The POLAR-RCT
The Prophylactic hypOthermia trial to Lessen trAumatic bRain injury-Randomised Controlled Trial
(NCT 00987688 & ACTRN12609000764235)

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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
Prof Jamie Cooper Principal Investigator, ANZIC-RC
Ms Lynne Murray Research Manager, ANZIC-RC
Prof Alistair Nichol Professor, ANZIC-RC
Prof Andrew Forbes Head Biostatistics Unit, DEPM, Monash University
Prof. Chris Reid Head, Monash Centre of Cardiovascular Research and Education in Therapeutics (CCRET), Monash University
Mr Tony Trapani Project Manager, ANZIC-RC
A/Prof Michael Bailey Biostatistician, ANZIC-RC

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
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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

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4. ABBREVIATIONS

AE  Adverse event
AKI  Acute Kidney Injury
ANZ  Australia and New Zealand
ANZIC-RC  Australian and New Zealand Intensive Care Research Centre
ANZICS  Australian and New Zealand Intensive Care Society
ARC  Australian Research Council
ARR  Absolute risk reduction
ATBIS  Australasian Traumatic Brain Injury Study
BTF  Brain trauma foundation
CCM  Critical Care Medicine
CCRET  Centre of Cardiovascular Research and Education in Therapeutics
CI  Confidence interval
CPP  Cerebral Perfusion Pressure
CRF  Case report form
CSF  Cerebrospinal fluid
CTG  Clinical Trials Group
CVP  Central venous pressure
DEPM  Department of Epidemiology and Preventive Medicine
DSMC  Data Safety Monitoring Committee
ED  Emergency Department
ETT  Endotracheal tube
HDEC  Human Disability Ethics Committee
HREC  Human Research Ethics Committee
HTS  Hypertonic saline
ICP  Intracranial Pressure
ICU  Intensive Care Unit
IMV  Invasive mechanical ventilation
IV  Intravenous
NEJM  New England Journal of Medicine
NHMRC  National Health and Medical Research Council
NNT  Number needed to treat
NOK  Next of kin
QOL  Quality of life
NS  National statement
RGC  Research Governance Committee
RCT  Randomised controlled trial
RRI  Relative risk increase
RRR  Relative risk reduction
RSI  Rapid sequence intubation
SAE  Serious adverse event
SF  Short form
TBI  Traumatic brain injury
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.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 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 adults². In a recent analysis of an international database of 2664 patients with severe TBI, mortality was 28%.³ 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) 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)7 trial, ACTRN12605000177851), 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. 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). 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 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. 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.

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. 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. 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.

### 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. 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 (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

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.\(^{40}\)

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\(^9\) 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\(^{32}\). 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.\(^4\) 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.

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 ‘normothermic’ care, is associated with an increased proportion of favourable neurological outcomes six months after severe TBI.

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.

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
- 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
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 > 2.5 hrs
- Able to be intubated without drugs
- Systolic BP < 90 mmHg
- Heart rate > 120 bpm
- 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:
  - 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
- 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 fulfill 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 re instituted** 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 RICH26 and other25 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 re-warming (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 de-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 24 hours, 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.\(^{30}\) (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 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, 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 adults 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. 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. 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. 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. Controlled slow rewarming will give the kidneys time to excrete any 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 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. Adrenalin). 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. 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. 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. Barbtsurates 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 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. This approach has proven successful for 5 previous NHMRC funded randomised trials (including TBI and pre-hospital trials) - (SAFE, RSI, RICH, out of hospital cardiac arrest and HTS 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 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
- Type and volume of fluid therapy including blood
- Bleeding incidents
- Brain injury management interventions
- CT Brain scan (Marshall score\textsuperscript{33})
- Injury severity score

**Intensive Care Admission**
- Vital signs, Glasgow coma scale
- Haematological and biochemical parameters
- Hourly core temperature
- Type and volume of fluid therapy including blood
- Urine output/fluid balance
- ICU interventions
- Brain injury management interventions
- Feeding; delivery method
- Feeding tolerance
- Infection surveillance
- Bleeding incidents

**Hospital discharge**
- Length of mechanical ventilation
- Length of stay
- Discharge destination
- Vital status 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

**General data collection**
- Withdrawal from study protocol

**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\textsuperscript{11}, RSI\textsuperscript{7}, ATBIS\textsuperscript{4}, SAFE-TBI\textsuperscript{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 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\(^5\) 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.\(^11\) 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)\(^4\) <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 \( \pm 1.996 \) SD (\( P = 0.0459 \)) rather than \( \pm 1.96 \) 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., 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.

