Pediatric Traumatic Brain Injury Consortium:
Hypothermia

Supported by:

The National Institute of Neurological Disorders and Stroke (NINDS)

Grant Number - 1U01NS052478-01A2
ClinicalTrials.gov Identifier: NCT00222742
### Pediatric Traumatic Brain Injury Consortium: Hypothermia

<table>
<thead>
<tr>
<th>Role</th>
<th>Name</th>
<th>Contact Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Principal Investigator</td>
<td>P. David Adelson, MD</td>
<td>1919 East Thomas Road, Building B, 4th Floor, Phoenix, AZ 85016, Phone: (602) 933-0923, Email: <a href="mailto:dadelson@phoenixchildrens.com">dadelson@phoenixchildrens.com</a></td>
</tr>
<tr>
<td>Co-Principal Investigator</td>
<td>John Beca, MD</td>
<td>127 Parran Hall, 130 DeSoto Street, Pittsburgh, PA 15213, Phone: 412-624-5218, Fax: 412-624-3775, Email: <a href="mailto:JohnBeca@adhb.govt.nz">JohnBeca@adhb.govt.nz</a></td>
</tr>
<tr>
<td>Clinical Coordinating Center</td>
<td>Sue R. Beers, PhD</td>
<td>3811 O'Hara Street, Phone: 412-246-5419, Fax: 412-246-5425, Email: <a href="mailto:beerssr@upmc.edu">beerssr@upmc.edu</a></td>
</tr>
<tr>
<td>Data Management and Analysis Center</td>
<td>Stephen Wisniewski, PhD</td>
<td>127 Parran Hall, 130 DeSoto Street, Pittsburgh, PA 15213, Phone: 412-624-5218, Fax: 412-624-3775, Email: <a href="mailto:wisniew@edc.pitt.edu">wisniew@edc.pitt.edu</a></td>
</tr>
<tr>
<td>Pediatric Neurosurgery</td>
<td>S. Danielle Brown, RN, MS</td>
<td>1919 East Thomas Road, Building B, 3rd Floor, Phoenix, AZ 85016, Phone: 602-933-0956, Email: <a href="mailto:dbrown4@phoenixchildrens.com">dbrown4@phoenixchildrens.com</a></td>
</tr>
<tr>
<td>Data Management and Analysis Center</td>
<td>Laurie Silfies, BS</td>
<td>127 Parran Hall, 130 DeSoto Street, Pittsburgh, PA 15213, Phone: 412-624-5218, Fax: 412-624-3775, Email: <a href="mailto:silfiesl@edc.pitt.edu">silfiesl@edc.pitt.edu</a></td>
</tr>
<tr>
<td>Neuropsychological Outcomes Center</td>
<td>Anthony Fabio, MPH, PhD</td>
<td>3520 Forbes Avenue, PARKV 203, Pittsburgh, PA 15261, Phone: 412-848-3901, Fax: 412-802-6505, Email: <a href="mailto:fabioa@upmc.edu">fabioa@upmc.edu</a></td>
</tr>
<tr>
<td>Epidemiology Data Center</td>
<td>Deborah Hirtz, MD</td>
<td>6001 Executive Blvd., MSC 9525, Bethesda, MD 20892, Phone: 301-496-5821, Fax: 301-480-1080, Email: <a href="mailto:hirtzd@ninds.nih.gov">hirtzd@ninds.nih.gov</a></td>
</tr>
<tr>
<td>Epidemiology Data Center</td>
<td>Richard Towbin, MD</td>
<td>1919 East Thomas Road, Phoenix, AZ 85016, Phone: 602-933-1146, Email: <a href="mailto:rtowbin@gmail.com">rtowbin@gmail.com</a></td>
</tr>
<tr>
<td>Project Manager</td>
<td>Laurie Silfies, BS</td>
<td>127 Parran Hall, 130 DeSoto Street, Pittsburgh, PA 15213, Phone: 412-624-5218, Fax: 412-624-3775, Email: <a href="mailto:silfiesl@edc.pitt.edu">silfiesl@edc.pitt.edu</a></td>
</tr>
<tr>
<td>Project Manager</td>
<td>Anthony Fabio, MPH, PhD</td>
<td>3520 Forbes Avenue, PARKV 203, Pittsburgh, PA 15261, Phone: 412-848-3901, Fax: 412-802-6505, Email: <a href="mailto:fabioa@upmc.edu">fabioa@upmc.edu</a></td>
</tr>
<tr>
<td>Data Management and Analysis Center</td>
<td>Deborah Hirtz, MD</td>
<td>6001 Executive Blvd., MSC 9525, Bethesda, MD 20892, Phone: 301-496-5821, Fax: 301-480-1080, Email: <a href="mailto:hirtzd@ninds.nih.gov">hirtzd@ninds.nih.gov</a></td>
</tr>
<tr>
<td>Epidemiology Data Center</td>
<td>Richard Towbin, MD</td>
<td>1919 East Thomas Road, Phoenix, AZ 85016, Phone: 602-933-1146, Email: <a href="mailto:rtowbin@gmail.com">rtowbin@gmail.com</a></td>
</tr>
</tbody>
</table>
### Clinical Sites and Principal Investigators – Enrolling Sites

<table>
<thead>
<tr>
<th>Michael Bell, MD</th>
<th>J. Paul Muizeelaar, MD, PhD</th>
</tr>
</thead>
<tbody>
<tr>
<td>University of Pittsburgh</td>
<td>University of California, Davis</td>
</tr>
<tr>
<td>Pittsburgh, PA 15213</td>
<td>Sacramento, CA 95817</td>
</tr>
<tr>
<td>Pamela Okada, MD</td>
<td>William Tsai, MD</td>
</tr>
<tr>
<td>University of Texas Southwestern</td>
<td>Carolinas Medical Center</td>
</tr>
<tr>
<td>Dallas TX 75390</td>
<td>Charlotte, NC 28203</td>
</tr>
<tr>
<td>Neal J. Thomas, M.D., M.Sc.</td>
<td>Jose Pineda, MD</td>
</tr>
<tr>
<td>Pennsylvania State University</td>
<td>Washington University</td>
</tr>
<tr>
<td>Hershey, PA 17033</td>
<td>St. Louis, Missouri 63110</td>
</tr>
<tr>
<td>Gerald Grant, M.D.</td>
<td>Richard Ellenbogen MD FCCM FACS</td>
</tr>
<tr>
<td>Duke University Medical Center</td>
<td>University of Washington</td>
</tr>
<tr>
<td>Durham, NC 27710</td>
<td>Seattle, Washington 98104-2499</td>
</tr>
<tr>
<td>Karin Bierbrauer, MD</td>
<td>Steven J. Schneider, MD, FACS, FAAP</td>
</tr>
<tr>
<td>Cincinnati Children's Hospital Medical Center</td>
<td>Cohen Children's Hospital</td>
</tr>
<tr>
<td>Cincinnati, OH 45229-3039</td>
<td>New Hyde Park, NY 11042</td>
</tr>
<tr>
<td>Sandra Buttram, MD</td>
<td>Stuart Friess MD</td>
</tr>
<tr>
<td>Phoenix Children’s Hospital</td>
<td>Children’s Hospital of Philadelphia</td>
</tr>
<tr>
<td>Phoenix, AZ 85016</td>
<td>Philadelphia, PA 19104</td>
</tr>
<tr>
<td>John Ragheb, MD</td>
<td>John Beca, MD</td>
</tr>
<tr>
<td>University of Miami</td>
<td>Starship Children’s Hospital</td>
</tr>
<tr>
<td>Miami, FL 33136</td>
<td>Auckland, New Zealand</td>
</tr>
<tr>
<td>Simon Erickson, MD</td>
<td></td>
</tr>
<tr>
<td>Princess Margaret Hospital</td>
<td></td>
</tr>
<tr>
<td>Perth, Australia</td>
<td></td>
</tr>
</tbody>
</table>

### Clinical Sites and Principal Investigators – Screening Sites

<table>
<thead>
<tr>
<th>Chani Traube, MD</th>
<th>Nathan Dean, MD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weill-Cornell Medical Center</td>
<td>National Children’s Medical Center.</td>
</tr>
<tr>
<td>New York, NY 10065</td>
<td>Washington, DC 20010</td>
</tr>
<tr>
<td>Peter Skippen, MD</td>
<td>Annemarie Guerguerian, MD</td>
</tr>
<tr>
<td>British Columbia Children’s Hospital</td>
<td>Hospital for Sick Children</td>
</tr>
<tr>
<td>Vancouver, Canada</td>
<td>Toronto, Canada</td>
</tr>
<tr>
<td>Ari Joffe, MD</td>
<td>Warwick Butt, MD</td>
</tr>
<tr>
<td>Stollery Children’s Hospital</td>
<td>Royal Children’s Hospital</td>
</tr>
<tr>
<td>Edmonton, Canada</td>
<td>Melbourne, Australia</td>
</tr>
<tr>
<td>Shelly Timmons, MD, PhD</td>
<td>George Jallo, MD</td>
</tr>
<tr>
<td>University of Tennessee</td>
<td>Johns Hopkins Medical Center</td>
</tr>
<tr>
<td>Memphis, TN</td>
<td>Baltimore, MD</td>
</tr>
<tr>
<td>Bradford Harris, MD</td>
<td>Grace Arteaga, MD</td>
</tr>
<tr>
<td>University of North Carolina</td>
<td>Mayo Clinic</td>
</tr>
<tr>
<td>Chapel Hill, NC</td>
<td>Rochester, MN</td>
</tr>
</tbody>
</table>
Clinical Sites and Principal Investigators – Additional Sites Interested in Participating

<table>
<thead>
<tr>
<th>Name</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mark Peters, MD</td>
<td>Great Ormond Street Hospital</td>
</tr>
<tr>
<td></td>
<td>London, England</td>
</tr>
<tr>
<td>Andreas Schibler, MD</td>
<td>Mater Children’s Hospital</td>
</tr>
<tr>
<td></td>
<td>South Brisbane, Australia</td>
</tr>
<tr>
<td>Anthony Slater, MD</td>
<td>Royal Children’s Hospital</td>
</tr>
<tr>
<td></td>
<td>Brisbane, Australia</td>
</tr>
<tr>
<td>Gary Williams, MD</td>
<td>Sydney Children’s Hospital</td>
</tr>
<tr>
<td></td>
<td>Sydney, Australia</td>
</tr>
<tr>
<td>Melissa Parker, MD</td>
<td>McMaster Children’s Hospital, Hamilton Hospital</td>
</tr>
<tr>
<td></td>
<td>Hamilton, Ontario</td>
</tr>
<tr>
<td>Peter-Marc Fortune, MD</td>
<td>Royal Manchester Children’s Hospital</td>
</tr>
<tr>
<td></td>
<td>Manchester, England</td>
</tr>
<tr>
<td>Anthony Figaji, MD</td>
<td>University of Cape Town</td>
</tr>
<tr>
<td></td>
<td>Cape Town, South Africa</td>
</tr>
<tr>
<td>Distur, MD</td>
<td>UTSW Parkland</td>
</tr>
<tr>
<td></td>
<td>Dallas, TX</td>
</tr>
<tr>
<td>Miriam Beauchamp, PhD</td>
<td>Ste-Justine Hospital</td>
</tr>
<tr>
<td></td>
<td>Montreal, Quebec, Canada</td>
</tr>
<tr>
<td>Marino Festa, MD</td>
<td>Children’s Hospital of Westmead</td>
</tr>
<tr>
<td></td>
<td>Sydney, Australia</td>
</tr>
<tr>
<td>Wilson, MD</td>
<td>Southampton University Hospitals Trust</td>
</tr>
<tr>
<td></td>
<td>Southampton, UK</td>
</tr>
<tr>
<td>Michael Yung, MD</td>
<td>Women’s &amp; Children’s Hospital</td>
</tr>
<tr>
<td></td>
<td>North Adelaide, S Australia</td>
</tr>
<tr>
<td>Kevin Morris, MD</td>
<td>Birmingham Children’s Hospital</td>
</tr>
<tr>
<td></td>
<td>Birmingham, England</td>
</tr>
<tr>
<td>Richard Edwards, MD</td>
<td>Frenchay Hospital</td>
</tr>
<tr>
<td></td>
<td>Bristol, England</td>
</tr>
<tr>
<td>Marianne Nellis, MD</td>
<td>Chaim Sheba Medical Center</td>
</tr>
<tr>
<td></td>
<td>Tel Aviv, Israel</td>
</tr>
</tbody>
</table>
# TABLE OF CONTENTS

