with significant disability each year amounts to nearly a billion dollars. Even a small increase in the number of TBI patients who have favourable rather than unfavourable neurological outcomes, would yield major human and economic savings.

### 7.1.2. Prophylactic hypothermia: a treatment for severe TBI

Current management of TBI is supportive and focuses on prevention and treatment of cerebral hypoxia using sedation, intravenous fluids, monitoring and manipulation of oxygen, intra-cranial pressure (ICP) and cerebral perfusion pressure (CPP)\(^9\). Despite decades of research investigating novel pharmacological therapies for patients with TBI, clinical trials of novel therapies to date have not demonstrated substantial improvements in outcomes\(^10\)-\(^12\). However, the recent landmark paper in the *New England Journal of Medicine* (NEJM)\(^5\) reported that the choice of fluid therapy after primary brain injury may positively influence long term neurological outcomes by decreasing secondary brain injury. This paper restored optimism that it is feasible to decrease secondary brain injury and improve long term outcomes.

Currently, a therapy with great potential to reduce neurological damage and improve outcome after severe TBI is the application of early prophylactic hypothermia\(^13\). This therapy involves the rapid reduction of core body temperature after injury to 33°C, to attenuate brain injury. This treatment is commonly used in Australia and New Zealand to decrease brain injury in patients with severe neurological injury following out-of-hospital cardiac arrest\(^13\).

There is extensive scientific rationale supporting early prophylactic hypothermia as a treatment following TBI including extensive laboratory data, supportive clinical trials and meta-analyses.

### 7.1.3. Laboratory studies of hypothermia in TBI

Many experimental studies have confirmed that moderate hypothermia confers protection against ischaemic and non-ischaemic brain hypoxia\(^14\). Many post-traumatic adverse events that occur in the injured brain at a cellular and molecular level are highly temperature-sensitive and are a good target for induced hypothermia. Hypothermia has demonstrated powerful neuroprotective effects in experimental models and influences multiple biochemical cascades that are set in motion after TBI (secondary brain injury)\(^14\). These mechanisms are multifactorial and include: reduction in brain metabolic rate, positive effects on cerebral blood flow, blockade of excitotoxic mechanisms, calcium antagonism, decrease in oedema, modulation of the inflammatory response and modulation of apoptosis\(^14\). Furthermore, experimental models also suggest that a ‘therapeutic window’ exists where the induction of hypothermia soon after the primary TBI may provide optimal neurological protection leading to improved outcomes\(^15\)-\(^18\).

### 7.1.4. Clinical studies of hypothermia in TBI

Over the past two decades, clinical trials of prophylactic hypothermia in TBI have been conducted and supported a likely benefit\(^13\). These include single centre trials\(^19\)-\(^23\) and a single multi-centre trial\(^1\). Furthermore, a meta-analysis of the highest quality clinical trials of hypothermia in severe TBI was conducted in 2007\(^24\) by the Brain Trauma Foundation (BTF), the recognised international medical body which promulgates evidence-based guidelines for the management of TBI. This meta-analysis reported a significant increase in long term favourable neurological outcomes (Relative Risk (RR) 1.46, 95% confidence interval (95% CI) 1.12 to 1.92, \(p=0.006\), figure 1) with no significant decrease in mortality.
(RR 0.76, 95% CI 0.05 to 1.05, p=0.18) in patients treated with prophylactic hypothermia compared to normothermia.

Figure 1

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Hypothermia nN</th>
<th>Control nN</th>
<th>RR (random) 95% CI</th>
<th>RR (random) 95% CI</th>
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<td>8/22</td>
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<td>76/276</td>
<td>1.01 (0.80, 1.28)</td>
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<tr>
<td>Jiang, 2000</td>
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<td>12/44</td>
<td>1.71 (0.96, 3.04)</td>
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<td>Marion, 1997</td>
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<td>16/42</td>
<td>1.02 (1.02, 3.55)</td>
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<tr>
<td>Qiu, 2005</td>
<td>29/43</td>
<td>16/43</td>
<td>1.75 (1.12, 2.73)</td>
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<tr>
<td>Total (95% CI)</td>
<td>354</td>
<td>344</td>
<td>1.46 (1.12, 1.92)</td>
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</tr>
</tbody>
</table>

The only published multi-centre hypothermia trial reported no improvement in outcomes in patients treated with prophylactic hypothermia. This trial was well conducted but had key methodological limitations.

First, there was an average delay of 8.4 hours in attaining the target temperature. This delay was largely due to inferior cooling technology and this may have confounded detection of a protective effect. The subgroup of patients in this trial who were initially hypothermic and then randomised to hypothermia had a significant long-term neurological advantage compared to normothermia. Future trials should induce hypothermia as early as possible and ideally at the location of the traumatic event. There is considerable Australian and international experience with paramedic-initiated early hypothermia for cardiac arrest, and this experience can be applied to severe TBI patients.

Second, in severe TBI the generalised swelling of brain tissue frequently persists for over 48 hours. It is therefore likely that therapeutic levels of hypothermia lasting for only 48 hours (in the Clifton trial) were insufficient. This assertion is supported by the BTF meta-analysis finding that trials of prophylactic hypothermia longer than 48 hours were associated with significantly reduced mortality (RR 0.51; 95% CI 0.34 to 0.78).

Therapeutic levels of hypothermia should be induced in excess of 48 hours, which has been well tolerated in patients with severe TBI.

Third, the Clifton trial withdrew hypothermia on a time-based trigger rather than according to a physiological trigger. Rewarming of patients despite increases in intracranial pressure is not considered optimal clinical practice. Hypothermia should be withdrawn using a physiological trigger (i.e. ICP) and over a prolonged period to avoid uncontrolled intracranial hypertension.

Fourth, the Clifton trial induced and maintained hypothermia using cooling blankets and bags of ice. This practice is associated with difficulty achieving a constant patient temperature and problems targeting gradual re-warming. The recent development of electronically controlled surface (skin) cooling pads through which cold water is channelled has revolutionised the controlled induction, maintenance and ultimate emergence from hypothermia.

Finally, the lack of a ‘run in’ period, lack of protocolised brain specific care, the inclusion of low-enrolment centres and the large inter-centre variance in the Clifton trial may have further confounded the detection of a protective effect. Interestingly, when the problematic Clifton trial was excluded from the BTF meta-analysis, a pooled estimate demonstrated a significant reduction of mortality (RR 0.64; 95%CI 0.46 to 0.89).

### 7.1.5. Potential adverse effects and complications of hypothermia

Despite a temperature of 33°C being perhaps the ideal balance of therapeutic effect and potential adverse side-effects, it is important to consider the potential complications, specifically coagulopathy and infection. Hypothermia may prolong clotting times and alter platelet function and this could lead to increased blood loss. However, this may not significantly increase bleeding in the context of severe TBI.

Future trials of prophylactic hypothermia such as this one should include a strategy to minimise potential risks of bleeding. For example, induction of mild hypothermia (minimum temperature 35°C) in the field to optimise brain protection, while limiting the risk of coagulopathy prior to a robust assessment of bleeding in the Emergency Department (ED). Meta-analyses reported increased pneumonia in patients cooled for prolonged periods. While it has previously been demonstrated in a small study that this increased rate of infection did not increase mortality, any future trial should incorporate optimal standard of care measures to reduce infectious complications.

Hypothermia decreases clearance of drugs that are cleared by the liver. These include propofol, midazolam and morphine which will accumulate over time unless doses are reduced.
The cooling phase of hypothermia is associated with hypokalaemia and hypomagnesaemia. The rewarming phase is associated with hyperkalaemia and hypermagnesimia.\textsuperscript{40}

\textbf{7.1.6. The requirement for a multi-centre phase III trial of prophylactic hypothermia in severe TBI}

Methodological shortcomings of the Clifton trial, together with limited evidence in recent meta-analyses\textsuperscript{9} has led to prophylactic hypothermia for the first time being suggested as a possible therapy in the international BTF guidelines, but not a "standard of care". Meta-analyses are best considered as hypothesis generating and should never form the basis for changes in clinical practice. Therefore, despite this recommendation, few if any clinicians are likely to implement prophylactic hypothermia owing to lingering concerns of efficacy, logistics, and increased costs. A large, multi-centre randomised controlled trial with the capacity to demonstrate benefit is required.

Currently, 2 multi-centre phase III trials of prophylactic hypothermia in severe TBI are underway (USA; NCT00178711, Japan; NCT00134472). However, there are a number of reasons why an Australian multi-centre phase III trial of prophylactic hypothermia in severe TBI is urgently required. First, these trials may not succeed, being underpowered to detect a plausible improvement in patient-centred outcomes, and by repeating previous methodological concerns such as insufficient duration of hypothermia, time based triggers for rewarming and the lack of a national hospital / ICU research network. Second, there are substantial differences in organisational and training structures of pre-hospital care and transport, emergency departments and ICUs between Australia and other countries\textsuperscript{32}. Finally, the standard of emergency and ICU care in Australia and New Zealand is high. The ATBIS survey found that Australian and New Zealand TBI patients are more likely than European patients to receive invasive monitoring.\textsuperscript{4} Therefore, if prophylactic hypothermia was shown to be beneficial in a setting where care levels are high, it would likely change practice not only in Australia and New Zealand but also internationally.

\textbf{7.2. Significance}

If prophylactic hypothermia is found to improve neurological outcomes, given the high disability rate, at least 200 patients per year will have significantly improved neurological outcomes in Australia/New Zealand by the widespread application of prophylactic hypothermia. If standard ‘normothermic’ care is shown to be equivalent, or even superior to prophylactic hypothermia, patients will be able to continue to receive less invasive and less expensive care and the features of Australian/New Zealand standard care can be used to inform practice worldwide.

\section{8. OBJECTIVES}

\textbf{8.1. Aim}

The primary aim of the study is to determine whether early and sustained prophylactic hypothermia, compared to standard ‘normothermic’ care, is associated with an increased proportion of favourable neurological outcomes six months after severe TBI.

\textbf{8.2. Null Hypothesis}

That there is no difference in the proportion of favourable neurological outcomes six months after severe traumatic brain injury in patients treated with early and sustained hypothermia, compared to standard normothermic management.

\section{9. STUDY OUTCOME MEASURES}

\textbf{9.1. Primary outcome}

The proportion of favourable neurological outcomes (Glasgow Outcome Score Extended: GOSE 5 to 8) at six months following injury

\textbf{9.2. Secondary outcome}

- Probability of an equal or greater GOSE level at 6 months compared to the probability of a lesser GOSE level, using a proportional odds model
- Probability of an equal or greater GOSE level at 6 months compared to the probability of a lesser GOSE level using the “sliding dichotomy” method
- Quality of life assessments (QOL)
  - EQ5D
- SF12

- Proportion of favourable (GOSE 5-8) neurological outcomes in survivors at six months following injury
- Mortality (all cause) at
  - six months
  - hospital discharge
- Incidence of adverse events, specifically:
  - Bleeding
  - Infection.
- Health economic evaluation
- Test for interaction between time to reach 33°C and dichotomised GOSE scores in the hypothermic group
- Test for interaction between the effect of cooling on neurological function at 6 months and the presence of surgically evacuated mass lesions.

10. OVERALL STUDY DESIGN

10.1. Study population
Patients with severe blunt traumatic brain injury.

10.2. Pre-hospital Inclusion Criteria
- Blunt trauma with clinical diagnosis of severe TBI and GCS <9
- Estimated age ≥ 18 and < 60 years of age
- The patient is intubated or intubation is imminent

10.3. Pre-hospital Exclusion Criteria
- Clinical diagnosis of drug or alcohol intoxication as predominant cause of coma
- Randomisation unable to be performed within 3 hrs of estimated time of injury
- Estimated transport time to study hospital >2.5hrs
- Able to be intubated without drugs
- Systolic BP <90mmHg
- Heart rate > 120bpm
- Cardiac arrest at the scene or in transit
- GCS=3 + un-reactive pupils
- Penetrating neck/torso injury
- Known or obvious pregnancy
- Receiving hospital is not a study site
- Evidence of current anti-coagulant treatment
- Known to be carer dependent due to a pre-existing neurological condition

10.4. Emergency Dept Inclusion Criteria
- Blunt trauma with clinical diagnosis of severe TBI and GCS <9
- Estimated age ≥ 18 and < 60 years of age
- The patient is intubated or intubation is imminent

10.5. Emergency Dept Exclusion Criteria
- Clinical diagnosis of drug or alcohol intoxication as predominant cause of coma
• Randomisation unable to be performed within 3 hrs of estimated time of injury
• Able to be intubated without drugs
• Persistent Systolic BP <90mmHg
• GCS=3 + un-reactive pupils
• Cardiac arrest at the scene or in transit
• Clinically significant bleeding likely to require haemostatic intervention, for example:
  o Bleeding into the chest, abdomen or retro-peritoneum likely to require surgery +/- embolisation
  o Pelvic fracture likely to require surgery +/- embolisation
  o More than two long bone fractures requiring operative fixation
• Penetrating neck/torso injury
• Positive urine or blood pregnancy test
• Evidence of current anti-coagulant treatment
• Known to be carer dependent due to a pre-existing neurological condition
• In the treating clinician’s opinion, “cooling” is not in the patient’s best interest

10.6. Co-enrolment
Co-enrolment of participants in other randomised controlled trials will not be permitted.
11. PARTICIPATING STUDY SITES

Australia and New Zealand
- Alfred Hospital, Melbourne, Australia
- Royal Melbourne Hospital, Melbourne, Australia
- Princess Alexandra Hospital, Brisbane, Australia
- Gold Coast University Hospital
- Royal Perth Hospital, Perth, Australia
- Sir Charles Gairdner Hospital, Perth, Australia
- Auckland City Hospital New Zealand
- Waikato Hospital, Hamilton, New Zealand

International
- Hôpital Jean Minjoz, Besancon, France
- Hôpital Gabriel Montpied, Clermont-Ferrand, France
- Hôpitaux Universitaires de Strasbourg, Strasbourg, France
- Hôpital de La Cavale Blanche, Brest, France
- King Abdullahaziz Medical City, Riyadh, Kingdom of Saudi Arabia
- Bern University Hospital, Bern, Switzerland
- Hamad General Hospital, Doha, Qatar

12. STUDY PROCEDURES

12.1. Pre-hospital assessment of patient for study suitability
Patients will be assessed by study trained and affiliated ambulance paramedics &/or physicians. If they fulfil the inclusion criteria and have no exclusion criteria they will be randomised by opening the next opaque envelope in the randomisation series kept in each participating ambulance. The envelopes will contain a wristband to be placed on the patient and a label which designates the study number and treatment allocation. A small number of details will be completed on the wristband and label (Patient's initials, Date and time of randomisation). The label will be placed in the patient's hospital medical record on hospital arrival. The ambulance paramedics/physicians will also document the randomisation of the patient on the ambulance case report form. The wristband and label in the patient's medical record will alert hospital staff to the patient's enrolment in the study.

12.2. Pre-Hospital Standard study care (normothermia - control group)
Patients randomised to the standard care arm, will be transferred to the nearest participating centre with no exposure and no cold fluids during transport. If the patient's core temperature is <36.5°C the patient will be transported covered by blankets in a heated vehicle in accordance with usual clinical practice.

12.3. Pre-hospital study intervention- Induction of hypothermia
The prophylactic hypothermia protocol will be commenced at the scene. Hypothermia will be induced pre-hospital by exposure and by intravenous (IV) infusion of ice-cold (4°C) 0.9% sodium chloride (similar to the RICH26 and other27 trials) to achieve a target core temperature of 35°C during transport.

To avoid fluid overload the volume of cold fluid administered will be dependent on intubation status
- Randomised after intubation – give 1000ml cold normal saline (100mls/min)
- Randomised before intubation – give 2000ml cold normal saline (100mls/min)
If the patient’s temperature is <35°C the patient will not receive cold fluid however they will be transported to hospital with a light covering.

12.4. Patient review on ED arrival
On arrival in the emergency department the patients randomised to the “cooling arm” will be assessed for:

Clinically significant bleeding including but not limited to:
- Bleeding into the chest, abdomen or retro-peritoneum likely to require surgery +/- embolisation
- Pelvic fracture likely to require surgery +/- embolisation
- More than two long bone fractures requiring operative fixation

If in the treating clinician’s opinion there is clinically significant bleeding (or a high risk of clinically significant bleeding), further cooling will be withheld and the patient maintained at a core temperature of 35-37°C. Hypothermia will be re-instituted as soon as possible following successful control of bleeding.

If hypothermia cannot be reinstituted within 48hrs of the injury the patient will be withdrawn from the “cooling arm” protocol and will follow standard management.

12.5. Drug and/or alcohol affected patients with normal CT brain
Patients who are clinically significantly drug or alcohol affected with a normal brain (or minor injury only) on CT imaging, will have the study intervention of active cooling withheld until they can be clinically assessed. Whilst waiting for drugs and alcohol to clear the patient will be kept sedated and at 35°C. Sedation will be weaned and a clinical assessment performed at the clinician’s discretion. If during clinical assessment the patient shivers significantly they may be warmed to a core temperature of 36°C.

The patient will have the study intervention of cooling withdrawn and will receive standard management if:
- They localise or obey when clinically assessed, and or
- In the treating clinician’s opinion they do not have a severe TBI, and or

In the treating clinician’s opinion they do not require an ICU admission. Data will be collected and the follow up assessment performed on all patients who have the study intervention withdrawn.

If the patient’s motor score is withdrawal or worse (GCS(m)<4) they will be re-sedated, have the surface cooling vests/wraps applied and will continue in the “cooling arm”.

12.6. Hospital assessment of patient for study suitability
Patients who have not been enrolled in the study pre-hospital will be assessed for study suitability on arrival in the ED. If they fulfil the inclusion criteria and have no exclusion criteria they will be randomised by opening the next opaque envelope in the randomisation series kept in the ED. The envelopes will contain a wristband to be placed on the patient and a label which designates the study number and treatment allocation. A small number of details will be completed on the wristband and label (Patient’s initials, Date and time of randomisation). The label will be placed in the patient’s hospital medical record. The wristband and label in the patient’s medical record will alert hospital staff to the patient’s enrolment in the study.

12.7. ED study intervention – Induction of hypothermia
The prophylactic hypothermia protocol will commence immediately following randomisation. Hypothermia will be induced by exposure and intravenous infusion (IV) of ice-cold (4°C) 0.9% sodium chloride (similar to the RICH20 and other21 trials) to achieve a target core temperature of 35°C.

To avoid fluid overload the volume of cold fluid administered will be dependent on intubation status
- Randomised after intubation – give 1000ml cold normal saline (100mls/min)
- Randomised before intubation – give 2000ml cold normal saline (100mls/min)

12.8. Temperature control system
Temperature control of the “cooling arm” patients will be achieved using a temperature control console and surface temperature control vests/leg wraps/blankets which facilitate thermal transfer. The vests/leg wraps/blankets will be applied by nursing staff to approximately 40% of the body surface area. Temperature control will be initiated in the ED after the patient has been reviewed.
12.9. Standard study care (normothermia – control arm group)
The core temperature of 36.5-37.5°C will be targeted in the control group patients. Active warming with blankets and other standard measures may be required to achieve the target temperature. Febrile patients (defined as temperature >38°C will be treated by paracetamol if clinically suitable, and by the application of temperature control vests/wraps/blankets with a target core temperature of 37 (+0.5°C)

12.10. Study intervention (hypothermia – cooling arm group)
The temperature control vest/wraps/blankets will be applied as soon as possible with a target core temperature of 33°C to be achieved by rapid cooling.

12.10.1. Withholding (temporary cessation) hypothermia
If a patient allocated to hypothermia develops clinically significant bleeding at any time, cooling will be withheld and they will be rewarmed (to 35°C - 37°C core temperature). Patients in whom any such bleeding is controlled may resume the hypothermic protocol (to 33°C) within 48 hours of the initial injury. Patients with bleeding controlled but requiring surgery will have hypothermia withheld and will be rewarmed to 35°C - 37°C. They will be reviewed for significant bleeding following the surgery and will resume the hypothermia protocol as soon as possible if there are no bleeding concerns.

12.10.2. Withdrawal (permanent cessation) of hypothermia
Patients with:
- Significant bleeding which prevents initiation of cooling within 48hrs post injury
- Positive urine or blood pregnancy test
- Normal CT Brain scan and patient localising or obeying after decreased sedation
- In the treating clinician’s opinion, the patient does not require an ICU admission
- In the treating clinician’s opinion, hypothermia is not in the patient’s best interest

Will have cooling permanently withdrawn and will follow the standard care control group protocol.

Data will be collected and the follow up assessment performed on all patients who have the study intervention withdrawn.

12.11. Rewarming protocol
72 hours after randomisation, the hypothermic patient will be assessed for suitability for controlled, active, gradual rewarming (0.17°C per hour) to 37°C. It is imperative that rewarming occurs slowly. The recommended maximum rate of rewarming using the Gaymer Meditherm III is 0.5°C every 3 hours. It is imperative that core temperature is utilised. (See “Appendix F: Cooling and Rewarming Guidelines”).

Prior to commencing rewarming assess the patient’s ICP, haemodynamic and electrolyte status (esp. potassium and magnesium which may alter during rewarming). Correct any abnormalities. Rewarming should only commence if the ICP is <20mmHg and stable. If at any time during the rewarming process there is a sustained rise in ICP (>20mmHg for > 5mins) the patient will be re-cooled to a temperature that controls the ICP (minimum core temperature 33°C). The patient will remain at this temperature until the clinician determines it is appropriate to recommence warming of the patient. Assessment for further rewarming will occur daily or earlier at the clinicians’ discretion. Transient rises in ICP due to suctioning, turning and coughing may not require cessation of rewarming.

Patients will be carefully monitored to ensure that hypotension is promptly treated with an initial small fluid bolus and/or by vasopressors. If the patient continues to be haemodynamically unstable rewarming will cease until stability is achieved.

Patient’s electrolyte status (esp. potassium and magnesium) should be monitored and electrolyte levels corrected during rewarming.

During rewarming there is an increased risk of shivering (esp. between 34°C to 35°C). As shivering greatly increases metabolic demand it is vital that shivering is monitored and managed quickly and aggressively. (See Appendix F: cooling and rewarming Guidelines)

The maximum protocolised period of hypothermia will be 7 days.

Once a patient has completed re-warming and reached 37°C, they will be maintained at normothermia (below 38°C) using the surface cooling pads up to a maximum of 7 days or until the patient is discharged from ICU if prior to 7 days.

In the control group pyrexia above 38°C should be avoided, for up to 96 hours post randomisation. After 96 hours post randomisation patients should be managed as per unit protocol. (Surface cooling systems may be utilised for control patients)
12.12. TBI management & ICU management

Patients enrolled in both the hypothermia and normothermia groups will be managed according to current international evidence based guidelines\(^9\) including insertion of an ICP monitor unless sedation and clinical assessment is planned or insertion is contraindicated (note: ICP monitor should not be removed in the hypothermia group until rewarming has been completed). This protocolised care (as previously used by ANZICS CTG TBI network in DECRA and HTS\(^{11}\) trials) includes a stepped regimen for both the management of increased intra-cranial pressure (ICP) (>20mmHg) and severely lowered cerebral perfusion pressure (CPP) (<60mmHg), and targets for fluid management.

ICU management guidelines to ensure optimal standard of care and reduction of infectious complications have been developed.

See Appendix D

12.12.1. Fluid management

Fluid overload may contribute to cerebral oedema. Therefore after resuscitation during the first 24hours, positive daily fluid balances > 500mls should be avoided. In the absence of hypovolaemia, periods of relative hypotension should be managed primarily with vasopressors (adrenaline/noradrenaline).

12.13. CT Brain scans

On conclusion of recruitment the admission CT Brain scan will be assessed by a Neurosurgeon or Neuroradiologist blinded to the treatment group using the Marshall Grading system.\(^{32}\)(De-identified CT brain scans will be forwarded to the coordinating centre for assessment).


To ensure appropriate treatment, participants must be monitored closely and investigation results known to the treating clinical staff. As patient safety is paramount, and a key patient vital sign (temperature) is due to the treatment itself, it is not possible to blind clinical staff as to the patient’s treatment allocation. Bias will be minimised by concealed treatment allocation prior to randomisation, by protocolised treatment in both groups, and by assessment of the primary outcome by centralised, blinded and trained research staff (as accomplished successfully in recent studies including SAFE\(^6\), SAFE-TBI\(^5\), HTS\(^4,11\), and ATBIS\(^4\)). The primary outcome measure is robust and subject to minimal ascertainment bias.

12.15. Contamination

Contamination will be minimised by using:

- Standardised and protocolised patient management in both groups by paramedics and emergency department staff
- Clearly distinct temperature goals.

Patients in the normothermia group who develop a strong clinical indication for induced hypothermia, such as for the therapy of refractory intracranial hypertension not responsive to other measures, will be permitted to receive a therapeutic reduction in core temperature below 37°C, down to a minimum of 35°C.

12.16. Study pilot/run-in phase

A study pilot/run in phase will be conducted at the lead site. This will involve enrolling 4 patients in the ED. The 4 pilot/run in phase patients will be allocated to receive hypothermia. The pilot/run in phase will allow the co-ordinating centre to optimise and refine the protocol paying particular attention to inclusion/exclusion criteria, safety assessment on hospital admission and administration of the cooling, rewarming protocol and resolving any unforeseen logistical issues.

A study run-in phase will also be conducted at all other sites. The first two patients at each site will be allocated to hypothermia in the ED. The purpose of this run-in period is to allow the co-ordinating centre to check site adherence to the prescribed protocol to ensure minimum site variance in management and to allow site feedback before commencing the study.

12.17. Randomisation

Randomisation will be performed by the paramedics/physicians using a closed envelope system including block randomisation (RSI\(^7\) and RICH\(^{26}\) trials). Treatment allocation will be stratified by 2 strata:

- A four level variable of Victoria / Queensland / Western Australia / New Zealand
- A two level variable of pre-hospital enrolment or emergency department enrolment

Eligible patients will be randomised to normothermia (standard care) or prophylactic hypothermia in a 1:1 ratio.
12.18. Table of events
See Appendix A

13. ETHICS

13.1. Guiding principles
This study will be performed in accordance with the ethical principles of the Declaration of Helsinki (June 1964 and amended 1975, 1983, 1989, 1996, 2000, 2008 and Note of Clarification 2002 and 2004), ICH GCP Notes for Guidance on Good Clinical Practice (CPMP/ICH/135/95) annotated with Therapeutic Goods Administration comments and NHMRC National Statement on Ethical Conduct in Research Involving Humans (March 2007).

13.2. Ethical issues of the study
The two ethical considerations in this study are:

- Emergency research and consent
- The risk/benefit ratio of the study treatment.