Fax number
+ 61 3 9903 0071

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

Chief Investigator:
Prof Jamie Cooper +61 3 9076 3036 / + 61 3 9076 0672 / +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), 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.
## 20. RESEARCH TIMELINES

<table>
<thead>
<tr>
<th>Time frame indicators</th>
<th>Milestone</th>
</tr>
</thead>
<tbody>
<tr>
<td>January 2008</td>
<td>Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS CTG) endorsement obtained</td>
</tr>
<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>
</tr>
<tr>
<td>January 2009</td>
<td>Commence study organisation</td>
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<tr>
<td>April 2009</td>
<td>Protocol finalised</td>
</tr>
<tr>
<td>April 2009</td>
<td>The Alfred HREC submission</td>
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<td>April 2009</td>
<td>Participating sites finalised</td>
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<td>June 2009</td>
<td>Monash University HREC submission</td>
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<td>September 2009</td>
<td>Participating sites HREC submission</td>
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<td>January 2010</td>
<td>Pilot phase commences at The Alfred</td>
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<tr>
<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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<td>August 2010</td>
<td>Ambulance paramedic training completed</td>
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<tr>
<td>September 2010</td>
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**Estimated**

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<td>Aug 2018</td>
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<td>Oct 2018</td>
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<tr>
<td>Jan 2019</td>
<td>Submission of initial manuscript</td>
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# The time lines will be reviewed at each interim analysis
## 21. APPENDIX A: TABLE OF EVENTS

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<th>Pre-hospital</th>
<th>ED Admission</th>
<th>ICU Admission</th>
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<th>Day 2</th>
<th>Day 3</th>
<th>Day 4-6</th>
<th>Day 7</th>
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<th>Follow Up 6 months</th>
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<td>Event</td>
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<td>ED Admission</td>
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<td>Day 8-14</td>
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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 >2.5hrs
- Able to be intubated without drugs
- Systolic BP <90mmHg
- Heart rate > 120bpm
- 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

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

**NORMOTHERMIA**
Standard care
Aim for temperature 36.5-37.5 °C.

**HYPOTHERMIA**
Apply surface cooling pads ASAP
Target 33 °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 >80mmHg until ICP known (then to achieve CPP with minimum MAP of 70mmHg), using fluids and vasopressor (type of vasopressor is clinician’s choice) if required
- After initial resuscitation in otherwise stable patients, positive daily fluid balances>500mls 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 sufentanil (0.2 to 1mcg/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 <20mmHg
- CPP target >60mmHg
• 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 >20mmHg

- 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)

ICP Stable and <20mmHg **

YES (Proceed)

No (sustained ICP>20mmHg)

Manage ICP
Reconsider warming in 12 hours

Haemodynamic and electrolyte status stable

No

YES (Proceed)

Status Corrected

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 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.

# 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.
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

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### Patient lost to follow up: ☐

### Patient alive (unscorable): ☐

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### Extended Glasgow Coma Scale

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

#### 16.2 Respondent:
- ☐ Patient alone
- ☐ Relative or friend or carer alone
- ☐ Patient and relative, friend or carer together
- ☐ Patient lost to follow up

#### 16.3 The injured person is:
- ☐ Out of hospital
- ☐ In hospital, rehabilitation centre or residential care

#### 16.4 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 crossing one box, which best answers the question.

#### 16.5 Is the injured person able to obey simple commands, or say any words?
- ☐ Yes
- ☐ No (2 - Vegetative state)

#### 16.6 Before the injury was the injured person able to look after themselves at home?
- ☐ Yes
- ☐ No

#### 16.7 As a result of the injury does the injured person now need someone to help look after them at home?
- ☐ Yes
- ☐ No

*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.