## 1.0 INTRODUCTION AND HYPOTHESIS

1.1 Preliminary Studies ............................................ 8

1.2 Hypotheses and Specific Aims ................................. 8

## 2.0 BACKGROUND AND SIGNIFICANCE

2.1 Overview ......................................................... 9

2.2 The Need for Pediatric Specific TBI Trials ................. 9

2.3 Unique Response to Injury and Treatment in Children .... 10

2.4 Hypothermia Laboratory Studies ............................ 10

2.5 Clinical Trials of Hypothermia for Neurologic Injury in Children 10

## 3.0 PRELIMINARY DATA

3.1 Patient Accrual and Attrition by Aim ....................... 11

3.2 Treatment Performance ....................................... 11

3.3 Safety of HYPO Treatment Protocol ........................ 12

3.3.1 Mortality: .................................................. 12

3.3.2 Complications: ............................................. 12

3.3.3 Intracranial Pressure and Cerebral Perfusion Pressure 13

## 4.0 STUDY DESIGN, ELIGIBILITY, AND CLINICAL PROTOCOLS

4.1 Overview of Phase III Study- Inclusion and Exclusion criteria 14

4.2 Run-in Period: .................................................. 14

4.3 Randomization Procedures: .................................... 14

4.3.1 Eligibility ................................................... 15

4.3.2 Time to cooling: ............................................ 15

4.3.3 Recruitment: ............................................... 15

4.3.4 Randomization: ............................................. 15

4.4 Conventional Management: .................................... 16

4.4.1 Acute Management Protocol: ............................. 16

4.4.2 Evaluation in the Emergency Department: .............. 16

4.4.3 Transfer to ICU or Operating Room: ..................... 16

4.4.4 ICP Monitoring and Management of Intracranial Hypertension: 16

4.4.5 Fluids and Electrolytes ................................... 17
4.4.6 Discharge:

5.0 HYPOTHERMIA PROTOCOL

5.1 Cooling:

5.2 Rewarming:

5.3 Normothermia

5.4 Compliance with Protocol:

5.5 After Study Treatment:

6.0 OUTCOME ASSESSMENT

6.1 Primary Outcome Measures: Mortality:

6.2 Secondary Outcome Measures:

6.3 Rationale for Selection of Outcome Measures:

6.4 Selection of the Outcome Time-points:

6.5 Description of the Outcomes Test Battery:

   6.5.1 Global measures:

   6.5.2 Cognition and Behavior:

6.6 Baseline Procedures:

6.7 Procedures to Mitigate Attrition in the Outcome Phase:

6.8 Mitigation of Drug Effects:

6.9 Testability of Patients:

6.10 Supervision and Blinded Status of Outcome Staff:

6.11 Scoring of the GOS/ GOS-E Peds:

6.12 Scoring of Neuropsychological Tests

7.0 SAFETY MONITORING and RADIOLOGY

7.1 Medical Safety Monitor

7.2 Efficacy on ICP Elevations:

7.3 Radiology Monitor

8.0 ADMINISTRATIVE AND STUDY OVERSIGHT

8.1 Trial Oversight and Coordinating Center (CC):

   8.1.2 Clinical Oversight Center:

   8.1.3 The Steering Committee:

   8.1.4 Neuropsychological Outcomes Center (NOC)
8.1.5 Safety Oversight Center:

8.1.5.1 Data Safety Monitoring Board (DSMB)

8.1.6 Communication between Centers:

9.0 DATA COLLECTION, MANAGEMENT, AND OVERSIGHT

9.1 Data Management Center (DMAC)- Administrative Overview:

9.2 Data Management Systems:

9.3 Data Security:

9.4 Intervention Training and Quality Control:

10.0 ANALYSIS

10.1 Sample size calculation

10.2 Statistical methods

10.3 Interim monitoring plan

11.0 LITERATURE CITED

Appendix 1: Description of Acute, Family Functioning and Outcome Measures and Other Scales

Appendix 2: Outcome time points, test instruments and age ranges

Appendix 4: Organizational Chart
1.0 INTRODUCTION AND HYPOTHESIS

1.1 Preliminary Studies

Despite preventative measures, traumatic brain injury (TBI) remains the leading cause of death and disability in children. While most pediatric treatment regimens for TBI to date are derived from adult studies, no therapeutic regimen has been particularly successful in improving outcome in children. In response to “priority areas” initiative for clinical research in Pediatric TBI by the National Institute of Health (NIH) [77] and our commitment, a Pilot Clinical Trial (PCT) was initiated and completed “to obtain preliminary data and conduct studies to support the rationale for a subsequent full-scale clinical trial” in children after severe TBI. The PCT utilized moderate hypothermia (HYPO) (32-33°C) as a model intervention, showed the safety and consortium performance of HYPO following severe TBI in children, and the application of novel pediatric specific initial and outcome assessments and were published [7].

Laboratory studies by the Principal Investigator (PI) and others [4,5,8,9,10,27,30,37,67] utilizing moderate HYPO (32-33°C) in mature and immature animals, successful Phase II and III clinical studies [28,68] in adult patients for 24 to 48 h after TBI, and a number of trials in children of HYPO following hypoxia-ischemic encephalopathy (HIE) brain injuries [43,44,90] have supported the efficacy of this intervention. The recently published trial of treatment with HYPO for HIE within 6 hours showed significant improvement in outcome, [87] particularly in mortality, as compared to severe disability. While the multi-center Phase III randomized controlled clinical trial (RCT) of moderate HYPO in adults was stopped early due to futility but not lack of efficacy, the secondary analysis did highlight that younger adult patients (< 40 y) tended toward improved outcome compared to older subjects [31]. This finding along with a trend toward improved outcomes with early cooling (< 6 hours) has resulted in a funded HYPO clinical trial specifically inclusive of patients ages 16-45 years and early pre-hospital cooling that has recently begun (G Clifton, personal communication). Because of this trend toward improvement in younger patients and since children have unique primary and secondary mechanisms of injury, pathophysiologic sequelae [11], and outcomes, [66], the lack of positive outcome in the adult study and the recently initiated study that have excluded children and adolescents cannot be extrapolated to children and provides the impetus for a pediatric trial. Additionally, in “Guidelines for the Acute Medical Management following Severe Traumatic Brain Injury in Infants, Children, and Adolescents”, [1], the conclusions on temperature regulation underscored the need for a study of the effect of HYPO in children following TBI.

Our goal has been to answer the question whether HYPO in children could improve outcome following severe TBI. The first step toward this goal was the PCT. The PCT successfully brought together a consortium/network of centers for the study of pediatric TBI and showed the safety of HYPO. It also importantly provided the initial evidence of the potential efficacy of HYPO in children following TBI, helped develop age-dependent pediatric specific outcomes measures for TBI, and standardized pediatric critical care management for these centers as well as highlighted the consistency and compliance of the participating centers utilizing HYPO as a model intervention. The data from the PCT [7] and its secondary analysis showed a trend toward decreased mortality and improved recovery potential in memory and learning and supports this larger study of the efficacy of this treatment on mortality and neurocognitive outcome using a highly focused battery of tests.

1.2 Hypotheses and Specific Aims

The Primary Hypothesis for this multicenter Phase III RCT is that induced early cooling (within 6 hours) with moderate HYPO (32-33°C) after severe TBI in children and maintained for a minimum of 48 h will improve mortality as compared to normothermia (NORM) (36.5-37.5°C).

Specific Aim 1 To determine the effect of early induced moderate HYPO (32-33°C) within 6 hours after severe TBI in children on mortality at 3 months post injury.

The Secondary Hypotheses are that early HYPO after severe TBI in children and maintained for a minimum of 48 hours:

1) will improve global function as measured by the Glasgow Outcome Scale (GOS)/GOS-Extended Pediatrics (GOS-EPeds) and neurocognitive status using measures of intellectual ability/development, memory and learning, and behavior at 6 and 12 months after injury;
2) will lessen intracranial hypertension and the intensity of therapy necessary for control of ICP.
Specific Aim 2 To determine the effect of early induced moderate HYPO (32-33°C) after severe TBI in children on global function and neurocognitive outcomes in the areas of intellectual ability/development, memory and learning, and behavior at 6 and 12 mos post injury.

Specific Aim 3 To determine the effect of early induced moderate HYPO after severe TBI in children of different age ranges (< 6y; 6-<16y; and 16-<18y) on mortality and 6 and 12 mos functional and neurocognitive outcomes.

Specific Aim 4 To determine the effect of early moderate HYPO after severe TBI in children on reducing intracranial hypertension and maintaining adequate cerebral perfusion pressure (CPP).

2.0 BACKGROUND AND SIGNIFICANCE

2.1 Overview
Trauma, especially head injury, remains a significant societal and public health problem in the United States (US), particularly in children, with an estimated incidence of 230/100,000 [53,55] affecting approximately 150,000 children annually (US Census Bureau estimate 3/31/98; www.census.gov/population/estimates). Although the vast majority of these injuries are mild and do not require hospitalization, approximately 10-15% of childhood TBI are severe and result in death or permanent brain damage [66]. TBI is a leading cause of death and disability in children [41] and is greater than all other causes combined [66]. With over 7000 deaths, there are approximately 20,000 children permanently disabled each year in the US [53-55] primarily due to the associated cognitive deficits, deficient academic achievement, motor impairments, psychiatric disturbances, and compromised adaptive behavior following severe TBI alone. Primary mechanisms of TBI vary with age and include: neonatal birth injuries, child abuse and falls in infants, bicycle, falls, and pedestrian collisions in preadolescents, and motor vehicle collisions and assaults in the adolescent age group. The sequelae of secondary mechanisms of brain injury likely add to the morbidity and mortality of TBI. The economic cost to society of children who suffer severe TBI with long-term or permanent disabilities is believed to exceed $30 billion per year, an estimated cost likely to continue to increase annually due to improved survival rates and the need for subsequent support including rehabilitation, outpatient care, and special education. While the societal financial burden is enormous and continues to grow [32, 41], the tremendous loss to families and society in terms of productivity for the victims and their caregivers has an even greater impact.

2.2 The Need for Pediatric Specific TBI Trials
Though it has been generally believed that the immature brain recovers more fully by virtue of its greater “neural plasticity,” studies now suggest that TBI in preschool age children (< 6 years), may actually result in higher mortality rates and more severe motor and cognitive deficits [50,59,61,66]. While improvements in morbidity and mortality outcomes have come with modern principles of pre-hospital care, rapid triage, and modern intensive care, there has been a relative stagnation in the outcome statistics in regard to mortality and functional outcome over the past 10 years [66]. The reasons for this lack of therapeutic improvement remain unclear but a change in thinking in regard to the management of children following TBI is necessary, particularly as it relates to the unique pediatric response to injury. This altered perspective requires an emphasis on “pediatric” clinical research that utilizes “pediatric” inclusion criteria and “pediatric” outcome measures to ensure comparable pediatric study groups rather than reliance on adult criteria and outcomes. To date, there has been a lack of pediatric specific RCTs looking at TBI. While this is likely due to multiple factors, impediments to pediatric clinical research in TBI include a lack of: an understanding of the unique secondary sequelae after pediatric TBI; a dedicated consortium/network of pediatric TBI research centers; reliable and valid measures of acute TBI severity; and age appropriate functional outcome assessments in infants and young children. While the long term goal of improved outcome in children following severe TBI may be facilitated by developing novel therapeutic and pediatric specific interventions to lessen the secondary injury cascade, pediatric specific clinical trials are necessary to better understand the impact that presently available therapies have on the developing brain. We therefore postulate that since children are unique in their response to injury, adult studies that have had only adult inclusion criteria and adult outcome data cannot be directly extrapolated to children. For these reasons, the assessment of therapeutic interventions in the pediatric age group needs to be performed in children in randomized controlled studies prior to becoming standard therapy and stratified by age. In addition, the literature would suggest the need to analyze the differences between the pediatric group by age < 6 y to ensure against age at injury effects in response to injury...
and treatment. This perspective has been further validated in the “Guidelines for the Acute Medical Management following Severe TBI in Infants, Children, and Adolescents” by the PI and others [1].

2.3 Unique Response to Injury and Treatment in Children

In approximately half of the cases of severe TBI in children, diffuse cerebral swelling (DCS) is the major radiographic and pathophysiologic finding [11]. DCS is the most common cause of brain death following severe TBI in both adults and children [15,70], and 3.5 times more common in children than adults, with up to 44% of children with severe TBI exhibiting this phenomenon [10,11,17,104]. The etiology of this difference between adults and children remains unclear. A number of hypotheses have been postulated and have included: cerebrovascular dysfunction, edema [19,20], disturbances of vascular reactivity and autoregulation [2,3,74,76,88], cerebral ischemia [2], altered CO2 vasoreactivity excitotoxicity, inflammation, free radical formation, lipid peroxidation, and early and late cell death [4,5,8,9,10,72,92]. Since the primary injury to the brain following TBI is believed not to be amenable to treatment, the goal of conventional management has been to prevent second insults and secondary brain injury. Since second insults that contribute to increased morbidity and mortality following TBI in children and adults include hypoxia, hypotension, and raised intracranial pressure (ICP) and intracranial hypertension, management guidelines for adult and pediatric patients with TBI include maintaining adequate mean arterial pressure (MAP), oxygenation, cerebral perfusion pressure (CPP), and aggressively treating raised ICP [1,97] using cerebrospinal fluid (CSF) drainage, hyperventilation, osmolar therapy using mannitol/ furosemide or hypertonic saline, and barbiturates [1,6]. Although aggressive management of severe TBI is believed to improve outcomes in children by lessening these second insults, conventional management has not been documented to be efficacious specifically in children and may indeed be associated with iatrogenic side effects [70,75]. At times, aggressive approach to ICP reduction may actually worsen brain injury (e.g.) hyperventilation leading to ischemia. While therapeutic interventions for severe TBI have been utilized for the past 20 y and many therapeutic adult trials have been attempted, no new additional treatment regimens have been shown to be particularly efficacious [21], nor specific to children.

2.4 Hypothermia Laboratory Studies

Moderate HYPO (32-33°C) is one therapy that has been shown to be consistently neuroprotective and efficacious in alleviating secondary brain injury and swelling typically seen following acute brain insults in laboratory studies in both adult and immature animal models of injury including TBI [22,26,30,34,58,61,67,73,81,93]. Moderate HYPO initiated immediately following experimental TBI in adult rats significantly reduced behavioral deficits [30] and lower temp (30°C) was more effective in mitigating these deficits than either 33°C or 36°C [30]. HYPO has also been shown to lessen mortality [27], mitigate behavioral deficits, and reduce histologic damage and contusion volume in other experimental TBI models [37]. Although the mechanisms by which HYPO preserves tissue, improves physiology, and/or enhances outcome have not been clearly established, it is thought that HYPO attenuates the numerous pathophysiologic responses that follow TBI or ischemic injury, particularly those derived from the biochemical cascade that potentiates secondary brain injury, by reducing excitotoxicity [22,49,80], preserving the integrity of the blood brain barrier [49,52] and diminishing the inflammatory-like response of the brain and neutrophil infiltration [100]. While these studies have for the most part been in adult animal models, we have shown significant improvements in cognitive/ memory function using the Morris Water Maze in our experimental models of TBI in the immature rat treated post injury with moderate HYPO. This improved functional effect was observed in different ages at injury (postnatal day [PND] 7 and 17 rats) [91], was long lasting and also importantly, for this trial, improved outcomes were observed even with a delay in the initiation of treatment [35] suggesting that delay in the initiation of HYPO treatment may still be efficacious in the immature.

