Attachment 1 -- Synopsis of Clinical Protocol

Study Title	*ARCTIC: Acute Rapid Cooling Therapy for Injuries of the spinal Cord*
Clinical Phase	Confirmatory Phase
Sponsor:	Miami Project to Cure Paralysis (MPCP), University of Miami (1095 NW 14th Terrace, Miami, FL, 33136. MPCP is responsible to ensure adherence to the trial procedures according to the protocol and current good clinical practices. Funding Agency: National Institute of Neurological Disorders and Stroke (NINDS)
Study Coordinating Center(s)	The Neurological Emergencies Treatment Trials (NETT) network. NETT Clinical Coordinating Center University of Michigan Department of Emergency Medicine 24 Frank Lloyd Wright Dr. Suite H3100 Ann Arbor, MI 48106 734-232-2142 734-232-2122 - Fax NETT Statistical and Data Management Center Medical University of South Carolina Department of Medicine Division of Biostatistics and Epidemiology 135 Cannon Street, Ste 303 Charleston, SC 29425 Trial Scientific and Protocol Leadership University of Miami

Attachment 1 -- Synopsis of Clinical Protocol

Enrollment Sites	University of Arizona Hub, University Medical Center, Scottsdale Healthcare Osborn Medical Center, Banner Good Samaritan Medical Center, Phoenix; University of Cincinnati Hub, University Hospital; Emory University Hub, Grady Memorial Hospital; Henry Ford Health System Hub, Henry Ford Hospital; University of Kentucky Hub, University of Kentucky Hospital; University of Maryland Hub, R Adams Cowley Shock Trauma Center ; University of Minnesota Hub, Hennepin County Medical center; New York Presbyterian Hub, New York Hospital-Cornell; Oregon Health Sciences University Hub, OHSU Hospital; Stanford University Hub, Stanford Unversity Medical Center; Temple University Hub, Temple University Hospital, Thomas Jefferson University; University of Texas Hub, Hermann Hospital Texas Medical Center; University of California San Francisco Hub, San Francisco General Hospital Medical Center; University of Pennsylvania Hub, Hospital of the University of Pennsylvania, Christiana Care Health System; Virginia Commonwealth University Hub, Virginia Commonwealth University Health System; Wayne State University Hub, Detroit Receiving Hospital, William Beaumont Hospital, Sinai-Grace Hospital; Medical College of Wisconsin Hub, Froedtert Memorial Lutheran Hospital; University of Miami, Jackson Memorial Hospital.
Investigators	Principal Investigators: Michael Wang, MD, FACS W. Dalton Dietrich , PhD William Barsan, MD Robert Silbergleit, MD Valerie Durkalski, PhD Scott Berry, PhD Co-investigators: Barth A Green, MD Allan D Levi, MD, PhD Steven Vanni, DO Diana Cardenas, MD Andrew Sherman, MD And the NETT Clinical Trial Investigators

Attachment 1 -- Synopsis of Clinical Protocol

Study Rationale	Spinal cord injury (SCI) is a devastating disease which exerts a disproportionate medical, social, and economic toll on society. However, to date, no therapeutic intervention has been demonstrated to definitively improve neurological outcomes or mitigate the effects of secondary neural injury.
	The current acute treatment of SCI is limited to the medical stabilization of the patient, surgical decompression of the involved neural elements, and stabilization of an unstable spinal column to prevent further mechanical injury. In addition, the maintenance of normal circulation and tissue oxygenation can reduce the likelihood of additional insults to the spinal cord. However, these measures remain supportive and there is little that can be done to protect the spinal cord itself. Neuroprotection, aimed at minimizing secondary neural injury and improving the chances for native recovery has been a major goal of neuroscientists and clinicians for the management of acute insults to the central nervous system. While restorative and adaptive approaches hold great promise for patients afflicted with these disorders, effective neuroprotection will likely remain a cornerstone of the early intervention needed to maximize a patient's functional status, and this remains a high priority in translational neuroscience research.
	Mild hypothermia has been shown to improve neurological function and mitigate neuronal loss in numerous animal models. Hypothermia has been shown to improve clinical outcomes after brain injury from cardiac arrest and neonatal hypoxia/ischemia. Clinical experiences of intravascular cooling in the treatment of acute brain injury after cardiac arrest and ischemic stroke have shown this method of inducing therapeutic hypothermia to be safe and feasible. Our pilot (Phase I) clinical study has shown therapeutic hypothermia by endovascular cooling to be a safe and potentially efficacious intervention for SCI patients.
	Based upon this promising evidence, the proposed confirmatory clinical trial will be a randomized, prospective, multi-center study investigating the use of intravascular cooling to 33º C. Hypothermic subjects will be compared with normothermic control patients. The primary objective will be to determine if this intervention results in neurological improvement in cooled patients, as measured by the change from baseline in the 12-month ASIA motor score. A difference in the mean change score of 10 points or greater between control and treatment is considered clinically relevant. Secondary objectives will include assessments of safety, as well as the effect of hypothermia on the ASIA sensory score, functional abilities, pain, and quality of life.
Trial Design	• Randomized, controlled, open label (with blinded outcome assessment) • Adaptive, two-stage Bayesian study design • Multiple sites (approximately 18 sites) • Informed Consent will be obtained prior to enrollment in the study