13.2.1. Emergency research and consent
Some research must necessarily be performed on patients in emergency (definition is unexpected) situations when they are unable to provide consent, as with all other categories of patients. The principle of justice requires this to be the case. This study constitutes emergency research. Principle 29 of the Declaration of Helsinki acknowledges that some clinical research will involve patients who are physically incapable of giving consent “Research on individuals from whom it is not physically possible to obtain consent, including proxy or advance consent, should be done only if the physical or mental condition that prevents obtaining informed consent is a necessary characteristic of the research population”.

To be eligible for recruitment in this study patients will be unconscious (GCS<9) and consequently will be unable to consent to participation. The study intervention must be instigated as soon as possible by the paramedics/physicians in the field or ED; thus consent/assent cannot be sought from the participant’s next of kin (NOK)/person responsible. The National Statement (NS) on Ethical Conduct in Research Involving Humans (March 2007) acknowledges in section 4.4 that research involving patients who are heavily dependent on medical care in emergency circumstances, such as the patients in this study, may proceed when the participants ability to give consent is nonexistent. This requires approval from the appropriate ethical body to waiver or defer consent (section 7.3).

13.2.2. Risk/benefit ratio of study treatment
As discussed previously in section 7.1 current literature supports a likely benefit from the use of prophylactic hypothermia in severe TBI1.2 These include single centre trials19-23 and a single multi-centre trial1. Furthermore, a meta-analysis of the highest quality clinical trials of hypothermia in severe TBI was conducted in 20079 by the Brain Trauma Foundation (BTF), the recognised international medical body which promulgates evidence-based guidelines for the management of TBI. This meta-analysis reported a significant increase in long term favourable neurological outcomes (RR 1.46, 95% CI 1.12 to 1.92, p=0.006, figure 1) with no significant decrease in mortality (RR 0.76, 95%CI 0.05 to 1.05, p=0.18) in patients treated with prophylactic hypothermia compared to normothermia. The only published multi-centre hypothermia trial in adults1 reported no improvement in outcomes in patients treated with prophylactic hypothermia. This trial was well conducted but had methodological limitations discussed previously in section 7.1.

As with most treatment interventions there are some potential associated risks. Patients with severe TBI are at increased risk for ventilator-associated pneumonia (VAP) and it is thought that the risk may potentially increase with hypothermia.36 The risk of VAP and other infections in this study will be minimised by utilising guidelines for optimal standards of care to reduce infectious complications.

Coagulopathy can also occur with cooling although to date none of the large clinical trials in patients with TBI has reported significantly increased risk of bleeding associated with hypothermia.37 However to minimise potential risks of bleeding, induction of mild hypothermia (minimum core temperature 35°C) in the field will be utilised to optimise brain protection, while limiting the risk of coagulopathy prior to a robust assessment of bleeding in the ED. Once admitted to hospital the participant will be reviewed to ensure that there is no significant bleeding and that it is safe to continue to receive the study intervention. Patients randomised in the field to the hypothermia group with haemodynamic instability presumed secondary to bleeding will be rewarmed until bleeding is controlled. Patients in whom bleeding is clearly controlled (i.e. correction of surgically-isolated lesions), will later resume the hypothermic protocol.
Over time low electrolyte levels may develop in the induction phase of cooling due to increased renal excretion and intracellular shift.38 Electrolytes are measured regularly as part of standard intensive care and abnormalities can be treated accordingly. Potassium levels may rise during the rewarming phase as potassium that was transferred into the cell in the induction phase is released.38 Controlled slow rewarming will give the kidneys time to excrete any excess potassium. Hypovolemia can occur due to "cold diuresis" during the induction phase.38 Haemodynamic parameters will be monitored carefully and if instability develops a fluid challenge test would be warranted.

Cardiac arrhythmias have been linked to cooling however there is no hypothermia-induced risk for severe arrhythmias unless core temperature decreases to <30°C.39 Bradycardia may occur when the core temperature drops below 35.5°C. The bradycardia may not require treatment however, bradycardia (<50 beats/min) associated with hypotension may respond to a low dose chronotropic agent (e.g. Adrenaline). Temperature will be tightly controlled at 33°C i.e.; above the temperature range known to cause harmful arrhythmias. Patients will have constant cardiac monitoring as part of standard intensive care.

Hypothermia can simultaneously decrease insulin sensitivity and reduce insulin secretion by pancreatic islet cells. Patients treated with hypothermia will be at a higher than average risk for developing hyperglycaemia.39 Patients have blood glucose tests performed regularly and control of hyperglycaemia forms a part of regular intensive care.

There is an increased risk of feeding intolerance in patients with traumatic brain injury.40 The risk may increase with hypothermia as cooling may impair bowel function and delay gastric emptying. Feeding rates and tolerance will need to be carefully monitored and appropriate measures instituted if feeding intolerance develops.

Hypothermia decreases drug clearance and may lead to drug accumulation. Sedation is utilised during hypothermia induction to minimise shivering. Once 35°C has been reached consideration should be given to ceasing propofol and dose reducing opiates. Fentanyl may also be considered as an alternative to morphine for pain control. Barbiturates can be considered for ICP control as required.

Hypothermia can also alter the movement of electrolytes such as potassium and magnesium, during the cooling and rewarming phases. Electrolyte levels will be monitored.

13.3. Ethics committee approval
In Australia, this protocol will be submitted to a Human Research and Ethics Committee constituted according to the NHMRC National Statement on Ethical Conduct in Research Involving Humans (March 2007) for each institution. In New Zealand, this protocol will be submitted to the appropriate Health and Disability Ethics Committee, accredited by the Health Research Council and constituted in accordance with the Operational Standard for Ethics Committees March 2006. Ethical clearance from the appropriate legal body will be required from any participating sites in other countries. Approval will also be sought using the appropriate legislative requirements for each state and country. Approval of the protocol, plans for obtaining consent, and related documents will be obtained prior to the start of the study at each site.

It is the investigator’s responsibility to ensure that all conditions for approval of the study are met and that amendments to the protocol or serious adverse events are also reported to the HREC (or equivalent) as required by that committee.

13.4. Confidentiality of patient data
Patients will be randomised either pre-hospital or in ED and will receive a study number. The Research Coordinator will compile a study enrolment log which will link the study number to the patient name. Subsequent data will be identified by the study number. The enrolment log and study data will be kept separately. Follow up details of the patient and their family will be collected including name, address and contact telephone numbers. The contact details will be forwarded to the co-ordinating centre. The co-ordinating site will perform the follow up assessments to ensure consistency and accuracy. All data collected in the follow up assessment will be identified by the study code. The follow up contact details and study data will be kept separately. Study data will be entered into a password protected database managed by the CCRET (Monash University). 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 site.

13.5. Informed consent
Unconscious patients with severe head injury will not be able to provide informed consent. This trial will therefore use deferral of consent, in accordance with section 4.4 of the NS.34 This approach has proven successful for 5 previous NHMRC funded randomised trials (including TBI and pre-hospital trials) - (SAFE6, RBI7, RICH28, out of hospital cardiac arrest41 and HTS5 trials).
As soon as is reasonably possible and appropriate the patient’s NOK/person responsible will be informed of the patient's inclusion in the research and will be informed of the option to withdraw the patient from it without any reduction in quality of care (NS 4.4.14). If the NOK/person responsible chooses to withdraw their consent for continued participation they will be asked for permission to use the data collected up to that time.

Patients who recover sufficient cognition to understand the explanation of the study will be asked to consent to continue in the study or be offered the chance to withdraw. If the patient chooses to withdraw from the study, they will be asked for permission to use their data up to the time of withdrawal (as per 4.4.14).

All interaction between research staff and participants and their relatives will take into consideration the stress or emotional factors associated with critical illness and ensure that the dependency of potential participants and their relatives on medical personnel providing treatment does not compromise their actual or perceived freedom of decision making to participate (as per 4.4.11).

14. DATA MANAGEMENT

14.1. Data collection methods
All data will be collected by trained staff at each study site using a paper source document developed by the coordinating centre. Data will then be entered into a website designed by the CCRET. Data queries will be automatically generated via the website.

Randomised patients will be followed up to death or six months post-randomisation. Data collection will be restricted primarily to those variables necessary to define clinical patient characteristics including: baseline demographics, primary diagnoses, physiological parameters, diagnostic interventions, therapeutic interventions and documentation of deaths and other serious adverse events.

Patients and/or their legal surrogates will be asked to provide 3 possible points of contact (home and close family contact details) to the research staff prior to discharge. For patients discharged alive from ICU, follow-up will be restricted to information concerning duration of hospital stay and vital status at hospital discharge and six months. Full protocol data will be collected in all patients including those excluded at any stage. In addition, patients who are alive at 6 months after randomization (or a proxy – generally a close family member) will be interviewed by a single, trained and blinded assessor. This blinded assessor will use a standardized structured telephone questionnaire to measure the eight-grade GOSE, and a QOL assessment EQ5D and SF12. Neurological outcomes will then be defined as favourable (GOSE 5 to 8; moderate disability and good recovery) or unfavourable (GOSE 1 to 4; death and severe disability). Patients allocated to the prophylactic hypothermia group in whom hypothermia is subsequently withdrawn for any reason (i.e. bleeding) will be followed up, according to the study follow-up schedule and analysed on an intention-to-treat principle.

Health economic data related to utilisation of medical services post hospital discharge will be collected. The transport accident commission and accident compensation corporation will assist with provision of health economic data.

14.2. Data variables collected

**Pre-hospital**
- Patient identifier(s)
- Baseline demographics
- Incident details
- Pre-hospital vital signs, Glasgow coma scale and temperature
- Date and timing of cooling intervention
- Type and volume of fluid therapy

**Hospital admission**
- Vital signs, Glasgow coma scale
- Pregnancy test (female)
- Date & time of surface temperature control vests/leg wrap application
- Haematological and biochemical parameters
- Hourly core temperature
Data management will be performed by the CCRET. Streamlined data collection instruments and procedures will be developed using experience from our previous TBI trials (HTS^11, RSI^7, ATBIS^4, SAFE-TBI^5).

**Data management**

Prior to study commencement, a start-up meeting will be held for study staff. During the study, the project manager will make one monitoring visit following the study run-in phase and at least one other monitoring visit to each site during the recruitment period. The purpose of these visits is to ensure the study is conducted according to the protocol, all applicable guidelines and regulations, and to perform source data verification.
A monitoring report will be prepared following each visit and reviewed by the management committee. A copy of the report will be sent to the principal investigator and study coordinator at the site and will be filed in the site investigator file.

Medical records, any other relevant source documents and the site investigator files must be made available to the monitor for these monitoring visits during the course of the study and at the completion of the study as needed.

14.5. Aims of monitoring visits:
- Check the accuracy of the database by performing source data verification of the CRF against the original source documents.
- Check for protocol violations or deviations and report these to the chief investigator as necessary.
- Review secondary outcome data available for each patient.
- Confirm the consent procedures approved by the site’s HREC have been followed and view each original signed consent form.
- Check data security and access.
- Review all serious adverse events (SAEs) and follow up all reported SAEs.
- Review investigator site files for completeness and accuracy.
- Assist the study staff with any queries or problems they may have in relation to the study.

15. STATISTICAL CONSIDERATIONS

15.1. Sample size calculation

15.1.1. Sample size and power calculations (primary outcome)

The recent prospective studies (RSI\(^7\), SAFE-TBI\(^8\) and ATBIS\(^4\)) found a weighted mean rate of current favourable neurological outcomes of 50% in Australian and New Zealand patients with severe TBI.

15.1.2. Original sample size calculations

A beneficial effect of prophylactic hypothermia in severe TBI of 30% relative risk increase (RRI) from 50% to 65% (15% absolute risk increase (ARI)) in favourable neurological outcome at 6 months following injury would be a clinically relevant and important effect. Based on these figures, a study of fixed size with full compliance and follow-up would require 364 patients (182 in each of two treatment arms) to have an 80% two-sided power to detect a 15% ARI (from 50% to 65%) in favourable neurological outcome at 6 months following injury. This is a plausible and conservative estimate, based on:

A recent meta-analysis\(^1\) in severe traumatic brain injury comparing prophylactic hypothermia to normothermia which demonstrated a 46% improvement of favourable outcomes (RR 1.46, 95% CI 1.12 to 1.92, p=0.006).

A finding of a 50% increase (p=0.02) in favourable outcomes in a sub-group of patients with severe traumatic brain injury <45 years of age who were hypothermic on arrival and subsequently randomised to hypothermia versus normothermia.\(^1\,\,9\)

A 30% RRI in favourable neurological outcomes is approximately two-thirds of the RRI demonstrated elsewhere.\(^1\,\,11\) If prophylactic hypothermia were proven to be beneficial, such a difference in neurological outcomes would be highly clinically significant (NNT=7) and would lead to a widespread change in management of severe TBI patients in Australia and internationally.

To ensure availability of the required number of evaluable patients, the sample size will be inflated to account for losses to follow-up, withdrawal of hypothermia, due to contraindications and interim data analysis. Allowing an overall proportion of 5% loss to long term follow up (previous CTG studies and HTS of 1%), expands the sample size to 384 patients. Furthermore, based on pilot data (ATBIS\(^4,\,11\)), allowance for a 12% rate of withdrawal of the hypothermic intervention for patients randomised to hypothermia (8% bleeding, 2% withdrawal of surrogate / physician consent (previous pre-hospital trials (HTS)\(^1\,\,\,11\) <1%), and an estimated 2% rate of inappropriate paramedics enrolment (i.e. cardiovascular accident not TBI) increases the sample size to 496 patients. In addition the trivial 0.7% sample size inflation factor associated with use of two interim Haybittle-Peto analysis adds a requirement for two more subjects. The trial recruitment target is 500 subjects.
15.1.3. Final sample size justification to accommodate additional interim analyses
The original POLAR trial sample size of 364 fully evaluable patients was appropriately inflated to a practically required target of 500 patients to maintain 80% power to find the anticipated beneficial effect of prophylactic hypothermia while accommodating anticipated losses to follow up (maximum 5%) and noncompliance (crossover from cooling to control and related losses, maximum 12%). Also incorporated was a much smaller (0.7%) inflation necessary to accommodate the originally anticipated interim analyses of both mortality and the proportion of unfavourable neurological outcomes using Haybittle-Peto 3SD group sequential boundaries at two recruitment points (one quarter \(n = 125\) and one half \(n = 250\)) [7].

Following the October 2015 publication of the EUROTHERM3235 study [6], the POLAR DSMC required a further substantial increase in interim monitoring, namely at increments of 50 patients from \(n = 300\) to \(n = 450\) inclusive. Ten of eleven planned interim analyses will be of both mortality and the proportion of unfavourable neurological outcomes, while at the penultimate \(n = 450\) assessment short term 28-day mortality alone will be assessed due to time constraints. These extra analyses implied a sample size inflationary requirement (4% - 0.7% = 3.3% extra) [39] which may be accommodated within the originally planned sample size, provided losses to follow up and noncompliance remained below anticipated limits.

From calculations using East trial design software [40] based upon an approximate Chi-square test, the trial power was only slightly diminished at 82.3% (down from 83%) with 366 fully evaluable subjects and 11 interim Haybittle-Peto 3SD interim analyses. In the absence of early stopping, the final analysis would be properly conducted at ±1.996 SD (\(P = 0.0459\)) rather than ± 1.96 SD (\(P = 0.05\)). This level of significance will not be adjusted for multiplicity; however, the primary trial outcome is clearly defined. Unless otherwise specified, all hypothesis tests and accompanying significance levels (that is, \(P\) values) will be two-sided, with 95% CI.

15.1.4. Sample size and power calculations (secondary outcomes)
The secondary outcome analysis using proportional odds has been included because although more complex for clinicians to understand, have the potential to increase power of our study to detect an effect in our primary outcome measure. For example, using the proportional odds model, this study of 182 evaluable subjects in each of two treatment groups would have a one-sided power of 96% to detect this magnitude of reference improvement as statistically significant with type I error (alpha) = 0.05.

15.2. Statistical analysis plan
A detailed statistical analysis plan will be developed and published separately from this trial protocol. This plan defines the intention-to-treat full analysis set, as well as exploratory analyses in “as treated” and “per protocol” subsets, accompanied by an analysis seeking to estimate the average causal effect of cooling in the presence of noncompliance with the cooling intervention [17].

An intention-to-treat analysis will be performed based on all randomly assigned patients except those withdrawing consent for use of all trial data and those not fulfilling inclusion criteria and never receiving the intervention. Baseline variables will be summarised using descriptive statistics.

The primary outcome, the midpoint dichotomised GOSE, will be modelled as a binomial random variable, and reported as an unadjusted risk ratio with associated 95% confidence interval (CI), and also as the risk difference with 95% CI and odds ratio with 95% CI.

Multiple secondary outcomes will be assessed. These include:

- GOSE as an ordinal variable, compared between treatment arms using a proportional odds model or a partial proportional odds model [31, 32].
- Binary variables (including hospital and six-month mortality and adverse events) will be analysed with log-binomial [33] and identity-binomial regression models [34] to estimate risk ratios and risk differences with 95% CIs, respectively.
- Quality of life measures and other continuous variables will be analysed with linear regression, using robust standard errors to accommodate potential non-normality and unequal error variation.
- The comparison of favourable GOSE between hypothermia and control in the presence of mortality will be measured by the survivor average causal effect (SACE), defined as the effect of treatment on the outcome among the subpopulation that would have survived under either treatment arm [35].
- Analyses of time-to-event outcomes will use Kaplan-Meier plots and log-rank tests, as well as unadjusted and adjusted Cox proportional hazard regression models returning hazard ratios with 95% CIs.
Cost-effectiveness from the health-care payer perspective will be calculated as a cost per additional patient with a favourable neurological outcome at 6 months following randomisation (defined as GOSE 5–8) and the cost per additional quality-adjusted life year, with quality-adjusted life years calculated using utility scores derived from the EQ-5D-3L conducted at 6 months post randomisation. Costs will be determined based on resource use during the intensive care, acute and post-acute periods up to six months post-randomisation.

Pre-specified subgroup analyses will be conducted according to (i) Marshall computerised tomography scan classification V, and (ii) Marshall V or VI. These will be performed using appropriate covariate by treatment interaction terms in the relevant regression models.

Sensitivity analyses of the primary and secondary outcomes will be performed using regression models adjusting for pre-specified baseline covariates as well as any covariate exhibiting substantial imbalance between randomisation arms, as recommended [36].

Sensitivity analyses of the primary and secondary outcomes will be performed in the subset of compliant patients assigned to cooling compared to all patients assigned to the control ("per protocol" analysis) and (ii) according to the actual treatment received ("as treated" analysis).

16. SAFETY

16.1. Data Safety Management Committee

An independent data safety monitoring committee (DSMC), comprising experts in clinical trials, biostatistics, emergency medicine and intensive care has been established. The committee chaired by Associate Professor Jamie Hutchinson (University of Toronto, Canada) will monitor the trial primary outcome, total mortality and serious adverse events at each interim analysis.

16.1.1. Adverse events

Adverse events (AEs) are defined as any untoward medical occurrence in a patient or clinical investigation subject administered an investigational intervention and which does not necessarily have to have a causal relationship with this treatment (adapted from the Note for Guidance on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (CPMP/ICH/377/95 July 2000)).

It is recognised that the patient population with severe traumatic brain injury will experience a number of common aberrations in laboratory values, signs and symptoms due to the severity of the underlying injury and the impact of standard therapies. These will not necessarily constitute an adverse event unless they require significant intervention or are considered to be of concern in the investigator's clinical judgement.

In all cases, the condition or disease underlying the symptom, sign or laboratory value should be reported e.g. renal failure rather than hyperkalaemia, and agitation rather than self-extubation.

16.1.2. Serious adverse events

Serious Adverse Events (SAE) are defined in accordance with the Note for Guidance on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (CPMP/ICH/377/95) (July 2000) as any untoward medical occurrence that:

- Results in death
- Is life-threatening
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event which may require intervention to prevent one of the previously listed outcomes.

In this study all SAEs will be reported regardless of suspected causality. However, consistent with the advice of Cook et al.,53 adverse events already defined and reported as study outcomes (total mortality) will not be labelled and reported a second time as serious adverse events.

16.1.3. Interim analyses

Planned interim safety analyses were initially scheduled by the DSMC at six months following 25% (n=125) and 50% (n=250) patient recruitment. There is no plan for early trial stopping for apparent futility.
After publication of the Eurotherm 3235 trial, the DSMC requested more frequent monitoring of the trial at 300, 350, 400 and 450 patients. The DSMC specified measuring at 180 days (six months) the primary outcome, the (proportion of favourable neurological outcomes) and mortality, except for n=450 when 28 day mortality will be assessed.

16.1.4. Reporting
Separate case report forms will be developed to record adverse events and serious adverse events. SAEs which occur from the time of commencement of study treatment to 7 days post cessation of study treatment will be reported to the coordinating centre (ANZIC-RC) by faxing the supplied SAE form. SAEs should be reported to the ANZIC-RC within 24 hours of study staff becoming aware of the event.

Minimum information to report will include:
- Patient initials and study number
- Nature of the event
- Commencement and cessation of the event
- An investigator’s opinion of the relationship between study involvement and the event (unrelated, possibly, probably or definitely related).
- Whether treatment was required for the event and what treatment was administered.

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Chief Investigator:
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SAEs must be reported on the fax form but may also be discussed with the ANZIC RC staff or chief investigator if necessary.

Coordinating centre staff will be responsible for following-up SAEs to ensure all details are available. It is the responsibility of each site to inform their HREC of all SAEs which occur at their site, in accordance with local requirements.

17. FUNDING
The POLAR study is funded by a project grant from the National Health and Medical Research Council (NHMRC) (Project grant no. 545901), and the Victorian Neurotrauma Initiative. The ANZIC-RC will supply infrastructure and administrative support.

18. SUB-STUDIES

18.1. Renal sub study (Appendix J)
The Renal Sub study is composed of 2 parts.
- POLAR-Acute Kidney Injury: Minimal data collection.
- Renal Biomarkers: Measurement of specific renal biomarkers (The Alfred and Royal Melbourne Hospital).

18.2. POLAR BEAR sub study (Appendix K)
The POLAR BEAR sub study will assess the energy expenditure of patients enrolled in the POLAR study (The Alfred and Auckland Hospital).
18.3. The Biomarker and Excito-toxicity POLAR sub study (Appendix L)
The specific aim of this sub-study is to determine the level of biomarkers in patients with TBI following hypothermia or normothermia treatment and evaluate the efficacy in predicting long-term outcome. We hypothesise that treatment with hypothermia after TBI will ameliorate neurological deficit and reduce the secretion of brain injury markers in the blood of TBI patients (The Alfred Hospital).

18.4. The POLAR TEG sub study (Appendix M)
The specific aim of this sub-study is to investigate changes in coagulation and in particular platelet function in patients with TBI. (The Alfred Hospital)

18.5. The POLAR Propofol PK sub study (Appendix N)
The specific aim of this sub-study is to determine the impact of therapeutic hypothermia (core body temperature 34.0 to 35.0°C) on propofol plasma pharmacokinetics in severely head-injured critically ill patients. (The Alfred Hospital)

19. AUTHORSHIP AND PUBLICATION
The study will be conducted in the name of the POLAR RCT investigators, the ANZIC RC, and the ANZICS CTG. The central project coordination and data management will be provided by the ANZIC-RC at Monash University, Melbourne. The principal publication from the study will be in the name of the POLAR RCT Investigators with full credit assigned to all collaborating investigators, research coordinators and institutions. Where individual names are required for publication these will be that of the writing committee, with the chair of the writing committee listed first and subsequent authors listed alphabetically.

19.1. Sub study publication
The manuscripts will be submitted for publication after approval by the CTG executive and trial investigators according to CTG and ANZIC-RC policy. The authorship will be under the names of the sub study investigators on behalf of the POLAR investigators.
<table>
<thead>
<tr>
<th>Time frame indicators</th>
<th>Milestone</th>
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<tbody>
<tr>
<td>January 2008</td>
<td>Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS CTG) endorsement obtained</td>
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<tr>
<td>March 2008</td>
<td>NHMRC funding application submitted</td>
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<tr>
<td>October 2008</td>
<td>NHMRC funding application approved</td>
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<tr>
<td>January 2009</td>
<td>Commence study organisation</td>
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<tr>
<td>April 2009</td>
<td>Protocol finalised</td>
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<tr>
<td>April 2009</td>
<td>The Alfred HREC submission</td>
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<tr>
<td>April 2009</td>
<td>Participating sites finalised</td>
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<tr>
<td>June 2009</td>
<td>Monash University HREC submission</td>
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<tr>
<td>September 2009</td>
<td>Participating sites HREC submission</td>
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<tr>
<td>January 2010</td>
<td>Pilot phase commences at The Alfred</td>
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<td>February 2010</td>
<td>Ambulance Research Governance Committee approval</td>
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<td>February 2010</td>
<td>Study start up meeting</td>
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<tr>
<td>August 2010</td>
<td>Ambulance paramedic training completed</td>
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<tr>
<td>September 2010</td>
<td>Study recruitment commences</td>
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<tr>
<td>August 2011-June 2012</td>
<td>25% recruitment completed</td>
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<td>March 2013</td>
<td>1st interim analysis</td>
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<td>August 2014</td>
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**Estimated**
- Feb 2018: Estimate Patient recruitment completed
- Aug 2018: 6mth follow up of 100% recruitment completed
- Aug 2018: Query resolution and data cleaning completed
- Sept 2018: Database lock
- Oct 2018: Complete data analysis
- Jan 2019: Submission of initial manuscript

# The time lines will be reviewed at each interim analysis
## 21. APPENDIX A: TABLE OF EVENTS

<table>
<thead>
<tr>
<th>Event Description</th>
<th>Pre-hospital</th>
<th>ED Admission</th>
<th>ICU Admission</th>
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(#{) Rewarming will be dependent on ICP control
22. APPENDIX B: PRE-HOSPITAL STUDY PROCESS

Assess patient for study suitability

22.1. Inclusion Criteria
- Blunt trauma with clinical diagnosis of severe TBI and GCS < 9
- Estimated age ≥ 18 and < 60 years of age
- The patient is intubated or intubation is imminent

22.2. Exclusion Criteria
- Clinical diagnosis of drug or alcohol intoxication as predominant cause of coma
- Randomisation unable to be performed within 3 hrs of estimated time of injury
- Estimated transport time to study hospital > 2.5 hrs
- Able to be intubated without drugs
- Systolic BP < 90 mmHg
- Heart rate > 120 bpm
- Cardiac arrest at scene or in transit
- GCS=3 + un-reactive pupils
- Penetrating neck/torso injury
- Known or obvious pregnancy
- Receiving hospital is not a study site.
- Evidence of current anti-coagulant treatment
- Known to be carer dependent due to a pre-existing neurological condition

If no exclusion criteria proceed to RANDOMISATION

Select the randomisation envelope in numerical order
Document all study parameters
Attach study wristband to patient

HYPOTHERMIA
Keep patient exposed.
If temp > 35°C : give chilled 0.9% NaCl IV at 100mls/min
Randomised after intubation - give 1000mls
Randomised before intubation - give 2000mls
If temp < 35°C : no cold fluid.