2.5 Clinical Trials of Hypothermia for Neurologic Injury in Children including the PCT

Recently, positive clinical trials using HYPO as a neuroprotective therapy for different neurologic injuries besides TBI in children and adults including cardiac arrest and hypoxic ischemic encephalopathy (HIE) [18,87] have shown the efficacy of this therapy and have received strong recommendation for its use [78]. Specifically for children, in the pediatric HIE RCT of over 200 patients treated with 72 h of HYPO, a poor outcome (death or moderate or severe disability), was reduced from 62% to 44% when HYPO was started within 6 h. Mortality consisted of 14% of this 18% improvement. They concluded that whole body HYPO within 6 h of neurologic injury reduces the risk of death and disability in infants with moderate or severe HIE [87]. Clinical studies of HYPO in children following severe TBI have been lacking. We are aware of a pilot Phase III multicenter RCT of only 24 h of moderate HYPO in children and adolescents with severe TBI in progress in Canada and Europe (PI- James Hutchison). This trial started in October 1998 and has to date shown perfor-
mance and feasibility across centers with no increased complications in cooled patients. (J. Hutchison- Personal communication). To further our understanding in this area, we have previously evaluated the effect of HYPO on physiologic and biochemical parameters in infants and children [14,89]. Through the funding of the PCT (NIH PCT initiative PAR 97-103; http://grants.nih.gov/grants/guide/pa-files/PAR-97-103.html), along with our parallel single institution study of safety and performance, the results of a Phase II RCT for HYPO following severe TBI in children were published [7] showing the safety of HYPO and potential efficacy in children (0-17 y), even with a delay to initiation of therapy up to 24 h after admission. Further analysis (III.D.1.) has identified a population of patients (< 16 y, cooling within 6 h, and GCS 4-8) that would more likely benefit and serves as the basis of the present proposal with a reduction in mortality from 17% to 5%, a 12% difference, similar to the 14% difference found in HIE [87]. These preliminary data in the framework of the PCT and the successful consortium of pediatric trauma centers have helped to define, refine, and develop the approach to pediatric TBI clinical research, providing the design and rationale for a full scale RCT of HYPO. Since the completion of these trials, the next step, as defined by the NIH initiative following the “planning” phase, is to proceed to the full scale Phase III prospective RCT of moderate HYPO following severe TBI in children.

3.0 PRELIMINARY DATA

The following preliminary data comes from the published [7] results of the PCT (“HYPO 1”) and a parallel, concurrent, single institution study at Children’s Hospital of Pittsburgh (CHP) (“HYPO 2”) instituted to test the safety in excluded categories (e.g.) ages 13- 17 y. In this study, we were able to show the ability of the clinical centers to form a consortium, the safety and performance of HYPO following severe TBI in the proposed pediatric age groups, and the potential efficacy of HYPO as a therapeutic intervention for mortality and functional outcome. In addition, we have added further data in support of this application, in particular, a secondary analysis of children up to 16 y, within 6 h of injury, and excluding children with an admission GCS=3. This group of patients had the largest effect of the study treatment and serves as the basis for the proposed RCT. Lastly, we have collected the data of the reference population from the clinical sites for the proposed trial, confirming the ability to meet accrual for the power and sample size estimate necessary for the RCT.

3.1 Patient Accrual and Attrition by Aim

Two goals of the PCT were to identify strategies to maximize accrual and limit attrition for future RCTs in children. For the HYPO PCT, accrual of severely injured children was 29%. Of children meeting inclusion criteria, accrual was >90%. Reasons for exclusion included: unknown time of injury (child abuse), age >12y, and inability to obtain consent within 6 hours (unavailability of parents/ guardian or delay to transfer to study center). Throughout all of the study centers, there was only one refusal of consent of eligible patients from a non English speaking family. If the inclusion criteria were extended to children < 16 y and with emergency waiver of consent, an additional 25 patients would have been randomized for the PCT and accrual would have been 41%. Note: Of randomized patients, the 3 mo outcome assessment for the primary outcome variable and completion of the study was achieved in 98% and the 6 mo assessment, 96%. (Table 1) This data highlights that the sites for the planned RCT can achieve the requisite sample size and accrual with the proposed criteria, with minimal drop out, and excellent follow up and completion of the primary and secondary measures.

<p>| Table 1: Accrual and Completion of Outcome Assessments for the PCT |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|</p>
<table>
<thead>
<tr>
<th>Number Randomized</th>
<th>Total Severe TBI</th>
<th>Refused</th>
<th>Percent Randomized</th>
<th>Completed Follow up</th>
<th>%</th>
<th>Completed Follow up</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>48</td>
<td>165</td>
<td>1</td>
<td>29%</td>
<td>45</td>
<td>98%</td>
<td>44</td>
<td>96%</td>
</tr>
</tbody>
</table>

3.2 Treatment Performance

For all HYPO patients, the average time post-injury when cooling was initiated was 8.53 ± 6.7 h; average time post-injury in HYPO 1 = 4.62 ± 1.09 h and HYPO 2 = 15.03 ± 7.08 h. The average time from randomization to reaching target temp of 32-33°C was 13.78 ± 7.23 h for all HYPO patients and 9.57 ± 2.81 h and 20.78 ± 6.92 h for HYPO 1 and HYPO 2 respectively. The average time for re-warming to NORM was 16.67 ± 2.1 h. There were 26 patients with deviations from the target temp during the first 48 h of temp regulation in the multicenter study, equally distributed between groups, HYPO = 15, NORM = 10. There were approximately 2 deviations (>2°C) per patient, minimal and easily correctable.

To improve treatment performance and to test the effect of rapid cooling and slow rewarming as proposed in the present proposal, the Pittsburgh site instituted a more rapid cooling protocol. In addition to instituting external measures of cooling, “iced” (4°C) intravenous (IV) saline, 10- 20 ml/ kg over 30 min [78] was added...
at randomization. In 10 patients, the time to target temp from initiation of cooling was reduced by close to an hour to 4.07 ± 0.74 h from the PCT (4.95± 2.59 h). In addition, rewarming time was extended as per the proposed protocol (1ºC/ 12 hrs); the average time for re-warming to NORM in this more recent group was 48.75 ± 11.66 h, a marked increase from the PCT. There were no complications from this change in protocol including arrhythmias which did not occur in any patient. In contrast to the literature regarding rapid cooling with concern of hypotension, one patient became slightly hypertensive, which resolved upon reaching target temp. Importantly, there were no “rebounds” in ICP > 20 mm Hg as experienced in the PCT. These data preliminarily show that our alterations in the HYPO protocol with iced saline infusion and slow rewarming resulted in improved time to target temp and decreased incidence of rebound intracranial hypertension without an increase in complications.

3.3 Safety of HYPO Treatment Protocol (PCT and Single Institution)

3.3.1 Mortality:

From the results of the PCT, combined with the ongoing single-center randomized trial conducted in Pittsburgh, we identified a total of 50 subjects who had been randomly assigned to either HYPO (N=20) or NORM (N=30), who presented < 6 h after injury, were < 16 y, and a presenting GCS 4 - 8. Of these patients, five (17%) of the NORM patients and one (5%) of the HYPO patients did not survive (GOS=5) (p=.24 Fisher’s Exact Test). There was no loss to follow up for mortality at 3-mo. Additionally, examining the overall distribution of the GOS between the 2 therapies at 6-mo in these patients indicates relatively similar rates of those with poor outcome (severe disability and persistently vegetative state [GOS=3 and 4]) and good outcome (no disability and mild disability [GOS=1 and 2]) (Table 2) though there was a trend toward increased good outcomes (GOS= 1, 2) in the HYPO subjects. This relationship holds even when restricting the sample to younger children, (< 12 y). Our results indicate that there was a decrease in mortality and improved outcome in children up to 16 y with a GCS at presentation of 4- 8, treated with HYPO within 6 h of injury and serves as the basis for our primary and secondary outcome measures for the proposed Phase III RCT.

<table>
<thead>
<tr>
<th>Table 2: GOS by Treatment</th>
<th>GOS (6 mos post injury)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1/ 2  3/ 4  5</td>
</tr>
<tr>
<td>All Subjects (&lt;16 y)</td>
<td></td>
</tr>
<tr>
<td>NORM</td>
<td>62%  21%  17%</td>
</tr>
<tr>
<td>HYPO</td>
<td>70%  25%  5%</td>
</tr>
<tr>
<td>Subjects (&lt; 12 y)</td>
<td></td>
</tr>
<tr>
<td>NORM</td>
<td>65%  23%  12%</td>
</tr>
<tr>
<td>HYPO</td>
<td>70%  24%  6%</td>
</tr>
</tbody>
</table>

3.3.2 Complications:

Of the primary complications studied, there were no differences between treatment groups with respect to coagulopathy, arrhythmias, or infection. Average PT and PTT in HYPO 1 for HYPO patients were 14.09 ± 1.98 sec and 30.50 ± 3.37 sec, respectively, whereas the average PT and PTT for NORM were 13.51 ± 1.25 seconds and 29.17 ± 3.68 sec, respectively, demonstrating no difference between treatment groups. In HYPO 2, average PT and PTT for HYPO were 13.81 ± 1.64 sec and 30.24 ± 2.43 sec, respectively, whereas for NORM, mean PT and PTT were 12.95 ± 1.43 sec and 28.83 ± 4.28 sec, again demonstrating no difference between treatment groups. Thirteen patients (18%) exhibited abnormal coagulation parameters during their ICU course (NORM, n = 6; HYPO, n = 7). In both groups, there were equal numbers of incidents of early and delayed intracerebral hemorrhage (2/ group). One other coagulation anomaly noted was that 13 (18%) of 75 patients had a documented deep vein thrombosis requiring treatment, which was also not significantly elevated in either treatment group; note that this incidence may be lower than the actual incidence because only symptomatic children underwent diagnostic testing. There were 11 patients with infections in the acute treatment period (≤ 5 d after injury), 5 in the NORM group, and 6 in the HYPO group, the majority of which were pneumonia (n=8). Two patients had urinary tract infections (UTI) and 1 patient a ventriculitis. An additional 17 patients had late infections (equal number in both groups), most as a result of pneumonia (n=10), although late UTI, pancreatitis, bacteremia, and ventriculitis were also noted. In HYPO 2, there were 2 early infections (both pneumonia) and 15 late infections in 8 patients, again, equally distributed between the treatment groups (HYPO, n=4; NORM, n=4). In determining whether HYPO would lead to increased instances of cardiac arrhythmias, we found that there was an increased trend to arrhythmias in HYPO when compared with NORM. In HYPO 1, there were seven patients who had arrhythmias in the acute period: two in NORM and 5 in HYPO. In HYPO 2, there was 1 patient who had an arrhythmia, HYPO. Most (6 of 8 patients) of the “arrhythmias” had a sinus tachycardia that resolved with fluid administration with no change in the temp protocol. However, 2 patients had ventricular ectopy, one from each group and one that required rewarming before completion of the protocol; there was no associated hypotension or other complication. One other
complication of note was post-traumatic seizures that occurred in 8 patients, 4 in each study, 6 (75%) were in NORM. Two other patients underwent a decompressive craniectomy for intractable intracranial hypertension (HYPO, n=1; NORM, n=1). Of the primary complications studied, there were no differences between treatment groups with respect to coagulopathy, arrhythmia or infection. There were also no significant differences in the number of episodes of any of the secondary complications evaluated; anemia, aspiration, cardiac arrest, diabetes insipidus, extra-axial or intra-parenchymal hematoma, hyperglycemia, hypokalemia, hypotension, hypoxemia, hydrocephalus, pneumothorax, or pulmonary edema.

3.3.3 Intracranial Pressure (ICP) and Cerebral Perfusion Pressure (CPP)

Children treated with HYPO tended to have a lower ICP early in the study period (< 48 h) compared with NORM (HYPO, 16.4 ± 20.4 mm Hg; NORM, 18.3 ±18.3 mm Hg). Overall, there was no difference in mean ICP between the groups during the 5 d period (P = 0.37) except within the first 24 h, when ICP was significantly less (p=0.024). When comparing the treatments on an hourly basis, HYPO had a decreased mean hourly ICP in 106 of 120 h compared to NORM. The exception was after the cooling period during rewarming, when HYPO patients had a rebound elevation of ICP as compared to NORM for 10 - 12 h. Similarly, in HYPO 2, mean ICP during the acute period of monitoring (120 h) was lower in HYPO (HYPO, 9.9 ± 2.3 mm Hg; NORM, 13.1 ± 3.4 mm Hg), and HYPO had a decreased mean hourly ICP for 69 of 72 h, with a comparable rebound after rewarming for 4- 6 h. HYPO decreased the number of hours and percent time > 20 mm Hg as compared to NORM during the first 24- 48 h (10.1% vs. 15.2%), indicating decreased severity of intracranial hypertension during the cooling phase and overall during the acute phase (first 120 h). Lastly, NORM patients had a slight decreasing trend in ICP during the 5 d period while HYPO patients had a lower ICP early on and then exhibited a more level trend. HYPO showed less variability in ICP measurements than NORM.
4.0. STUDY DESIGN, ELIGIBILITY, AND CLINICAL PROTOCOLS
(Note: While this section provides a detailed study design and methods, further operational details can be found in the Manual of Operations)

4.1 Overview of Phase III Study- Moderate Hypothermia for Children Following TBI
The Primary design of this study is a multi-center Phase III randomized controlled clinical trial to evaluate the effect of moderate HYPO (32-33°C) treatment in conjunction with standardized head injury management, as compared to NORM, following severe TBI in children on mortality and functional outcome.

1. Inclusion/Exclusion Criteria:

   **Inclusion Criteria**
   1. Diagnosed Traumatic Brain Injury
   2. GCS <= 8 (post-resuscitation)
   3. Glasgow Motor Score < 6 (post-resuscitation)
   4. Age 0 – < 18 years (216 months)

   **Exclusion Criteria**
   1. Unavailable to initiate cooling within 6 h of injury
   2. Glasgow Coma Scale (GCS) score = 3 and abnormal brainstem function
   3. Normal initial CT scan (no blood, fracture, swelling, and/or shift)
   4. Penetrating brain injury
   5. No known mechanism of injury
   6. Unknown time of injury
   7. Uncorrectable coagulopathy (PT/PTT >16/40 sec, INR >1.7)
   8. Hypotensive episode (Systolic Blood Pressure < 5th percentile for age > 10 min)
   9. Documented Hypoxia episode (O2 saturation < 90% for > 30 min.)
   10. Pregnancy

(No inclusions or exclusions will be based on gender or ethnicity.)