Attachment 1 -- Synopsis of Clinical Protocol

Approximate Duration of Patient Participation	• Participants will be monitored throughout a 12 month evaluation period for the occurrence of Adverse Events (acute, delayed, and/or cumulative), as well as for changes in clinical status, neurological status. • Scheduled safety and efficacy assessments will be performed at 4, 8, 16, 26 and 52 weeks post-treatment.
Approximate Duration of Study	• 60 months from First Subject Initial Visit until Last Subject Final Visit. • End of Study is Defined as Last Subject Final Visit
Study Objective(s)	**Primary:** To determine the efficacy of mild hypothermia (cooling to $33.0 \pm 0.2°$ C) initiated within 6 hours of SCI for improving neurological outcomes as compared to normothermic patients (maintained at $37.0°$ Celsius for 72 hours using the same intravascular thermoregulatory device) following ASIA A & B cervical (C4 to C8) SCI. **Secondary:** 1. To assess the safety of mild hypothermia administration following SCI. 2. To assess the relative efficacy of 3 different durations of cooling, 24, 48, and 72 hours. 3. To assess the clinical efficacy of mild hypothermia with cooling to $33.0 + 0.2°$ Celsius for improving the ASIA sensory score when comparing between treatment arms. 4. To assess the clinical effects of mild hypothermia on functional abilities as measured by the Spinal Cord Independence Measure (SCIM-3) score. 5. To assess the clinical effects of mild hypothermia on neuropathic pain following spinal cord injury as measured by the International Spinal Cord Injury Pain Basic Data Set (ISCIPDS:B) instrument.
Main Criteria for Inclusion	**Major Inclusion Criteria:**

Inclusion Criteria	Measure	Rationale
Age ≥ 15	Years of age	Higher rates of neurological recovery than in adults.
Age ≤ 65	Years of age	Different injury patterns and higher risk of complications
AIS Grades A & B	Neurological exam	Severe injuries with a poor prognosis warranting aggressive intervention
Level of injury C4-C8	Neurological exam	Eliminates thoracic level injuries, which exhibit different recovery rates

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Attachment 1 -- Synopsis of Clinical Protocol

	Major Exclusion Criteria:		
	Exclusion Criteria	**Measure**	**Rationale**
	Rapidly improving exam in ED	Clinical examination	Patients likely to be in spinal shock
	Severe non-CNS injury	Injury severity score > 30	Higher risks of complications from cooling body temperature
	Significant traumatic brain injury	GCS $\leq$ 13 or abnormal head CT	Head injury alters rehabilitation potential
	Penetrating SCI	History and clinical examination	Patients unlikely to recover with any therapy
	Unable to give informed consent	Clinical examination	Protection of human subjects
Main Criteria for Exclusion	Prisoner or ward of the state	History	Vulnerable population
	Pregnancy	Urine or serum pregnancy test	Risk to fetus
	Unknown time of injury	Paramedic run report	Need for timely initiation of cooling therapy
	Previous SCI	History and clinical examination	Patients unlikely to recover with any therapy
	ASIA motor exam unobtainable	ASIA Motor Score	Baseline scoring needed for determination of change in score
	History of cardiac arrhythmia	History and ECG tracing	Higher risks of arrhythmia with cooling
	Unknown cause for impairment	History & radiographic imaging	Highly variable rates of recovery
	Languages without local expertise	Family history	Lack of personnel or appropriate outcomes scales
Approximate Number of Patients	A maximum of 240 participants with acute ASIA Impairment Scale (AIS) Grade A or B spinal cord injury.		
Approximate Number of Study Centers	Eighteen (18) Hub sites.		