NORMOTHERMIA
Standard care.
Aim for temperature 36.5-37.5°C
23. APPENDIX C: EMERGENCY DEPARTMENT STUDY PROCESS

PATIENTS RANDOMISED PRE-HOSPITAL

23.1. Normothermic – control group:
Follow standard temperature management, target temperature 37°C
Follow brain injury guidelines

23.2. Hypothermic – cooling group:
The patient will be assessed before progressing to active cooling

TEMPORARILY WITHOLD cooling protocol if:
In the clinician’s opinion the patient has clinically significant bleeding or risk of significant bleeding including but not limited to:

- Bleeding into the chest, abdomen or retro-peritoneum likely to require surgery +/- embolisation
- Pelvic fracture likely to require surgery +/- embolisation
- More than two long bone fractures requiring operative fixation
- Rewarm to 35-37°C and correct coagulopathy if present.
- Perform any interventions to control bleeding.
- Follow cooling protocol ASAP when bleeding controlled

The patient is drug or alcohol affected with a normal CT brain.

- Hold patient at 35°C while drugs and alcohol clear (can be warmed to 36°C if shivering an issue).
- Reduce sedation.
- Check neurological function

IF NONE OF THE ABOVE PRESENT CONTINUE WITH COOLING PROTOCOL:

- Apply surface temperature control vests/leg wraps/blankets
- Connect to temperature control module
- Commence temperature control to target temperature 33°C

PERMANENTLY WITHDRAW THE PATIENT FROM THE COOLING PROTOCOL AND FOLLOW STANDARD MANAGEMENT IF THE FOLLOWING IS PRESENT:

- Significant bleeding which prevents initiation of cooling within 48hrs post injury
- Positive urine or blood pregnancy test
- Normal CT Brain scan & patient localising or obeying (GCS(M) >5) after decreased sedation
- In the treating clinician’s opinion the patient does not require an ICU admission
- In the treating clinician’s opinion, cooling is not in the patient’s best interest.
Patients not previously randomised will be assessed for study eligibility by ED staff.

23.3. Inclusion Criteria
- Blunt trauma with clinical diagnosis of severe TBI and GCS <9
- Estimated age ≥ 18 and < 60 years of age
- The patient is intubated or intubation is imminent

23.4. Exclusion Criteria
- Clinical diagnosis of drug or alcohol intoxication as predominant cause of coma
- Randomisation unable to be performed within 3 hrs of estimated time of injury
- Able to be intubated without drugs
- Persistent Systolic BP <90mmHg
- Clinically significant bleeding likely to require haemostatic intervention, for example:
  - Bleeding into the chest, abdomen or retro-peritoneum likely to require surgery +/- embolisation
  - Pelvic fracture likely to require surgery +/- embolisation
  - More than two long bone fractures requiring operative fixation
- GCS=3 + un-reactive pupils
- Cardiac arrest at scene or in transit
- Penetrating neck/torso injury
- Positive urine or blood pregnancy test
- Evidence of current anti-coagulant treatment
- Known to be carer dependent due to a pre-existing neurological condition
- In the treating clinician’s opinion, cooling is not in the patient’s best interest.

If no exclusion criteria proceed to RANDOMISATION

Select the randomisation envelope in numerical order

HYPOTHERMIA
Administer chilled 0.9% NaCl IV @ 100mls/min
Randomised after intubation - give 1000mls
Randomised before intubation - give 2000mls

HYPOTHERMIA
Apply surface cooling pads ASAP
Target 33°C.

NORMOTHERMIA
Standard care
Aim for temperature 36.5-37.5°C.
24. APPENDIX D: SEVERE TBI & ICU MANAGEMENT GUIDELINE

24.1. Lines/Fluids
- Arterial line and central line in place
- CVP target 8-12 mmHg (if CVP transduced)
- Crystalloid preferred resuscitation fluid, avoid albumin
- MAP target >80 mmHg until ICP known (then to achieve CPP with minimum MAP of 70 mmHg), using fluids and vasopressor (type of vasopressor is clinician’s choice) if required
- After initial resuscitation in otherwise stable patients, positive daily fluid balances >500 mls should be avoided.

24.2. Ventilation/Oxygenation
- SpO2 > 95%
- PaO2 > 90 mmHg
- PaCO2 35-40 mmHg

24.3. Patient Position
- Position 15-30 degrees head up, avoiding venous obstruction in the neck.
- Position flat if shock prominent and this improves CPP

24.4. Sedation
Recommended agents:
- Benzodiazepine, e.g. Midazolam 0-15 mg/h
- Opiate, e.g. Fentanyl 0-100 mcg/h, or sufentanyl (0.2 to 1 mcg/kg/h)
- Barbiturate infusions can be used at clinician’s preference (second tier therapy for ICP control)
- **ESSENTIAL TRIAL RULES WHEN PROPOFOL PRESCRIBED:**
  - Propofol 1-2 mg/kg/h when patient temperature ≥ 35°C
  - REDUCE dose if prolonged infusion (> 24h)
  - CEASE propofol after 24h when patient temperature < 35°C
  - CEASE propofol if commencing barbiturate infusion
  - CEASE propofol if patient develops clinical changes consistent with Propofol Infusion Syndrome (PRIS)
- Neuromuscular Blockade
  - As per clinician’s preference (generally for ICP control)

24.5. Glycaemic Control
- Maintain BSL 6-10 mmol/L

24.6. Serum Electrolytes
- Serum Na target 140-150 mmol/L
- Serum Potassium as per unit protocol. Monitor 2 hrly during rewarming
- Serum Magnesium as per unit protocol. Monitor prior to rewarming, mid rewarming and when normothermia is reached.

24.7. ICP Monitoring and CPP control
- Monitor ICP – EVD preferred, Codman parenchymal catheter acceptable
- ICP target <20 mmHg
- CPP target >60 mmHg
• Do not remove ICP monitor before completion of rewarming
See Appendix E – ICP control

24.8. Nutritional Support
• Aim to commence enteral nutrition within 24 hrs and to achieve full nutrition within 72hrs

24.9. DVT, Ulcer, Seizure prophylaxis
• As per clinician’s choice
# 25. APPENDIX E: ICP CONTROL FOR BOTH STUDY GROUPS

- **ICP > 20 mmHg**
  - Optimise ventilation, sedation (including neuromuscular blockade if clinically indicated) & position
  - **ICP > 20**
    - Drain CSF if EVD is present
  - **ICP > 20**
    - Consider hypertonic saline or mannitol bolus
  - **ICP > 20**
    - Reconsider EVD if not in place
    - Consider repeat CT brain scan

### HYPOTHERMIA PATIENTS

If ICP remains > 20
- Consider Thiopentone bolus +/- infusion to a maximum of burst suppression

### CONTROL PATIENTS

If ICP remains > 20
- Consider Thiopentone bolus +/- infusion to a maximum of burst suppression.
- And / Or
- Consider cooling to 35°C
26. APPENDIX F: COOLING AND REWARMING GUIDELINES

26.1. Purpose
This guideline outlines the management of patients enrolled in the POLAR study who are allocated to therapeutic hypothermia.

26.2. Indication
Patients enrolled in the POLAR study (see Inclusion/Exclusion document).

26.3. Hypothermia Management

26.3.1. Temperature control
- Commence therapeutic hypothermia as soon as possible following randomisation.
- During ambulance transport and in the Emergency Department: Expose the patient to promote environmental cooling. Infuse up to 2000mL ice cold crystalloid (0.9% saline at 4°C) at 100mls/min. Temperature goal during transport is 35°C. (Tympanic temperature)
- IN ED /ICU: Apply surface cooling using MEDITHERM III vests and leg wraps (see MEDITHERM III instructions for use) as soon as possible.
- Set target temperature on cooling console to 33°C to institute rapid cooling with the auto rapid (hare) setting.
- Turn down the temperature of inspired gas heating to the Non-Invasive Ventilation setting (34°C).
- Monitor core temperature using bladder temperature (preferred) or oesophageal temperature.
- This temperature is ideally to be maintained for a period of 72 hours after severe head injury.
- A target temperature of 32.5°C to 33.5°C (ideally 33°C) represents the optimal balance between clinical effectiveness and adverse side effects. In addition, at this temperature, there is generally minimal shivering. This generally means that further muscle-relaxants may be withheld.
- Should the core temperature rise to 33.5°C:
  - Check the temperature setting and circulating water temperature on the cooling machine.
  - Check that there is cold water flow through the jacket.
  - Increase sedation and/or administer further neuromuscular blocking agent as required for shivering. See Management of Shivering in this appendix.
- Should the core temperature fall below 32.5°C:
  - Check the temperature setting and circulating water temperature on the cooling machine.
  - Check that there is warm water flow through the jacket.

26.3.2. Respiratory
- Adjust ventilator to provide arterial blood gases (not corrected for temperature).
  - pO2 >90mmHg
  - pCO2 35-40mmHg (Hypothermia decreases CO2 production thus this pCO2 usually requires a decrease in minute volume of about 30%, i.e.: tidal volume of 8ml/kg and a rate of 8bpm).

26.3.3. Cardiovascular
- In severe traumatic brain injury, the CPP should be maintained at a minimum of 60mmHg.
- The MAP target is 80 mmHg if an ICP monitor is not inserted. Increase MAP initially with crystalloid resuscitation fluids (avoid albumin).
- A decreased heart rate (<50 beats/minute) is a physiological effect of hypothermia. Low dose adrenaline may be considered to keep heart rate >50 beats/min if hypotension (absolute or relative). The electrocardiograph may show prolonged QT interval and Osbourne waves.
- If an inotrope is required to increase blood pressure, an adrenaline infusion should be commenced. If the dose exceed 5mic/min or the lactate level is increasing, then an infusion of noradrenaline...
should be used. If a further fluid challenge is required for CVP<12mmHg, infuse a bolus (i.e. 500mL) of 0.9% saline

- Lactate levels may initially be increased by an adrenaline infusion. This hyperlactaemia is not an indication to stop cooling.

26.3.4. Neurological:
- On-going sedation is required to prevent shivering. Options include midazolam/ morphine infusion. If shivering occurs despite sedation, a non-depolarising neuromuscular blocking drug may be administered as required.
- Magnesium may decrease shivering threshold, we suggest that magnesium be corrected to upper normal range, prior to cooling (if possible) and before commencing rewarming.
- Calcium infusions are toxic to injured neurones, thus calcium should not be routinely administered to correct asymptomatic hypocalcaemia in patients with neurological injury.

26.3.5. Renal
- Frequent monitoring and appropriate correction of electrolytes (K+, Mg++, PO4-) is required. In particular, hypokalaemia is usual during cooling, therefore carefully monitor K+ and replace for a potassium level >4.0 mmol/L. During rewarming, the potassium level increases however this generally does not require treatment.

26.3.6. Gastrointestinal
- Aim to commence enteral nutrition within 24hrs and to achieve full nutrition within 72hrs.
- Commence target feeding at 70% of predicted because of the decreased metabolic rate.
- Gut motility may be decreased during hypothermia and high gastric residual volumes should be expected. Follow site ICU protocol for gastric intolerance.

26.3.7. Endocrine
- Hyperglycaemia is common during hypothermia due to decreased insulin release and should be treated according to the site ICU Insulin protocol (generally BSL-6-10 mmol/L)

26.3.8. Skin Integrity
- Cooling causes vasoconstriction in the skin and may increase the risk of wound infection

26.3.9. Infection
- Cooling can decrease the number and function of leucocytes and may potentially be associated with higher infection risk. Clinicians should be alert to the masking of increased temperature and the potential blunting of the leukocyte response as markers of infection
- The diagnosis of pneumonia is difficult during therapeutic hypothermia, since fever is masked and there may be no increase in the white cell count. The use of antibiotics should be considered if a new pulmonary infiltrate develops

26.3.10. Haematology
- In traumatic brain injury, anticoagulation is not generally used during the first 7 days
- Hypothermia increases clotting times although the measured INR and APTT may appear normal since the samples are warmed prior to analysis
- Prolonged therapeutic hypothermia (>5 days) leads to gradual decreases in the platelet and white cell counts
26.4. Rewarming from hypothermia

72 hours post randomisation? #

YES (Proceed)  
NO (Do Not Proceed)

ICP Stable and <20mmHg **

YES (Proceed)  
No (sustained ICP>20mmHg) Manage ICP Reconsider warming in 12 hours

Haemodynamic and electrolyte status stable

YES (Proceed)  
No

The rewarming rate aim is 0.17C/hr
Ensure patient in Tortoise Mode (Gaymer Meditherm III) ‘Set Point Control’ to 0.5C above present set temperature.(i.e.: increase to 33.5°C).
DO NOT remove wraps or turn off cooling machine.
DO NOT allow patient to rewarm passively.
Constantly monitor patient temperature and ensure rewarming does not occur faster than required.

# If cooling commenced late we require a minimum of 48hrs of cooling to have occurred prior to considering rewarming.

** Transient rises in ICP >20mmHg such as during suctioning, turning, moving, etc are not relevant to this dot point.

If at any time during rewarming there is a sustained ICP instability (ICP >20mmHg) - Despite medical treatment Transient rises in ICP>20 mmHg such as during suctioning, turning, moving etc. are not relevant.
Halt rewarming procedure and manage ICP instability.

If required
Re cool to a point where ICP stability is maintained.
Reassess in 12 hours for suitability to re-commencement of rewarming procedure.

Continue to monitor (ICU Management guidelines= Appendix D and E) For alterations in Potassium and Magnesium.
Haemodynamic instability.
ICP instability
Infection (Temperature spikes (>38°C) are common post rewarming.)

Repeat rewarming process increasing Meditherm III “set point control” by 0.5C every 3 hours.
26.5. Management of Re-Warming

The rewarming of a patient is a critical period. The aim is to reach 37°C +/- 0.5 degrees. It is critical that rewarming occurs slowly and in a controlled manner. If rewarming occurs too quickly it may cause damage to neural cells.

- Ensure the water level is above the green line in Gaymer Mediterm III.
- Ensure all cooling device connections are open.
- Ensure temperature probe is connected and appropriately connected to the patient.
- Choose the tortoise mode on the Gaymer Mediterm III and “set point control” temperature at 0.5 degrees above current setting (i.e. 33.5°C). The Tortoise mode will allow cooling to occur at 0.17 degrees per hour.
- DO NOT remove wraps or turn off machine.
- DO NOT allow patient to rewarm passively.
- After 3 hours increase the “set point control” by another 0.5°C. Continue this increase every 3 hours until patient reaches 37.0°C.
- Rewarming to 37°C should take approximately 24 hours.

Continue to OBSERVE patient temperature as rewarming occurs.

If rewarming is occurring too quickly, it may be necessary to increase set point by 0.2 per 2 hours. The slower rewarming rate may increase risk of shivering.

26.5.1. Rewarming Special considerations

- In urgent situations (uncontrolled bleeding or urgent theatre) a faster rewarming rate may be necessary and should be led by the intensivist, but wherever possible utilise the slower rewarming rate.
- When transporting the patient consideration should be given to continuing cooling while the patient is undergoing a procedure or being transported.
- Gaymer Meditherm III is able to be utilised in theatre. Consideration should be given to utilising the device during theatre to maintain a patient temperature.
- DO NOT PRE COOL PATIENT for expected transport
- AVOID sudden cessation of cooling and removal of cooling warps.
Changes in Potassium and magnesium occur during rewarming.

- Check potassium 2/24hrly
- Check magnesium prior to commencement, half way and at the end of rewarming.
- Haemodynamic instability may occur. Small doses of adrenaline may be required.

Haemodynamic instability may occur during rewarming

- Try and avoid fluid boluses
- Consider increase in inotropes
- Blood if Hb<9
- Hold rewarming until patient stable (clinicians discretion)

ICP instability

- See ICP management guidelines / flowchart

Infection (Temperature spikes (>38.3°C) are common post rewarming.)

- Clinicians should treat febrile patients as per the site ICU Guideline for the Management of Fever. A full septic screen is recommended.
- Keep wraps available or on patient for a total of 96 hours.
- Utilise Gaymer Meditherm III to regulate temperature to normothermia if there is a temperature spike.
- The maximum protocolised period of hypothermia will be 7 days. Once a patient has completed the re-warming protocol and reached 37°C, they will be maintained at normothermia (below 38°C) using the surface cooling pads for 96 hours post randomisation. After this time the will be managed according to ward protocol.
- Pyrexia above 38°C should also be avoided in all patients, for up to 96 hours post randomisation, by application of surface cooling systems after this time patients should be managed according as per unit protocol.

26.6. Management of Shivering

- Shivering is most pronounced at temperatures between 34°C and 35.5°C but may be seen beyond these points.
- Shivering will significantly increase metabolic demand and increase ICP.
- Review sedation and neuromuscular blockade prior to rewarming
- Shivering must be immediately treated with additional sedation/muscle relaxant.
- Sedation can be weaned if ICP is stable once core temperature is >36.0°C
- It is important to monitor for shivering at all times but it is most important during initial cooling and during rewarming phases as patient temperature passes shiver point.
- As rewarming (which is slow) will take longer than initial cooling (which is rapid), shivering may be prolonged during the slow rewarming phase (0.17°C per hour).
- Shivering should be monitored continually and managed immediately and aggressively.

26.6.1. Shivering Assessment

- There are shivering assessment tools that can grade the amount of shivering. In this study we desire no shivering. The Bedside Shivering Assessment Scale (BSAS) can be used to monitor shivering if desired.
- It is important to monitor for shivering at all times but it is most important during initial cooling and during rewarming phases as patient temperature passes shiver point.
- Shivering observations should be done:
  - During induction of hypothermia, maintain continuous surveillance for shivering and conduct a formal shivering assessment hourly until target temperature (33°C) is reached.
  - During maintenance of hypothermia continuous surveillance for shivering should continue and a formal shivering assessment should be conducted 2 hourly
During rewarming hypothermia, maintain continuous surveillance for shivering and conduct a formal shivering assessment hourly until target temperature (37°C) is reached.

- The suggested method to assess for shivering is
  - Observe patient for 2 minutes during which time the jaw, neck, chest, arms and legs should be visually inspected and palpated for shivering.

### 26.6.2. Pharmacological management

- Manage serum magnesium at upper level of normal
- Consider active skin counter-warming (using warm wraps or hot air blower on hand, feet and face)
- Maximise sedation. Options include midazolam, morphine, fentanyl
  - Recommendations (only) are:
    - Benzodiazepine, e.g. Midazolam 0-15 mg/h
    - Opiate, e.g. Fentanyl 0-100 mcg/h, or sufentanyl (0.2 to 1mcg/kg/h)
  - Barbiturate infusions can be used at clinician’s preference (second tier therapy for ICP control)
- If shivering continues despite these agents consideration should be given to adding
  - Pethidine 50mgs/4hrly
    - And also consider
  - Clonidine 75micrograms (only if blood pressure allows)

Neuromuscular blockade can also be utilised to manage shivering. Clinicians should consider seizure activity monitoring if NMB are utilise

### 26.6.3. Cooling phase

Once a patient has reached 34°C consideration should be given to decreasing medications that have been utilised to manage shivering. Reduced metabolism and decreased shivering are likely at this temperature.

### 26.6.4. Rewarming Phase

Once a patient has reached 35.5°C consideration should be given to decreasing medications that have been utilised to manage shivering.
## 27. APPENDIX G: GLASGOW OUTCOME SCALE

### 6 Month Follow Up

<table>
<thead>
<tr>
<th>Date of follow up:</th>
<th>dd</th>
<th>mm</th>
<th>yyyy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient lost to follow up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient alive (unsolicited)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Extended Glasgow Coma Scale

The questions can be answered by the patient or close, relative, friend or by rehabilitation / nursing staff if appropriate

<table>
<thead>
<tr>
<th>Respondent:</th>
<th>Patient alone</th>
<th>Relative or friend or carer alone</th>
<th>Patient and relative, friend or carer together</th>
<th>Patient lost to follow up</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>The injured person is:</th>
<th>Out of hospital</th>
<th>In hospital, rehabilitation centre or residential care</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>What is the most important factor in recovery?</th>
<th>Effects of head injury</th>
<th>Effects of illness or injury to another part of the body</th>
<th>A mixture of these</th>
</tr>
</thead>
</table>

Please answer by crossing one box, which best answers the question.

<table>
<thead>
<tr>
<th>Is the injured person able to obey simple commands, or say any words?</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>(2 - Vegetative state)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Before the injury was the injured person able to look after themselves at home?</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>(3 - Low dependence)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Before the injury was the injured person able to buy things at shops without help?</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>(4 - Upper SD)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>As a result of the injury does the injured person now need help to buy things at shops?</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>(4 - Upper SD)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Before the injury was the injured person able to travel without help?</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>(4 - Upper SD)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>As a result of the injury does the injured person now need help to travel?</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>(4 - Upper SD)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Need help to travel, but not because of the injury | |

Polar_Frm15_6MonthFUbyCA_V1
15.12 Employment before the injury?  
☐ Working  ☐ Studying as a student  
☐ Looking for work  ☐ Retired  
☐ Looking after family  ☐ None of these

15.13 As a result of the injury has there been a change in the injured person's ability to work?  
(Or to study, or to look after your family)  
Cross one box only:  ☐ Still do the same work  
☐ Still work, but at a reduced level (5 - Upper MD)  
(eg. Change from full time to part time or change in level of responsibility)  
☐ Am unable to work, or only able to work in sheltered workshop (6 - Lower MD)  
☐ Ability to work has changed, but not because of the injury

15.14 Before the injury did the injured person take part in social and leisure activities outside home?  
☐ Yes  ☐ No  
At least once a week. Examples include going out with or visiting friends, going to the cinema or live performances, attending sporting events or participating in sporting events, attending religious ceremonies or services.

15.15 As a result of the injury has there been a change in the ability of the injured person to take part in social or leisure activities outside the home?  
Cross one box only:  ☐ Take part about as often as before  
☐ Take part a bit less but at least half as often (7 - Lower GR)  
☐ Take part much less, less than half as often (6 - Upper MD)  
☐ Do not take part at all (5 - Lower MD)  
☐ Ability to take part has changed, but not because of the injury

15.16 Before the injury did the injured person have any problems getting on with friends and family?  
☐ Yes  ☐ No

15.17 As a result of the injury does the injured person have any emotional or behavioural problems which cause difficulties in relationships with friends or family?  
Examples include quick temper, irritability, mood swings, depression, anxiety, insensitivity to others, rigid thinking, unreasonable or childish behaviour.  
Cross one box only:  ☐ Things are still much the same  
☐ There are occasional problems (less than one a week) (7 - Lower GR)  
☐ There are frequent problems (once a week or more) (6 - Upper MD)  
☐ There are constant problems (problems everyday) (5 - Lower MD)  
☐ There are problems for some other reason, not because of the injury

15.18 Are there currently any other problems resulting from the injury?  
Problems sometimes reported after head injury include headaches, dizziness or balance problems, tiredness or sleeping disturbances, sensitivity to noise or light, slower speed of thinking, trouble with memory, concentration problems.

Cross one box only:  ☐ No current problems  
☐ Some problems (7 - Lower GR)  
☐ Some problems for other reasons, not because of the head injury

15.19 Before the injury were similar problems present?  
☐ No problems or they were minor problems  
☐ Similar problems before

15.20 Comments:  Add extra page if required
### Extended Glasgow Coma Scale

#### Glasgow Outcome Scale - Extended

16.21 Tick appropriate score:
- [ ] 1 - Dead
- [ ] 2 - Vegetative state (VS)
- [ ] 3 - Lower severe disability (Lower SD)
- [ ] 4 - Upper severe disability (Upper SD)
- [ ] 5 - Lower moderate disability (Lower MD)
- [ ] 6 - Upper moderate disability (Upper MD)
- [ ] 7 - Lower good recovery (Lower GR)
- [ ] 8 - Upper good recovery (Upper GR)

#### Glasgow Outcome Score

16.22 Tick appropriate score:
- [ ] 1 - Dead
- [ ] 2 - Vegetative state (VS)
- [ ] 3 - Severe disability (SC)
- [ ] 4 - Moderate disability (MD)
- [ ] 5 - Good recovery (GR)
## 28. APPENDIX H: EURO QUALITY OF LIFE (EQ5D)

### EQ-5D

**By placing a cross in one box in each group below, please indicate which statements best describe your own health state today.**

#### 16.23 Mobility:
- [ ] I have no problems in walking around
- [ ] I have some problems in walking around
- [ ] I am confined to bed

#### 16.24 Personal care:
- [ ] I have no problems with personal care
- [ ] I have some problems washing or dressing myself
- [ ] I am unable to wash or dress myself

#### 16.25 Usual activities:
- [ ] I have no problems with performing my usual activities
- [ ] I have some problems with performing my usual activities
- [ ] I am unable to perform my usual activities

#### 16.26 Pain / discomfort:
- [ ] I have no pain or discomfort
- [ ] I have moderate pain or discomfort
- [ ] I have extreme pain or discomfort

#### 16.27 Anxiety / depression:
- [ ] I am not anxious or depressed
- [ ] I am moderately anxious or depressed
- [ ] I am extremely anxious or depressed

### Health state scale:

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your current health state is.

Your own health state today

Your own health state today
### 29. APPENDIX I: ASSESSMENT OF QUALITY OF LIFE (SF-12)

**SF-12**

**INSTRUCTIONS:** This questionnaire asks for your views about your health, how you feel and how well you are able to do your usual activities. Please answer every question by crossing one box. If you are unsure about how to answer please give the best answer you can.

<table>
<thead>
<tr>
<th>Question</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>16.29 In general, would you say your health is:</td>
<td>Excellent</td>
</tr>
<tr>
<td>16.30 The following questions ask about your activities you might do during a typical day. If so, how much?</td>
<td>Yes limited a lot</td>
</tr>
<tr>
<td>16.30.1 Moderate activities: (such as moving a table, pushing a vacuum cleaner, bowing or playing golf)</td>
<td></td>
</tr>
<tr>
<td>16.30.2 Climbing several flights of stairs:</td>
<td></td>
</tr>
<tr>
<td>16.31 During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health? Yes</td>
<td>No</td>
</tr>
<tr>
<td>16.31.1 Accomplished less than you would like:</td>
<td></td>
</tr>
<tr>
<td>16.31.2 Were limited in the kind of work or other activities:</td>
<td></td>
</tr>
<tr>
<td>16.32 During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your emotional problems? (such as feeling depressed or anxious) Yes</td>
<td>No</td>
</tr>
<tr>
<td>16.32.1 Accomplished less than you would like:</td>
<td></td>
</tr>
<tr>
<td>16.32.2 Didn’t do work or other activities as carefully as usual:</td>
<td></td>
</tr>
<tr>
<td>16.33 During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)? Not at all</td>
<td>A little bit</td>
</tr>
</tbody>
</table>

These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling.