4.2 Run-in Period:
Based on the experience of the PCT and the adult Phase III trial, a 3 mo run-in period will be used for all sites that have not had experience with induced hypothermia to assure high performing centers and to avoid jeopardizing patient safety and data quality. Using this objective mechanism, poorly-performing centers can be eliminated before they compromise the data, drain the budget, and distract the CC’s resources from high-performing centers. In addition, this provides for adequate practice of the protocols and optimizes performance of well-performing centers. Requirements to “pass” the run-in period will include receiving IRB approval, entry of 1 patient assigned to HYPO and managed according to protocol, and transfer of all necessary data to the DMAC. This patient’s data will not be included in the analysis but will be audited by the PI, MSM, OM, DMAC and SC for quality and protocol compliance. Data quality must meet 95% accuracy with no protocol violations to be certified to begin entering patients into the study. Any protocol deviation must have documentation supporting it as a specific response to individual clinical needs of the patient and may require further justification prior to acceptance. Failure to pass the audit will result in termination from the trial. Once a clinical center has passed the audit, all further randomized patients will be included in the analysis. Clinical centers may also be dropped from the trial for: 1) failure to randomize any patients during the 3 mo run-in period; 2) failure to meet expected accrual during any 6 mo period; 3) failure to complete follow up functional outcomes testing within the timeframe dictated by the study protocol. If extenuating circumstances, a clinical center may appeal a termination in writing to the PI, CC, and EAC.

4.3 Randomization Procedures:
At each clinical center, all severely closed head injured patients with a GCS 4-8, who are less than 18 y of age and within 6 h of injury who have no exclusion criteria will be eligible for randomization into the study.
4.3.1 Eligibility:
All patients with a closed head TBI admitted to the Emergency Department (ED) of the participating centers will be screened for study entry. Eligibility is assessed immediately post-resuscitation in the ED. Injury severity and time from injury will be determined by examination of the site PI, site coordinator, neurosurgical Co-I, intensivist Co-I, or ED attending physician pre-qualified by the PI of each center. The Site Coordinator is responsible for completing a Screening Form for each screened patient to ensure that qualifying patient populations are expeditiously entered and accurately collected at each institution.

The racial, gender, and ethnic characteristic of the proposed subject population will reflect the demographics of the surrounding areas of each clinical site and the patient population each medical center. No exclusion criterion will be based on race, ethnicity, or gender. There will be no exclusion of women or minorities in this study; however, pregnant or lactating women are not eligible because of the unknown effects of HYPO on an unborn child.

4.3.2 Time to cooling:
Time to the initiation of cooling will be defined as: the time from injury (as indicated by either paramedic or eyewitness report) to the time that cooling/warming measures are started and must begin BEFORE 6 hours.

4.3.3 Recruitment:
All of the clinical sites will be required to establish and maintain a call system so that a member of the research team will be available to evaluate all potential subjects as soon as possible. Informed consent will be obtained from the parents/legal guardians of the patient prior to randomization if the family is available. If the family is not available and in order to meet the 6 h time window, attempts at obtaining “emergency waiver of consent” will be made at each study site. Family members will have the option to withdraw from the study once they are available for consent.

CHP has obtained “emergency waiver of consent” for this study through the Institutional Review Board (IRB). Previously adverse, the IRB at University of Pittsburgh has been helpful in developing model applications and informed consents for Site IRB review. Data will be collected as to the numbers of patients that met inclusion criteria, were randomized but then withdrawn. Tracking of time of injury to initiation of cooling will be recorded to obtain an accurate time for initiation of the protocol.

4.3.4 Randomization:
Following hemodynamic and pulmonary stabilization in the ED, patients that meet inclusion criteria will be randomized to either HYPO or NORM for a minimum of 48 h. Randomization will occur using a Computer program system developed by the DMAC that is available 24 h daily to the site PIs and coordinators. After all necessary information is entered, the next treatment is selected from a table. In the event that randomization cannot occur via the web site, all sites will be provided with randomization envelopes provided by the DMAC.

Once the patient is randomized, all emergency treatment procedures that would otherwise be done will be carried out without interruption. A rectal temp probe will be placed and cooling will be initiated to those subjects randomized to hypothermia. Additional temp monitoring probes, such as esophageal, bladder and/or brain, may also be placed in addition to the rectal probe. Various methods can be used to cool the subject including the use of a temp-controlled cooling/warming blanket placed below the patient in order to reach the target core body temp for HYPO (32-33°C) or NORM (36.5-37.5°C), iced (4°C) intravenous fluids (10-20 ml/kg over 30 min), ice packs, and/or occasionally gastric lavage with iced saline. A second cooling blanket placed above the patient may also be useful during initial cooling. These aggressive measures result in a more rapid time to target temp. Once the patient reaches target, the temp is maintained at this level for a minimum of 48 h period; rewarming will be initiated at 48 hours if ICP is under control. If ICP is elevated, rewarming will begin 72 h after reaching target. Rewarming will be at a rate of 1°C every 12-24 h.

4.4 Conventional Management:
4.4.1 Acute Management Protocol:
All patients transported to the participating centers will be treated as per protocol for the Level I Trauma Center. Specific guidelines for head injury management in children are set by the “Guidelines for Acute Medical Management following Severe TBI in Infants, Children, and Adolescents”[1] and in numerous publications authored and co-authored by the PI[1,6,51] and the protocol detailed in the MOP. Management of severe TBI patients will follow the algorithms in these guidelines and those of the American College of Surg-
4.4.2 Evaluation in the Emergency Department:
All patients will be treated (as per ATLS/ PALS/ Pediatric Guidelines protocols) with the identification and treatment of all life-threatening injuries, endotracheal intubation as necessary (if not already done prior to admission), pulmonary and hemodynamic stabilization, initial injury severity assessment by the site PI (GCS, motor score), cervical spine series (AP, lateral, open mouth) as possible, CT scan of the head, and to the operating room (OR) as necessary for evacuation of mass lesion or other traumatic injury. An ICP monitor will be placed and other monitoring modalities will also be placed as indicated at the discretion of the site PI at the individual institutions.

4.4.3 Transfer to ICU or Operating Room:
The severe TBI protocol/ algorithm for basic physiologic support includes:
- the head of bed at 0-30°
- isotonic crystalloid (without glucose), colloid or blood products as indicated for fluid expansion to maintain an adequate central venous pressure (CVP)
- continuous monitoring of peripheral O2 saturation, mean arterial pressure (MAP), and pulse
- enteral or parenteral nutrition is initiated after 48 h from injury.

The primary goals of therapy in the ICU/ OR are to maintain:
- MAP at ± 2 SD for age,
- peripheral O2 saturation > 94%,
- ICP < 18 mm Hg (< 6 y), ≤ 20 mm Hg (≥ 6 y),
- CPP > 45 - 55 mm Hg if < 6 y, or 50- 60 mm Hg if ≥ 6y,
- Rectal temp at 36.5- 37.5°C (except those randomized to HYPO).

Patients may undergo another head CT scan after admission if concern of the presence of surgical intracranial mass lesions after the initial CT scan or immediately after any sudden, severe rise in ICP as per standard protocol.

4.4.4 ICP Monitoring and Management of Intracranial Hypertension:
All patients with a severe TBI and randomized to the study will have ICP monitoring with the use of a ventriculostomy and/or a fiberoptic ICP catheter. CPP measures have gained importance recently and may at times be used more often than ICP. In children, the present protocol maintains adequate age appropriate CPP and ICP and will be initiated for
- elevated ICP > 18 mm Hg (< 6y) or > 20 mm Hg (≥ 6y) for > 5 min
- reduced CPP < 45-55 mm Hg (<6y) or < 50-60 (≥ 6y) for > 5 min
- a CPP > 40 mm Hg may be acceptable for children < 2y
ICP measurements will be obtained continuously and will be recorded on an hourly basis.

a. Tiered ICP Protocol for ICP Elevations for > 5 Minutes  ** Note: this protocol, as a consensus algorithm, is in accordance with the “Guidelines for the Acute Medical Management following Severe TBI in Infants, Children, and Adolescents” [1], and is defined operationally in the MOP. The Tiered Protocol will be followed in a stepwise manner with failure of one therapy dictating escalation to the next highest therapy on the algorithm. An electronic version of the MOP will be made available [password protected] on the study website (http://www.CoolKidsTrial.org).

Tier 1:
- Head in a neutral position at 0-30° elevation
- Intermittent and/ or continuous ventricular drainage of CSF, (Note that if CSF is drained continuously, then it is recommended that ICP will be monitored by a second ICP monitor)
- Systemic neuromuscular paralysis (Pancuronium/ Vecuronium) with sedation or sedation alone with a continuous infusion of narcotic
CoolKids Trial
PTBIC: Hypothermia

Tier 2
- Mannitol, initially at 0.25 g/kg q 4-6 h as needed for ICP elevations, with escalation to 1/2 - 1 g/kg until serum osmolality ≥ 320 mOsm/L and/or
- Hypertonic Saline - Intermittent bolus doses of 3ml/kg and/or a continuous drip, initiated at 0.1-0.5 ml/kg, up to 1.0 ml/kg, titrated to effect to maintain serum osmolality ≤ 360 mOsm/L

Tier 3:
- Barbiturates, initially 5 mg/kg q 4-6 h and/or infusion of 1-5mg/kg/hr, with escalation to coma with 80-90% burst suppression by continuous EEG monitoring 10 second epochs. (Note: Pressors and further volume expansion are often required to maintain CVP, CPP and MAP during barbiturate coma)
- Decompressive craniectomy- Unilateral and/or temporal lobectomy or Bilateral Frontal w/ duraplasty
- Hyperventilation (see below)
- Lumbar drain

***The order in which tier 3 therapies are utilized may be varied by local preference/protocols and individualized for the specific patient. However it is essential that all centers have a clearly stated preferred sequence.

Data regarding ICP will be recorded up to 7 d of ICU data collection. The mean, median and percent time of ICP elevations > 18, or 20 mm Hg for the different age groups will be calculated during the treatment period to determine the differences between study groups. Previously [59], it has been shown that a higher percent time of ICP elevation was associated with a poor outcome with increased mortality.

b. Controlled Ventilation and PaCO2 Management: Hyperventilation in the management of TBI has been avoided due to the concern that chronic hyperventilation may result in cerebral ischemia due to metabolically induced arteriolar constriction [75].
- PaCO2 will be routinely maintained at 35-40 mm Hg (4.7-5.3 kPa) during the study period by adjusting the ventilator rate and tidal volumes.
- To maintain O2 saturation greater than 94% at all times, FiO2 and PEEP (< 15 mmHg) will be adjusted.
- For periods of intracranial hypertension, moderate hyperventilation to PaCO2 30-34 mmHg (4-4.5 kPa) may be needed and used as third tier therapy. Measurement of SjO2 or brain tissue PO2 is recommended if hyperventilation is undertaken.
- Severe hyperventilation to lower PaCO2 < 30 mmHg (< 4 kPa) may only be used in an acute crisis situation to temporarily lower ICP until other measures can be instituted [1,86].

4.4.5 Fluids and Electrolytes
Electrolytes, serum osmolality, and arterial blood gases will be measured every 6 hours throughout the protocol. Magnesium, potassium and phosphate will all be maintained in the normal range. Laboratories are repeated as frequently as clinically indicated.

Intravenous “maintenance fluid” solutions in the first 48 h are to be crystalloid, either normal saline or other isotonic balanced salt solutions at appropriate maintenance for body weight. Dextrose solutions should be avoided unless:

A dextrose solution (D5W) should be used in the first 48 hours ONLY when:

a) Children < 2 years – Serum glucose < 80 mg/dl (4.4 mmol/L)
b) Children ≥ 2 years – Serum glucose < 70 mg/dl (3.9 mmol/L)

HYPO may produce mild hyperglycemia with usual dextrose infusions, probably due to decreased metabolic rate. Hyperglycemia is to be controlled with insulin infusion or sliding scale as standard practice at the clinical site. There should be close monitoring of serum glucose levels once glucose-containing solutions are introduced.

Intravenous solutions may have glucose in them after 48 h and patients are begun on parental or jejunal feedings 48 h after injury and subsequent management will be the same as for the control NORM patients. Indications for re-warming prior to the 48 h window include:
- ventricular arrhythmias unresponsive to fluids (atrial or ventricular tachycardia were experienced early in the PCT but were responsive to fluid boluses)
- delayed intracranial hemorrhage
- intra-abdominal or intra-thoracic bleeding.

4.4.6 Discharge:
Discharge from the ICU will be based on hemodynamic stability of pulmonary status as well as adequate control of intracranial hypertension as determined by the site PI.

On the general neurosurgical unit as per routine, TBI patients are evaluated in consultation by physicians from Physical Medicine and Rehabilitation for the decision for placement and/or discharge from the acute care unit. The length of stay in the acute care facility will be documented to evaluate differences in treatment regimens, mechanisms of injury, age and severity.

5.0 HYPOTHERMIA PROTOCOL

5.1 Cooling:
The goal of the cooling protocol is rapid cooling and slow rewarming. The target temp should be reached within 2 hours of randomization and is to be maintained at 32-33°C for the HYPO and 36.5-37.5°C for NORM patients. Once the patient is randomized to either NORM or HYPO, a dedicated temp control unit guided by a rectal probe will be used to facilitate the cooling (or warming) as needed in addition to routine measures listed below.

Recommended cooling protocol must be initiated immediately upon randomization to the protocol.

Measures that can be employed include:
1. Cooling unit and blanket set to target temperature
2. Iced (4°C) intravenous (IV) saline, 20-30 cc / kg over 30 min; repeat x 2 as needed
3. Gastric lavage as needed
4. Sedation with paralysis is standard in all patients with severe TBI and is continued throughout the 48 h cooling and re-warming period to avoid shivering.
5. Surface ice packs and/or a second cooling blanket above the patient
6. Cool ventilator air
7. Warm towels and fans

5.2 Rewarming:
Following a minimum of 48 h of cooling, re-warming is initiated by increasing the temp on the cooling system to achieve a temperature change of 1°C every 12-24 hours so as to reach NORM in approximately 48-72 hours depending on response of ICP. Slower re-warming may be necessary due to intracranial hypertension.