Attachment 1 -- Synopsis of Clinical Protocol

Concomitant Medication	Concomitant medications and treatments or procedures pertinent to the study treatment or to any adverse events will be recorded including: 1) name of drug, treatment, or description of procedure, 2) start and end dates and times, and 3) clinical indication and/or findings. Investigational drugs and any other intervention (not part of the guidelines for management of SCI) known to have a potential impact on outcome will be prohibited.

Attachment 1 -- Synopsis of Clinical Protocol

Study Intervention (Device Usage Protocol, Randomization, Adoptive Design)	
Treatment Protocol	Patients presenting acutely to trial centers with a history and mechanism consistent with acute traumatic spinal cord injury will be assessed clinically with respect to AIS grade. Patients with no motor function in their lower extremities (AIS grades A & B) and tetraplegic at the C4 to C8 levels identified within 6 hours of injury will be offered enrollment into the study. Because the timeliness of intervention has been associated with successful neuroprotection, inclusion into the study will require consent and initiation of cooling protocol within 6 hours of the injury. At the time of enrollment an ASIA motor examination will be performed by trained and certified study personnel. This metric will be utilized as the baseline measure of neurological function.
	Following baseline measurements and consents, all **ARCTIC** subjects will undergo placement of an intravascular heat exchange catheter into the femoral vein. Subjects will then be randomized to receive either: 1) maintenance of normothermia at 37.0º C, or 2) intravascular cooling at a target temperature of 33.0º + 0.2 C for a total of 24, 48 or 72 hours. While the rate of cooling is variable, target temperatures can typically be achieved in awake patients between 2 and 5 hours after the initiation of cooling. However, to speed cooling, the patients randomized to the hypothermia treatment arm will receive a 2 liter bolus of iced saline. Control patients will receive an equivalent volume of room temperature saline (Figure 1below).
	Figure 1

Attachment 1 -- Synopsis of Clinical Protocol

<table>
<tr><td rowspan="3">Treatment groups</td><td>Cohort</td><td>Treatment</td><td>Time limit</td></tr>
<tr><td>1</td><td>Mild hypothermia (33.0± 0.2° C)</td><td>24, 48, and 72 hours + 24 hour rewarming will be utilized (total 96 hours of temperature control).</td></tr>
<tr><td>2</td><td>Normothermia (37.0± 0.2° C)</td><td>96 hours</td></tr>
<tr><td>Rehabilitation Protocol</td><td colspan="3">Following stabilization in the acute setting, patients will be transferred to an inpatient rehabilitation facility. In this environment it is expected that in addition to physical conditioning, patients will receive, full intensive acute multi-disciplinary rehabilitation treatment individually tailored to their injury patterns to allow for maximizing functional reintegration into society. Patients also procure the necessary adaptive equipment and are made aware of the medical and community resources available to them following discharge. Education of family members and caregivers occurs, and a psychosocial support structure is developed. For ARCTIC enrollees clinical evaluations will continue to occur during this phase of their treatment, including the initial functional (SCIM-III), pain (ISCIPDS:B), and quality of life (SCI-QOL & SF-36) measures. Active monitoring of adverse events will also continue, as patients are still at risk for the early sequelae of SCI, including respiratory problems, infections, and problems at the surgical site</td></tr>
<tr><td>Frequency</td><td colspan="3">One-time administration of mild hypothermia as described.</td></tr>
<tr><td rowspan="4">Safety Evaluation</td><td colspan="3">The NINDS will appoint an independent Data and Safety Monitoring Board (DSMB). The investigators and a medical safety monitor will review adverse events and report them to the DSMB. The DSMB will review adverse events and safety outcomes throughout the trial.</td></tr>
<tr><td colspan="3">1) Although preclinical data and clinical experience suggests mild hypothermia is relatively safe, several adverse events are possible and will be noted, including bradycardia, pneumonia, deep venous thrombosis, coagulopathy, and infection.</td></tr>
<tr><td colspan="3">2) Full ASIA motor assessments done at admission/enrollment, 4, 8, 16, 26 & 52 weeks post-treatment will monitor for any deterioration in neurological function during the study.</td></tr>
<tr><td colspan="3">3) Pain Assessments will evaluate development of neuropathic pain syndromes using the ISCIPDS:B</td></tr>
<tr><td>Secondary outcomes</td><td colspan="3">1) Functional Independence Measures: SCIM III