<table>
<thead>
<tr>
<th>Question</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>16.34 How much of the time during the past 4 weeks...</td>
<td>All of the time</td>
</tr>
<tr>
<td>16.34.1 Have you felt calm and peaceful?</td>
<td></td>
</tr>
<tr>
<td>16.34.2 Did you have a lot of energy?</td>
<td></td>
</tr>
<tr>
<td>16.34.3 Have you felt down?</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Question</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>16.35 During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities?</td>
<td>All of the time</td>
</tr>
<tr>
<td>(like visiting friends, relatives, etc.)</td>
<td></td>
</tr>
</tbody>
</table>
30.APPENDIX J: RENAL SUB-STUDY

30.1. POLAR-Acute Kidney Injury (AKI)
This is a study of the effects of early and sustained hypothermia on renal function in patients with traumatic brain injury (TBI) to be conducted on all patients in the POLAR trial.

30.1.1. Aims
Acute kidney injury (AKI) is a complication of TBI, which makes its management more complex and costly, and exposes TBI patients to a greater risk of dialysis-related cerebral edema. We plan to investigate changes in renal function and biomarkers in patients with TBI in this substudy of the POLAR trial.

The specific aim of POLAR-AKI is to determine whether in patients with TBI, early and sustained hypothermia reduces the risk for, severity of, and duration of AKI, compared to normothermia.

30.1.2. Background
AKI as classified by the RIFLE criteria (acronym for Risk, Injury, Failure, Loss, End-stage)\textsuperscript{54} may occur in approximately 9\% of TBI patients in Australia (Risk, Injury and Failure categories).\textsuperscript{55} Trauma patients compose almost 1 in 10 of those admitted to Australian ICUs and over 42\% have TBI.\textsuperscript{56} AKI increases the risk of aggravating cerebral edema,\textsuperscript{57} and is associated with increased mortality\textsuperscript{58} and prolonged length of stay.\textsuperscript{59} Severe cases require costly treatments and can result in prolonged kidney dysfunction and delayed recovery, escalating the human and financial costs of TBI.\textsuperscript{60} Treatment of AKI with dialysis is associated with significant fluctuations in osmolarity which expose the patient to an increased risk of cerebral edema.\textsuperscript{57} Accordingly, we consider it a priority to investigate treatments which simultaneously may protect the brain and kidney after neurotrauma.

Evidence suggests that mild hypothermia (32-35°C) in the first hours after an ischemic event can prevent or ameliorate permanent injury not only in the brain as for TBI but also in the kidneys.\textsuperscript{59} Some mechanisms through which hypothermia may protect the brain and kidneys include: the blockade of excitotoxic mechanisms, modulation of the inflammatory response and modulation of apoptosis.\textsuperscript{14} Hypothermia (~33°C) has been shown to reduce the risk of renal failure after induced renal ischemia-reperfusion injury in animals.\textsuperscript{58,61-64} There has been little clinical investigation of the renal effects of hypothermia and no such study in patients with TBI. The POLAR trial presents a unique opportunity to clinically investigate the influence of hypothermia on kidney function in TBI patients at minimal cost.

30.1.3. Methods
Inclusion and exclusion criteria for the Renal Substudy will be the same as for POLAR. Degree of AKI post trauma will be categorised using the GFR and urine output criteria of the RIFLE classification system\textsuperscript{54} and comparisons made. Maximal change in serum creatinine from baseline in the first 7 days post-trauma will be used and urine output data will be collected for 7 days while in ICU. RIFLE outcome criteria ‘Loss of kidney function’ and ‘End stage renal failure’ will not be used. The RIFLE criteria have been validated in critically ill populations.\textsuperscript{58,63,64} Creatinine collection will continue for 10 days to allow assessment of treatment/ post treatment effect, and duration of AKI. The patient’s weight will be estimated if not known to calculate urine output data in ml/kg/hr. Data will also be collected on the need for Renal Replacement Therapy / Dialysis while in hospital and days when this is received as it affects creatinine level and will be assessed as an outcome.

30.1.4. Power calculations and sample size
The POLAR trial recruitment target is 500 patients. With 250 subjects per group this study will have an 80\% power to show a difference in a continuous normally-distributed outcome, equivalent to 25\% of one standard deviation with a 2-sided p-value of 0.05. Given one standard deviation is equivalent to about 24\% across a range of data, this difference could be thought to equate to a difference of approximately 6\%. With 250 subjects per trial group receiving cooling / normothermia, POLAR-AKI will have an approximately 80\% power to show a change in proportion of 6\% in those with any degree of AKI (9\% v. 3\%) with a two sided p-value of 0.05. We estimate that 9\% of TBI patients will develop AKI (Risk/Injury/Failure) based on a preliminary study.\textsuperscript{55}

30.1.5. Primary outcomes
Severity of AKI (measured as Percent decline in eGFR from baseline to worst eGFR up to day 10 OR increase in serum creatinine from baseline to peak value while in ICU over 10 days)

30.1.6. Secondary outcomes
Cumulative proportion in Risk/Injury/Failure RIFLE categories in those receiving cooling v. normothermia.
Duration of AKI measured as AKI free days (number of days not in Risk/Injury/Failure categories) for 10 days or duration of data collection.

### 30.1.7. Analysis of results
Data will be analysed using Intercooled Stata, version 9 or later (Statacorp, Tx, USA). Data will initially be assessed for normality and log-transformed where appropriate. Univariate analyses will be conducted using appropriate tests. Multivariate analysis will be performed adjusting for baseline imbalances and known covariates. Where sufficient data exists, multiple logistic regression will be used for AKI as a binary outcome. Multivariate analysis on log-transformed biomarkers will be performed using multiple linear regression, while time to event data will be analysed using Cox regression and displayed with Kaplan Meier curves. A two sided p-value of 0.05 will be considered statistically significant.

### 30.1.8. Significance
POLAR-AKI will provide unique prospective information on the incidence, severity and duration of AKI in patients with TBI. It also presents a unique opportunity to evaluate the benefit of early and sustained hypothermia (a potential kidney protective therapy for AKI) to decrease the occurrence, severity and duration of AKI in TBI patients. The POLAR trial provides a unique opportunity to investigate a kidney protective therapy for AKI in TBI at minimum cost.

### 30.2. POLAR-Renal Biomarkers
This is a study of the effects of early and sustained hypothermia on renal biomarkers in patients with TBI to be conducted only at The Alfred and Royal Melbourne Hospitals in Melbourne, Victoria.

#### 30.2.1. Aims
The specific aims of POLAR-Biomarkers are to determine whether in patients with TBI:

- Early and sustained hypothermia reduces the release of biomarkers NGAL, cystatin C and L-FABP compared to their release in those receiving normothermia.
- The release of these biomarkers predicts the occurrence, severity, duration of and recovery from AKI.

#### 30.2.2. Background
Levels of NGAL, cystatin C and L-FABP rise early in AKI compared to creatinine. No study has analysed these biomarkers in patients with TBI, or studied their response to therapy over a period of up to 72 hours. If their value as early renal biomarkers is confirmed in patients with TBI and other populations, they may change the definition, diagnosis, prognosis and timing of therapy for AKI in TBI. The POLAR trial provides a unique opportunity to analyse the biomarker response to cooling which could elucidate mechanisms involved in the body’s response to this therapy.

#### 30.2.3. Methods
Inclusion and exclusion criteria for POLAR-Biomarkers will be the same as for POLAR. Urine and blood specimens will be collected as soon as practicable after randomisation and at 24, 48 and 72 hours after these first specimens, from the first 50 participants recruited between the Alfred and Royal Melbourne hospitals. Renal biomarker levels in some samples will be measured with point-of-care assays (plasma NGAL) and remaining samples will be processed, freeze-stored and later transported for measurement to Monash Medical Centre laboratory (cystatin C); Dr Yasushi Takigawa, CIMC Co. laboratories, Tokyo, Japan (L-FABP); and Cincinnati Children’s Hospital Medical Centre laboratories, Cincinnati, USA (urine NGAL). Investigation into novel biomarkers is at an explosive stage, and other compounds may in a short space of time emerge as solid predictors of renal function. In view of this, two samples of urine and plasma for all 4 time-points from each participant will be stored and kept for future measurement of other biomarkers.

#### 30.2.4. Power calculations and sample size
With 50 subjects from the POLAR trial, POLAR-Biomarkers will have an 80% power to detect a correlation coefficient of \( r = 0.4 \) between continuous variables on any given day with a two-sided p-value of 0.05. Whilst the addition of repeat measures data will increase the power to detect relationships between continuous variables, as the within patient correlation between data points is unknown, it is impossible to calculate the exact increase in power.

By considering a change in values between days 1 and 3, with 25 subjects per group POLAR-Biomarkers will have an 80% power to detect a difference between groups in continuously normally distributed variables, equivalent to 80% of one standard deviation with a two-sided p-value of 0.05. As additional repeat measures will once again increase the power of the study, this is a conservative estimate.
30.2.5. Primary outcomes
Levels of biomarkers NGAL, cystatin C and L-FABP in those receiving cooling v. normothermia; and comparison of urine and serum samples.

30.2.6. Secondary outcomes
Relationships between biomarkers and change in eGFR, serum creatinine, RIFLE classes Risk/Injury/Failure, and survival.

30.2.7. Analysis of results
Data will be analysed using Intercooled Stata, version 9 or later (Statacorp, Tx, USA) and assessed for normality and log-transformed where appropriate. We anticipate that biomarkers (NGAL, cystatin C, L-FABP) will be well approximated by a log-normal distribution. Multivariate analysis will be performed adjusting for baseline imbalances and known covariates using repeat measures analysis of variance. We will determine changes in response over time between treated / untreated groups by fitting an interaction between treatment and time. Relationships between biomarkers and change in eGFR, serum creatinine, RIFLE class Risk/Injury/Failure, and survival, will be determined using logistic regression and reported using area under the curve for receiver operating characteristic curves.

30.2.8. Significance
POLAR-Biomarkers will provide unique information on the pattern of renal biomarker release in response to cooling and in AKI, in patients with TBI. The POLAR trial provides a unique opportunity to investigate this potential kidney protective therapy and new diagnostic approaches to AKI in TBI at minimum cost.
30.2.9. Renal sub study contact details
Ms Elizabeth Moore
Department of Epidemiology and Preventive Medicine
School of Public Health and Preventive Medicine
Monash University
Level 6, The Alfred Centre
99 Commercial Rd
Melbourne, Vic, 3004
Australia
 Fax Number: +61 3 990 30071
 Mobile Number: +61 400 971 948
 Email Address: Elizabeth.moore@monash.edu
31. APPENDIX K: (POLAR BEAR)

31.1. POLAR Basal Energy Assessment Research (POLAR BEAR) – a POLAR sub-study

This is a study of the effects of early and sustained hypothermia in TBI patients on resting energy requirements with TBI to be conducted at The Alfred and Auckland City Hospital.

31.1.1. Background and Rationale

Traumatic Brain Injury (TBI), defined as an external insult to the head resulting in damage to the brain, is one of the leading causes of hospitalisation, death and disability worldwide, particularly in young adults. In 2004-2005 there were over 22,000 hospitalisations in Australia for TBI, many of whom required a period in intensive care due to the severity of their injury and the consequences resulting from it. In a recent analysis of an international database of 2664 patients with severe TBI, mortality was 28% and only 52% of these patients had favourable neurological outcomes (good recovery or moderate disability) and were able to live independently at 6 months.

Given the young age of many patients with severe TBI and the long term prevalence of major disability, the economic and social cost to the community is very high.

Current management of TBI is supportive and focuses on multiple interventions for the prevention and treatment of secondary brain injury hypoxia including sedation, intravenous fluids, monitoring and manipulation of oxygen, intra-cranial pressure (ICP) and cerebral perfusion pressure (CPP). Despite decades of research investigating novel therapies for patients with TBI, recent clinical trials have not demonstrated substantial improvements in outcome. One intervention with great potential to reduce neurological damage and improve outcome after severe TBI is the application of early prophylactic hypothermia. This therapy involves the rapid reduction of core body temperature to 33°C and is commonly used in Australia to treat patients with severe neurological injury following out-of-hospital cardiac arrest.

There is a compelling scientific rationale to further investigate whether early prophylactic hypothermia is efficacious in TBI. On the background of extensive laboratory data, clinical trials over the past two decades have supported a likely benefit. Furthermore, a 2007 meta-analysis of the highest quality clinical trials of hypothermia in severe TBI reported a significant increase in long term favourable neurological outcomes (relative risk (RR) 1.46, p=0.006) with no significant decrease in mortality (RR 0.76, 95% confidence interval (CI) 0.05 to 1.05, p=0.18) in patients treated with prophylactic hypothermia compared to normothermia.

The only published multi-centre hypothermia trial reported no improvement in outcomes in patients treated with prophylactic hypothermia. Whilst the trial was well conducted, it had key methodological limitations including a prolonged time until commencement of hypothermia (an average of 8 hours) and a short duration of hypothermia (48 hours). In addition, the trial induced and maintained hypothermia using cooling blankets and bags of ice, a practice which is renowned for difficulty in achieving constant patient temperature and targeting gradual re-warming. The recent development of electronically controlled surface (skin) cooling pads has significantly advanced the controlled induction, maintenance and ultimate emergence from hypothermia.

Members of the ANZICS Clinical Trials Group have designed a large, multi-centre randomised controlled trial to investigate the efficacy of prophylactic hypothermia in patients with TBI. The POLAR (the Prophylactic hypOthermia trial to Lessen trAumaticbRain injury) study will enrol 500 patients and has been designed to address the major limitations of the previous multicentre study by inducing prophylactic hypothermia early (in the ambulance) and maintaining it for a prolonged period (minimum of 3 up to 7 days) using well controlled surface cooling pads.

Nutrition therapy in the critically ill setting is an essential element of patient care. It has now been clearly demonstrated to reduce complication rates and improve morbidity and mortality. Enteral nutrition (EN) is preferred over parenteral nutrition as it is associated with better clinical outcomes, especially in patients with trauma. It is also recommended that EN is commenced within 24-48 hours of admission to the ICU in the critically ill.

Whilst the route of delivery and timing of nutrition therapy has become increasingly understood, the amount and composition that should be delivered is more difficult to define. The primary goal of providing nutrition therapy during critical illness is to supply adequate macro and micronutrients to meet metabolic demands, which are usually significantly increased in the presence of injury or illness. One of the biggest challenges in administration of nutrition therapy is the prediction of each patient’s true nutritional needs. Assessment of the individual patient’s total energy requirements is most commonly performed using mathematical equations which estimate energy requirements using age, gender, height, weight and severity of illness. Such predictive equations were derived many decades ago and

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are potentially inaccurate in the critically ill population. The most commonly used formula in Australia, the Schofield equation,\textsuperscript{76} was developed in 1985, and is based on a meta-analysis of 100 studies which included 7000 healthy subjects, almost half of whom were Italian soldiers, and is therefore likely to be significantly unhelpful in an ICU.\textsuperscript{76,78} In addition there is considerable variation in energy expenditure depending on the time course of the illness and the interventions that are applied. Therefore it is likely that single predictions are inaccurate for all phases of critical illness.

The gold standard for prediction of energy expenditure is indirect calorimetry, a machine attached to the patient's ventilator circuit, which measures the utilisation of oxygen and production of carbon dioxide to obtain a value for resting energy expenditure.\textsuperscript{79,80} Because the lungs are the sole source of oxygen intake and carbon dioxide excretion, changes in the concentration of these gases reasonably reflect energy metabolism. An indirect calorimetry measurement of only 15 minutes duration can successfully predict energy requirements with less than a 4% error. This allows for quick, accurate and real-time determination of the metabolic response to injury in mechanically ventilated and critically ill individuals.\textsuperscript{80} Essentially this technology could eliminate the error associated with a predictive equation and transform current nutrition practices by allowing adjustment of the nutrition regime accordingly.\textsuperscript{79-81}

A significant concern in the provision of nutrition therapy is that patients are often inadequately nourished and receive significantly less than their predicted requirements, due to a number of patient-related and logistic factors, thereby putting patients at risk of malnutrition.\textsuperscript{82,83} The inverse of this is over-nourishment, however the consequences may not be as serious as prolonged under-nourishment. In a retrospective analysis of 55 mechanically ventilated patients, only 40\% of patients received the amount they required when using predictive equations alone, compared to using indirect calorimetry measurements. A quarter of the patients were classified as inadequately nourished by the predictive equation and 35\% were over-nourished.\textsuperscript{84} In TBI patients, inadequate nourishment in the form of delayed nutritional therapy has been shown to be associated with a prolonged acute phase response and poor outcomes.\textsuperscript{85} Inadequate nourishment is a significant problem given the inaccuracy of clinical tools for prediction of energy expenditure in the critically ill, intolerance of EN due to gastrointestinal dysmotility and the regular interruptions of nutrition regimes which are common place in the ICU.\textsuperscript{82,83} We have recently demonstrated in a large international survey of 2850 ICU patients that the average proportion of predicted energy requirements that were actually delivered was 58\%.\textsuperscript{88}

It could be expected that hypothermia would reduce energy expenditure, however there is sparse data in the literature to support this. One study of 10 patients who had brain injury from stroke demonstrated that hypothermia to 33°C for 3 days led to a total energy expenditure fall of between 25 and 29\%.\textsuperscript{86} More recently, a study of 5 TBI patients showed that hypothermia to 32°C led to a total reduction of 30.3\% in energy expenditure such that on average a 1°C reduction in temperature led to 5.9\% less energy expenditure\textsuperscript{88}. Neither of these studies had a control group of normothermic patients to determine whether other interventions may have contributed to these changes.

It therefore seems likely that significant reductions in energy expenditure do occur during hypothermia, but how much and what this might mean remains unknown. It is also unknown what happens during the rewarming phase after a period of prophylactic hypothermia in TBI patients. A study from over 20 years ago showed that rewarming after hypothermia during surgery (for cardiopulmonary bypass) led to increased energy expenditure \textsuperscript{88} but this has not been measured in TBI patients. Indeed the metabolic response to all phases of illness and intervention in TBI patients remains poorly understood. Whilst there have been studies in this area, most were conducted 15-20 years ago when the management of TBI patients was often quite different and there have been no studies in an Australasian population.

Understanding energy expenditure in TBI patients has critical implications for setting nutrition therapy targets. Although less nutrition may be required during hypothermia, hypothermia may have adverse effects on the tolerance of nutrition therapy. An understanding of energy expenditure by severe TBI patients, including during hypothermia, is of fundamental importance to nutritional management in TBI. It will be of even greater importance if hypothermia becomes the standard of care. This study will allow us to measure energy expenditure throughout the intensive care period of TBI care. We anticipate that energy expenditure will change considerably over time as injury and treatment varies.

The POLAR study will therefore allow us to study energy expenditure in TBI patients with 2 predominant objectives. The first of these is that we will specifically investigate the effects of hypothermia on energy expenditure and the second is that we will investigate the energy expenditure response over the entire course of ICU treatment of TBI patients. We can also observe in these patients the actual nutrition therapy received and how well this matches both their predicted and measured requirements.
The research questions we therefore aim to address are (1) “how is energy expenditure affected by treatment with prophylactic hypothermia in severe TBI patients”, and (2) “what is the daily energy expenditure in severe TBI patients over the course of their illness, whether they receive hypothermia or not”?

31.1.2. Significance

Traumatic Brain Injury is one of the leading causes of hospitalisation, death and disability worldwide, particularly in young adults. Prophylactic hypothermia is a highly promising intervention which may become a standard of care if the POLAR study shows a beneficial effect on neurological outcomes.

Nutrition therapy is another important intervention that is not well understood. Determining the optimal amount of nutrition therapy to deliver to critically ill TBI patients is a significant challenge, especially as treatments such as hypothermia can affect their energy expenditure, and therefore their nutritional requirements.

Discovering how energy expenditure changes both in response to hypothermia and throughout the course of the post-hypothermia period will allow clinicians to accurately determine optimal nutritional goals. Optimising nutrition delivery and maximising its benefits requires accurate assessment of the patient’s nutritional needs to avoid the complications of over and under-nourishment.

This study will provide us with this information to enable dietitians to improve nutritional delivery and will be particularly pertinent if hypothermia becomes a standard of care for TBI. The POLAR BEAR study will be the only one of its kind to our knowledge that can provide this information. The nature of this research lends itself to generate further hypotheses and we hope that the POLAR BEAR study will be the first of a series of nutrition and TBI research projects led by the ANZIC-RC, in conjunction with The Alfred Hospital so that we can emerge as a leader in research and best practice for nutrition for the critically ill adult.

31.1.3. Objectives

Hypothesis

Our primary hypothesis is that TBI patients who receive prophylactic hypothermia will have reduced energy expenditure (measured by indirect calorimetry) of at least 20% during the initial 72 hour period of treatment compared to patients who receive standard care.

Objectives

Our primary objective is to assess the daily energy expenditure (as measured by indirect calorimetry) in TBI patients over the first 72 hours after enrolment in the POLAR study so as to compare patients who receive prophylactic hypothermia with those who receive standard care.

Our secondary objective is to assess the daily energy expenditure (as measured by indirect calorimetry) in TBI patients who receive either prophylactic hypothermia or standard care until the end of their period on mechanical ventilation.

Other objectives are:

(1) To assess the daily energy expenditure (as measured by indirect calorimetry) in TBI patients during rewarming after prophylactic hypothermia.

(2) To assess the daily energy expenditure (as measured by indirect calorimetry) in TBI patients in the period after warming from prophylactic hypothermia.

(3) To assess the daily energy expenditure (as measured by indirect calorimetry) in TBI patients who have fever.

(4) To assess the difference in daily energy expenditure between measurements with indirect calorimetry and estimations using the Schofield predictive equation at The Alfred and fixed prescription (cal/kg) at Auckland City in TBI patients.

(5) To assess the amount of energy that is actually delivered by nutrition therapy in TBI patients as a proportion of both estimated and measured energy expenditure.

31.1.4. Study outcome measures

Primary outcome

The primary outcome for this study will be:

Mean daily energy expenditure as measured by indirect calorimetry over the first 72 hours after enrolment into the POLAR study.
Secondary outcome

Secondary outcomes will be:

Mean daily energy expenditure as measured by indirect calorimetry over the first 7 days after enrolment into the POLAR study

Mean daily energy expenditure as measured by indirect calorimetry over defined periods of intervention: (1) period of prophylactic hypothermia; (2) period of rewarming; (3) period of post-hypothermia treatment; and (4) periods of fever (defined as periods where body temperature > 39°C)

Mean daily energy expenditure as estimated by the Schofield equation and fixed prescription as a proportion of mean daily energy expenditure as measured by indirect calorimetry

Actual delivered energy by nutrition therapy as a proportion of mean daily energy expenditure as estimated by the Schofield equation and fixed prescription methods Actual delivered energy by nutrition therapy as a proportion of mean daily energy expenditure as measured by indirect calorimetry

31.1.5. Study design

This will be a sub-study of all patients who are enrolled into the POLAR study in 2 participating centres (Alfred Hospital and Auckland City Hospital) – a prospective, randomised controlled trial.

Inclusion Criteria:

40 consecutive patients admitted to the Alfred Hospital or Auckland City Hospital who are enrolled in the POLAR study and who also meet the following criteria:

Informed consent is obtained for the sub-study

Indirect calorimetry can commence within 24 hours of enrolment

Exclusion criteria:

Intercostal catheter with air leak

Known air leak in ventilation circuit

31.1.6. Methods

All patients meeting eligibility criteria at the Alfred Hospital ICU, Melbourne, Australia and Auckland City Hospital, Auckland, New Zealand will be enrolled in the study subject to obtaining informed consent. The patients will follow all trial procedures of the POLAR study.

Indirect calorimetry (using the Quark RMR Nutritional Assessment Device, Cosmed, Rome, Italy at The Alfred Hospital and the Deltatrac II, DatexOhmeda, Madison, USA at Auckland City Hospital) will be attached to the mechanical ventilator circuit and will be commenced within 24 hours of enrolment into the study.

As per previous validation studies for indirect calorimetry, a steady respiratory and physiological state defined as 5 consecutive minutes where VO2 and VCO2 change by less than 10% will be achieved for 5-10 minutes prior to indirect calorimetry measurements. The first and last 5 minutes of each test will be discarded for accuracy. If deemed necessary measurements may be extended to ensure a steady state is achieved. Detailed information about the patients clinical state will be collected to allow correlation of indirect calorimetry measurements during the time course of prophylactic hyperthermia or normothermia.

Indirect calorimetry measurements will then be performed over a 30 minute time period twice daily at a specified time point (am and pm) until day 7 or until extubation, death or discharge from the ICU. After day 7, indirect calorimetry will be performed over a 30 minute time period once every 2 days until extubation, death or discharge from the ICU.

No other procedures will be necessary and nutritional support will not be influenced by any of these measurements as they will not be made available to clinical staff. Nutrition will be prescribed as per the main POLAR study protocol (described above).

In addition to the main POLAR study data collection and these indirect calorimetry measurements, data will be collected on several other aspects of nutritional therapy prescription and delivery including timing of commencement, route of delivery, amount prescribed, amount delivered, gastric residual volumes, use of promotility drugs, serum albumin, serum glucose and bowel actions. These will only be collected if they are measured as part of routine care.

31.1.7. Participating study sites

The Alfred Hospital, Melbourne
31.1.8. Ethics

This study will be performed in accordance with the ethical principles of the Declaration of Helsinki (June 1964 and amended 1975, 1983, 1989, 1996, 2000, 2008 and Note of Clarification 2002 and 2004), ICH GCP Notes for Guidance on Good Clinical Practice (CPMP/ICH/135/95) annotated with Therapeutic Goods Administration comments and NHMRC National Statement on Ethical Conduct in Research Involving Humans (National Statement) (March 2007).

Patients will be enrolled into the study at the same time as for the POLAR study.

The ethical implications of the study are that the patients will have a severe traumatic brain injury and will be incapable of consenting to participate at the time of enrolment. The study intervention (indirect calorimetry) does not pose any additional risks or discomforts to the patient. However, as the indirect calorimetry must be commenced within 24 hours of the patient being enrolled into the POLAR study, there may not be sufficient time for the patient's Person Responsible to be contacted and discuss the study with the researcher without causing additional distress.