If ICP is elevated at 48 hours, hold rewarming for an additional 24 hours and begin rewarming 72 hours after reaching target. If ICP becomes elevated during rewarming, slow rewarming rate to 1°C every 24-36 hours and institute other measures for ICP control. The goal is to rewarm the patient to a minimum of 36.5°C. Maintain temperature 36.5-37.5°C.

If, despite all first and second tier therapies, the patient is not able to be rewarmed to > 35°C within 72 hours of commencing rewarming, a decompressive craniectomy is strongly recommended. Meticulous management during this phase is critical. Instability may worsen brain injury and outcome. Therefore the rate of rewarming should be guided by physiology (ICP, MAP, CPP) first and time second. Hypotension during rewarming should be managed aggressively with intravenous fluids and vasoconstrictors. Any increase in ICP should also be managed rapidly by the algorithm and concurrently the rate of rewarming should be slowed.

5.3 Normothermia
Normothermic patients are to be kept 36.5-37.5°C, and the lower end of this range is recommended. Hyperthermia should be prevented and must be treated aggressively. Active cooling measures (cold saline
IV, cooling blanket, ice packs, etc) will usually be required to maintain normothermia. Passively re-warm patient to ≥ 36.5°C if temperature drops, preferably with blanket cover but be more aggressive if this does not work. Rewarm no quicker than 1°C every 3-4 hours once temp is below 36.0°C.

5.4 Compliance with Protocol:
Expected breaches of protocol may require removal of the patient from treatment. These will include:
- major injuries discovered after randomization requiring removal from cooling;
- atrial or ventricular cardiac arrhythmias;
- bleeding diathesis with an intracerebral or other sustained hemorrhage;
- inability to cool within the first 8 h after randomization;
- inability to maintain the projected temp for the full 48 h.

The instances of breaches and/or complications during the study period will be recorded and assessed as to site performance.

5.5 After Study Treatment:
Often due to the severity of injury, many patients will require rehabilitative care in the chronic period. Details of rehabilitation management will not be prospectively kept for each patient, but a final report from the rehabilitation facility will be entered into the database for each patient as part of their outcome assessment. Communication with the rehabilitative staff is essential to ensure that medications and other potential interventions are well defined.

6.0 OUTCOME ASSESSMENT TO DETERMINE EFFICACY OF HYPOTHERMIA FOR SEVERE TBI
6.1 Primary Outcome Measures: Mortality:
The primary outcome measure will be mortality and will be assessed acutely and at 3 months post severe TBI after treatment with HYPO for 48 hours vs. NORM.

6.2 Secondary Outcome Measures:
The secondary outcome measures will encompass the variables of global function, intellectual ability, memory and learning, and behavior and will be administered at 6 and 12 months to compare the sequelae and pattern of recovery of severe TBI after treatment with HYPO. These measures are described in detail (Appendix 1). Children who are not native English speakers will not be given any neurocognitive tests. Parents will participate in behavior surveys and questionnaires provided translations are available. For example, in the PCT we obtained Spanish translations for these instruments.

6.3 Rationale for Selection of Outcome Measures:
Mortality was chosen as the primary outcome measure based on the results from our preliminary data and the literature showing the largest effect of HYPO on mortality in pediatric brain injury. In our preliminary data, we have been able to show the reliability and validity of the GOS/ GOS- E Peds for its use in assessing global pediatric outcome. As previously noted, in the PCT, we were able to obtain 6 month outcomes in 96% of the patients at all centers and our outcome results identified consistent results with respect to tests of memory and learning, suggesting this area should be included in a focused outcome battery.

In contrast to adult outcome measures, and because of necessary developmental considerations, there is no IQ measure that spans the age range of this study. To address this issue, we will use normative information and compute a z-score for each IQ/developmental variable so that the underlying construct of intellectual ability can be compared across the age ranges [38]. All outcomes testing will be completed by technicians and/or neuropsychologists blinded to treatment group status.

6.4 Selection of the Outcome Time-points:
The primary outcome measure, mortality, will be assessed throughout the “acute” period and conclude at 3 months post injury. This allows for an objective measure of outcome within a time frame that the patient remains under the care of the neurosurgical service. The only other addition to the assessment battery for the acute period will include a retrospective assessment of baseline premorbid behavior and family function as well as a comprehensive review of medical and educational history. Sensitive to patient and family burden,
we have eliminated the 3-month outcome assessment with the exception of the primary outcome measure, mortality and GOS/GOS-E peds.

For the secondary outcome measures, testing at the 6- and 12-month outcome points will include a focused cognitive battery. Our PCT demonstrated differing patterns of outcome at the 6 month assessment in that recovery patterns diverged for the treatment groups (HYPO vs. NORM) at 6 months post injury. In addition, coupled with the literature that developmental differences in recovery for children of different ages (as discussed earlier) indicates that several time-points during the active recovery period would optimize the information obtained regarding the effect of treatment on recovery and the suggestion that 12 months marks the end of the most active recovery period [103], we have chosen the 12-month post injury as the specific endpoint of the secondary outcomes analysis. Secondary analyses will not only include differential results of the outcome testing at each time-point but also a comparison of the recovery rate over time. In summary, for this RCT we propose a brief retrospective assessment of behavior and family function at the acute injury period, assessment of the primary outcome measure at 3 months and then global functional assessment and neurocognitive assessment of intellectual ability, memory and learning, and behavior (including assessment of family function) at the 6- and 12-month time points (Appendix 2).

6.5 Description of the Outcomes Test Battery:

6.5.1 Global measures:

GOS/ GOS-E Peds: The GOS is the standard outcome measure in adult TBI studies and are categorical outcome scales that have wide acceptance, established validity, and moderate inter-rater reliability (kappa of .77). Despite its limitations in children [62], the GOS and the GOS- E Peds will be used as a functional outcome measure. Consistent with its use in adult studies of TBI, the primary outcome analysis will dichotomize the GOS categories of SD/PVS/D as a poor or unfavorable outcome and GR/MD as a good or satisfactory outcome as well as analyzing all five categories. In addition, we will secondarily apply the eight GOS-E Peds categories to track recovery of function over time and compare recovery curves between HYPO and NORM.

6.5.2 Cognition and Behavior:

The focused neuropsychological tests and behavior measures are based according to four categories (e.g.) IQ, memory and learning, behavior, and age of administration. Validity and reliability information on each instrument is included in the MOP. Measures were chosen based on our experience during the PCT and relevance to educational and social functioning. The estimated total time (parents): initial hospitalization is 40 min and the total time (parents) at 6 and 12 mo < 45 min; Total time (subjects) < 3 y is 40 min, 3 - 6 y 60 min, and for 6- <18y < 80 min. Rest breaks will be provided.

6.6 Baseline Procedures:

Baseline assessment of premorbid status is completed while on the acute ward prior to transfer to rehabilitation or discharge. Developmental history will be obtained for all children to assess the child's pre-injury functioning. Family function will be evaluated using the General Functioning Scale of the McMaster Family Assessment Device [23]. The parent and/or caregiver will complete the PRS to assess the pre-injury level of behavior and emotional status.

6.7 Procedures to Mitigate Attrition in the Outcome Phase:

In the PCT, efforts by the investigators and outcome staff to establish rapport with the family during the initial hospitalization enhanced compliance with follow-up. In the PCT, we obtained 92% participation of survivors in the outcome assessments in the randomized groups (PCT: Aim 1) and 81 % of the non-randomized, outcomes only severe TBI patients (PCT: Aim 3). We expect to exceed these percentages with the addition of the Outcomes Monitor (OM) for oversight of the Clinical Centers. Patients unable to return for follow-up testing within the time windows, regardless of the reason, will be evaluated at home or at school provided that the parents give permission. Providing feedback to the parents, reimbursement for travel expenses as possible, written reports and consultation (without charge) concerning the child’s school placement, and assistance in referrals for medical and psychiatric services will directly benefit the child and enhance participation. Central monitoring of all follow-up examinations by the DMAC will alert the staff at each site of patients entering the window and provide assistance to facilitate completion of examinations in complicated cases. Based on the experience in the PCT, the following arrangements will be implemented to enhance compliance with follow-up.

a. Study Nurse: Early introduction to the family of the designated “Study Nurse” at each center by the patient's neurosurgeon or intensivist (Site PI) while the patient is hospitalized provides an oppor-
tunity to establish rapport with the family and to explain the project and timeline of treatment, acute care, and outcome assessments. The study nurse maintains contact with the patient and family through monthly telephone calls and the sending of birthday and holiday greeting cards.

b. Patient Tracking System: The data management system includes a Patient Tracking Report which indicates upcoming appointments to be scheduled each month and their associated follow-up windows as well as dates of completed visits. Appointment letters are followed by telephone calls. Based on HIPAA regulations, sites will be notified of patient's upcoming appointments by Study ID number and the site will be responsible for coordinating specific appointments for outcome assessment.

c. Follow-up Schedule: To facilitate compliance with follow-up, all outcome measures will be scheduled whenever possible to coincide with neurosurgery clinic visits at the participating centers and completed by 3 mo (+ 2 wks) for the primary outcome measure, mortality, and 6 (+ 1) month and 12 (+ 1) month follow-up examinations for the secondary outcome measures. The window surrounding each follow-up interval will provide flexibility in accommodating the family's schedule. Incorporating the experience of the Phase III trial of HYPO in adults with severe TBI [85], it was an over 90% follow-up for both 3 and 6 month outcomes assessments in the randomized patients.

d. Reimbursement: To provide an incentive to participate and to defray expenses, we will pay all subjects for participation. Families will be paid $25 for completing the baseline portion of the study. Payments for the 6-and 12-mos evaluations will be paid on a graduated scale at $50 and $75, respectively. Subjects and families who complete the entire study will be paid a total of $150.

e. Home Visits: Home visits will be arranged for patients unable to return to the study center for follow-up.

f. Feedback: The neuropsychologist will discuss the purposes of the assessment procedures with the family, describe the results of the tests to the patient and family at the time of participation in this phase of the project, provide general feedback concerning progress as reflected by the neurobehavioral findings, and offer a written report at no charge.

g. Non English Speaking: Due to the concern of reliable and valid Non English translations for the neuro-cognitive outcome measures, Non English speaking subjects will be excluded from the secondary analysis except through tests given by questionnaires and surveys and only when translators are available.

6.8 Mitigation of Drug Effects:

Our experience in pediatric outcome research indicates that 13.5% of TBI patients were taking prescribed psychoactive drugs at 3 mos post-injury, including 6.9% who were taking anticonvulsants (AED) and are seriously monitored by their physicians for toxicity. The neuropsychological performance of AED-treated, non-medicated severe TBI patients showed slower motor speed on Grooved Pegboard as the only difference in neuropsychological performance, consistent with a study of epileptic children that found minimal effects of AED monotherapy on reaction time and attention provided serum levels were in the therapeutic range. All medications and doses at each endpoint in the proposed project are documented. Scientific concern about measuring cognitive and behavioral effects of brain insult uncontaminated by medication is balanced by ethical and medical issues surrounding the need for the medications that frequently have to be given for a period of weeks to be effective (e.g., serotonin reuptake inhibitors) and have a long washout period [57]. Consequently, we will: (1) encourage families to have their child monitored carefully for all psychoactive medications; and (2) check for adverse effects at follow-up visits.

6.9 Testability of Patients:

Since mortality can be completed by interviewing the parent or guardian at a standard post discharge follow up visit to the clinic or by telephone, we expect complete and accurate data for the primary outcome measure. For the GOS/ GOS-E Peds, it too can be obtained by interview and in patients even with severe cognitive, behavioral, or motor deficits. These scales can also be administered by telephone if required. This latter method of data collection will be used as a last resort when the family is unavailable for a home visit and can-
not return to the clinical center. Other outcome measures completed by the parent (e.g. Conner’s PRS) can be completed while the Outcomes Technician tests the child. Consequently, the time used to complete the functional and behavior measures does not prolong the patient’s total assessment duration. Based on our experience in the neurocognitive follow-up of children in the PCT, of adults with severe TBI in the Traumatic Coma Data Bank [59] and the adult Phase III RCT of HYPO [85], we anticipate that 25- 33% of the severely injured children in this project will be unable to complete portions of the 6 and 12 mo assessments. Procedures have been developed during the secondary analysis for the data of children with missing test scores.

6.10. Supervision and Blinded Status of Outcome Staff:
The supervising site neuropsychologist will be blind to treatment status, is responsible for the quality of the outcome data, and is to certify that the data are accurate and complete. They are to supervise the Outcomes Technicians to make sure that subjects are recalled and examined at the proper time, that subjects are assessed by blinded examiners, and that outcome measures are administered properly. They check the demographic and medical history forms for completeness and coding errors. The neuropsychologist ensures that data packets are mailed to the OM within one week of the evaluation date. The supervising neuropsychologist reviews and approves all neuropsychological reports sent to parents. A psychometrician, blind to the experimental group of each patient and thoroughly trained in the administration of neuropsychological tests to head-injured children, will complete the assessment battery.

6.11. Scoring of the GOS/ GOS-E Peds:
Training and certification procedures for the GOS/ GOS-E Peds are included in MOP and the Outcomes Training Manual. During the outcome phase, the OM will review GOS interview notes and test results used to make the GOS rating and also co-score every 5th GOS/ GOS-E Peds protocol to prevent examiner drift. Immediate contact will be made with the site should problems become evident.

6.12. Scoring of the Neuropsychological Tests:
Packets containing the original test protocols will be mailed to the CC/ Outcomes Oversight Center (OOC) for scoring and quality control procedures. The OOC and OM will score all the neuropsychological instruments from all sites to maintain consistency and accuracy and be responsible for reviewing each for non-standard or inaccurate test administration, providing further training as required.

7.0 SAFETY MONITORING and RADIOLOGY MONITORING

7.1 Medical Safety Monitor
The determinants of safety for children will be determined by the number of serious adverse events (SAE) that occur during the treatment period and will be monitored by the DSMB and the Medical Safety Monitor (MSM). Each site and the overall study will be guided by the Data Safety Monitoring Plan(s) individually implemented at each site and by the CC for study oversight. The published complications that can occur following TBI and/or its treatment with HYPO and will be included as an AE are pneumonia, sepsis, cardiac arrhythmias, hemorrhage, and coagulopathy. The decision for whether an AE is serious is at the discretion of the site PI and be reported on the AE form.