2) Quality of life measures: SCI-QoL & SF-36</td></tr>
</table>

Attachment 1 -- Synopsis of Clinical Protocol

Statistical Considerations and Analysis	
Primary Efficacy Outcome Measure	The primary efficacy outcome is change in the ASIA motor score from baseline to 52-weeks.
Sample Size & Power	Clinical experience and controlled studies have estimated that a 10-point difference in the mean change score between the two treatment arms is clinically relevant.[54] The trial is designed to have high power when there is a duration arm with at least a mean change from baseline in ASIA motor score of 10 points above the control arm. If the cooling duration arms have a high probability of having less than a 7 point difference compared to the control arm then the trial will be stopped for futility or entry criteria adjusted. Based on the review of the Sygen data by Fawcett et al, the estimated standard deviation of the change score (52wks – Baseline) is 15 points for AIS A cervical patients and 25 points for AIS B cervical patients[111].
	We use these estimates to simulate the adaptive design. The adaptive design has a maximum sample size of 240 subjects. The design has 97.4% power to select a duration and conclude it is superior to the control if all durations have a 10pt advantage over the control. If each duration has an 8 point advantage the power is 89.3%. If there is variation in the effect size across arms this power will vary. If the 48-hour duration has a mean change of 10pts and the 24 and 72 hour durations have a mean change of 5 points, the design has 83.3% power. Additionally the design has a 70.8% probability to determine the 48-hour duration is the best and it is superior to the control arm. If there is no effect to cooling—for any durations—then there is a probability of 75.3% of stopping for futility or adjusting the entry criteria.

Attachment 1 -- Synopsis of Clinical Protocol

Randomization	A web-based central randomization system will be developed by the SDMC and installed on the WebDCU™ ARCTIC study website. The objective of subject randomization is to prevent possible selection bias by providing random treatment assignment to each subject, and to prevent accidental treatment imbalances for the known prognostic variables. During the burn-in stage of the trial and in Stage 2, the randomization scheme will be balanced (1:1) and will control imbalances in the following baseline covariates between the two treatment groups: AIS Grade (A versus B), gender, level of injury (C4-C8), age and hub. During the adaptive randomization phase of the trial (subjects 61-140) in Stage 1, response adaptive randomization will be utilized with the goal of allocating subjects to the most likely effective durations. During this phase there will be no covariate balancing, it will be driven entirely by the response-adaptive randomization.
	To ensure proper randomization, the unblinded statistical programmer will have access to the randomization information in order to oversee the quality control of the computer program. Randomization will occur via the study-specific password-protected website accessed by an authorized research coordinator or investigator at the clinical site. If, in rare circumstances, the web system is not available, the coordinator or investigator will have access to emergency randomization procedures that will allow the site to randomize the patient. Upon randomization by the authorized person at each center, an e-mail notification will be sent to the Study Executive Committee, Site PI, Site Primary Study Coordinator and relevant NETT CCC and SDMC personnel. Subjects will be considered enrolled in this trial at the time of randomization, regardless of whether or not they start or complete study treatment. The entire randomization process will be blind to all study team members. Only the SDMC programmer will have access to the randomization information in order to oversee the quality control of the computer program.