The POLAR study will enrol patients utilising the provisions for emergency research included in the National Statement.

Some research must necessarily be performed on patients in ‘emergency’ (the definition is ‘unexpected’) situations when they are unable to provide consent, as with all other categories of patients. To be eligible for recruitment in the POLAR study patients will be unconscious (GCS<9) and consequently will be unable to consent to participation. The National Statement acknowledges in section 4.4 that research involving patients who are heavily dependent on medical care in emergency circumstances, such as the patients in this study, may proceed when the participants ability to give consent is non-existent. This requires approval from the appropriate ethical body to waiver or defer consent (section 7.3).

The Alfred Research and Ethics Committee has approved the POLAR study, including the use of emergency consent. Application for an amendment will be made to the Committee if funding is secured for this study, and the Committee will be asked to approve the inclusion of this POLAR BEAR study using the same consent provisions.

As soon as is reasonably possible and appropriate the patient’s Person Responsible will be informed of the patient’s inclusion in the research and will be asked to consent to the patients continuation in the study. Patients who recover sufficiently to understand the explanation of the study will also be asked to consent to continue in the study or be offered the chance to withdraw.

31.1.9. Data management

Data Collection Methods

All data will be collected by trained staff at each study site using a paper source document developed by the coordinating centre. Data will then be entered into a website designed by the CCRET. Data queries will then be automatically generated via the website. Some of the variables will be obtained from the POLAR trial and others are only relevant to the POLAR BEAR sub study and will be collected in addition.

Data variables collected

**Pre hospital**
- Patient identifier(s)
- Baseline demographics
- Inclusion and exclusion criteria (POLAR BEAR)
- Pre-hospital vital signs, Glasgow coma scale and temperature
- Date and timing of cooling intervention

**Hospital admission**
- Vital signs, Glasgow coma scale
- Date and time of surface temperature control vests/leg wrap application
Biochemical parameters
Hourly core temperature
Injury severity score

**Intensive Care Admission**
- Vital signs, Glasgow coma scale
- Height
- Weight
- Date and time nutrition commenced
- Biochemical parameters
- Hourly core temperature
- Energy and protein requirements as per usual prediction method
- Total daily sedation dose

**Nutrition (daily)**
- Type of nutrition received and if EN, the route delivered
- Formulation name (EN and/or PN)
- Daily volume, energy and protein prescription (EN and/or PN)
- Actual volume, energy and protein received (EN and/or PN)
- Gastric residual volume total on that study day
- Promotility drug use
- Number of bowel actions
- Indirect calorimetry measurements (twice daily days 1-7 and once every second day from Day 7 until discharge, extubation or death)
- Bed side shivering assessment scale twice daily during indirect calorimetry measurements until cooling is removed or day 7 (whichever comes first)

**Hospital discharge**
- Length of mechanical ventilation
- Length of stay
- Discharge destination
- Vital status at ICU and hospital discharge
- Treatment limitations/withdrawal

**Outcome data**
- 6 month GOSE
- EQ5D
- SF12®
- Health Economic evaluation data

**Clinical costing**
- Duration of rehabilitation stay
- Duration of nursing home stay
- Level of home care

### 31.1.10. Data monitoring
Data monitoring for POLAR BEAR will be conducted by the Project Manager
31.1.11. Monitoring
Each POLAR site will be monitored once 50% of the total number of required patients has been enrolled into the study.

31.1.12. Statistical considerations
Sample size calculation
Sample size calculations were based on our observational cohort of 478 trauma patients. Based on a mean predicted energy requirement of 2000 calories and a standard deviation of 400 calories this study will require a minimum of 16 subjects per group to have an 80% power to detect a difference in total energy expenditure over the first 72 hours between the standard care and hypothermic patients of 400 calories with a two-sided p-value of 0.05. A difference of this magnitude (20% absolute reduction) has been chosen as a conservative estimate from previous studies86-88 which showed that hypothermia may reduce energy expenditure by between 25-30%. Allowing a further 20% for non-completion, this study will recruit a total of 20 patients per group.

Statistical and analytical plan
Data analysis will be performed by a statistician at the Australian and New Zealand Intensive Care Research Centre (ANZIC-RC). Reports will be issued to the sub-study and the main POLAR study investigators. Appropriate statistical techniques will be used for comparison of normally distributed and non-parametric data.

31.1.13. Safety
As Per the POLAR trial. There are no additional risks posed by the POLAR BEAR sub-study.

31.1.14. Funding
POLAR BEAR is supported by a $5000 grant (AuSPEN) for statistical services and data management and $20,000 (The Alfred Foundation) for salary support of the project manager. The ANZIC-RC will provide infrastructure and administrative support.

31.1.15. Publication
The study will be conducted in the name of the AuSPEN Clinical Research Group, the ANZICS Clinical Trials Group (pending endorsement) and the ANZIC-RC on behalf of the POLAR investigators. Authorship will be under the names of the sub-study investigators on behalf of the POLAR investigators.

31.1.16. POLAR BEAR contact details
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32. APPENDIX L: BIOMARKER AND EXCITOTOXICITY POLAR SUB-STUDY

32.1. The Biomarker and Excitotoxicity POLAR Sub-Study

32.1.1. Aims
TBI increases the release of the cellular injury markers, S100β, neuron specific enolase (NSE), and myelin basic protein (MBP) into the serum. These markers have been shown to reflect the degree of neurological impairment after injury and have substantial prognostic value of long-term outcome. We plan to investigate the changes in these biomarkers in patients with TBI as a sub-study of the POLAR trial.

The specific aim of this sub-study is to determine the level of biomarkers in patients with TBI following hypothermia or normothermia treatment and evaluate the efficacy in predicting long-term outcome. We hypothesise that treatment with hypothermia after TBI will ameliorate neurological deficit and reduce the secretion of brain injury markers in the blood of TBI patients.

32.1.2. Background
There has been considerable work on the potential use of brain specific proteins as markers for tissue damage as well as markers of prognostic value for outcome. The identification of markers following TBI in blood serum would be of great benefit for all patients, as this would provide clinicians with additional molecular diagnostic parameters to improve monitoring and potentially the treatment provided to TBI patients.

**S100β:** S100β is a family member of acidic low molecular weight calcium binding proteins that are found primarily in astrocytes (S100β) within the CNS. We and others have previously found S100β levels to be dramatically increased following TBI. The utility of the use of S100β as a prognostic tool has been reinforced by studies by Petzold et al showing that the levels of S100β correlate with outcome.

**Glial fibrillary acidic protein (GFAP):** GFAP represents the major constituent of the cytoskeleton of astrocytes and is found only in glial cells of the CNS. Astrogliosis is a hallmark of astrocytes activation and occurs in both TBI and hypoxic brain damage. In animal models, the increases in GFAP are associated with the degree of astrogliosis and was shown in this model by immunohistochemistry.

**Neuron specific enolase (NSE):** NSE is glycolytic enzyme found in high concentrations in neuroendocrine cells, platelets and neurons. Increased CSF and serum levels of NSE are usually associated with acute neurodegeneration. Raised levels of NSE following TBI have been correlated with contusion size and cerebral inflammation with very high levels being associated with death. Also, following hypoxia-ischemia, plasma NSE correlated with clinical outcome.

**Myelin basic protein (MBP):** In the CNS, 30% of the myelin is composed of myelin basic protein (MBP). Human MBP has been shown to be released into the CSF by the destruction of myelin, and is therefore a marker of demyelination activity. Elevated levels of MBP in CSF have been observed in patients with head trauma and neurological diseases.

32.1.3. Methods
Inclusion and exclusion criteria for the Biomarker Sub-study will be the same as for POLAR. Blood samples (10 ml) will be collected daily for 5 days post-injury in a subset of 80 patients enrolled in POLAR trial which will be divided into 40 treated with hypothermia and 40 untreated control patients. Blood samples will be spun at 2000g and serum frozen at -70°C. Serum samples will be stored and managed in the laboratory at National Trauma Research Institute by our associate investigators. S100β, NSE, and MBP will be measured in serum using commercial ELISA kits (R&D Systems, CanAg). The results will be correlated with patient’s neurological outcome scores assessed at 6 month post-injury (GOSE) to allow comparisons between patients treated with hypothermia and control normothermic patients. GOSE will be provided by the clinicians managing the POLAR-RCT.

32.1.4. Power calculations and sample size
Our preliminary data based on MBP measurements showed a r=0.4542 of Spearman Rank Correlation Coefficient between concentration of MBP in serum and GOSE. Based on this, a study of 40 patients (per group: hypothermia and normothermia) will have >80% power with r=0.45 and a two sided p-value of 0.05.

32.1.5. Analysis of results
Data will be analysed using GraphPad Prism 5. Continuous outcomes will be assessed for normality and log-transformed where appropriate. Multivariate analysis on normal or log-transformed biomarkers will be performed using multiple linear regression analysis while group comparisons over time using 2-way ANOVA. A p-value of 0.05 will be considered statistically significant.
32.1.6. Outcomes
The purpose of the experiments of this sub-study is to explore whether improvement of neurological deficit in TBI patients following hypothermia will coincide with attenuated release of brain injury markers in blood serum as compared to TBI patients kept under normothermic conditions. Therefore differences in the concentration of serum markers will be assessed between the treatment groups and correlated with the neurological GOSE scores. If our hypothesis will prove correct these markers may become applicable in future clinical trials as prognostic tool of long term neurological outcome.

32.1.7. Contact details
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33. APPENDIX M: POLAR TEG

33.1. POLAR TEG

33.1.1. Aims
We plan to investigate changes in coagulation and in particular platelet function in patients with TBI in this sub study of the POLAR trial.

33.1.2. Background
Therapeutic Hypothermia and POLAR.

Therapeutic hypothermia is used in patients with severe TBI to improve outcomes, both as a prophylactic therapy to reduce secondary brain injury, and also as one of only 3 possible “second tier” therapies for refractory rises in intracranial pressure. We are, at present, testing hypothermia in a rigorous NHMRC funded randomised trial (POLAR - ACTRN 1260500009617).

One concern with this therapy is the effect of hypothermia on coagulation. Most haematologists agree that hypothermia adversely affects coagulation status and studies in animals and in vitro confirm this. Accordingly, trauma patients are often hypothermic on arrival at an emergency department and are routinely aggressively rewarmed during emergency resuscitation using sophisticated massive transfusion devices.

Strangely, little clinical work has been done to inform us of the direct effect of hypothermia in the severe TBI population. Review articles state that hypothermia to 35°C is generally safe and that 33°C is not usually associated with bleeding complications in TBI patients however, there is little to support these contentions in the original research literature.

Hypothermia impairs coagulation by inhibiting temperature dependent enzymes involved in the coagulation cascade. Hypothermia also causes platelet dysfunction, but the temperature at which these elements become clinically relevant and or predominant has not been studied in trauma patients and is completely unknown.

There have been no reports of increased bleeding in patients suffering severe TBI and managed with hypothermia, but coagulation was not studied in detail and has generally been de-emphasised by hypothermia advocates. Haemostasis in cardiac arrest patients treated with hypothermia has been studied by Spiel et al, and it has been concluded that the potential bleeding complications of therapeutic hypothermia are “minimal”. However and obviously, cardiac arrest patients do not have the same traumatic tissue injuries at risk of bleeding as trauma, and specifically TBI patients.

There has been little clinical investigation of the effects of hypothermia on coagulation and no such study of this type in patients with severe TBI. The POLAR trial presents a unique opportunity to clinically investigate the influence of hypothermia on TBI patients at minimal cost. POLAR gives us an opportunity to study the effects of hypothermia on coagulation in severe TBI patients. As this work has never been done in TBI patients especially those receiving hypothermia, it will have direct clinical applicability.

33.1.3. Laboratory Testing
The most common routine laboratory-based coagulation tests International Normalised Ratio (INR), Activated Partial Thromboplastin Time (APTT) and platelet numbers are used to inform clinicians of the patients’ coagulation status but may be poor indicators of in vivo coagulation in hypothermic patients. These samples test plasma (blood minus cells) rather than whole blood which excludes the contribution of the cellular elements to the in vivo coagulation process. The assays are also performed at a standard temperature of 37°C (regardless of the patient’s actual temperature) which likely underestimates the effects of hypothermia on coagulation. Thromboelastography (TEG) has been previously used in bleeding cardiac surgical patients to measure coagulation deficits and we will use this technology in TBI patients. It can be performed at the patient bedside (Point-of-Care) and also at the patient’s temperature. We can therefore, for the first time, get an clearer picture of the effect of patient temperature on coagulation in the patient group of concern.
33.1.4. Significance
There has been little clinical investigation of the effects of hypothermia on coagulation and no such study of this type in patients with severe TBI. POLAR gives us an opportunity to study the effects of hypothermia on coagulation in severe TBI patients. As this work has never been done in TBI patients especially those receiving hypothermia, it will have direct clinical applicability.

33.1.5. Objectives
Hypothesis
TBI patients who receive prophylactic hypothermia will have alterations in their coagulation status as measured by the TEG.
Primary Outcome
The coagulation status of a group of trauma patients enrolled in the POLAR study will be compared to a group of non-POLAR trauma patients.
Secondary Outcome
Hypothermic patient’s coagulation status will be compared with the same patient’s blood tested at normothermia.

33.1.6. Study Design
An observational sub study of patients enrolled in the POLAR RCT plus another 20 patients from the general trauma population not enrolled in POLAR.

Recruiting Site
The Alfred Hospital Melbourne

Inclusion criteria
- POLAR cohort (Hypothermic and control POLAR patients)
  - Enrolment in the POLAR study
  - Age ≥18 years
- Non POLAR Cohort
  - Adult patients admitted to the ICU with diagnosis of trauma
  - Blunt trauma with injury severity score >16

Exclusion Criteria
- Death is imminent
- Patient on Heparin or Clexane
- Inability to cool POLAR “hypothermia” patient
- Likely to be discharged from the ICU in <48 hours

33.1.7. Ethics and consent
The Alfred Research and Ethics Committee has approved the POLAR study, including the use of emergency consent. The Alfred HREC have agreed to include the POLAR TEG study using the same consent provisions.

The POLAR plain language and information form includes details about the sub study including the study design, methodology and significance. A separate plain language and information form will be used for the non POLAR cohort.

Consent from the non POLAR group will be prospective and sought from the participant’s Person Responsible/ Next of Kin or appropriate delegate, as soon as practical, and from the participant themselves when competent. If a Person Responsible is not found and the participant is not competent then procedural authorisation under section 42T will be requested. Procedural authorisation will always...
be followed by participant or Person Responsible consent as soon as possible. Patients will have the opportunity to withdraw consent to participate at any time.

They will be informed that refusal to participate in the study will not prejudice their current/future treatment.

33.1.8. Research plan and Methods

20 trauma patients recruited into POLAR and 20 non POLAR trauma patients will be recruited. Wherever possible eligible patients will be enrolled consecutively, however logistical constraints may preclude this.

Demographic data and baseline data will be gathered from patient notes and the coagulation profile will be drawn from routine sampling of patients. Information about the pre-injury use of non-steroidal anti-inflammatory medication will be collected. Patients will undergo TEG analysis as per TEG schedule and TEG analysis methodology. Patients will exit this observational study upon completion of the final blood sample.

33.1.9. TEG analyser technology

The TEG analyzer has a sample cup that oscillates back and forth constantly at a set speed through an arc of 4°45'. Each rotation lasts ten seconds. A whole blood sample of 360 ul is placed into the cup, and a stationary pin attached to a torsion wire is immersed into the blood. When the first fibrin forms, it begins to bind the cup and pin, causing the pin to oscillate in phase with the clot. The acceleration of the movement of the pin is a function of the kinetics of clot development.

The torque of the rotating cup is transmitted to the immersed pin only after fibrin-platelet bonding has linked the cup and pin together. The strength of these fibrin-platelet bonds affects the magnitude of the pin motion, such that strong clots move the pin directly in phase with the cup motion. Thus, the magnitude of the output is directly related to the strength of the formed clot. As the clot retracts or lyses, these bonds are broken and the transfer of cup motion is diminished. The rotation movement of the pin is converted by a mechanical-electrical transducer to an electrical signal which can be monitored by a computer.

The resulting hemostasis profile is a measure of the time it takes for the first fibrin strand to be formed, the kinetics of clot formation, the strength of the clot (in shear elasticity units of dyn/cm²) and dissolution of clot.

Normal TEG trace
**R time** – reaction time - the initiation phase of coagulation / clotting time (clotting factors)

**A angle** – rate of clot formation/strengthening (speed of fibrin build up and crosslinking)

**MA** - maximum amplitude – reflects the ultimate strength of the clot (fibrinogen, platelet count and function).

**A30** – amplitude at 30 mins - reflects clot stability/breakdown (fibrinolysis)

### 33.1.10. TEG schedule

#### Sample 1

POLAR hypothermia patients will have TEG blood samples taken while at 33°C and prior to rewarming (48 to 72hrs hours post POLAR randomisation). Samples will be analysed using the TEG at both 33°C and 37°C (see TEG analysis methodology). At each temperature (33°C and 37°C) standard and functional fibrinogen assays will be performed. Standard, functional fibrinogen and Platelet Mapping (PM) at 33°C will be tested followed by standard, functional fibrinogen and Platelet Mapping (PM) at 37°C. The second analysis will require the patient to have a fresh sample taken.

Control patients will have blood taken 48 to 72hrs hours post POLAR randomisation and analysed at 37°C using the TEG. Standard, functional fibrinogen and Platelet Mapping (PM) assays will be performed at 37°C (see TEG analysis methodology) Non POLAR patients will have blood taken 48 to 72hrs hours post hospital admission and analysed at 37°C using the TEG. Standard, functional fibrinogen and Platelet Mapping (PM) assays will be performed at 37°C (see TEG analysis methodology)

#### Sample 2

Hypothermia patients will have blood taken 120 hrs +/- 12hrs post randomisation once they have reached 37°C. Samples will be analysed using the TEG at 37°C. Standard, Fibrinogen and PM TEG Assay will be performed (see TEG analysis methodology).

Control patients will have blood taken 120 hrs +/-12hrs post randomisation and analysed at 37°C using the TEG. Standard, fibrinogen and PM TEG Assay will be performed (see TEG analysis methodology).

Routine laboratory testing includes International Normalised Ratio (INR), Activated Partial Thromboplastin (APTT) & Platelet count.

<table>
<thead>
<tr>
<th></th>
<th>Hypothermic therapy patient</th>
<th>Standard therapy patient</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sample 1</strong></td>
<td>48 and 72hrs hours post POLAR randomisation</td>
<td>Standard, Fibrinogen and PM assay at 33°C followed by, Standard, Fibrinogen and PM assay at 37°C</td>
</tr>
<tr>
<td><strong>Sample 2</strong></td>
<td>120 +/-12hrs post POLAR randomisation</td>
<td>Standard, Fibrinogen and PM assay at 37°C only.</td>
</tr>
</tbody>
</table>

### 33.1.11. TEG analysis methodology:

Samples for analysis will be drawn from the arterial catheter and must be used within 4 minutes.

The collection of samples will, wherever possible, coincide with routine blood collection to minimise fluid and blood loss to the patient. A 10ml aliquot will be collected and discarded to eliminate the dilutional effect of saline in the arterial line (standard practice). The sample for testing is then collected.
Standard Assay
- Set temperature of analyser
- Load plain test pin and cup
- Collect 1ml of blood from arterial line (follow unit standard practice)
- Deliver 1ml aliquot into kaolin vial
- Mix carefully by inversion (not pill rolling as this may warm the sample).
- Pipette 360µl of kaolin mixture into loaded plain test cup
- Commence computer program

Fibrinogen Assay
- Set temperature of analyser
- Load plain test pin and cup
- Collect 0.5ml of blood from arterial line (follow unit standard practice)
- Deliver 0.5ml aliquot into functional fibrinogen assay vial
- Mix carefully by inversion (not pill rolling as this may warm the sample).
- Pipette 360µl of kaolin mixture into loaded plain test cup
- Commence computer program

Platelet Mapping Assay
- Set temperature of analyser
- Load plain test pins and cups, only 2 can be analysed at one time
- Prepare cups and pins with:
  - 1 – Activator
  - 2 – Activator + AA
  - 3 – Activator + ADP
- Collect 3ml of blood from arterial line into a heparin tube
- Deliver 360µl aliquots of blood from the heparin tube into each cup and pin
- Mixed by pipetting half the volume of the blood and activator mix into the pipette tip and ejecting 3 times
- Commence the computer program

Analysis shall be performed with the computerised thromboelastograph coagulation analyser (Haemoscope Corp., Skokie, IL). The coagulation profile is displayed on a computer running TEG analytic software which is connected to the analyser via an A/D interface box. The values of normal controls are displayed enabling comparison.

33.1.12. Quality Control

*Routine* quality control should be performed prior to patient testing if it has not been performed in the last 7 days.

33.1.13. Data variables
- Gender
- Date of Birth
- Injury time
33.1.14. Data analysis and statistics
Both conventional (INR and APTT) and TEG related (platelet function and fibrinogen) indices of coagulation will be compared between treatment and control groups at two time points 1) between 48 and 72hrs hours post POLAR randomisation, 2) 120 hours (+/- 12hrs) post randomisation. These indices will also be compared in the same samples at both 33C and 37C, in the treatment group patients. All data will be analysed using SAS version 9.2 (SAS Institute Cary, NC, USA). Data will be assessed for normality and log-transformed where appropriate. Comparisons within and between groups will be performed using mixed linear modelling accounting for repeat measures with individual patients treated as random effects. Should any indices have insufficient symmetry to satisfy the assumption of normality, changes from baseline will firstly be considered followed by non-linear modelling if required. A two-sided p-value of 0.05 will be considered to be statistically significant.

33.1.15. Safety
As Per the POLAR trial. There are no additional risks posed by the POLAR TEG sub-study. The results of the study will be forwarded to the DSMC.

33.1.16. Funding
Funding for the sub-study has been obtained from the Institute for Safety, Compensation and Recovery Research.

33.1.17. Publication
The study will be conducted in the name of the ANZIC-RC on behalf of the POLAR investigators. Authorship will be under the names of the sub-study investigators on behalf of the POLAR investigators. Publication of results will be embargoed until publication of the main study results unless specific permission for early publication is given by the POLAR management committee.
34. APPENDIX N: POLAR PROPOFOL PK SUB-STUDY

34.1. POLAR Propofol PK sub-study

34.1.1. Aims

To determine the impact of therapeutic hypothermia (core body temperature 34.0 to 35.0°C) on propofol plasma pharmacokinetics in severely head-injured critically ill patients.

34.1.2. Background: Therapeutic Hypothermia, Traumatic Brain Injury and Propofol

Propofol (2,6-diisopropylphenol) is a potent intravenous hypnotic agent with a rapid onset, short recovery time and generally favourable side effect profile, making it an ideal sedative for the intensive care unit (ICU) environment. In healthy, normothermic patients, propofol is rapidly and extensively redistributed, and has high clearance.\(^{115-117}\) It is frequently used in the management of traumatic brain injury (TBI) for sedating and anticonvulsant effects, as well as reduction in cerebral metabolic demands and control of intracranial pressure (ICP).\(^9\)

Systematic cooling of patients (therapeutic hypothermia) is a therapy that is also used in patients with severe TBI to improve outcomes, both as a prophylactic therapy to reduce secondary brain injury and also as a “second tier” therapy for refractory rises in intracranial pressure.\(^9,36,118\) However, little is known about the effect of hypothermia on the pharmacokinetics (PK) of propofol in the Intensive Care setting.

Propofol Infusion Syndrome (PRIS) is a rare and frequently fatal complication of propofol administration, comprising a constellation of metabolic derangements and organ dysfunction resulting from interruption of mitochondrial respiratory chain function.\(^119\) Since the initial paediatric case reports\(^120\) in the early 1990s, a number of articles have attempted to characterise the syndrome but there is still a great deal not known about this disease.

There remains no laboratory test of sufficient specificity to accurately diagnose PRIS; hence estimates of incidence vary considerably from 1%\(^121\), 2.9%\(^122\), and even 33%\(^123\) depending on the clinical diagnostic criteria used. PRIS has a number of clinical features with progressive cardiac dysfunction the most common clinical sign noted in both adults and children. There is uncertainty regarding the onset and triggers for PRIS. Vasile\(^124\) suggests that the syndrome requires two essential elements; a priming factor such as a critical illness, and a triggering factor (use of high dose (>4mg/kg/hr) for prolonged periods (>48hrs), concurrent catecholamine, or steroid use).

34.1.3. Possible effects on Propofol Pharmacokinetics

Hypothermia is known to reduce the clearance of many medications; however the effects of hypothermia on propofol remain poorly studied. In a small cohort study, Leslie et al\(^125\) showed that a drop of 3°C in core hypothermia (37 to 34°C) was associated with higher propofol blood concentrations than normothermia. Leslie et al found that cooling to 34°C led to an approximate 28% increase in propofol levels in 6 healthy patients.\(^125\) In 2001, Myburgh et al\(^126\) suggested that more research regarding the application of propofol in critically ill patients was required. Very little work has been published on the use of propofol in severely ill TBI patients, and no work on severely ill TBI patients receiving hypothermia.

Reports of PRIS in adults, generally those that are critically unwell and requiring high dose Propofol, e.g. patients with status epilepticus or TBI, continue to be found in the literature. Despite these reports, propofol use remains widespread in ICU and in patients with TBI. It appears possible that decreased clearance associated with hypothermia may predispose these critically ill patients to an increased risk of PRIS.
34.1.4. Significance

There has been very little clinical research on the effect of hypothermia on propofol PK, and no research in patients with severe TBI. The POLAR-RCT gives us a unique opportunity to study the effects of hypothermia on the PK of propofol in patients with severe TBI. As this work has never been done in TBI patients, especially those receiving hypothermia, it will have direct clinical applicability.

34.1.5. Objectives

Hypothesis

In severely head-injured critically ill patients receiving therapeutic hypothermia (body temperature of 34.0 to 35.0°C), total body clearance (CL\textsubscript{TOT}) of propofol will be significantly reduced when compared to normothermia (36.5 to 38.0°C), resulting in higher plasma concentrations.

**Primary Outcome**
- Plasma propofol concentrations

**Secondary Outcomes**
- Propofol pharmacokinetic parameters
- CL\textsubscript{TOT}
- Volume of distribution (V\textsubscript{d})
- Elimination half-life (T\textsubscript{1/2B})

34.1.6. Study Design

This will be a nested observational pharmacokinetic sub-study of patients enrolled in the POLAR-RCT.

34.1.7. Recruiting Site

Intensive Care Unit, The Alfred Hospital, Melbourne

34.1.8. Inclusion criteria

All patients enrolled in the POLAR-RCT, randomized to receive therapeutic hypothermia, and getting propofol by continuous infusion as clinician directed sedation.