Although there were no statistical differences in the rate of these complications in the PCT, a record of each laboratory study for each complication will be kept to calculate the complication rate for each patient. Life-threatening SAE, adverse events/ complications, accrual and mortality rates will be monitored by the PI and the DMAC on a continuous basis. The data from each clinical center will be entered directly via the study website to the DMAC at the time of patient entry and at the occurrence of any SAE. As a standard, the DMAC will provide bi monthly reports to the MSM and every 25 patients to the DSMB for each of the following data items: mortality, incidence of SAE, and 6 and 12 months GOS/ GOS-E Peds. Additionally, blinded data provided monthly to the PI, MSM, and the DSMB from the DMAC will include:

1) mortality and complication rates,
2) follow-up rates,
3) hourly temp measurements of all randomized patients for the first 72 h,
4) time to protocol cooling,
5) patient accrual rates,
6) time from admission to randomization for each patient.
7.2 **Efficacy on ICP Elevations:**
To determine the effect of HYPO on ICP elevations, hourly ICP and physiologic data in the intensive care unit (ICU) during the acute clinical course will be collected and analyzed. The incidence of ICP elevations for age, the percent time of elevated ICP, and average ICP over the study period will be calculated for each patient.

7.3 **Radiology Monitor**
Radiologic images (e.g.) CT Head, from all clinical sites will be DICOM compliant and all personal health information (PHI) will be stripped out per HIPAA requirements. All images will be sent to the CC electronically for central analysis. The DMAC will maintain a repository of all images on a separate server behind the DMAC firewall. Images will be uploaded directly to this server via secure FTP from the clinical site. The Radiology Monitor (RM) will receive an automated email message each time new scans are uploaded to the server and are ready for his review. The RM will then grade and categorize each image and enter the completed Radiology form into the project database via MATRIX.

8.0 **ADMINISTRATIVE AND STUDY OVERSIGHT**

8.1 **Trial Oversight and Coordinating Center (CC):**
There will be 6 areas of oversight for the Phase III RCT: As PI and through the CC, Dr. Adelson will have direct and overall oversight and ultimate responsibility of the RCT of the clinical study centers, and the 4 other Centers of Oversight. These “Oversight Centers” include:

8.1.1. **Clinical Oversight Center:**
The clinical centers have been identified through their expressed interest in participating and their ability to provide adequate patient numbers to the study. The PI, the SC, the MSM and the Steering Committee will have overall responsibility for the oversight of the clinical implementation of the HYPO protocol at each of the clinical centers. The PI will primarily oversee study progression, implementation and center performance and compliance. The SC and the MSM will primarily oversee the day to day clinical care of the patients entered into the study throughout all of the centers and adherence to standard protocols. The DMAC will provide daily updates to the SC of those patients entered in the study and management. The DMAC will provide weekly to monthly reports to the MSM and will work in conjunction with the EAC, DMAC and DSMB to ensure adherence and compliance to the study protocols.

8.1.2 **The Steering Committee:**
The Steering Committee will consist of the Study PI, Dr. Adelson, the NIH Scientific Advisor Dr. Hirtz, Ms. Brown (SC), and Drs. Wisniewski (Statistics and Data Management) and Beers (Outcomes). The specific duties include the general design and conduct of the study, the scientific and clinical protocol, review of the essential study documents including the MOP and data collection forms, review of data collection and practices, changes in study producers, appointments to subcommittees, review of study progress, review of clinical site performance and review and implementation of recommendations from the DSMB.

8.1.3 **Neuropsychological Outcomes Center (NOC):**
The PI, Dr. Beers as the OM and the Outcomes Advisory Center (OAC) will primarily oversee the outcomes assessment performance and adherence to the standard testing protocols. The OAC is composed of the OM, external Neuropsychology Consultant, and senior neuropsychologist(s) from key sites. The NOC will review the training and certification procedures, oversee all outcome processes, and supervise local sites on an as needed basis. The NOC will meet at least twice a year, but more frequently if the need arises, through electronic mail, teleconference or in person meetings. The OM will make periodic visits to each site to observe follow-up evaluations, examine records, and assess whether the conditions of the protocol have been met (e.g.) blinded status. Some follow-up evaluations will be scheduled to coincide with these visits. The OM will work with the OAC to oversee outcomes assessment protocols and performance.

8.1.5 **Safety Oversight Center:**
The study PI, the MSM, and DSMB will primarily oversee the ongoing safety of the RCT.

8.1.5.1 **Data Safety Monitoring Board (DSMB):**
An independent DSMB will be formed to assure subject safety and human subject protection policies are followed, recommend protocol modification, recommend recruitment initiation, and monitor all aspects of the study. The DSMB will be formed by the NIH as per policy for Phase III trials and identified prior to the start of
the study. The PI will work with the NIH to identify members of the DSMB that will likely include experts in the
treatment of TBI, biostatistics, and ethics. Once the DSMB has been identified, the IRB at each site will be
notified of the members of the DSMB and specific responsibilities. At its initial meeting, the DSMB will review
the protocol (e.g., interventions, data collection, sample size determination, and monitoring plan) and the official
interim monitoring approach of the study and recommend changes. The DMAC will work with the MSM
and DSMB to assure that the interim monitoring approach best suits the proposed study. The DSMB will then
meet on a semi-annual basis either in person or via conference call, more or less frequently based on the
decision of the members of the DSMB and the NIH, and review the progress of the study, review interim re-
ports (e.g., recruitment by race/ethnicity at each site, protocol deviations, intervention adherence, adverse
events, site visit summaries, data quality, attrition, descriptive characteristics of the population at baseline by
intervention group, and efficacy of the intervention) and discuss any concerns with the PI. The members of
the DSMB along with the PI, the Statistician, and the SC will be in attendance at these meetings. If it be-
comes clear that one treatment is clearly superior to the other, it is not ethical to continue enrolling partici-
pants into the trial. The overall alpha-level for each interim report will be adjusted to maintain an overall type I
error rate of .05 using group sequential methods. To avoid potential bias, research staff (e.g., nurse coordina-
tors, neuropsychologists, neurosurgeons) will not review these results.

8.1.6 Communication between Centers:

The channels of communication are particularly important in a multi-center study. The investigators in the
PCT developed a collaborative and communicative network through the Internet, email, fax, phone and in
person meetings at the major neurosurgical and trauma meetings over the past 7 y to discuss, plan, revise
and formulate an optimal approach to the investigation of acute TBI in children. These lines of communication
will continue and be further developed in the growth of the pediatric consortium/ network for the Phase III
RCT and future collaborative research. The DMAC also has proven experience in the development and
maintenance of communication systems for multi-center trials. The RCT web site
(http://www.CoolKidsTrial.org) will serve as the information dissemination hub for this project and will be used
for all day-to-day communications among the members of the trial. The RCT Website will be comprised of
two main areas, an area open to the public and a private area. The information contained on the public
website will be targeted for the general public, those interested in pediatric TBI (e.g., parents of patients) and
external members of the research community. The private area of the RCT website will be restricted to the
study investigators, research staff and committee members and will be used to enhance the communication,
collaboration, and management among the study sites. The private area involves individual web panels,
each representing a single feature or tool (e.g., email, web-based data entry, Help Desk, Calendar, etc.),
which will vary in presentation and tool availability based on a user’s defined role (e.g., investigator, neuro-
psychologist, etc.) and group associations (e.g., Publications Subcommittee). We believe that a web panel
that mimics MSN Messenger will encourage real-time correspondence among collaborating investigators and
other personnel. We anticipate that this option will also encourage closer communication between the CC
and the sites. This site will be monitored daily by the DMAC and SC to maintain and enhance communication
between the PI and the sites. The tools available on the RCT website include:

a. Directory: A directory of each individual’s contact information will be available with a directory web panel
of the most frequently used contacts for each user and a link to the complete project directory.
b. Calendar: A calendar system will be included where study events (e.g., EAC or DSMB conference call)
may be scheduled or modified from multiple locations and by multiple project personnel. The calendar web
panel will list the next several meetings/events relevant to the current user and will provide a link to the com-
plete calendar of events.
c. Committee Resources: Committee resources will be accessible from a single web panel and will list
committees (e.g., Outcomes Committee) or groups (e.g., neuropsychologists), based on a user’s members-
ship. The committee area is designed to organize and provide easy access to information including meeting
agendas, minutes, and manuscripts by committee or group. In addition, specialized tracking systems may be
developed to aid specific committees. To assist the Publications Subcommittee, a web-based Publications
and Presentations Monitoring System (P&P) will be used to monitor the progress of manuscripts through to
publication. The P&P will provide all investigators with a standard process for the submission, management,
and refinement of concepts as progress is made toward publication or presentation. After concepts are ap-
proved by the P&P committee, a working group identification number is assigned to the submission, which will
begin the process of documenting and monitoring the progress of the working group. Details such as modifi-
cations to working group authors, the DMAC statisticians assigned, the stage or status of the manuscript, and
general correspondence will all be recorded via the P&P system.

d. **Document Sharing:** Document sharing areas will be available for the sharing of manuscripts, operations memos, data collection forms, and training materials.

e. **Reports:** Several types of reports will be provided to the study investigators through a protected area of the RCT Website and will include static reports updated on a routine schedule, dynamic reports generated from a database at the time of request, and user-configurable reports that are customized to manage the data in the database. Other reports will be used to summarize the progress the study, including recruitment and retention, schedule of upcoming interviews, quality of the data and procedures for a given protocol.

f. **RCT Update:** A RCT Update will be posted weekly via email to all study personnel. The RCT Update will keep study personnel informed of project activities by briefly summarizing all study activities during the course of the past week as well as providing reminders for upcoming deadlines (e.g., review of the manuscript from the Publications Subcommittee is due by next Wednesday) or activities.

g. **Help Desk:** A Help Desk/Frequently Asked Questions (FAQ) web panel will be used to assist researchers when attempting to obtain answers to questions (e.g., clarification on inclusion/exclusion criteria) or to request assistance (e.g., register IP for a new computer).

h. **Training, Orientation and Reference Materials:** A web panel, tailored to the user, will be dedicated for easy access to training, orientation and reference materials including the MOP for all researchers. For example, a neurosurgeon would access the HYPO protocol training and documentation while a neuropsychologist would have access to training and documentation of the administration of the outcome measures.

i. **Data Management:** A web panel will display data management tools for staff authorized to access the web-based data management system.

9. **DATA COLLECTION, MANAGEMENT, AND OVERSIGHT** (Full Details in MOP: III Data Management Administrative Center)

9.1 **Data Management Center (DMAC) - Administrative Overview:**

The DMAC in Pittsburgh is already well-versed in the HYPO protocol as CC and DMAC for the PCT and as a study site for the Phase II and III adult trials for HYPO. Administrative arrangements for this RCT are based on the established expertise of Drs. Adelson, Beers, and Wisniewski and relative ease and security of data transmission by internet and e-mail.

9.2 **Data Management Systems:**

A contemporary data management system will be used for this trial. The Epidemiology Data Center (EDC) at the University of Pittsburgh, Graduate School of Public Health has a long history of utilizing state-of-the-art data management tools. This includes web-based data entry systems, optical recognition systems and interactive voice recognition systems (IVR). The MATRIX data management system is a Web-based communications and data entry system. The core of this data management and communications system is a study Web site, which includes public and private areas, a restricted shared document section, and a system area. Public web areas include items such as a home page with the project description, a bibliography page, and current news regarding the study. The private Web site areas include items such as a personnel directory (including individual and group electronic mail, telephone/voice mail and U.S. mail information) and additional dynamic utilities such as a calendar in a month-at-a-glance format, which can provide information regarding scheduled events such as conference calls. The Shared Document section of the Web site is a restricted area for study-related manuscripts, operations memos, training documentation, and news bulletins. Password authentication and Internet Protocol address (IP) verification via the WWW server will be necessary to access the private area. The PNTC at the Children’s Hospital of Pittsburgh is a model site for a multi-project, multi-site collaborative research program ([http://www.edc.gsp.h.pitt.edu/pntc/](http://www.edc.gsp.h.pitt.edu/pntc/)) and for multicenter RCT. The Data Management panel of the Web site is the interface for the MATRIX Data Management System. MATRIX is a data management system (DMS) designed and developed at the EDC to manage multiple medical research projects and is a complete Web-based DMS built on Internet and Oracle RDBMS technologies. MATRIX exploits the intuitive format of Internet/Web technologies providing an easy to use interface on the client-side (clinical centers, other data collection sites), while providing the performance and reliability of Oracle on the server-side (DMAC). This interface provides data personnel at the sites with a comprehensive set of data management tools to perform data management processes such as data entry, data verification, data editing, data updating, and report generation. Additionally, clinical center personnel are able to query patient compliance data from the database and generate and view up-to-the-minute specialized reports.
9.3 Data Security:
Access to secure areas of the Web site is controlled by enforcing digest authentication and IP verification via the Web server. All information transmitted to and from the DMAC is encrypted by the use of Secure Sockets Layer (SSL) protocol and therefore unreadable during transit. Data entry takes place at the clinical centers to take advantage of the enhanced quality control and greater efficiency that can be achieved with a distributed data entry system. MATRIX prohibits duplicate entries, allows for double-entry verification on a form-by-form basis, and utilizes real time data checking (e.g., ID verification, range and type verification) to ensure complete and highly accurate data are transmitted promptly to the main project database. Identifying data inconsistencies at time of entry allows for more efficient and timely resolution of errors. With on-site data entry, medical charts are readily available, events are current and data collectors are accessible so that rigorous point-of-entry checks can be resolved immediately, before transmission to the main project database. More extensive edit checks for completeness, accuracy, and consistency are executed on the main project database and immediate feedback in the form of an on-line edit report is provided to the user. The report may be used as an interface to make updates in the current session, or may be printed for resolution at a later time using the MATRIX Update module. Authorized users may recreate these edit reports on-line at any time. Form and protocol documentation is available on the Web site to aid in error resolution. The DMAC enforces a comprehensive security policy with network defenses that include IP restriction, basic or digest authentication, and elimination of anonymous FTP to protect the data system and database from common network intrusions. A firewall provides an additional barrier between the Internet community and the DMAC network and study database by restricting, monitoring, and logging Internet traffic in and out of the DMAC, and alerts system administrators of potential security threats. Regularly scheduled backups and archives at the DMAC will protect central and local information from hard disk failures. Permanent archives of critical project files are created and stored in a secured, climate controlled off-site facility to prevent data loss due to catastrophic events. Routine virus detection and virus shields will be enforced for all DMAC computers. All critical information regarding database transactions will be logged and stored in journal files. In the event of inappropriate use of the project database, a previous database state may be restored from backup media or journal files. All servers used for this project will be connected to uninterruptable power supplies to protect equipment and data from damage resulting from electrical surges and outages. A secured, raised-floor computer room in an area with a burglar alarm will house all project server equipment.