Cross one box only:
- ☐ 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

#### 16.8 Before the injury was the injured person able to buy things at shops without help?
- ☐ Yes
- ☐ No

#### 16.9 As a result of the injury does the injured person now need help to buy things at shops?

Cross one box only:
- ☐ Do not need help to shop
- ☐ 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

#### 16.10 Before the injury was the injured person able to travel without help?
- ☐ Yes
- ☐ No

#### 16.11 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.

Cross one box only:
- ☐ Do not need help to travel
- ☐ Need help to travel (4 - Upper SD)
- ☐ Need help to travel, but not because of the injury
### Extended Glasgow Coma Scale

<table>
<thead>
<tr>
<th>15.12</th>
<th>Employment before the injury?</th>
<th>Working</th>
<th>Studying as a student</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Looking for work</td>
<td>Refined</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Looking after family</td>
<td>None of these</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>15.13</th>
<th>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)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cross one box only:</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>15.14</th>
<th>Before the injury did the injured person take part in social and leisure activities outside home?</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>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.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>15.15</th>
<th>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?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cross one box only:</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>15.16</th>
<th>Before the injury did the injured person have any problems getting on with friends and family?</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>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?</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Examples include quick temper, irritability, mood swings, depression, anxiety, insensitivity to others, rigid thinking, unreasonable or childish behaviour.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cross one box only:</td>
<td>Things are still much the same</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>There are occasional problems (less than one a week) (7 - Lower GR)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>There are frequent problems (once a week or more) (6 - Upper MD)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>There are constant problems (problems everyday) (5 - Lower MD)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>There are problems for some other reason, not because of the injury</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>15.18</th>
<th>Are there currently any other problems resulting from the injury?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td>Cross one box only:</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| 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 |

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Multi-centre POLAR study_ANZIC-RC/DJC003 Version 9 _ 11 July 2017
### 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 (SD)
- [ ] 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:

<table>
<thead>
<tr>
<th>16.23 Mobility:</th>
</tr>
</thead>
<tbody>
<tr>
<td>I have no problems in walking around</td>
</tr>
<tr>
<td>I have some problems in walking around</td>
</tr>
<tr>
<td>I am confined to bed</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>16.24 Personal care:</th>
</tr>
</thead>
<tbody>
<tr>
<td>I have no problems with personal care</td>
</tr>
<tr>
<td>I have some problems washing or dressing myself</td>
</tr>
<tr>
<td>I am unable to wash or dress myself</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>16.25 Usual activities:</th>
</tr>
</thead>
<tbody>
<tr>
<td>I have no problems with performing my usual activities</td>
</tr>
<tr>
<td>I have some problems with performing my usual activities</td>
</tr>
<tr>
<td>I am unable to perform my usual activities</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>16.26 Pain / discomfort:</th>
</tr>
</thead>
<tbody>
<tr>
<td>I have no pain or discomfort</td>
</tr>
<tr>
<td>I have moderate pain or discomfort</td>
</tr>
<tr>
<td>I have extreme pain or discomfort</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>16.27 Anxiety / depression:</th>
</tr>
</thead>
<tbody>
<tr>
<td>I am not anxious or depressed</td>
</tr>
<tr>
<td>I am moderately anxious or depressed</td>
</tr>
<tr>
<td>I am extremely anxious or depressed</td>
</tr>
</tbody>
</table>

#### 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

Worst imaginable health state

Best imaginable health state
## 29. APPENDIX I: ASSESSMENT OF QUALITY OF LIFE (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.

### 16.29 In general, would you say your health is:

- [ ] Excellent
- [ ] Very good
- [ ] Good
- [ ] Fair
- [ ] Poor

### 16.30 The following questions ask about your activities you might do during a typical day.

#### 16.30.1 Does your health now limit you in these activities? If so, how much?

- [ ] Yes limited a lot
- [ ] Yes limited a little
- [ ] No

#### 16.30.2 Climbing several flights of stairs:

- [ ] Not limited at all

### 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?

#### 16.31.1 Accomplished less than you would like:

- [ ] Yes
- [ ] No

#### 16.31.2 Were limited in the kind of work or other activities:

### 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)

#### 16.32.1 Accomplished less than you would like:

- [ ] Yes
- [ ] No

#### 16.32.2 Didn't do work or other activities as carefully as usual:

### 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
- [ ] A little bit
- [ ] Moderately
- [ ] Quite a bit
- [ ] Extremely

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.