34.1.9. Exclusion criteria
- Death is imminent
- Inability to effectively achieve therapeutic hypothermia
- Clinical features consistent with PRIS
- Concomitant red cell transfusion at the time of plasma sampling
- Propofol infusion running for <60-min prior to sampling
- Change to or cessation of propofol infusion, or administration of a bolus dose within 30-min of plasma sampling

34.1.10. Ethics and consent
The Alfred Research and Ethics Committee has approved the POLAR study, including the use of emergency consent. A single-site amendment will be sought from The Alfred HREC to enrol patients in the POLAR Propofol PK Sub study using the same consent provisions.

The POLAR plain language and information form includes details about the sub study including the study design, methodology and significance. They will be informed that refusal to participate in the study will not prejudice their current/ future treatment.

34.1.11. Methods

Sample size

A convenience sample of 10 patients with severe TBI recruited into the POLAR-RCT. Wherever possible eligible patients will be enrolled consecutively, however logistical constraints may preclude this.

Data collection

Demographic and baseline data (including injury mechanism and severity) is already collected and forms part of core data collection for the POLAR study. This sub study will require additional data describing propofol dosage and blood sampling times.

Blood Samples

Sampling will occur on two occasions (each patient will act as their own control):

**Occasion A** – during provision of therapeutic hypothermia (body temperature 34.0 to 35.0°C)

**Occasion B** – when the patient is normothermic (body temperature 36.5 to 38.0°C)

All patients enrolled in the study will receive propofol by continuous intravenous infusion (0-200mg/h) as per local study and management guidelines (Traumatic brain injury (TBI) management guideline, Prompt Doc No: AHG0000643 v3.0, Approval Date: August 2014 and Appendix D: Severe TBI and ICU Management Guideline, POLAR-RCT Protocol Amendment). The treating clinician will determine dosing.

**Occasion A:**

As per the recent POLAR-RCT study protocol amendment (Dated 28 May 2015), propofol infusion should be discontinued at a body temperature <35.0°C. Propofol PK will initially be determined at this point, by obtaining serial plasma concentrations via an indwelling intra-arterial cannula (inserted for clinical monitoring). The first sample will be drawn immediately prior to discontinuing the infusion. Subsequent samples will then be obtained at 5, 10, 15, 30, and 60min. See Figure 1 below. The arrow marks the point at which the propofol infusion is stopped.
Occasion B:

Once the patient is allowed to passively re-warm to normothermia (as per the POLAR-RCT Study Protocol), propofol continuous intravenous infusion may be provided as a short-acting sedative to facilitate ongoing care. Dosing is at the discretion of the treating clinician, although is typically interrupted at some point to allow a sedation free period of neurological assessment. Propofol PK will be determined at this point, using the same sampling regime as outlined in Occasion A. The clinical team will determine the timing of occasion B.

Patients will exit the study upon completion of the final blood sample.

Data variables will include:

- Demographic and baseline:
- Gender
- Date of Birth
- Patient weight and height
- Pre-existing comorbidities, especially chronic liver disease
- Injury time
- Blood pressure / heart rate
- Fluid and Blood component Input and output
- Glasgow coma scale
- Pupil reaction
- Date and timing of cooling intervention (commenced and ceased)
- APACHE II
Multi-centre POLAR study_ANZIC-RC/DJC003 Version 9 _ 11 July 2017

- AIS Head (max)
- CT brain scan – Marshall score
- Treatment data
- Temperature profile over each sampling period
- Propofol infusion rate
- Cumulative propofol dose in the 60-min prior to sampling.
- Other medications and fluids provided
- Blood samples
- Liver enzymes
- Renal function tests
- Plasma propofol concentrations
- Creatinine Kinase
- Lactate

34.1.12. Data analysis and statistics

Plasma propofol PK will be determined by both non-compartmental analysis and non-linear mixed effects modelling (NONMEM, GloboMax LLC, Hanover, MD, USA). The plasma concentration measured immediately prior to discontinuing the infusion will be assumed to represent steady-state (C_{SS}). Total body clearance (CL_{TOT} - L/h) will be calculated by dividing the total dose of propofol administered in the 60 minutes (mg/h) prior to this, by C_{SS} (mg/L). The area under the plasma concentration-time curve (AUC_{0-∞}) will be determined using the linear trapezoidal rule, and extrapolated to infinity by adding the product of the last measured plasma concentration multiplied by the terminal slope.

NONMEM will be employed to develop a baseline population physiologically-based-pharmacokinetic (PBPK) model, in an attempt to quantify between subject variability (BSV) and within subject variability, particularly in relation to body temperature. The influence of demographic, clinical, and therapeutic will be tested in the model.

Continuous data will be presented as the mean (SD) or median [IQR] where appropriate. Categorical data will be presented as counts (%). Within subject comparisons will utilize a paired Student’s T-test, Wilcoxon Sign Rank test, or a McNemar test, where analysis assumptions are met. All analyses will employ SPSS version 22 (IBM Corporation, Armonk, NY, USA).

34.1.13. Safety

As Per the POLAR trial.

There are no additional risks posed by the POLAR Propofol PK sub-study. A small amount of blood (approximately 12mls on each occasion of sampling) will be taken from an arterial line that is already in place for clinical reasons. The results of the study will be forwarded to the DSMC.

34.1.14. Funding

Funding for this sub-study will be sought from competitive external research grants.
34.1.15. Publication

The study will be conducted in the name of the ANZIC-RC on behalf of the POLAR investigators. Authorship will be under the names of the sub-study investigators on behalf of the POLAR investigators. Publication of results will be embargoed until publication of the main study results unless specific permission for early publication is given by the POLAR management committee.
35. BIBLIOGRAPHY

7. Bernard SA. The effects on outcome at 6 months of pre-hospital rapid sequence intubation compared with no intubation in patients with severe head injury Australian New Zealand Clinical Trials Registry 2005;ACTRN12605000177651.
50. Cummings P. Converting an adjusted odds ratio to a risk ratio will produce biased estimates. BMJ 2014;348:f7450/rr/684808.
51. Grant RL. Converting an odds ratio to a range of plausible relative risks for better communication of research findings. BMJ 2014;348:f7450.
66. !!! INVALID CITATION !!!


114. Jackson GNB, Ashpole KJ, Yentis SM. The TEG(R) vs the ROTEM(R) thromboelastography/thromboelastometry systems. Anaesthesia 2009;64:212-5.


Summary of POLAR protocol changes from Version 1 to Version 2

<table>
<thead>
<tr>
<th>Summary of POLAR protocol changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-hosp inclusion/exclusion reworded</td>
</tr>
<tr>
<td>Exclude if unable to randomise within 2.5 hrs post injury</td>
</tr>
<tr>
<td>Added ED randomisation</td>
</tr>
<tr>
<td>ED inclusion/exclusion criteria same as pre-hospital except for exclusion of patients with clinically significant bleeding likely to require haemostatic intervention eg:</td>
</tr>
<tr>
<td>ED randomisation: Infuse up to 2L of cooled fluid in ED</td>
</tr>
<tr>
<td>ED assessment of randomised cooled pts reworded, treatment withheld in patients with clinically significant bleeding. Temp maintained at 35-37°C</td>
</tr>
<tr>
<td>If cooling cannot be reinstituted within 48hrs the patient will be withdrawn from the cooling arm and will follow standard management</td>
</tr>
<tr>
<td>Patients who are clinically significantly drug or alcohol affected with a normal brain (or minor injury only) on CT imaging, will have active cooling withheld until they can be clinically assessed. Whilst waiting for drugs and alcohol to clear the patient will be kept sedated and at 35°C and then desedated and clinically assessed at the treating clinician’s discretion. If during clinical assessment the patient shivers significantly they may be warmed to 36°C. The patient will be withdrawn from the “cooling arm” and receive standard management if</td>
</tr>
<tr>
<td>• They localise or obey when clinically assessed, or</td>
</tr>
<tr>
<td>• In the treating clinician’s opinion they do not have a severe TBI, or</td>
</tr>
<tr>
<td>• In the treating clinician’s opinion they do not require an ICU admission</td>
</tr>
<tr>
<td>If the patient’s motor score is withdrawal (or worse) they will be re-sedated, have the surface cooling pads applied and will continue in the “cooling arm”</td>
</tr>
<tr>
<td>Standard management: The temperature of 36.5-37.5°C will be targeted in the control group patients. Febrile patients (defined as temperature &gt; 38°C) will be treated by paracetamol and application of temperature control pads with a target temperature of 37°C</td>
</tr>
<tr>
<td>Withdrawal of hypothermia:</td>
</tr>
<tr>
<td>Patients with:</td>
</tr>
<tr>
<td>• Significant bleeding which prevents initiation of cooling within 48hrs post injury</td>
</tr>
<tr>
<td>• Positive urine or blood pregnancy test</td>
</tr>
<tr>
<td>• Normal CT Brain scan &amp; patient localising or obeying after decreased sedation</td>
</tr>
<tr>
<td>Will have cooling permanently ceased and will follow the standard care control group protocol.</td>
</tr>
<tr>
<td>Study run in phase: A study run-in phase will be conducted at the lead site. This will involve enrolling 6 patients. The study run in phase will allow the co-ordinating centre to check and refine the protocol paying particular attention to inclusion/exclusion criteria, pre-hospital cooling, safety assessment on hospital admission, administration of the cooling and rewarming protocol. Although a study run-in phase will not occur at the other sites each site will be carefully monitored following the enrolment of the first patient to the hypothermia arm once again paying particular attention to inclusion/exclusion criteria, pre-hospital cooling, safety assessment on hospital admission, administration of the cooling and rewarming protocol.</td>
</tr>
</tbody>
</table>
Changed AQoL to SF12

**Economic evaluation data**
- Clinical costings
- Length of rehabilitation stay
- Length of nursing home stay
- Level of home care

Jeff Presneill has reviewed sample size & power section.

**RENAI substudy**
Data collection for complete study: daily for 21 days
- Creatinine
- Urine output

**Biomarker study (Alfred, RMH)**
Collect bloods post baseline
- 12, 24, 48, 72hrs
1. APPENDIX D: SEVERE TBI & ICU MANAGEMENT GUIDELINE

LINES/FLUIDS
- Arterial line and central line in place
- CVP target 8-12 mmHg (if CVP transduced)
- Crystalloid preferred resuscitation fluid, albumin preferably avoided.
- MAP target >80mmHg until ICP known (then to achieve CPP with minimum MAP of 70mmHg), using fluids and vasopressor (type is clinicians choice) if required

VENTILATION/OXYGENATION
- $S_aO_2 > 95\%$
- $P_aO_2> 90\, \text{mHg}$
- $P_aCO_2 35-40\, \text{mmHg}$

PATIENT POSITION
- Position 15-30 degrees head up, avoiding venous obstruction in the neck.
- Position flat if shock prominent and this improves CPP

SEDATION
- Sedate as per clinicians choice
- Neuromuscular blockade as per clinicians choice (preferably reserved for difficult ICP control)

GLYCAEMIC CONTROL
- Maintain BSL 6- 10 mmol/L

SERUM SODIUM
- Serum Na target 140-150 mmol/L

ICP MONITORING & CPP CONTROL
- Monitor ICP - EVD preferred, Codman parenchymal catheter acceptable
- ICP target <20mmHg
- CPP target >60mmHg
- See Appendix E – ICP control

NUTRITIONAL SUPPORT
- Aim to commence enteral nutrition within 24 hrs and to achieve full nutrition within 72hrs
- DVT, Ulcer Seizure prophylaxis as pre clinician’s choice

2. APPENDIX E: ICP CONTROL
ICP >20mmHg
Follow step wise progression

Optimise ventilation, sedation (including neuromuscular blockade if clinically indicated) & position
ICP still >20

Intermittantly drain CSF if EVD in place.
Consider increasing length and frequency of drainage
ICP still >20

Consider hyperonic saline or mannitol
ICP still >20

Reconsider EVD if not in place

Consider repeating CT brain for indications for surgery.
If surgery not required & ICP still >20
*cooling arm move to last step

Consider reducing temperature in control group
(not below 35C)
ICP still >20

Consider thiopentone
**7th July 2010: POLAR study protocol changes (update from version 2 to version 3)**

Note: Changes have been tracked. Any changes that are duplicated in later sections of the protocol have not been tracked.

<table>
<thead>
<tr>
<th>Location of change</th>
<th>Change</th>
<th>Reason</th>
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<tbody>
<tr>
<td>Header</td>
<td>Change version number and date to Version3 dated 1st June 2010 (Also changed on management committee authorisation page &amp; Investigator protocol agreement signature page)</td>
<td>Amended to correspond to the revised version</td>
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<tr>
<td>Titlepage</td>
<td>Assoc/Professor Michael Bailey added</td>
<td>Assoc/Professor Michael Bailey will provide statistical advice in conjunction with Prof Andrew Forbes</td>
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<tr>
<td>Titlepage</td>
<td>Amended title from Dr to Assoc/Prof Alistair Nichol</td>
<td>Correct title</td>
</tr>
<tr>
<td>Titlepage</td>
<td>Mr Michael Stephenson added</td>
<td>Mr Stephenson will provide support and advice regarding the pre hospital component of the research.</td>
</tr>
<tr>
<td>Titlepage</td>
<td>Amended title from Dr to Assoc/Prof Steve Webb</td>
<td>Correct title</td>
</tr>
<tr>
<td>Titlepage</td>
<td>Deleted Mr Ian Patrick</td>
<td>Mr Patrick is no longer employed by Ambulance Victoria and his position on the MC has been taken by Mr Michael Stephenson</td>
</tr>
<tr>
<td>P9</td>
<td>Added Ms Gillian Syre to staff</td>
<td>Updating staff list</td>
</tr>
<tr>
<td>P9</td>
<td>Added Mr Carl Costolloe</td>
<td>Updating staff list</td>
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### 7th July 2010: POLAR study protocol changes (update from version 2 to version 3)

Note: Changes have been tracked. Any changes that are duplicated in later sections of the protocol have not been tracked.

<table>
<thead>
<tr>
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<tr>
<td>P13</td>
<td>Amended patient number from 512 to 500</td>
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<td></td>
<td>The 512 number included pilot and run in patient numbers. The actual randomised trial will be 500</td>
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<tr>
<td></td>
<td>patients.</td>
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<tr>
<td>P17</td>
<td>Secondary outcome section:</td>
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<td>Deleted ICU discharge</td>
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<td>Not required</td>
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<td>P17</td>
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<td></td>
<td>Corrected wording</td>
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<td>Added to secondary outcome section;</td>
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<td></td>
<td>• Health economic evaluation</td>
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<td>A health economic evaluation of the intervention will be performed on completion of the study.</td>
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<tr>
<td>P17</td>
<td>Added to secondary outcome section;</td>
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<tr>
<td></td>
<td>• Test for interaction between time to reach 33C and dichotomised GOSE scores in the hypothermic</td>
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<tr>
<td></td>
<td>group</td>
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<tr>
<td></td>
<td>• Test for interaction between the effect of cooling on neurological function at 6 months and the</td>
</tr>
<tr>
<td></td>
<td>presence of surgically evacuated mass lesions</td>
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<tr>
<td>P17</td>
<td>Added to pre-hospital exclusion criteria:</td>
</tr>
<tr>
<td></td>
<td>Estimated travel time &gt;2.5hrs</td>
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<tr>
<td></td>
<td>The aim of the study is to test early cooling. Patients will not be suitable if the study</td>
</tr>
<tr>
<td></td>
<td>procedures are going to be delayed due to long transport times.</td>
</tr>
</tbody>
</table>
### 7th July 2010: POLAR study protocol changes (update from version 2 to version 3)

Note: Changes have been tracked. Any changes that are duplicated in later sections of the protocol have not been tracked.

<table>
<thead>
<tr>
<th>P17</th>
<th>Pre hospital exclusion criteria:</th>
<th>Amended following review of pre-hospital data (Ambulance Victoria - time critical guidelines)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Changed BP&lt;100 to 90 mmHg</td>
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</table>

<table>
<thead>
<tr>
<th>P17</th>
<th>Pre hospital exclusion criteria</th>
<th>Management committee decision. Cardiac arrest is a confounder in the study.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Added cardiac arrest at the scene or in transit</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>P18</th>
<th>Pre hospital exclusion criteria</th>
<th>Management committee decision. Pre-existing neurological condition is a confounder in the study.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Known to be carer dependent due to a pre-existing neurological condition</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>P18</th>
<th>Emergency dept exclusion criteria:</th>
<th>Amended following review of pre-hospital data (Ambulance Victoria - time critical guidelines)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Changed BP&lt;100 to 90 mmHg</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>P18</th>
<th>Emergency dept exclusion criteria:</th>
<th>Management committee decision. Cardiac arrest is a confounder in the study.</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Added cardiac arrest at the scene or in transit</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>P18</th>
<th>Emergency dept exclusion criteria</th>
<th>Management committee decision. Pre-existing neurological condition is a confounder in the study.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Known to be carer dependent due to a pre-existing neurological condition</td>
<td></td>
</tr>
</tbody>
</table>

| P18 | Added Sir Charles Gairdner Hospital as a participating site |                                                                                     |

<table>
<thead>
<tr>
<th>P18 &amp; 19</th>
<th>Added “wristband to be placed on the patient”</th>
<th>Added as an additional means of identifying enrolled patients.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>“The wristband and label in the patient’s medical record will</td>
<td></td>
</tr>
<tr>
<td></td>
<td>be recorded”</td>
<td></td>
</tr>
</tbody>
</table>
7th July 2010: POLAR study protocol changes (update from version 2 to version 3)

Note: Changes have been tracked. Any changes that are duplicated in later sections of the protocol have not been tracked.

<table>
<thead>
<tr>
<th></th>
<th>Added to pre hospital study intervention:</th>
<th>Amended as a safety measure to avoid possible fluid overload.</th>
</tr>
</thead>
<tbody>
<tr>
<td>P19</td>
<td>To avoid fluid overload the volume of cold fluid administered will be dependent on intubation status</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Randomised after intubation – give <strong>1000ml</strong> cold normal saline (100mls/min)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Randomised before intubation – give <strong>2000ml</strong> cold normal saline (100mls/min)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Added “Data will be collected and the follow up assessment performed on all patients who have the study intervention withdrawn”.</th>
<th>Added to clarify that data collection &amp; follow up is required on all patients entered into the study</th>
</tr>
</thead>
<tbody>
<tr>
<td>P19</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Added : “(GCS(m)≤4)”</th>
<th>Added for clarification.</th>
</tr>
</thead>
<tbody>
<tr>
<td>P19</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Amended the hospital assessment of patient for study suitability section:</th>
<th>Amended to include the use of a wristband for identification</th>
</tr>
</thead>
<tbody>
<tr>
<td>P20</td>
<td>If they fulfil the inclusion criteria and have no exclusion criteria they will be randomised by opening the next opaque envelope in the randomisation series kept in the ED. The envelopes will contain a wristband to be placed on the patient &amp; a label which designates the study number and treatment allocation. A small number of details will be completed on the wristband and label (Patient’s initials, Date and time of randomisation). The label will be placed in</td>
<td></td>
</tr>
</tbody>
</table>
**7th July 2010: POLAR study protocol changes (update from version 2 to version 3)**

Note: Changes have been tracked. Any changes that are duplicated in later sections of the protocol have not been tracked.

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>P20</td>
<td>Added to ED study intervention:</td>
<td>Amended as a safety measure to avoid possible fluid overload.</td>
</tr>
<tr>
<td></td>
<td>To avoid fluid overload the volume of cold fluid administered will be dependent on intubation status</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Randomised <strong>after intubation</strong> – give <strong>1000ml</strong> cold normal saline (100mls/min)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Randomised <strong>before intubation</strong> – give <strong>2000ml</strong> cold normal saline (100mls/min)</td>
<td></td>
</tr>
<tr>
<td>P20</td>
<td>Temperature control system:</td>
<td>Paediatric blankets will be supplied to use for cooling when leg wraps cannot be fitted.</td>
</tr>
<tr>
<td></td>
<td>Added blankets</td>
<td></td>
</tr>
<tr>
<td>P20</td>
<td>Standard study care:</td>
<td>Additional instructions added to assist the control arm with temperature control.</td>
</tr>
<tr>
<td></td>
<td>Added “Active warming with blankets and other standard measures may be required to achieve the target temperature”</td>
<td></td>
</tr>
<tr>
<td>P20</td>
<td>Withholding hypothermia:</td>
<td>Instructions were changed following MC discussion.</td>
</tr>
<tr>
<td></td>
<td>Changed 72hrs-48hrs</td>
<td></td>
</tr>
<tr>
<td>P21</td>
<td>Withdrawal of hypothermia:</td>
<td>Added for clarification.</td>
</tr>
</tbody>
</table>


7th July 2010: POLAR study protocol changes (update from version 2 to version 3)

Note: Changes have been tracked. Any changes that are duplicated in later sections of the protocol have not been tracked.

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Added “Data will be collected and the follow up assessment performed on all patients who have the study intervention withdrawn.”</strong></td>
<td></td>
</tr>
<tr>
<td><strong>P21</strong></td>
<td><strong>Instructions added to help avoid fluid overload.</strong></td>
</tr>
<tr>
<td><strong>Added “Fluid management</strong>** Fluid overload may contribute to cerebral oedema. Therefore after resuscitation during the first 24 hours, positive daily fluid balances &gt; 500mls should be avoided. In the absence of hypovolaemia, periods of relative hypotension should be managed primarily with vasopressors (adrenaline/noradrenaline).”**</td>
<td></td>
</tr>
<tr>
<td><strong>P22</strong></td>
<td><strong>Changed following review of the enrolment of the 1st 2 pilot patients. It is thought that 4 patients should be sufficient in the pilot phase</strong></td>
</tr>
<tr>
<td><strong>Study pilot/run in phase:</strong> Changed pilot study patient number from 6 to 4**</td>
<td></td>
</tr>
<tr>
<td><strong>P22</strong></td>
<td><strong>Changed following discussion by the study statisticians.</strong></td>
</tr>
<tr>
<td><strong>Randomisation:</strong> Changed wording to “stratified by 2 strata:**</td>
<td></td>
</tr>
<tr>
<td><strong>- a four level variable of Victoria / Queensland / Western Australia / New Zealand</strong></td>
<td></td>
</tr>
<tr>
<td><strong>- a two level variable of pre-hospital enrolment or emergency department enrolment</strong></td>
<td></td>
</tr>
<tr>
<td><strong>P24</strong></td>
<td><strong>Added to accurately reflect where the randomisation will take place and who will be involved.</strong></td>
</tr>
<tr>
<td><strong>Emergency research and consent</strong> Added “physicians” and “ED”</td>
<td></td>
</tr>
</tbody>
</table>
### 7th July 2010: POLAR study protocol changes (update from version 2 to version 3)

Note: Changes have been tracked. Any changes that are duplicated in later sections of the protocol have not been tracked.

<table>
<thead>
<tr>
<th>P25</th>
<th>Confidentiality of patient data.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Changed wording &quot;The ambulance paramedics/physicians will complete a randomisation form including name, address &amp; date of birth which will be forwarded to the Research Coordinator at each site. These details are required to notify the Research Coordinator that the patient is a participant in the trial. The Research Coordinator will compile a study enrolment log which will link the study number to the patient name using the details forwarded by the ambulance service/physicians.&quot;</td>
</tr>
<tr>
<td></td>
<td>Clarification of the use of the study log.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>P26</th>
<th>Data collection methods.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Added “Health economic data related to utilisation of medical services post hospital discharge will be collected. The transport accident commission and accident compensation corporation will assist with provision of health economic data.&quot;</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>P26</th>
<th>Data variables collected:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Deleted “Inclusion/exclusion criteria”</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>P26</th>
<th>Data variables collected:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Added “Pregnancy test (female)”</td>
</tr>
</tbody>
</table>
7th July 2010: POLAR study protocol changes (update from version 2 to version 3)

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<table>
<thead>
<tr>
<th>P27</th>
<th>Data variables collected:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Added &quot;General data collection&quot;</td>
</tr>
<tr>
<td></td>
<td>· Withdrawal from study protocol</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>P28</th>
<th>Sample size and power calculations:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Changed 0.3% to 0.7% sample size inflation factor</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>P28</th>
<th>Sample size and power calculations:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Changed one interim analysis to two</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>P28</th>
<th>Sample size and power calculations:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Changed sample size from 498 to 500</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>P28</th>
<th>Sample size and power calculations:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Deleted &quot;Including the ‘run in’ phase of two patients from each site and an additional four piloted at the lead site, the overall trial recruitment target is 512 subjects in total.&quot;</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>P28</th>
<th>Sample size and power calculations (secondary outcomes):</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Deleted “Assuming a proportional odds cumulative logit model applied to the eight-level GOSE outcome category vector, a reference improvement with therapy of ln(OR) = 0.62, and a one-sided linear rank test that the two multinomial populations had equal probabilities versus the</td>
</tr>
</tbody>
</table>

The wording was amended as the previous paragraph was difficult to understand and also included some personal communication between 2 of the investigators.
7th July 2010: POLAR study protocol changes (update from version 2 to version 3)

Note: Changes have been tracked. Any changes that are duplicated in later sections of the protocol have not been tracked.

Alternative that the treatment population was stochastically larger than the control, this study of 182 (Reason 183 vs 182 appeared here is simply that AI and I used different software, resulting in a small difference in starting sample size. This difference 182 vs 183 is trivial. I have checked, and power remains at 96% if sample per group is smaller by one at 182 rather than my original of 183 — so we can make POLAR protocol starting point = 182) evaluable subjects in each of two treatment groups would have a one-sided power of 96% to detect this magnitude of reference improvement as statistically significant with type I error (alpha) = 0.05”

Amended wording to “The secondary outcome analyses using proportional odds and the sliding dichotomy are included because although more complex for clinicians to understand, have increased power for outcome assessments in TBI patients. For example using the proportional odds model, this study of 182 evaluable subjects in each of two treatment groups would have a one-sided power of 96% to detect this magnitude of reference improvement as statistically significant with type I error (alpha) = 0.05”

<table>
<thead>
<tr>
<th>P29</th>
<th>Interim analyses:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Deleted “One planned interim safety analysis will be performed by the independent data and safety monitoring committee (DSMC) at 50% patient enrolment, using a</td>
</tr>
</tbody>
</table>

The wording has been changed as the two interim analyses will now be performed. Additional details have been added regarding stopping rules.
Haybittle-Peto rule applied to mortality data between treatment groups and the conventional 3-standard deviation threshold of a standardised statistic \(|Z_{est.}| \geq 3\) calculated from a normal approximation to the discrete binomial difference in mortality proportions. Assuming no early stopping, such a single interim Haybittle-Peto analysis will not, in practice, require adjustment (for repeated significance testing) to the conventional statistical significance level \((p<0.05)\) to be applied at the final analyses of the completed trial”

Amended wording to “There will be no analyses for futility.