9.4 Intervention Training and Quality Control:
For any multi-site intervention trial, it is essential that the intervention be implemented according to protocol across all sites. To achieve this goal, during the trial in the run-in period, the DMAC will work with the PI and the clinicians to: a) operationalize the intervention and provide instructions for its implementation, b) oversee the training and certification program for interventionists that must be successfully completed prior to entering the trial, and c) oversee the assessment protocol to assure that interventions are implemented consistently over time within and across sites.

10.0 DATA ANALYSIS

10.1 Sample size calculation:
For the Primary Hypothesis the goal is to be able to detect the minimum clinically significant difference in mortality between the two treatment groups. This value is defined as an absolute difference of 10%. Based on available data, the national rate of mortality after TBI is approximately 20%. In tertiary care settings, such as the sites for the proposed study, the mortality rate is lower, approximately 17%, which is consistent with our preliminary data (III.D.1.Table 2). Thus, the sample size estimates are based on the ability to detect a difference in the mortality rates of 17% in the normothermia group and 7% in the hypothermia group. In order to detect this difference, assuming a type I error rate of .045 (adjusted for 2 interim analyses), 80% power, a two-sided alternative hypothesis and using a logistic regression model, 170 patients would need to be enrolled in each of the 2 groups for a total of 340 patients. It is expected that 100% of the outcomes will be observed, thus no adjustments for attrition are needed. This is a reasonable assumption in that the prima-
ry outcome is obtained 3 mos post-injury and in that time patients with severe TBI are typically still in the care of the treating neurosurgeon.

10.2 Statistical methods:

The primary analysis will be conducted under the intention to treat principle that all patients will be included in the treatment group to which they were assigned regardless of whether the patient received treatment (e.g., patient randomly assigned to HYPO but died before treatment could be delivered) or received an adequate duration of treatment (e.g., patient randomly assigned to HYPO but died before the target temp could be achieved). The primary analysis will be conducted at the 3-mo time point. A logistic regression model will be fit to determine if there is an independent effect of treatment after controlling for the stratification variables.

For the analysis of the global functional outcomes (GOS, GOS- E Peds), an ordinal mixed effect logistic regression model will be used as these measures will be assessed at two time-points for each subject (6-mo, 12-mo). Models will include main effects for treatment, and time, as well as a two-way treatment-by-time interaction and stratification variables. The analysis of the intellectual ability and memory and learning is complicated by the fact that not all patients will be completely evaluated and the same test is not used for all subjects. With respect to the same test not being used for all age ranges, standardized scores (e.g., z-score) will be created for each test and then combined across age groups. With respect to not all subjects completing the evaluation, scores will be generated for these subjects based on their functional outcome. For example, a patient in a persistent vegetative state will not be able to complete the evaluation. The patients who cannot be evaluated will be assigned a score indicating the greatest impairment. For the WASI the worst possible standard score is 20. Patients in a persistent vegetative state at the time of the follow-up evaluation will be assigned a standard score of 19 and patient who died prior to the evaluation will be assigned a standard score of 18, which will then be converted to z-scores. This approach is necessary for the inclusion of all patients, thus maintaining the intention-to-treat approach of a RCT. The ranked scores for all subjects at both the 6-mo and 12-mo assessments will then be analyzed using a mixed-effects regression model which will include main effects for treatment, time, stratification variables and a two-way treatment-by-time interaction.

The analysis of memory and learning will be further complicated by a number of factors. One complication is that those children less than 5 y and those non-English speaking will not be tested and will be excluded from the analyses, thus limiting the generalizability of the results of the analysis to the sub-sample of the population of those over 5 y of age and English speaking. A second complication is that a single standardized score is not available to assess memory and behavior, but four key scores are generated to measure verbal memory (CVLT-C: List A Total Trials, List A Short Delay Free Recall, List A Long Delay Free Recall, Discriminability scaled scores) and two scores are generated to measure non-verbal memory (TOMAL Facial memory: Immediate Scaled Score, Delayed Scaled Score). To address this complication, multivariate statistical methods will need to be employed. Specifically a multivariate mixed effects model with main effects for treatment, time and stratification variables, as well as the two-way interaction between treatment and time will be fit. As was done in the analysis of intellectual ability, the outcome variable in the multivariate mixed effects model will be the ranked scores from the CVLT-C and TOMAL Facial Memory measures with scores for children who cannot be evaluated because of the severity of the injury being generated using the same approach as outlined above.

The analysis of behavior will parallel the analysis of intellectual ability. Identical approaches will be used to address the issue of the same test not being used for all ages as well generating scores for children who cannot be evaluated because of the severity of the injury. As was done for the analytic plan of intellectual ability, ranked z-scores will be analyzed using a mixed-effect model, which would include main effects for treatment, time, stratification variables and a two-way treatment-by-time interaction.

The analyses for Aim 3 will be repeated for the outcome variables identified above. The modeling approach will be consistent to those analyses, with the appropriate regression models for a given outcome variable (e.g., logistic regression, generalized linear mixed). To determine if there is a differential effect of treatment on different age groups, the models will include main effects for treatment, age (< 6y; 6-15y; and 16-<18y) and the stratification variables as well as the two-way treatment-by-age interaction.

ICP and CPP measures will be obtained hourly on each patient. Assuming that the number of observations per patient occurs at random, a mixed-effect regression model will be used to determine if there is an effect of treatment on the levels of ICP and CPP. Time will be included in the model as well as a time-by
treatment interaction to determine if there is a differential effect of treatment, over time, on ICP and CPP. Stratification variables will also be included in the model. Additional analyses will be conducted to analyze the peak ICP and CPP levels. Specifically, linear regression models will be used to assess the effect of treatment on the peak levels. As with the regression models described previously, variables will include indicators for treatment, the stratification variables. Survival analysis methods will also be used to assess the effect of treatment on time to peak ICP and CPP levels. Kaplan-Meier curves will be generated and a log-rank statistic will be computed to assess effect of treatment on time to peak ICP and CPP levels. Next, Cox-proportional hazards models will be used to determine if there is a effect after controlling for the effect of the stratification variables.

10.3 Interim monitoring plan:

The Lan and DeMets approach will be used for interim analyses. Interim analyses within subgroups will not be conducted. The Lan and DeMets approach does not fix the number of analyses prior to the start of the trial and spends the type I error as a function of time. For the study, interim analyses will be conducted every six months corresponding to the Data and Safety Monitoring Board meeting, in addition to the final analysis. The Lan and DeMets approach will focus on the comparison of the mortality rate across treatment groups after the completion of the 3-mo assessment. The overall Type I error rate for the study has been set to .05. We propose allocating .005 of the type I error rate to the interim monitoring and the remaining .045 for the final analysis. The spending function chosen for this study will yield critical values from the standard normal distribution defined as,

$$\alpha(t) = 2 - 2\Phi\left(\frac{\alpha/2}{\sqrt{t}}\right),$$

where \(t\) represents the proportion of patients enrolled in the trial and 0<1. This spends very little of the Type I error early in the course of the study, which leaves the majority of the Type I error in tact for the final analyses (similar to the O'Brien and Fleming approach but providing the flexibility to modify the number of interim analyses during the course of the trial). For the purpose of reserving .045 of the Type I error for the final analysis, we will set the spending function at the completion of the study equal to one (e.g.) \(\alpha(t=1) = .05\).
11.0. LITERATURE CITED


## Appendix 1
### Description of Acute, Family Functioning and Outcome Measures and Other Scales

<table>
<thead>
<tr>
<th>Task (Age/time)</th>
<th>Description and respondent [Child (C) or parent (P)]</th>
<th>Time points</th>
<th>Key Variables</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline Assessment Function Measures</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demographic Information (All ages/5’)</td>
<td>Provides demographic information about the subjects along with information to calculate socioeconomic status. (P)</td>
<td>Baseline</td>
<td>Demographic information &amp; SES</td>
</tr>
<tr>
<td>Developmental and Health History Questionnaire (All ages/10’)</td>
<td>Questionnaire reviews developmental and medical histories. Premorbid developmental status and medical history information is recorded. <strong>A follow-up form updates this information at 6- and 12-month time points.</strong> (P)</td>
<td>Baseline</td>
<td>Each variable coded in database</td>
</tr>
<tr>
<td>General Functioning Scale (All ages/5’)</td>
<td>This 12-item scale is part of the McMaster Family Assessment Device (FAD) and provides an overall measure of family functioning. The FAD has been shown to interact with TBI severity and outcomes. (P)</td>
<td>Baseline; 6/12</td>
<td>Total score</td>
</tr>
<tr>
<td><strong>Global Function</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GOS (All ages/10’ with GOS-E Peds)</td>
<td>The GOS is the standard outcome measure in adult TBI studies and are categorical outcome scales that have wide acceptance, established validity, and moderate inter-rater reliability (kappa .77). It was devised with the intention of assessing survival, social integration, and level of daily living. Despite its limitations in children, the GOS will be used as a functional outcome measure. Consistent with its use in adult studies of TBI, A 5-point scale that allows for the categorization. The secondary outcome analysis will dichotomize the GOS categories of SD/PVS/D as a poor or unfavorable outcome and GR/MD as a good or satisfactory outcome as well as analyzing all five categories. (C, P)</td>
<td>6/12</td>
<td>Good vs. poor outcome; GOS score (1-5)</td>
</tr>
<tr>
<td>GOS-E Peds (All ages)</td>
<td>An expansion of the original GOS to an 8-point scale, adding lower and upper ranges that make the scale more sensitive. We will secondarily apply the 8 GOS-E Peds categories to track recovery of function over time and compare recovery curves between groups. This version is a recent revision and includes a semi-structured interview with questions relevant to infants and children. (C, P)</td>
<td>6/12</td>
<td>Category score (1-8)</td>
</tr>
<tr>
<td><strong>Intellectual Ability (Age Appropriate Scale)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bayley Scale of Infant &amp; Toddler 3rd Ed. Cognitive and Language Scale (6-35.11 mo/30’ total test time)</td>
<td>A scale that measures development of children up to 3 yrs, this recent edition now provides a measure of cognitive function that includes visual preference, attention, memory, sensorimotor, exploration and manipulation, and concept formation. The language scale includes expressive and receptive subtests.</td>
<td>6/12</td>
<td>Cognitive Scale Score</td>
</tr>
<tr>
<td>WPPSI-III (3-6 y/30’)</td>
<td>A measure of cognitive functioning of children from ages 3-6 y, it includes a Verbal IQ (VIQ), Performance IQ (PIQ), and Full Scale IQ (FSIQ). Vocabulary, Information, Object Assembly and Block Design subtests of this instrument will provide an estimate of VIQ, PIQ and FSIQ.</td>
<td>6/12</td>
<td>Full Scale IQ; VIQ, PIQ; Vocabulary; Information; Object Assembly; Block Design</td>
</tr>
<tr>
<td>Test Name</td>
<td>Description</td>
<td>Administered Age</td>
<td>Scaled Score Version</td>
</tr>
<tr>
<td>-----------</td>
<td>-------------</td>
<td>------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>WASI (6 y and up/30’)</td>
<td>This abbreviated IQ test is a short and reliable measure of intelligence in clinical, psycho-educational, and research settings and is individually administered and designed for ages ≥ 6 y. Similar to the WPPSI, 4 sub-tests will be used to generate a VIQ, PIQ and FSIQ: Vocabulary requires the child to define words of increasing difficulty; Block Design assesses the child’s ability to construct two dimensional designs from multicolored blocks. Similarities asks the child to explain the similarity between common objects or concepts; Matrix Reasoning requires the child to complete a grid by inserting the appropriate design and provides a measure of nonverbal reasoning.</td>
<td>6/12</td>
<td>Full Scale IQ; VIQ; PIQ; Vocabulary; Block Design; Similarities; Matrix Reasoning</td>
</tr>
<tr>
<td>Memory and Learning</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NEPSY-2 Sentence Repetition (3 – 4.11 yrs/5’)</td>
<td>This NEPSY subtest assess recall of sentences that increase in length and complexity and are frequently used to assess children with developmental disorder and brain injury. It is particularly sensitive to aphasic disturbances. (C)</td>
<td>6/12</td>
<td>Scaled score</td>
</tr>
<tr>
<td>California Verbal Learning Test-Child version (5- &lt; 17 yrs/20’)</td>
<td>Assesses multiple strategies and processes in learning and recalling verbal material and tests both recall and recognition of words associated with verbal learning of a 15-word list over 5 trials. Target words include three semantic categories: toys, clothing, and foods. After an interference trial, children are asked to recall the original list immediately and after a 20-minute delay. We will record the multiple CVLT sub-scores, but the key variables used in the secondary analysis are noted here. (C)</td>
<td>6/12</td>
<td>List A Total Trials; List A Short Delay Free Recall; List A Long Delay Free Recall; Discriminability scaled scores</td>
</tr>
<tr>
<td>California Verbal Learning Test – 2nd Edition (17 yrs and up/20’)</td>
<td>Assesses multiple strategies and processes in learning and recalling verbal material and tests both recall and recognition of words associated with verbal learning of a 16-word list over 5 trials. Target words include four semantic categories: vegetables, modes of transportation, animals, and furniture. After an interference trial, subjects are asked to recall the original list immediately and after a 20-minute delay. We will record the multiple CVLT sub-scores, but the key variables used in the secondary analysis are noted here. (C)</td>
<td>6/12</td>
<td>List A Total Trials; List A Short Delay Free Recall; List A Long Delay Free Recall; Discriminability scaled scores</td>
</tr>
<tr>
<td>TOMAL-2 Object Recall (5- yrs and up /5’)</td>
<td>This test measure both verbal and visual memory by asking the child to remember a list of pictures that have been given verbal labels by the examiner. (C)</td>
<td>6/12</td>
<td>Total Recall score</td>
</tr>
<tr>
<td>TOMAL-2 Facial Memory (5- yrs and up/10’)</td>
<td>Non-verbal memory test that requires child to remember black and white photographs children’s faces. After exposure, the child identifies the target photograph from two distractors. A recognition memory task is completed after a brief delay. (C)</td>
<td>6/12</td>
<td>Immediate &amp; Delay scaled scores</td>
</tr>
<tr>
<td>Language</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bayley Scale of Infant &amp; Toddler 3rd Ed. Language Scale (6-35.11 mo/30’) see time above</td>
<td>The most recent revision of the Bayley includes an evaluation of language function with subscale scores that measure expressive and receptive language abilities. (C)</td>
<td>6/12</td>
<td>Language Scale Score; Expressive &amp; Receptive Communication subtest scaled scores</td>
</tr>
<tr>
<td>Clinical Evaluation of Language Fundamentals – Preschool - Following Directions (3 – 5.11 yrs/5’)</td>
<td>This measure assesses a child’s ability to interpret, recall, and execute oral commands of increasing length and complexity that contain concepts requiring logical operations with an emphasis on early development. (C)</td>
<td>6/12</td>
<td>Scaled score</td>
</tr>
</tbody>
</table>
### Clinical Evaluation of Language Fundamentals – 3rd Edition – Concepts and Directions (6 yrs and up/5’)