Attachment 1 -- Synopsis of Clinical Protocol

Analysis Plan	
Interim Futility and Enrichment Analyses	Interim analyses for futility will be conducted during the regular interim analyses in Stage 1 of the trial (every 4weeks after an initial burn-in period). If the likelihood of at least a 7-point advantage for the most-likely maximally effective duration is less than 10% then the trial will be analyzed for possible enrichment (See Attachment 3 for details). If the conditions for enrichment are not met the trial will be stopped for futility.
Interim Monitoring for Safety	The independent Medical Safety Monitor and DSMB will receive periodic safety reports of all adverse events and serious adverse events. Statistical monitoring for safety will be limited to specific serious adverse clinical events including death, neurological worsening as determined by the ASIA motor score and AIS grade/level, malignant arrhythmia, thromboembolism, pneumonia, wound infection, sepsis, and pressure ulcers. Death will be monitored throughout the 12-month study period using unadjusted relative risks. Stopping the trial due to harm may be considered by the DSMB if at any time the lower limit of the 95% confidence interval for the relative risk reaches or exceeds 1. The remaining specified events will be monitored during the treatment period, acute hospitalization and inpatient rehabilitation. The difference in event rates between the two treatment arms will be monitored using two-sided 95% confidence intervals.
Primary Analysis	The analysis of the primary outcome of change (Month 12–Baseline) in the ASIA motor score will use a Bayesian multiple linear regression model that will include entry AIS Grade (A versus B), gender, level of injury (C4-C8), and age (continuous) as model covariates. In addition a normal-dynamic linear model (NDLM) will be used to combine the results from all durations in the estimate of the efficacy of the target duration dose. The NDLM provides better estimates of individual duration mean responses and helps to prevent type I error from occurring when the null hypothesis of no effect is assumed.
Safety Outcome Analysis	In addition to the continual monitoring of adverse events by the safety monitor and DSMB and the planned statistical monitoring of specific events (described above), final analyses of primary and secondary safety outcomes will be compared between the two treatments. The primary safety outcome is all cause mortality. Secondary safety outcomes are: 1) neurological worsening, 2) thromoembolism, 3) sepsis, and 4) malignant arrhythmia. Because bradycardia, hypotension, and supraventricular arrhythmias are nearly universal following the sympathectomy effect of cervical SCI, malignant arrhythmia will be defined as: 1) asystole; 2) ventricular tachycardia or ventricular fibrillation; 3) any non-elective electrical cardioversion; 4) severe bradycardia requiring sustained electrical pacing for greater than 6 hours; and 5) third degree conduction blockade. All other cardiovascular events will still be documented as standard AE's.

Attachment 1 -- Synopsis of Clinical Protocol

Secondary Outcomes and Analyses	This study is designed to test the primary hypothesis. However, it also offers the opportunity to conduct analyses to evaluate important additional neurological and functional outcomes using the ASIA sensory score, Spinal Cord Independence Measure (SCIM), International Spinal Cord Injury Basic Pain Data Set (ISCIPDS:B), and SCI-QOL for quality of life assessment. All secondary analyses will be conducted using the ITT principle. The 12-month ASIA sensory score will be compared between the two treatment arms using a multiple linear regression model that will include entry AIS Grade (A versus B), gender, level of injury (C4-C8), and age (continuous) as model covariates. Unlike the ASIA motor score, a baseline sensory score can not be measured prior to treatment initiation; therefore an adjustment for a true baseline sensory measure cannot be conducted. However we will measure the sensory score at 12-36 hrs post randomization (during treatment) and at multiple time points during the follow up period. This information will be used in an additional analysis of longitudinal effects using a mixed effects model repeated measures analysis. Similar to the analysis of the ASIA motor score, the model will include the covariates listed above plus covariate*time and covariate*time*treatment. Statistical interactions will be judged at a 0.15 significance level. The SCIM total score ranges from 0-100 and will be assessed as a continuous outcome variable. The total score and the four subscales of the SCIM will be evaluated between the two treatment arms to provide information on specific areas of function (Self Care, Respiration and Sphincter Management, Mobility in Room and Toilet, and Mobility Indoors and Outdoors). In addition to comparison of functional measurements, the two treatment arms will be compared regarding pain and disability. The ISCIPIDS:B records information on location, intensity and frequency of pain in the last 7 days as well as information on disability due to pain. Each of these aspects of pain will be compared between the two treatment arms. Analyses of all secondary outcomes will adjust for the specific covariates that are listed above in the primary analysis section as well as additional covariates identified at the time of analysis.

Other Statistical Considerations	
Hub Effects	We have instituted several protocol procedures in order to minimize treatment differences between hubs, including investigator training modules to be performed prior to study initiation, and guidelines for acute SCI management. Although we do not anticipate significant hub/site effects, we will investigate potential associations and their effect on inferences from the primary model. The distribution of patient baseline characteristics, as well as treatment variables (time to initiation of cooling, timing of surgical intervention, and administration of high dose steroids) will be examined and as a secondary analysis of the primary outcome where hub and hub*treatment interaction will be added to the analysis model.
Missing Data	Although every attempt will be made to avoid missing outcome data, missing data is anticipated with any longitudinal study. The missing data can be defined as intermittent or dropout. Although every effort will be made to prevent subjects from missing visits or dropping out of this study, it is possible that the 12-month measurement will be missing. Reasons for missing data will be examined by comparing means and standard deviations for subjects that have and do not have the relevant missed visit data. The reason for missing data will be fully examined to confirm this assumption. Any missing data on the primary outcome (12-month ASIA motor score) will be imputed using a Bayesian multiple imputation method that creates a linear model between earlier visits (4, 8, 16, and 26 weeks) for multiply imputing the final visit. Sensitivity analyses will be conducted to assess the effect of the missing data method on the results. These analyses include including only completers, using last-observation carried forward, and worst-case scenarios, where the worst case change in ASIA motor is assumed for all subjects with missing 52-week data.