Two planned interim safety analyses for potential harm will be performed by the independent data and safety monitoring committee (DSMC) at 25% and 50% patient enrolment. The first (at 125 patients) will examine mortality only with a \(P\) value for stopping of \(P<0.005\). The second (at 256 patients) will examine mortality and proportion of favourable neurological outcomes. \((P<0.005)\) The analyses will use the Haybittle-Peto rule applied to mortality data between treatment groups and the conventional 3-standard deviation threshold of a standardised statistic \(|Z_{est.1}| \geq 3\) calculated from a normal approximation to the discrete binomial difference in mortality proportions. Assuming no early stopping, such a single interim Haybittle-Peto analysis will not, in practice, require adjustment (for repeated significance testing) to the conventional statistical
7th July 2010: POLAR study protocol changes (update from version 2 to version 3)

Note: Changes have been tracked. Any changes that are duplicated in later sections of the protocol have not been tracked.

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<table>
<thead>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>significance level ($p&lt;0.05$) to be applied at the final analyses of the completed trial”</td>
<td></td>
</tr>
</tbody>
</table>
| P29 | Data and safety monitoring committee:  
|     | Changed wording from “will be” to “has been” |
|     | Changed to show that the DSMC has been established. |
| P31 | Added “POLAR BEAR sub study (Appendix J)” |
|     | Introducing an additional sub study |
| P31 | Added “The biomarker and excito-toxicity POLAR substudy” |
|     | Introducing an additional sub study |
| P32 | Amended “research time lines” |
|     | Updated the current time lines. |
| P33 | Table of events: |
|     | A pregnancy test will be required for safety |
|     | Added “Pregnancy test (female)” |
| P34 | Table of events |
|     | Data required for health economic analysis |
|     | Added clinical costings at hospital discharge |
| P38 | Appendix D: |
|     | Instructions added to help avoid fluid overload |
|     | Added “After initial resuscitation in otherwise stable patients, positive daily fluid balances $>500$mls should be avoided” |
| P40-42 | Added Appendix F Cooling and rewarming guidelines |
|     | Added to assist with the management of the study patients |
7th July 2010: POLAR study protocol changes (update from version 2 to version 3)

Note: Changes have been tracked. Any changes that are duplicated in later sections of the protocol have not been tracked.
### 9th November 2010: POLAR study protocol changes (update from version 3 to version 4)

Note: Changes have been tracked. If

<table>
<thead>
<tr>
<th>Location of change</th>
<th>Change</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>Header</td>
<td>Change version number and date to Version4 dated 9th November 2010 (Also changed on management committee authorisation page &amp; Investigator protocol agreement signature page)</td>
<td>Amended to correspond to the revised version</td>
</tr>
<tr>
<td>Page 1, 6 &amp; 10</td>
<td>Deleted Prof John Myburgh</td>
<td>Prof Myburgh has resigned from the management committee due to increased time demands from his participation in other studies.</td>
</tr>
<tr>
<td>Page 1, 7 &amp; 10</td>
<td>Dr Stephen Rashford</td>
<td>Dr Rashford is an Intensivist and Medical Director of the Queensland ambulance service. He will provide support and advice regarding both the pre hospital &amp; ICU component of the research.</td>
</tr>
<tr>
<td>Page 1, 7, 9 &amp; 10</td>
<td>Mr Tony Trapani added</td>
<td>Mr Trapani will take over the role previously held by Ms Lynne Murray.</td>
</tr>
<tr>
<td>Page 9 &amp; 10</td>
<td>Deleted Ms Murray from staff list</td>
<td>Ms Murray has resigned as Project Manager but will continue to participate in the research as a management committee member.</td>
</tr>
<tr>
<td>Page 19, 20, 36 &amp; 38</td>
<td>Changed exclusion criteria:</td>
<td>A review of the screening logs at two centres</td>
</tr>
<tr>
<td>Date</td>
<td>Information</td>
<td></td>
</tr>
<tr>
<td>------------</td>
<td>-----------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>9th November 2010</td>
<td><strong>POLAR study protocol changes (update from version 3 to version 4)</strong></td>
<td></td>
</tr>
</tbody>
</table>

Note: Changes have been tracked. If

- Randomisation unable to be performed within **2.5** hrs of estimated time of injury to:
- Randomisation unable to be performed within **3** hrs of estimated time of injury to

Currently recruiting has demonstrated that 10% of patients were excluded because they were more than **2.5** hours post-injury but less than **3** hours. The Management Committee believe that enrolling patients and commencing the cooling process within 3 hours from injury will be sufficient to be considered as "early" hypothermia treatment and is appropriate for the study design.
### Summary of POLAR protocol changes

<table>
<thead>
<tr>
<th>Page number or Location</th>
<th>Change with Track changes from previous protocol (if applicable)</th>
<th>Discussion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Page 10</td>
<td>• Addition of an Executive Committee. The Executive Committee will have responsibility for day to day management of the study and will have direct accountability to the management committee. Some numbering changes will occur as a consequence of this addition.</td>
<td>Not previously available. This will ensure an increased efficiency in managing project questions and queries.</td>
</tr>
<tr>
<td>Page 12</td>
<td>• Change to Postal address and phone contacts from Lyn Murray to Tony Trapani.</td>
<td>Change of project manager (previous amendment).</td>
</tr>
<tr>
<td>Page 18</td>
<td>• The background section now includes a statement that hypothermia decreases clearance of medications that are cleared by the liver and the medications will accumulate over time unless doses are reduced.</td>
<td>Neither of these sections was previously mentioned. These changes will enhance background information available.</td>
</tr>
<tr>
<td></td>
<td>• A statement mentioning the changes in clearance that occur with some electrolytes (especially Potassium and Magnesium)</td>
<td></td>
</tr>
<tr>
<td>Page 23</td>
<td>• The rewarming protocol has been amended to include a statement that the patient will remain at a temperature that controls the ICP until the clinician determines it is appropriate to recommence rewarming.</td>
<td>Improve clarity in the management of pyrexia in both patient group</td>
</tr>
<tr>
<td></td>
<td>• A statement clarifying the management of pyrexia in these patients during the protocol period</td>
<td></td>
</tr>
<tr>
<td>Page 25</td>
<td>• An additional comment regarding the specific management of bradycardia has been added: “the bradycardia may not require treatment however, bradycardia (&lt;50 beats/min) associated with hypotension may respond to a low dose chronotropic agent (eg. Adrenaline)”.</td>
<td>Enhanced definition of bradycardia by suggesting hypotension a secondary sign. Suggestion to use low dose adrenaline in the management of bradycardia.</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Page 26</td>
<td>• Sedation is utilised during hypothermia induction to minimise shivering. “Once 34°C has been reached consideration should be given to ceasing or dose reducing propofol and opiates to decrease the risk of accumulation. Fentanyl may also be considered as an alternative to morphine for pain control. Barbiturates can be considered for ICP control as required”. • Hypothermia can also alter the movement of electrolytes such as potassium and magnesium, during the cooling and rewarming phases. Electrolyte levels will be monitored.</td>
<td>The risk/benefit section has been amended to include a statement that hypothermia decreases drug clearance and may lead to drug accumulation. It also discusses changes to electrolyte movement.</td>
</tr>
<tr>
<td>(PAGE 33 / 34 / 35)</td>
<td>• Typographical error change Sepembert to September • Typographical error change Admision to Admission • Typographical error change Suveillance to Surveillance</td>
<td>Typographical errors</td>
</tr>
<tr>
<td>(PAGE 39) Appendix D</td>
<td>• Sedation recommendations and doses have been amended • Benzodiazepine – midazolam 0-15 mgs/hour • Opiate – fentanyl 0-100 micrograms/hour • Propofol – 0-100 mgs/hour and cease when patient at 34°C • Serum Electrolytes • Change to heading</td>
<td>Change recommendations to • analgesia from Morphine to Fentanyl • propofol dose • electrolyte monitoring</td>
</tr>
<tr>
<td>(PAGE 42) Appendix E</td>
<td>Changes include:</td>
<td></td>
</tr>
<tr>
<td>---------------------</td>
<td>-----------------</td>
<td></td>
</tr>
<tr>
<td>• Thiopentone will be delivered to manage ICP. It is suggested that EEG be utilised to monitor for burst suppression. Thiopentone coma is maximal aim for ICP control.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Control boxes (2) have been blended into one (1) to remove ambiguity. Either thiopentone or cooling (to 35°C) or both can be utilised in the control arm, if required to control ICP &lt;20mmHg. Clinician will determine which therapy/s to utilise.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in terminology to remove ambiguity from the control of ICP diagram. -Thiopentone Max dose is burst suppression. Once burst suppression has been attained further dosing with Thiopentone will not assist in ICP management.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>(PAGE 43-45) Appendix E</th>
<th>Changes include:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• A decreased heart rate (&lt;50 beats/minute) is a physiological effect of hypothermia. Low dose adrenaline may be considered to keep heart rate &gt;50 beats/min if hypotension (absolute or relative).</td>
<td></td>
</tr>
<tr>
<td>• If an inotrope is required to increase blood pressure, an adrenaline infusion should be commenced. If the dose exceed 5mic/min or the lactate level is increasing, then an infusion of noradrenaline should be used. If a further fluid challenge is required for CVP&lt;12mmHg, infuse a bolus (i.e. 500mL) of 0.9% saline</td>
<td></td>
</tr>
<tr>
<td>• Lactate levels may initially be increased by an adrenaline infusion. This hyperlactaemia is not an indication to stop cooling.</td>
<td></td>
</tr>
<tr>
<td>Fine tuning suggestions for management of bradycardia and the use of inotropes.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>(Page 45)</th>
<th>Changes include:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Shivering often occurs between 34°C and 35.5°C. This may significantly increase metabolic demand and increase ICP. Shivering must be immediately treated with additional sedation/muscle relaxant. Sedation can be weaned if ICP is stable once core temperature is &gt;36.5°C</td>
<td></td>
</tr>
<tr>
<td>• Hypotension and bradycardia can occur during the three day cooling phase. As usual noradrenaline is the best first line medication, but if the heart rate &lt;50 beats/min low dose adrenaline (1-2 micrograms) or isoprenaline (1-2 micrograms) will usually correct bradycardia and prevent unnecessary fluid loading.</td>
<td></td>
</tr>
<tr>
<td>More detail concerning the management of hypothermia during rewarming.</td>
<td></td>
</tr>
</tbody>
</table>
- Routine fluid boluses (greater than 500mLs per day total) on day 2 and 3 should be avoided in hypothermia group patients. Consider starting low dose furosemide while patient still cooled.
- Be aware that many patients get ventilator associated pneumonia. The usual signs of purulent sputum, increased white cell count and pulmonary infiltrates should lead to consideration of cultures and broad spectrum antibiotics.
- Hypotension can occur during rewarming and should be treated immediately with more noradrenaline, blood product if Hb<9 and then crystalloid fluid challenge. Patients that are particularly unstable may also require the cessation of rewarming until the hypotension has been controlled.


Addition of reference to support additions
### POLAR study: Summary of protocol changes. (May 2011 to August 2012)

The **new marked up version** of the protocol will now be referred to in the header as:

Multi-centre POLAR study. Protocol ANZIC-RC/DJC003 Version 6. Date 1\textsuperscript{st} August 2012

**Previous version:** Multi-centre POLAR study. Protocol ANZIC-RC/DJC003 Version 5. Dated 6\textsuperscript{th} May 2011

#### Summary of POLAR protocol changes

<table>
<thead>
<tr>
<th>Page number or Location</th>
<th>Change with Track changes from previous protocol (if applicable)</th>
<th>Discussion</th>
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<tbody>
<tr>
<td><strong>Protocol</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Previously (ACTRN12605000009617)</td>
<td>Change to ANZ Clinical Trials Registry number</td>
</tr>
<tr>
<td></td>
<td>• Now (NCT00987688 &amp; ACTRN12609000764235)</td>
<td>Addition of ClinicalTrials.gov registry number</td>
</tr>
<tr>
<td>Page 23 (12.10.3)</td>
<td>• Clarification of guidelines for re-warming post therapeutic hypothermia.</td>
<td>Hospitals have requested more information about the management of rewarming and shivering. These additions are points of further clarification to the protocol.</td>
</tr>
<tr>
<td>Page 43 to 49</td>
<td>• Clarification of Rewarming and Shivering Guidelines.</td>
<td>Hospitals have requested more information about the management of rewarming and shivering. These additions are points of further clarification to the protocol.</td>
</tr>
<tr>
<td>Page 69 to 73</td>
<td>• Addition of Sub Study: POLAR TEG</td>
<td>Request to conduct a sub study at The Alfred Hospital</td>
</tr>
</tbody>
</table>
1. APPENDIX L: POLAR TEG

**Aims:**

We plan to investigate changes in coagulation and in particular platelet function in patients with TBI in this sub study of the POLAR trial.

**Background:**

**Therapeutic Hypothermia and POLAR.** Therapeutic hypothermia is used in patients with severe TBI to improve outcomes, both as a prophylactic therapy to reduce secondary brain injury, and also as one of only 3 possible “second tier” therapies for refractory rises in intracranial pressure. We are, at present, testing hypothermia in a rigorous NHMRC funded randomised trial (POLAR - ACTRN 1260500009617).

One concern with this therapy is the effect of hypothermia on coagulation. Most haematologists agree that hypothermia adversely affects coagulation status and studies in animals and in vitro confirm this (Watts, Trask et al. 1998, Dirkmann, Hanke et al. 2008, Polderman, Herold et al. 2009). Accordingly, trauma patients are often hypothermic on arrival at an emergency department and are routinely aggressively rewarmed during emergency resuscitation using sophisticated massive transfusion devices.

Strangely, little clinical work has been done to inform us of the direct effect of hypothermia in the severe TBI population. Review articles(Polderman 2009) state that hypothermia to 35C is generally safe and that 33C is not usually associated with bleeding complications in TBI patients however, there is little to support these contentions in the original research literature.

Hypothermia impairs coagulation by inhibiting temperature dependent enzymes involved in the coagulation cascade (Reed RL 1990, Rohrer and Natale 1992). Hypothermia also causes platelet dysfunction (Valeri, Feingold et al. 1987, Michelson, MacGregor et al. 1994), but the temperature at which these elements become clinically relevant and or predominant has not been studied in trauma patients and is completely unknown.

There have been no reports of increased bleeding in patients suffering severe TBI and managed with hypothermia (Clifton, Miller et al. 2001, Hutchison, Ward et al. 2008, Clifton, Valadka et al. 2011), but coagulation was not studied in detail and has generally been de-emphasised by hypothermia advocates. Haemostasis in cardiac arrest patients treated with hypothermia has been studied by Spiel et al, and it has been concluded that the potential bleeding complications of therapeutic hypothermia are “minimal” (Spiel, Kliegel et al. 2009). However and obviously, cardiac arrest patients do not have the same traumatic tissue injuries at risk of bleeding as trauma, and specifically TBI patients.

Severe TBI and severe trauma alone are known to have effects on platelet function. Recent studies have shown platelet dysfunction in TBI may more accurately predict poor outcomes than current laboratory measures of coagulation [Windelov et al]. Trauma-induced coagulopathy (TIC) occurs in approximately one-third of all trauma patients [Schochl et al]. The contribution of platelet dysfunction to TIC has not been studied extensively; however a preliminary study suggests almost all patients admitted to ICU after a critical injury will have platelet hypofunction at some time during their stay [Kutcher et al].POLAR TEG affords us the opportunity to study platelet function across a diverse group of trauma patients and more specifically the effects of therapeutic hypothermia.

There has been little clinical investigation of the effects of hypothermia on coagulation and no such study of this type in patients with severe TBI. The POLAR trial presents a unique opportunity to clinically investigate the influence of hypothermia on TBI patients at minimal cost. POLAR gives us an
opportunity to study the effects of hypothermia on coagulation in severe TBI patients and compare this to other non-POLAR trauma patients. As this work has never been done in TBI patients especially those receiving hypothermia, it will have direct clinical applicability.

**Laboratory Testing**

The most common routine laboratory-based coagulation tests International Normalised Ratio (INR), Activated Partial Thromboplastin Time (APTT) and platelet numbers are used to inform clinicians of the patients’ coagulation status (Whitten CW 2000) but may be poor indicators of *in vivo* coagulation in hypothermic patients (Whitten CW 2000). These samples test plasma (blood minus cells) rather than whole blood which excludes the contribution of the cellular elements to the *in vivo* coagulation process (Reed RL 1992, Valeri CR 1995, Felfernig, Blaicher et al. 2001). The assays are also performed at a standard temperature of 37°C (regardless of the patient’s actual temperature) which likely underestimates the effects of hypothermia on coagulation (Whitten CW 2000). Thromboelastography (TEG) has been previously used in bleeding cardiac surgical patients to measure coagulation deficits and we will use this technology in TBI patients (Westbrook, Olsen et al. 2009). It can be performed at the patient bedside (Point-of-Care) and also at the patient’s temperature. We can therefore, for the first time, get a clearer picture of the effect of patient temperature on coagulation in the patient group of concern (Ganter and Hofer 2008, Jackson, Ashpole et al. 2009).

**Significance**

There has been little clinical investigation of the effects of hypothermia on coagulation and no such study of this type in patients with severe TBI. POLAR gives us an opportunity to study the effects of hypothermia on coagulation in severe TBI patients. As this work has never been done in TBI patients especially those receiving hypothermia, it will have direct clinical applicability.

**Objectives**

**Hypothesis**

TBI patients who receive prophylactic hypothermia will have alterations in their coagulation status as measured by the TEG.

**Primary Outcome**

The coagulation status of a group of trauma patients enrolled in the POLAR study will be compared to a group of non-POLAR trauma patients

**Secondary Outcomes**

Hypothermic patient's coagulation status will be compared with the same patient’s blood tested at normothermia.
**Study Design**

An observational sub study of patients enrolled in the POLAR RCT plus another 20 patients from the general trauma population not enrolled in POLAR.

**Recruiting Site**

The Alfred Hospital Melbourne

**Inclusion criteria**

POLAR cohort (Hypothermic and control POLAR patients)

- Enrollment in the POLAR study
- Age ≥18 years

Non POLAR Cohort (Adult patients admitted to the ICU with diagnosis of trauma)

- Blunt trauma with injury severity score >16

**Exclusion Criteria**

- Death is imminent
- Patient on Heparin or Clexane
- Inability to cool POLAR “hypothermia” patient
- Likely to be discharged from the ICU in <48 hours
Ethics and consent

The Alfred Research and Ethics Committee has approved the POLAR study, including the use of emergency consent. The Alfred HREC have agreed to include the POLAR TEG study using the same consent provisions.

The POLAR plain language and information form includes details about the sub study including the study design, methodology and significance. A separate plain language and information form will be used for the non POLAR cohort.

Consent from the non POLAR group will be prospective and sought from the participant's Person Responsible/ Next of Kin or appropriate delegate. as soon as practical, and from the participant themselves when competent. If a Person Responsible is not found and the participant is not competent then procedural authorisation under section 42T will be requested. Procedural authorisation will always be followed by participant or Person Responsible consent as soon as possible. Patients will have the opportunity to withdraw consent to participate at any time.

They will be informed that refusal to participate in the study will not prejudice their current/ future treatment.

Research plan and Methods

20 trauma patients recruited into POLAR and 20 non POLAR trauma patients will be recruited. Wherever possible eligible patients will be enrolled consecutively, however logistical constraints may preclude this.

Demographic data and baseline data will be gathered from patient notes and the coagulation profile will be drawn from routine sampling of patients. Information about the pre-injury use of non-steroidal anti-inflammatory medication will be collected. Patients will undergo TEG analysis as per TEG schedule and TEG analysis methodology. Patients will exit this observational study upon completion of the final blood sample.

TEG analyser technology

The TEG analyzer has a sample cup that oscillates back and forth constantly at a set speed through an arc of 4°45'. Each rotation lasts ten seconds. A whole blood sample of 360 ul is placed into the cup, and a stationary pin attached to a torsion wire is immersed into the blood. When the first fibrin forms, it begins to bind the cup and pin, causing the pin to oscillate in phase with the clot. The acceleration of the movement of the pin is a function of the kinetics of clot development.

The torque of the rotating cup is transmitted to the immersed pin only after fibrin-platelet bonding has linked the cup and pin together. The strength of these fibrin-platelet bonds affects the magnitude of the pin motion, such that strong clots move the pin directly in phase with the cup motion. Thus, the magnitude of the output is directly related to the strength of the formed clot. As the clot retracts or lyses, these bonds are broken and the transfer of cup motion is diminished. The rotation movement of the pin is converted by a mechanical-electrical transducer to an electrical signal which can be monitored by a computer.
The resulting hemostasis profile is a measure of the time it takes for the first fibrin strand to be formed, the kinetics of clot formation, the strength of the clot (in shear elasticity units of dyn/cm²) and dissolution of clot.

**Normal TEG trace**

- **R time** – reaction time - the initiation phase of coagulation / clotting time (clotting factors)
- **A angle** – rate of clot formation/strengthening (speed of fibrin build up and crosslinking)
- **MA** - maximum amplitude – reflects the ultimate strength of the clot (fibrinogen, platelet count and function).
- **A30** – amplitude at 30 mins - reflects clot stability/breakdown (fibrinolysis)

**TEG schedule**

**Sample 1**

POLAR hypothermia patients will have TEG blood samples taken while at 33°C and prior to rewarming (48 to 72hrs hours post POLAR randomisation). Samples will be analysed using the TEG at both 33°C and 37°C (see TEG analysis methodology). At each temperature (33°C and 37°C) standard and functional fibrinogen assays will be performed. Standard, functional fibrinogen and Platelet Mapping (PM) at 33°C will be tested followed by standard, functional fibrinogen and Platelet Mapping (PM) at 37°C. The second analysis will require the patient to have a fresh sample taken.

Control patients will have blood taken 48 to 72hrs hours post POLAR randomisation and analysed at 37°C using the TEG. Standard, functional fibrinogen and Platelet Mapping (PM) assays will be performed at 37°C (see TEG analysis methodology).

**Sample 2**

Hypothermia patients will have blood taken 120 hrs +/- 12hrs post randomisation once they have reached 37°C. Samples will be analysed using the TEG at 37°C. Standard, Fibrinogen and PM TEG Assay will be performed (see TEG analysis methodology).

Control patients will have blood taken 120 hrs +/-12hrs post randomisation and analysed at 37°C using the TEG. Standard, fibrinogen and PM TEG Assay will be performed (see TEG analysis methodology).
Routine laboratory testing includes International Normalised Ratio (INR), Activated Partial Thromboplastin (APTT) & Platelet count.

<table>
<thead>
<tr>
<th></th>
<th>Hypothermic therapy patient</th>
<th>Standard therapy patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample 1</td>
<td>48 and 72hrs hours post POLAR randomisation</td>
<td>Standard, Fibrinogen and PM assay at 33C</td>
</tr>
<tr>
<td></td>
<td></td>
<td>followed by,</td>
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<tr>
<td></td>
<td></td>
<td>Standard, Fibrinogen and PM assay at 37C</td>
</tr>
<tr>
<td>Sample 2</td>
<td>120 +/-12hrs post POLAR randomisation</td>
<td>Standard, Fibrinogen and PM assay at 37C only.</td>
</tr>
</tbody>
</table>


TEG analysis methodology:

Samples for analysis will be drawn from the arterial catheter and must be used within 4 minutes.

The collection of samples will, wherever possible, coincide with routine blood collection to minimise fluid and blood loss to the patient. A 10ml aliquot will be collected and discarded to eliminate the dilutional effect of saline in the arterial line (standard practice). The sample for testing is then collected.

**Standard Assay**

- Set temperature of analyser
- Load plain test pin and cup
- Collect 1ml of blood from arterial line (follow unit standard practice)
- Deliver 1ml aliquot into kaolin vial
- Mix carefully by inversion (not pill rolling as this may warm the sample).
- Pipette 360µl of kaolin mixture into loaded plain test cup
- Commence computer program

**Fibrinogen Assay**

- Set temperature of analyser
- Load plain test pin and cup
- Collect 0.5ml of blood from arterial line (follow unit standard practice)
- Deliver 0.5ml aliquot into functional fibrinogen assay vial
- Mix carefully by inversion (not pill rolling as this may warm the sample).
- Pipette 360µl of kaolin mixture into loaded plain test cup
- Commence computer program

**PlateletMapping Assay**

- Set temperature of analyser
- Load plain test pins and cups, only 2 can be analysed at one time
- Prepare cups and pins with:
  - 1 – Activator
  - 2 – Activator + AA
  - 3 – Activator + ADP
- Collect 3ml of blood from arterial line into a heparin tube
- Deliver 360µl aliquots of blood from the heparin tube into each cup and pin
- Mixed by pipetting half the volume of the blood and activator mix into the pipette tip and ejecting 3 times
- Commence the computer program

Analysis shall be performed with the computerised thromboelastograph coagulation analyser (Haemoscope Corp., Skokie, IL). The coagulation profile is displayed on a computer running TEG analytic software which is connected to the analyser via an A/D interface box. The values of normal controls are displayed enabling comparison.
Quality Control

Routine quality control should be performed prior to patient testing if it has not been performed in the last 7 days.

Data variables

- Gender
- Date of Birth
- Injury time
- Blood pressure / pulse / Respiratory Rate / Blood sugar
- Fluid and Blood component Input and output
- Glasgow coma scale
- Pupil reaction
- Temperature
- Date & timing of cooling intervention (commenced and ceased)
- APACHE II
- AIS Head (max)
- CT brain scan – Marshall score
- INR
- APTT
- Platelet count
- TEG
  - R time
  - A angle
  - MA
  - A30
- Bleeding incidents
- Medications (pre injury and during ICU stay)

Data analysis and statistics

Both conventional (INR and APTT) and TEG related (platelet function and fibrinogen) indices of coagulation will be compared between treatment and control groups at two time points 1) between 48 and 72hrs hours post POLAR randomisation, 2) 120 hours (+/- 12hrs) post randomisation. These indices will also be compared in the same samples at both 33C and 37C, in the treatment group patients. If data will be analysed using SAS version 9.2 (SAS Institute Cary, NC, USA). Data will be assessed for normality and log-transformed where appropriate. Comparisons within and between groups will be performed using mixed linear modelling accounting for repeat measures with individual patients treated as random effects. Should any indices have insufficient symmetry to satisfy the assumption of normality, changes from baseline will firstly be considered followed by non-linear modelling if required. A two-sided p-value of 0.05 will be considered to be statistically significant.
Safety
As per the POLAR trial. There are no additional risks posed by the POLAR TEG sub-study. The results of the study will be forwarded to the DSMC.