This measure assesses a child’s ability to interpret, recall, and execute oral commands of increasing length and complexity that contain concepts requiring logical operations. (C)

<table>
<thead>
<tr>
<th>Attention &amp; Executive Functioning</th>
</tr>
</thead>
</table>
| **Behavior Rating Inventory of Executive Function – Preschool (BRIEF-P)** (2 - < 5 yrs/15’)
| This instrument measures a child’s ability and behavior in a variety of domains, with an emphasis on early development. The domains examined include the ability to initiate, plan, organize, and sustain problem solving in working memory. (P)  
6/12  General Executive Composite; Inhibitory Self-Control Index; Flexibility Index; Emergent Metacognition Index |
| **Behavior Rating Inventory of Executive Function – (BRIEF)** (5 - < 19 yrs/15’)
| This instrument measures the child’s ability to shift cognitive set and modulate emotions and behavior through age appropriate inhibition. Metacognition, or the child’s self-monitoring behavior that depends on the ability to initiate, plan, organize, and sustain problem solving in working memory is also evaluated. (P)  
6/12  General Executive Composite; Behavioral Regulation Index; Metacognition Index |
| **Behavior Rating Inventory of Executive Function – (BRIEF-A) Informant Report (19 and up/15’)**
| This instrument measures the subject’s ability to shift cognitive set and modulate emotions and behavior through age appropriate inhibition. Metacognition, or the child’s self-monitoring behavior that depends on the ability to initiate, plan, organize, and sustain problem solving in working memory is also evaluated. (P)  
6/12  General Executive Composite; Behavioral Regulation Index; Metacognition Index |
| **Visual-Spatial Skills** |
| **Test of Visual-Motor Integration (VMI) – 5th Edition (3 yrs and up/10’)**
| A developmental sequence of 24-geometric figures is presented to the child in booklet form. In the revised version of the VMI, the examiner draws the first three figures and the child imitates with his or her own drawing in the box provided on the test form. For the remainder of the test, the child copies figures from the test booklet. The child is supplied with a pencil that does not have an eraser and told to copy the designs as accurately as possible without turning the booklet. Because the forms to be copied are shapes rather than letters or numbers, the test authors report it to be a virtually culture free measure of visual-motor integration. Explicit scoring criteria are supplied. (C)  
6/12  Scaled score |
| **Motor Development or Psychomotor Speed** |
| **Bayley Scale of Infant & Toddler 3rd Ed. Motor Scale (6-35.11 mo/30’) see above**
| A developmental scale that measures sensorimotor, exploration and manipulation. The scale includes fine and gross motor measures. (C)  
6/12  Motor Scaled score; Fine motor scaled score; Gross motor scaled score |
| **NEPSY-2 Visuomotor Precision (3 – 5.11 yrs/5’)**
| This NEPSY subtest assesses fine motor speed and accuracy of eye-hand coordination. The child uses his or her dominant hand to draw a line inside a track at two difficulty levels. (C)  
6/12  Subtest scaled score |
| **WPPSI – III Coding**<br>(4 - 5.11 yrs/5')<br>**WISC-IV Coding**<br>(6 – <17 yrs/3')<br>**WAIS-III Coding**<br>(17 yrs. And up/3') | **WPPSI – III, WISC – IV, and WAIS-III Coding versions are determined by the age of the child. For children ages 4 to 7, an array of large symbols (e.g., star, circle, and triangle) is printed at the top of the page. One of another set of symbols is represented in the center of each larger figure. The remainder of the page includes a grid of the large symbols. The child’s task is to draw the correct small symbol into as many of the larger symbols as possible within a strict time limit. Children 8 and older are presented with a similar task, and complete the age appropriate version. However, they are given an array of nine numbers, each paired with a different geometric symbol. Beneath this array is a set of the numbers alone. The youngster completes this grid by writing the proper symbol beneath each number, as quickly as possible. This is a powerful test of the integrity of the CNS as a whole, as it demands speed, attention, visual scanning, and memory. (C) | 6/12 | Scaled score |
| **WISC-IV Symbol Search**<br>(6 - < 17yrs/3')<br>**WAIS-III Symbol Search**<br>(17yrs. And up/3') | For the Symbol Search subtest, the child is presented with one or two (depending on age) target stimuli, followed by an array of either 3 or 5 similar distractor stimuli. Both forms of the test consist of 45 items presented to the child on 3 pages. The child is asked to check the appropriate “yes” or “no” box to indicate whether or not the target (or either of the targets) appears among the array. For both of these tasks the child is instructed to work as quickly and accurately as possible for 120 seconds. The child’s score is the number of correct responses. (C) | 6/12 | Scaled score |

### Behavior (Age Appropriate Scale)

| **Bayley-III Social-Emotional Scale**<br>(3-36 mo/10') | The Bayley-III social-emotional assessment was developed by Stanley Greenspan, M.D., one of the world's leading experts in child development, and is based on his Social-Emotional Growth Chart. The parent or caregiver answers questions about how a child uses all capacities to meet needs, deal with feelings, think and communicate. (C) | 6/12 | Scaled score |
| **Conners’ Parent Rating Scale-R (3yrs. and up/15’)** | Commonly used in studies of TBI, it provides a summary of the child’s overall emotional status and assesses a wide range of childhood behavioral difficulties, including conduct disorders, problems of cognition, social difficulties, and anxiety. This 80-item questionnaire is completed by the parent or main caregiver who endorses each item according to a Likert scale. Questions describe concrete behaviors that are frequently observed in children with emotional dysfunction (e.g., Cries easily, steals, disturbs others, etc). (P) | 6/12 | Global Index score |
| **Vineland Adaptive Behavior Scale – II**<br>(6 – 35 mo/15') | The Vineland assesses personal and social sufficiency of individuals from birth to adulthood. The survey form is given to a respondent who is familiar with the child’s behavior, usually the child’s parent. The survey covers a broad range of behaviors that are subsumed under the Communication Domain, Daily Living Skills Domain, Socialization Domain In turn, the Communication, Daily Living Skills, and Socialization Domains are each further divided into 3 subdomains of functioning. Specific scoring criteria for each item are available in the test manual. (P) | 6/12 | Adaptive Behavior Composite score: Communication, Daily Living Skills, Socialization Scores, & Motor Skills |
**CoolKids Trial**

**PTBIC: Hypothermia**

**Primary outcome variables are in boldface.** Baseline of child behavior and family function completed at time of acute injury.

**Estimated Total Test Time:** Total time for parents at time of initial hospitalization: 20 min; Total time for parents at other outcome points ≤ 50 min; Total time for subjects < 36 mo: 40 min; Total time 3-5 yrs: 60 min; Total time older children: < 80 min.

**Abbreviations:** GOS = Glasgow Outcome Scale; WPPSI = Wechsler Preschool and Primary Scale of Intelligence; WASI = Wechsler Abbreviated Scale of Intelligence; CVLT-C = California Verbal Learning Test-Child version; TOMAL = Test of Memory and Learning.
### Appendix 2: Outcome time points, test instruments and age ranges.

<table>
<thead>
<tr>
<th></th>
<th>BL</th>
<th>Endpoints (mos)</th>
<th>Age Range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Outcome Measures</strong></td>
<td></td>
<td>3±0.5</td>
<td>6± 1</td>
</tr>
<tr>
<td>Mortality &amp; GOS-E Peds</td>
<td></td>
<td>SC</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Baseline Assessment</strong></th>
<th></th>
<th>3 years and up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Developmental &amp; Health History Form</td>
<td>PR</td>
<td>All ages</td>
</tr>
<tr>
<td>SES Form</td>
<td>PR</td>
<td>All ages</td>
</tr>
<tr>
<td>Conners’ Parent Rating Scale -- Revised Long Form</td>
<td>PR</td>
<td>All ages</td>
</tr>
<tr>
<td>McMaster General Function Subscale</td>
<td>PR</td>
<td>All ages</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Secondary Outcomes Assessment</strong></th>
<th></th>
<th>3 – 5.11 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOS-E Peds</td>
<td>SC, PR</td>
<td>All ages</td>
</tr>
<tr>
<td>Post-Injury Follow-up Form</td>
<td>OT</td>
<td>All ages</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Neuropsychological Assessment</strong></th>
<th></th>
<th>Birth – 2.11 years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intelligence</strong></td>
<td></td>
<td>Birth – 2.11 years</td>
</tr>
<tr>
<td>BSID-III Cognitive Scale</td>
<td>OT</td>
<td>All ages</td>
</tr>
<tr>
<td>WPPSI-III Vocabulary &amp; Block Design</td>
<td>OT</td>
<td>3 – 5.11 years</td>
</tr>
<tr>
<td>WASI Vocabulary &amp; Block Design</td>
<td>OT</td>
<td>6 years and up</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Language</strong></th>
<th></th>
<th>Birth – 2.11 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>BSID-III Language Scale</td>
<td>OT</td>
<td>All ages</td>
</tr>
<tr>
<td>CELF- Preschool 2nd Ed. Following Directions</td>
<td>OT</td>
<td>3 – 5.11 years</td>
</tr>
<tr>
<td>CELF3rd Ed. Concepts and Directions</td>
<td>OT</td>
<td>6 years and up</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Memory and Learning</strong></th>
<th></th>
<th>3 – 4.11 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEPSY-2 Sentence Repetition</td>
<td>OT</td>
<td>All ages</td>
</tr>
<tr>
<td>TOMAL 2nd Ed. Object Recall</td>
<td>OT</td>
<td>5 years and up</td>
</tr>
<tr>
<td>CVLT-C</td>
<td>OT</td>
<td>5 – 16 years</td>
</tr>
<tr>
<td>TOMAL 2nd Ed. Facial Memory</td>
<td>OT</td>
<td>5 years and up</td>
</tr>
<tr>
<td>CVLT-II</td>
<td>OT</td>
<td>17 years and up</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Attention &amp; Executive Function</strong></th>
<th></th>
<th>3 – 4.11 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRIEF-Preschool</td>
<td>OT</td>
<td>All ages</td>
</tr>
<tr>
<td>BRIEF-School age</td>
<td>OT</td>
<td>5 – 16 years</td>
</tr>
<tr>
<td>BRIEF - A</td>
<td>OT</td>
<td>17 and up</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Visual-Spatial Skills</strong></th>
<th></th>
<th>3 years and up</th>
</tr>
</thead>
<tbody>
<tr>
<td>VMI-5th Ed.</td>
<td>OT</td>
<td>All ages</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Motor &amp; Psychomotor Skills</strong></th>
<th></th>
<th>Birth – 2.11 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>BSID-III Motor Scale</td>
<td>OT</td>
<td>All ages</td>
</tr>
<tr>
<td>NEPSY-2 Visuomotor Precision</td>
<td>OT</td>
<td>3 – 5.11 years</td>
</tr>
<tr>
<td>WPPSI-III Coding</td>
<td>OT</td>
<td>4 – 5.11 years</td>
</tr>
<tr>
<td>WISC-IV Coding &amp; Symbol Search</td>
<td>OT</td>
<td>6 – 16 years</td>
</tr>
<tr>
<td>WISC-IV Processing Speed Index</td>
<td>OT</td>
<td>6 – 16 years</td>
</tr>
<tr>
<td>WAIS –III Coding and Symbol Search</td>
<td>OT</td>
<td>17 years and up</td>
</tr>
<tr>
<td>WAIS-III Processing Speed Index</td>
<td>OT</td>
<td>17 years and up</td>
</tr>
<tr>
<td>Behavior</td>
<td>PR</td>
<td>PR</td>
</tr>
<tr>
<td>---------------------------------------------------</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>BSID-III Social Emotional Scale</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vineland Adaptive Behavior Scale II</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Connors' Parent Rating Scale – Revised Edition Long Form</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BL = Baseline; PR = parent report; OT = Neuropsychological Outcomes Technician; SC = Site Coordinator; GOS-E Peds = Glasgow Outcome Scale-Extended Pediatric Version; BSID = Bayley Scales of Infant Development; WPPSI = Wechsler Preschool and Primary Scale of Intelligence; WASI = Wechsler Abbreviated Scale of Intelligence; CELF = Clinical Evaluation of Language Fundamentals; CVLT = California Verbal Learning Test; TOMAL = Test of Memory and Learning; BRIEF = Behavior Rating Inventory of Executive Functioning; VMI = Test of Visual-Motor Integration; WISC = Wechsler Intelligence Scale for Children.
Appendix 3: Organizational Chart

EAC  Executive Advisory Committee
NINDS  National Institute of Neurological Disorders and Stroke
DSMB  Data and Safety Monitoring Board
NOAC  Neuropsychological Outcomes Advisory Committee