Missing covariate data will be imputed using either the multiple imputation, regression method, or hot-decking, if needed. |
| **Analysis Samples** | All analyses will be conducted using the ITT population defined as all randomized patients regardless of whether they actually received the assigned intervention, or the full duration of their assigned intervention (See Attachment 3). As a sensitivity analysis, the primary and secondary analyses will be repeated using the 'per protocol' population, defined as all randomized patients who receive the assigned intervention as described in the protocol. If differences are present between this analysis and the ITT analysis, the characteristics of the two analysis populations will be examined to aid in explaining any discrepancies. |

Attachment 1 -- Synopsis of Clinical Protocol

Early Trial Termination	The study design incorporates planned interim analyses for futility. In addition to the futility analysis, we will work with our DSMB to establish stopping rules for safety in the event that interim monitoring and data analysis reveal a potentially high rate of adverse or negative events in the cooled compared to normothermic patients. This process will be overseen by the ARCTIC independent Medical Safety Monitor (Dr. Robertson) and the DSMB. Early trial termination will be considered in the event of a significantly higher rate of complications in the hypothermia groups as determined by the DSMB.
Trial Blinding	Because the effects of cooling will be easily identified in the patient's vital signs and potentially in his or her physiologic responses to hypothermia, it will be impossible to blind subjects and acute care study personnel to the assigned treatment group. However, post-treatment assessments following acute care will be undertaken with functional scoring by study personnel who are unaware of the treatment allocation. This process will be managed by blinding the outcomes scoring for the SCIM, SF-36, SCI-QOL, and ISCIPDS:B sections of the follow-up examinations. More critically, ASIA motor scoring at 12 months (primary outcome measure) will be performed by certified, blinded study personnel.
Subject Attrition	Because of the lengthy 12-month follow-up, efforts will be made to minimize the number of subjects lost to follow-up. Patients suffering an acute SCI are almost universally discharged to an inpatient rehabilitation facility. There will thus be ample opportunity to establish rapport with the patient and his/her social support network during the acute and rehabilitation hospitalizations. In addition, because of the nature of the re-integrative process following inpatient rehabilitation, patients are typically well-informed on medical and caregiver resources and thus maintain communication with their rehabilitation team. Patients injured and treated remotely from their domicile, who subsequently return home, can have their follow up performed by the closest NETT Hub rather than the enrolling site so that ASIA motor and sensory examinations can be performed with little patient or study team member travel. Telephone interviews can also be used to collect several outcome measures, including the SCIM, ISCIPDS:B, SCI-QOL, and SF-36. A member of the outcomes team will travel to the study subject for those not residing near a NETT Hub.

Attachment 1 -- Synopsis of Clinical Protocol

Treatment Variability and Standardization	Recognizing the impact of treatment at all stages on the outcome after SCI and because of the substantial variability in patient management following SCI we have instituted measures to minimize these effects on study outcome. To ensure compliance between ARCTIC centers each site's principal investigator, study personnel, treating physicians, inpatient nursing staff, and outcome assessment personnel will be fully in-serviced prior to study initiation. This will occur through an intensive training program which will be finalized by the site visit. Training decay will be minimized with semi-annual re-certification of outcomes personnel to ensure inter-rater reliability. Investigator meetings will occur once yearly. In addition, ARCTIC includes the following specific training programs: 1. Training program for hypothermia administration – To address the technical aspects of catheter placement, cooling protocol, control of shivering, re-warming protocol, and equipment in-service to ensure the safe and effective cooling of study patients. 2. Guidelines for acute SCI management – To address variability in the clinical practice of treating cervical SCI patients between centers. 3. Outcomes assessment training - To address the need for certification in the ASIA motor and sensory examinations. Training will involve DVD/video modules as well as training with testing of inter-reliability with patients. Re-training for certification renewal will occur every 6 months 4. Incorporating covariate balancing the randomization scheme – To avoid possible imbalances in key prognostic variables between the two treatment arms. 5. Annual investigator meetings – To address any impediments to subject enrollment, discrepancies in treatment between centers, and protocol violations of concern. In addition, this will afford an opportunity to discuss any changes in the standard of care during the study period. 6. Continual monitoring of inter-center variability – To ascertain significant site-specific deviations in subject treatment to be addressed at investigator meetings.