Funding
Funding for the sub-study has been obtained from the Institute for Safety, Compensation and Recovery Research.

Publication
The study will be conducted in the name of the ANZIC-RC on behalf of the POLAR investigators. Authorship will be under the names of the sub-study investigators on behalf of the POLAR investigators. Publication of results will be embargoed until publication of the main study results unless specific permission for early publication is given by the POLAR management committee.
2. BIBLIOGRAPHY


Multi-centre POLAR study_ANZIC-RCDJC003 Version 8_1st March 2016
(Summary of changes) Note: Changes have been tracked.

<table>
<thead>
<tr>
<th>Location of change</th>
<th>Change</th>
<th>Reason</th>
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<tr>
<td>Header</td>
<td>Multi-centre POLAR study_ANZIC-RC/DJC003 Version 8_1st March 2016</td>
<td>Amended to correspond to the revised versions</td>
</tr>
<tr>
<td>P1 Titlepage</td>
<td>Addition of Prof Capellier and Assoc/Prof Varma to POLAR management committee</td>
<td>Prof Capellier will lead the management of French sites and A/Prof Varma will perform all Marshall scoring. The addition of these investigators will strengthen collaborative ties, enhance study completion and ensure robust Marshal scoring.</td>
</tr>
<tr>
<td>Pages 1-13 Updated throughout document</td>
<td>Administrative changes (numerous) -- Includes post nominal, address, mobile changes -- Personnel and index changes -- Number, formatting, style</td>
<td>Since the study commenced there has been a number of changes to personnel, titles and phone numbers.</td>
</tr>
<tr>
<td>Section 11 Participating Study Sites</td>
<td>New sites have been added</td>
<td>The POLAR collaborative has been expanded and now includes sites in France. This will enhance recruitment and better generalize trial results.</td>
</tr>
<tr>
<td>Section 15 Statistical Considerations</td>
<td>Change to statistical and analytical plan and addition of modified intention to treat analysis.</td>
<td>The original protocol for the POLAR trial featured an intention to treat analysis where a full dataset of participants would be analysed. This form of analysis does not take into account participants who withdraw consent and participants who do not fulfil the inclusion criteria and never receive the intervention a situation which can occasionally occur in emergency trials where participants are enrolled pre-hospital. In the case of POLAR this refers to patients who have an altered conscious state due to alcohol or drugs rather than traumatic brain injury. Following extensive discussion the POLAR management has amended the protocol to a modified intention to treat analysis following the principles outlined in the E9 guideline titled Statistical Principles For Clinical Trials from</td>
</tr>
<tr>
<td>Section 15 Interim analysis</td>
<td>Alteration to Interim analysis to include Data Safety Monitoring committee recommendations</td>
<td>After publication of Eurotherm 3235 the Data Safety Board was asked to review POLAR patient safety. They recommended continuation with increase in monitoring for safety at 300,350,400,450 patients.</td>
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<tr>
<td>Section 16 Safety</td>
<td>Change in references</td>
<td>Updated references</td>
</tr>
<tr>
<td>Section 18 Sub-studies</td>
<td>Addition of POLAR TEG Sub Study (The Alfred Hospital Only)</td>
<td>The POLAR TEG sub study was a single centre study performed at the Alfred and previously submitted and approved by Alfred HREC. We are now informing all sites of this sub study and have embedded it in the protocol (rather than a separate appendix as submitted to Alfred). This sub study has now been completed.</td>
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<td></td>
<td>Addition of POLAR Propofol PK Sub Study (The Alfred Hospital Only)</td>
<td>The Propofol PK sub study is proposed for the Alfred only and will examine the effect of hypothermia on propofol pharmacokinetics, in patients with severe TBI.</td>
</tr>
<tr>
<td>Section 20 Research Timelines</td>
<td>Timeline estimates updated</td>
<td>Timeline estimates updated</td>
</tr>
<tr>
<td>Appendix D / F</td>
<td>Changes to Propofol guidelines</td>
<td>Removal of and changes to suggested doses of propofol in Hypothermic patients in order to minimise the occurrence of Propofol Infusion Syndrome (PRIS). Please see accompanying documents –2015 05 28 Alert to POLAR Site Investigators –2015 05 28 POLAR Protocol Amendment_FINAL This has been ratified by the Data Safety Monitoring Committee (DSMC)</td>
</tr>
<tr>
<td><strong>Appendix F to M</strong></td>
<td><strong>Correction to Appendix Labelling</strong></td>
<td><strong>Incorrect in previous versions</strong></td>
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<tr>
<td>Appendix N</td>
<td>Addition of POLAR Propofol PK Sub Study</td>
<td>Single site sub study – The Alfred, Melbourne</td>
</tr>
</tbody>
</table>
To all site PI and RC,

Please find attached a copy of the POLAR protocol V8 amendment documents. The documents include

- Multi-centre POLAR study_ANZIC-RCDJC003 Version 8_1st March 2015_Marked_up
- Multi-centre POLAR study_ANZIC-RCDJC003 Version 8_1st March 2015_Clean
- Summary of changes - POLAR protocol Summary Changes 1st Nov 2015

Sites please note.

**Protocol versions**

- V6 is the version you have been correctly utilising
- V7 was a single site amendment to the POLAR TEG sub-study (The Alfred Hospital, Victoria)
- We request that ALL sites now adopt V8 as their working protocol.

**Sub-study**

- There has been the addition of Propofol PK Sub-study. A single site sub study (The Alfred Hospital, Melbourne)

Many thanks for your continued support of POLAR

Tony
Multi-centre POLAR study_ANZIC-RCDJC003 Version 9 11th July 2017
(Summary of changes) Note: Changes have been tracked.

<table>
<thead>
<tr>
<th>Location of change</th>
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<td>Multi-centre POLAR study_ANZIC-RC/DJC003 Version 9 11th July 2017</td>
<td>Amended to correspond to the revised versions</td>
</tr>
<tr>
<td>P1 Titlepage</td>
<td>Addition of Ms Shirley Vallance</td>
<td>Ms Vallance has been involved in intensive care research for nearly 20 years. She is also the research Co-ordinator of the highest recruiting site.</td>
</tr>
<tr>
<td>Pages 8 - 13</td>
<td>Administrative changes</td>
<td>A number of changes to personnel and titles.</td>
</tr>
<tr>
<td>Section 11 Participating Study Sites</td>
<td>New sites have been added</td>
<td>The POLAR collaborative has been expanded and now includes sites in Middle east and Switzerland. This will enhance recruitment and better generalize trial results.</td>
</tr>
</tbody>
</table>
| Section 15 Statistical Considerations | The POLAR trial Statistical Analysis Plan was finalized in May 2017 and has been submitted to a scientific journal for editorial consideration of publication. Modifications in this latest version are incremental relative to the previous analysis plan, with no change to the trial primary outcome or most secondary outcomes. The main updates in this final statistical analysis plan include 1. a more detailed interim analysis schedule, and 2. a new statistical approach to a secondary outcome, that being estimation of the average Interim analysis schedule Interim safety analyses of 6-month mortality were initially scheduled at six months following 25% (n=125) and 50% (n=250) patient recruitment. There remains no plan for early trial stopping for apparent futility. After publication of the Eurotherm 3235 trial (Andrews PJ, Sinclair HL, Rodriguez A, et al. Hypothermia for Intracranial Hypertension after Traumatic Brain Injury. N Engl J Med 2015;373:2403-12), the POLAR trial independent Data Safety and Monitoring Committee (DSMC) requested more frequent monitoring of the POLAR trial. These were specified by the DSMC to be the 6-month outcomes observed with 300, 350, 400 and 450 randomized patients. The DSMC specified measuring the primary outcome (proportion of
causal effect among patients complying with cooling treatment

favourable neurological outcomes) and mortality, except for n=450 when 28 day mortality will be assessed.

Estimation of the average causal effect among patients complying with treatment

In trials with incomplete adherence to treatment, such as that anticipated in the cooling arm of POLAR, the intention-to-treat comparison only provides an estimate of the causal effect of treatment assignment rather than an estimate of the causal effect of treatment actually received. An additional exploratory secondary analysis has been added in this circumstance. This complier average causal effect (CACE) analysis will be conducted to estimate the average effect of cooling treatment on the primary outcome for patients who would comply with whichever cooling group they were assigned to, considering both the binary and continuous definitions of compliance with cooling.
30 August 2017

The chair of the Ethics committee

RE: The Prophylactic hypOthermia trial to Lessen trAumatic bRain injury-Randomised Controlled Trial - POLAR RCT (CTN 00987688)

POLAR has been recruiting since 2010 and we are now near the end of the recruiting phase of this very large international Randomised Control Trial.

The recruiting rate over the last twelve months has been steady at 8 patients/month and 15 patients were recruited in August. We are currently at 496 patients recruited.

In a review of recruited patients, the POLAR executive committee noted that the POLAR "consent withdrawn" (2.5% rather than 2% originally predicted) and "loss to follow-up" (7% rather than 5% originally predicted) are both higher than originally projected in 2009.

The POLAR executive committee has suggested increasing our total study size to 510 (now at 500) to compensate. This will add another month to our recruiting period, and shift our finish time by approximately 1 month, to late September/early October. We believe the addition of these patients will be important to the power of the study.

We ask that you support this decision and allow your site to continue recruiting until this point is reached. We have formally notified the Chair of the POLAR Data Safety Monitoring Board (Prof James S. Hutchison, Toronto, Canada).

Yours sincerely

DJ (Jamie) Cooper
On behalf of the POLAR-RCT Management Committee
BMBS MD FRACP FICCM FAAHMS
Professor of Intensive Care Medicine, Monash University
CI-A NHMRC #545901 POLAR-RCT
Director – ANZIC Research Centre, Monash University
2. PUBLISHED STATISTICAL ANALYSIS PLAN (SAP), SAP UPDATE INCLUDING SUMMARY OF AMENDMENTS, AND SAP UPDATE CORRECTION

Published Statistical Analysis Plan (SAP) – POLAR Trial


PMID: 29703266

POLAR SAP Update

The following should be read in conjunction with the published statistical analysis plan (SAP) for the POLAR randomised controlled trial. All additions to the planned analyses were made prior to data lock and prior to access to any unblinded data.

Dose effect / Intensity of cooling
To enable comparison with the existing large randomised controlled trials of prophylactic hypothermia in TBI we will also report intensity of cooling in intervention arm patients categorised according to the time after injury to first reach the core temperature thresholds of 35°C and 33°C.

As-treated and per-protocol analyses
In keeping with the clinical rationale for prophylactic hypothermia in the POLAR Protocol, these planned analyses will be conducted in addition to those in the published SAP.

The previous literature has suggested the optimal dose of prophylactic hypothermia to maximise clinical benefit is for a duration of “more than 48 hours”. This definition is concordant with the POLAR Protocol Version 9 (11 July 2017), Section 7.1.4. Therefore, our main per-protocol and as-treated analyses will be clinically relevant dose analyses (described below*) in addition to the previously described depth of hypothermia exploratory per-protocol and as-treated analyses (in the published SAP).

The clinically relevant dose and depth of hypothermia per-protocol and as-treated analysis subsets will comprise control and intervention patients who are demonstrated retrospectively to have suffered a severe TBI, thus excluding those with initially low GCS <9 not due to severe head injury but rather associated with transient influences, such as alcohol or drug effects. In addition, all patients who did not meet an inclusion criteria or who had an exclusion criteria present will be excluded from the per-protocol and as-treated analysis subsets (Figures 1 and 2).

Compliance with cooling in the clinically relevant dose per-protocol and as-treated analysis subsets will be defined as patients receiving >48 hours of cooling to ≤35°C within 96 hours of randomisation. Patients who survive at least 96 hours but who do not meet the compliance with cooling definition will be excluded from the per-protocol analysis subset. Patients who do not survive 96 hours but who are known to be noncompliant at the time of their death will be excluded. Patients who do not survive 96 hours but who are known to be compliant at their time of death, or whose compliance status is not completely determined, will be included in the per protocol analysis subset.

In the as-treated analysis subset, patients who meet the compliance with cooling criteria (regardless of randomisation category) will be analysed in the hypothermia group. Patients who did not meet the definition of the compliance with cooling, will be analysed with the standard care group. Patients who do not survive 96 hours but who are known to be noncompliant with their assigned treatment at the time of their death will be analysed in the opposite treatment arm to their assignment. Patients who do not survive 96 hours but who are known to be compliant at their time of death, or whose compliance status is not completely determined, will be analysed in their assigned treatment arm.

Professor D. Jamie Cooper
On behalf of the POLAR Management Committee

POLAR RCT ClinicalTrials.gov Identifier: NCT00987688 and
Australian and New Zealand Clinical Trials Registry Identifier: ACTRN12609000764235

POLAR SAP Update 12 June 2018
Figure 1. Per-protocol analysis

XXX Assisted to hypothermia group

XXX Assisted to standard care group

XXX Excluded, incorrect pre-hospital enrolment:
- X X hours
- X GCS 3 and unreactive pupils
- X HR >120; SBP <90
- X Other

XXX Excluded, incorrect hospital enrolment:
- X X3 hours
- X GCS 3 and unreactive pupils
- X Persistent SBP <90
- X Other

XXX Continued in hypothermia group in ICU

XXX Continued in standard care group in ICU

XXX Withdrawn in hospital <12 hours:
- X Pregnancy
- X Clinically significant bleeding
- X Physician decision
- X Not severe TBI
- X Other

XXX Withdrawn in ICU, surviving patients who receive<48 hours of core temperature ≥35°C

XXX Excluded at 6-month follow-up:
- X Withdraw consent
- X Lost to follow-up

XXX Included in 6-month patient outcome

Outcome analyses will only be adjusted for baseline extended IMPACT-TBI probability of 6-month unfavourable outcome

Figure 2. As treated analysis

XXX Assisted to hypothermia group

XXX Assisted to standard care group

XXX Excluded, incorrect pre-hospital enrolment:
- X X hours
- X GCS 3 and unreactive pupils
- X HR >120 or SBP <90
- X Other

XXX Excluded, incorrect hospital enrolment:
- X X3 hours
- X GCS 3 and unreactive pupils
- X Persistent SBP <90
- X Other

XXX Continued in hypothermia group in ICU

XXX Continued in standard care group in ICU

XXX Withdrawn in hospital <12 hours:
- X Pregnancy
- X Clinically significant bleeding
- X Physician decision
- X Not severe TBI
- X Other

XXX Withdrawn in hospital, not severe TBI

XXX Crossed over from standard care group:
- X X hours of core temperature ≥35°C

XXX Crossed over from hypothermia group:
- X X hours of core temperature ≥35°C

XXX Excluded at 6-month follow-up:
- X Withdraw consent
- X Lost to follow-up

XXX Included in 6-month patient outcome

Outcome analyses will only be adjusted for baseline extended IMPACT-TBI probability of 6-month unfavourable outcome

POLAR SAP Update 12 June 2018
References
SAP Update Correction – POLAR Trial

POLAR SAP Update Correction: Figures 1 and 2 aligned with text from 12 June 2018

Outcome analyses will only be adjusted for baseline extended IMPACT-TBI probability of 6-month unfavourable outcome.

Figure 1. Pre-protocol analysis
511 Were randomised pre-hospital and hospital

XX Excluded, incorrect pre-hospital enrolment:
X >3 hours
X GCS 3 and unreactive pupils
X HR >120 or SBP <90
X Other

XX Excluded, incorrect hospital enrolment:
X >3 hours
X GCS 3 and unreactive pupils
X Persistent SBP <90
X Other

XX Continued in hypothermia group
X Assigned to hypothermia group

XX Continued in standard care group
X Assigned to standard care group

XX Excluded, incorrect pre-hospital enrolment:
X >3 hours
X GCS 3 and unreactive pupils
X HR >120 or SBP <90
X Other

XX Excluded, incorrect hospital enrolment:
X >3 hours
X GCS 3 and unreactive pupils
X Persistent SBP <90
X Other

XX Continued in hypothermia group in ICU

XX Continued in standard care group in ICU

XX Withdrawn in hospital <12 hours:
X Pregnancy
X Clinically significant bleeding
X Physician decision
X Not severe TBI
X Other

XX Withdrawn in ICU:
X Surviving patients who received >48 hours of core temperature ≥33°C
X Patients who died at 48-96 hours who received >48 hours of core temperature ≥33°C

XX Excluded at 6-month follow-up:
X Withdraw consent
X Lost to follow-up

XX Included in 6-month patient outcome

Figure 2. Analytical analysis
511 Were randomised pre-hospital and hospital

XX Excluded, incorrect pre-hospital enrolment:
X >3 hours
X GCS 3 and unreactive pupils
X HR >120 or SBP <90
X Other

XX Excluded, incorrect hospital enrolment:
X >3 hours
X GCS 3 and unreactive pupils
X Persistent SBP <90
X Other

XX Continued in hypothermia group in ICU

XX Continued in standard care group in ICU

XX Crossed over from standard care group:
X Surviving patients who received >48 hours of core temperature ≥33°C
X Patients who died at 48-96 hours who received >48 hours of core temperature ≥33°C

XX Crossed over from hypothermia group:
X Surviving patients who received >48 hours of core temperature ≥33°C
X Patients who died at 48-96 hours who received >48 hours of core temperature ≥33°C

XX Excluded at 6-month follow-up:
X Withdraw consent
X Lost to follow-up

XX Included in 6-month patient outcome

Outcome analyses will only be adjusted for baseline extended IMPACT-TBI probability of 6-month unfavourable outcome.

POLAR SAP Update Correction 13 June 2018

Page 1 of 1
3. DATA AND SAFETY MONITORING COMMITTEE (DSMC) STOPPING RULES AND REPORTS


Statistical Monitoring Guidelines
Two planned interim analyses were scheduled by the DSMC at six months following 25% (n = 125) and 50% (n = 250) patient recruitment. There was no plan for early trial stopping for apparent futility.

A group sequential statistical approach was applied at both interim analyses to assess the trial primary outcome of dichotomized extended Glasgow Outcome Score (GOS-E) (or at the discretion of the DSMC, the differential patient mortality) between treatment groups. These interim analyses used a conventional Haybittle-Peto three standard deviation (|Zk| ≥3) sequential monitoring boundary for efficacy / safety, calculated from a normal approximation to the discrete binomial difference in outcome proportions (approximate P<0.001 in both cases).

At the discretion of the DSMC, comparative treatment group summary information were provided for any or all of the adverse events collected in the case report form, as listed below under paragraph 10.

After investigation of whether there appeared to be a safety risk at specific centres or across the POLAR centres as a whole, a recommendation to stop the study at specific centres or in its entirety could be made by the DSMC. In these deliberations, the DSMC will be mindful of the specified trial primary outcome, and the implications of multiplicity of statistical testing of trial data for inflation of type I error.

Assuming no early stopping, the negligible effect of the two interim analyses on expenditure of error (final critical value |Z3| ≥1.975 [P value .048], rather than 1.960) allowed the final analyses at full recruitment to be little affected by these interim analyses and consequently all final analyses were conducted with a Type I error alpha equal to 0.05. This level of significance was not be adjusted otherwise for multiplicity; however the primary trial outcome was clearly defined.

Additional Safety Data
The DSMC could request additional safety data (documented complications and SAEs) at other intervals as required.
Outcome (n=273 – 7 refused consent, 20 lost to follow up)

<table>
<thead>
<tr>
<th>Label</th>
<th>GROUPx (n=140)</th>
<th>GROUPy (n=133)</th>
<th>pvalue</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOSE=1 (Death)</td>
<td>19% (27)</td>
<td>20% (27)</td>
<td>0.83</td>
</tr>
<tr>
<td>GOSE=2</td>
<td>1% (1)</td>
<td>2% (2)</td>
<td>0.61</td>
</tr>
<tr>
<td>GOSE=3</td>
<td>18% (25)</td>
<td>21% (28)</td>
<td>0.5</td>
</tr>
<tr>
<td>GOSE=4</td>
<td>7% (10)</td>
<td>9% (12)</td>
<td>0.57</td>
</tr>
<tr>
<td>GOSE=5</td>
<td>23% (32)</td>
<td>23% (30)</td>
<td>0.95</td>
</tr>
<tr>
<td>GOSE=6</td>
<td>11% (15)</td>
<td>13% (17)</td>
<td>0.6</td>
</tr>
<tr>
<td>GOSE=7</td>
<td>14% (19)</td>
<td>7% (9)</td>
<td>0.06</td>
</tr>
<tr>
<td>GOSE=8</td>
<td>8% (11)</td>
<td>6% (8)</td>
<td>0.55</td>
</tr>
<tr>
<td>GOSE score</td>
<td>4.39 (2.23)</td>
<td>4.08 (2.11)</td>
<td>0.23</td>
</tr>
<tr>
<td>GOSE unfavourable score (1-4)</td>
<td>45% (63)</td>
<td>52% (69)</td>
<td>0.26</td>
</tr>
<tr>
<td>GOSE unfavourable survival (2-4)</td>
<td>26% (36)</td>
<td>32% (42)</td>
<td>0.28</td>
</tr>
</tbody>
</table>

180 day mortality in blocks of 25

Cumulative 180 day mortality

Downloaded From: https://jamanetwork.com/ by a Non-Human Traffic (NHT) User on 03/25/2020
180 day unfavourable outcome (GOSE 1-4) in blocks of 25

Cumulative 180 day unfavourable outcome (GOSE1-4)
Outcome (n=321 – 7 refused consent, 22 missing GOSE at 6 months)

Of the 22 missing GOSE, 6 month survival status has been determined for 20/22 (all survivors).

<table>
<thead>
<tr>
<th>Label</th>
<th>GROUPx</th>
<th>GROUPy</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOSE=1</td>
<td>34 (20%)</td>
<td>32 (21%)</td>
<td>0.88</td>
</tr>
<tr>
<td>GOSE=2</td>
<td>1 (1%)</td>
<td>2 (1%)</td>
<td>0.61</td>
</tr>
<tr>
<td>GOSE=3</td>
<td>33 (20%)</td>
<td>30 (20%)</td>
<td>0.99</td>
</tr>
<tr>
<td>GOSE=4</td>
<td>14 (8%)</td>
<td>16 (10%)</td>
<td>0.51</td>
</tr>
<tr>
<td>GOSE=5</td>
<td>36 (21%)</td>
<td>32 (21%)</td>
<td>0.91</td>
</tr>
<tr>
<td>GOSE=6</td>
<td>16 (10%)</td>
<td>20 (13%)</td>
<td>0.31</td>
</tr>
<tr>
<td>GOSE=7</td>
<td>22 (13%)</td>
<td>11 (7%)</td>
<td>0.08</td>
</tr>
<tr>
<td>GOSE=8</td>
<td>12 (7%)</td>
<td>10 (7%)</td>
<td>0.83</td>
</tr>
</tbody>
</table>

GOSE score

<table>
<thead>
<tr>
<th>Label</th>
<th>GROUPx</th>
<th>GROUPy</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOSE=1</td>
<td>4.27 (2.22)</td>
<td>4.10 (2.14)</td>
</tr>
<tr>
<td>GOSE unfavourable score (1-4)</td>
<td>82 (49%)</td>
<td>80 (52%)</td>
</tr>
<tr>
<td>GOSE favourable score (5-8)</td>
<td>86 (51%)</td>
<td>73 (48%)</td>
</tr>
</tbody>
</table>

GOSE unfavourable survival

<table>
<thead>
<tr>
<th>Label</th>
<th>GROUPx</th>
<th>GROUPy</th>
</tr>
</thead>
<tbody>
<tr>
<td>180 Mortality*</td>
<td>34 (19%)</td>
<td>32 (20%)</td>
</tr>
</tbody>
</table>

Denominator for GOSE=321, denominator for 6 month survival=341
180 day favourable outcome (GOSE 5-8) in blocks of 25

Cumulative 180 day favourable outcome (GOSE 5-8)
Outcome (n=364 – 8 refused consent, 28 missing GOSE at 6 months)

Of the 28 missing GOSE, 6-month survival status has been determined for 26/28 (all survivors).

<table>
<thead>
<tr>
<th>Label</th>
<th>n</th>
<th>GroupX</th>
<th>GroupY</th>
<th>pvalue</th>
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</thead>
<tbody>
<tr>
<td>GOSE=1</td>
<td>364</td>
<td>36 (19.6%)</td>
<td>35 (19.4%)</td>
<td>0.98</td>
</tr>
<tr>
<td>GOSE=2</td>
<td>364</td>
<td>1 (0.5%)</td>
<td>2 (1.1%)</td>
<td>0.62</td>
</tr>
<tr>
<td>GOSE=3</td>
<td>364</td>
<td>36 (19.6%)</td>
<td>36 (20.0%)</td>
<td>0.92</td>
</tr>
<tr>
<td>GOSE=4</td>
<td>364</td>
<td>16 (8.7%)</td>
<td>18 (10.0%)</td>
<td>0.67</td>
</tr>
<tr>
<td>GOSE=5</td>
<td>364</td>
<td>41 (22.3%)</td>
<td>39 (21.7%)</td>
<td>0.89</td>
</tr>
<tr>
<td>GOSE=6</td>
<td>364</td>
<td>17 (9.2%)</td>
<td>24 (13.3%)</td>
<td>0.22</td>
</tr>
<tr>
<td>GOSE=7</td>
<td>364</td>
<td>24 (13.0%)</td>
<td>13 (7.2%)</td>
<td>0.07</td>
</tr>
<tr>
<td>GOSE=8</td>
<td>364</td>
<td>13 (7.1%)</td>
<td>13 (7.2%)</td>
<td>0.95</td>
</tr>
<tr>
<td>GOSE score</td>
<td>364</td>
<td>4.3 (2.2)</td>
<td>4.2 (2.1)</td>
<td>0.65</td>
</tr>
<tr>
<td>GOSE unfavourable score</td>
<td>364</td>
<td>89 (48.4%)</td>
<td>91 (50.6%)</td>
<td>0.68</td>
</tr>
<tr>
<td>GOSE unfavourable survival</td>
<td>364</td>
<td>53 (28.8%)</td>
<td>56 (31.1%)</td>
<td>0.63</td>
</tr>
<tr>
<td>GOSE favourable score</td>
<td>364</td>
<td>95 (51.6%)</td>
<td>89 (49.4%)</td>
<td>0.68</td>
</tr>
<tr>
<td>180 day mortality</td>
<td>390</td>
<td>36 (18.0%)</td>
<td>35 (18.4%)</td>
<td>0.91</td>
</tr>
</tbody>
</table>

Denominator for GOSE=364, denominator for 6 month survival=390
180 day favourable outcome (GOSE 5-8) in blocks of 25

Cumulative 180 day favourable outcome (GOSE5-8)