### 16.34 How much of the time during the past 4 weeks...

#### 16.34.1 Have you felt calm and peaceful?

- [ ] All of the time
- [ ] Most of the time
- [ ] A good bit of the time
- [ ] A little of the time
- [ ] None of the time

#### 16.34.2 Did you have a lot of energy?

#### 16.34.3 Have you felt down?

### 16.35 During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities?  

<table>
<thead>
<tr>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</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 and prolonged length of stay.\textsuperscript{58} Severe cases require costly treatments and can result in prolonged kidney dysfunction and delayed recovery, escalating the human and financial costs of TBI.\textsuperscript{59} 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{39} 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{50,61-64} 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 72hours. 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 (a 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...
are potentially inaccurate in the critically ill population. The most commonly used formula in Australia, the Schofield equation, 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. 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. 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. 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.  

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. 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. 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. 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. 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%. 

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%.

There have been 2 small studies in TBI patients suggesting a similar response. The first investigated multiple metabolic parameters in 31 TBI patients who had prophylactic hypothermia and found that resting expenditure decreased by over 35% at 33°C. 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. 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 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 studies\(^86-88\) 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 that 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.

**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.

**NSE**: NSE is a 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.

**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 12605000009617).

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.\textsuperscript{37,40,99} 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\textsuperscript{100} 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.\textsuperscript{101,102} Hypothermia also causes platelet dysfunction,\textsuperscript{103,104} 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,\textsuperscript{1,105,106} 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”.\textsuperscript{107} 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\textsuperscript{108} but may be poor indicators of in vivo coagulation in hypothermic patients.\textsuperscript{108} 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.\textsuperscript{109-111} 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.\textsuperscript{108} Thromboelastography (TEG) has been previously used in bleeding cardiac surgical patients to measure coagulation deficits and we will use this technology in TBI patients.\textsuperscript{112} 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.\textsuperscript{113,114}
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 33C and prior to rewarming (48 to 72hrs hours post POLAR randomisation). Samples will be analysed using the TEG at both 33C and 37C (see TEG analysis methodology). At each temperature (33C and 37C) standard and functional fibrinogen assays will be performed. Standard, functional fibrinogen and Platelet Mapping (PM) at 33C will be tested followed by standard, functional fibrinogen and Platelet Mapping (PM) at 37C. 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 37C using the TEG. Standard, functional fibrinogen and Platelet Mapping (PM) assays will be performed at 37C (see TEG analysis methodology). Non POLAR patients will have blood taken 48 to 72hrs hours post hospital admission and analysed at 37C using the TEG. Standard, functional fibrinogen and Platelet Mapping (PM) assays will be performed at 37C (see TEG analysis methodology).

Sample 2
Hypothermia patients will have blood taken 120 hrs +/- 12hrs post randomisation once they have reached 37C. Samples will be analysed using the TEG at 37C. 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 37C 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>Sample 1</th>
<th>Hypothermic therapy patient</th>
<th>Standard therapy patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>48 and 72hrs hours post POLAR randomisation</td>
<td>Standard, Fibrinogen and PM assay at 33C followed by, Standard, Fibrinogen and PM assay at 37C</td>
<td>Standard, Fibrinogen and PM assay at 37C only.</td>
</tr>
</tbody>
</table>

| Sample 2 | 120 +/-12hrs post POLAR randomisation | Standard, Fibrinogen and PM assay at 37C only. | Standard, Fibrinogen and PM assay at 37C only. |

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

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 (CLTOT) 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
- CLTOT
- Volume of distribution (Vd)
- Elimination half-life (T1/2)

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
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 (CLTOT - 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-\infty}) 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.
25. Bernard SA. The effect on outcome at hospital discharge of paramedic cooling compared with hospital cooling after resuscitation from cardiac arrest. Australian New Zealand Clinical Trials Registry 2005;ACTRN12605000179639.
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.