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Award Number: W81XWH-07-1-0361

TITLE: North American Clinical Trials Network (NACTN) for Treatment of Spinal Cord Injury: A Consortium of Military, Veterans Administration and Civilian Hospitals

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REPORT DATE: March 2012

TYPE OF REPORT: Addendum to Final

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
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REPORT DOCUMENTATION PAGE				Form Approved OMB No. 0704-0188	
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1. REPORT DATE March 2012		2. REPORT TYPE Addendum to Final		3. DATES COVERED 1 January 2011 – 31 December 2011	
4. TITLE AND SUBTITLE North American Clinical Trials Network (NACTN) for Treatment of Spinal Cord Injury: A Consortium of Military, Veterans Administration and Civilian Hospitals				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER W81XWH-07-1-0361	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Robert G. Grossman, M.D.; Ralph Frankowski, Ph.D.; Elizabeth Toups, RN, MS; Susan Howley E-Mail: rgrossman@tmhs.org				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Christopher Reeve Foundation Short Hills, New Jersey 07078				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT Five hundred twenty-four acutely injured patients have been enrolled in the NACTN data registry as of 12/31/2011 and enrollment continues at the clinical centers. Thirty-six acutely injured patients were enrolled in the Riluzole Phase I safety study. Data analyses are ongoing and a decision to move forward to a Phase 2 efficacy study will be made when analysis is complete. NACTN has become a resource for the spinal cord injury field at large and is approached now by academic labs, biotech and pharma industries seeking guidance and collaboration; the network has several therapies under consideration for trialing, in addition to Riluzole. NACTN operates under formally adopted Governance Policies & Procedures (revised effective 11-2011) and works through established committees. Oversight for all NACTN operations is vested in its Executive Committee. Under the aegis of its Neurological Outcomes Committee (NOA), five contracts have been issued to develop and finalize new outcome instruments. A book chapter on NACTN is in press; a complications manuscript has been revised and submitted to Journal of Neurotrauma; in collaboration with AO Spine NA, NACTN PIs have written a series of papers that will be published (Summer 2012) in a J Neurosurgery-Spine supplement issue on SCI that is featuring the work of NACTN. NACTN is collaborating with the European EM-SCI and the North American STASCIS networks on a series of research questions involving discrete merged data. In addition, under the aegis of the AO Spine Knowledge Forum, NACTN is exploring a complete merge of international registries, including EM-SCI, STASCIS and Rick Hansen. Lastly, effective 1/1/2012, SAMMC will join NACTN as the second military hospital; given its catchment area and patient population, it is expected to be a prolific contributor to NACTN studies.					
15. SUBJECT TERMS Spinal cord injury, clinical trial, Riluzole, anti-Nogo, outcome / quantitative measures, military, functional recovery.					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
U	U	U	UU	423	19b. TELEPHONE NUMBER (include area code)

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INTRODUCTION: The 2009 release of the Reeve Foundation's population-based survey, "One Degree of Separation: Paralysis and Spinal Cord Injury in the United States," conducted by the University of New Mexico, changed the conversation in this country about paralysis and spinal cord injury (SCI). Until that time, the accepted wisdom was that an approximate 250,000 Americans were living with SCI. The survey revealed surprisingly larger numbers: 5,596,000 individuals are living with paralysis and of those, 1.275 million are spinal cord injured (Cahill et al., 2009). Lifetime care costs for a 25 year-old with a high cervical SCI are estimated to be three million dollars (Spinal Cord Information, 2008). Spinal cord patients are living near-normal life spans now, thanks to vastly improved medical care and rehabilitation but as of this writing, not a single intervention, acute or chronic, has been successfully tested in a rigorous randomized, controlled trial and brought to clinical application. Developing effective therapies and cures for these individuals has taken on new urgency in light of these startling numbers. Never has the need for the North American Clinical Trials Network (NACTN) for the Treatment of Spinal Cord Injury been greater.

The field of spinal cord research has blossomed in recent years with many academic laboratories in the United States and internationally dedicated fulltime to pursuit of strategies to repair the damaged spinal cord. More recently, a handful of biotech and pharmaceutical companies have expanded their portfolios to include spinal cord, and the field now has several biotechs focused on development of SCI interventions. The last several months alone have seen publication of a number of exciting new studies on the road to therapy development. These include, but are not limited to a stunning new technology to see inside the living spinal cord and create three-dimensional images of regenerating axons (Erturk et al, 2011), long nerve fiber survival post-SCI contusion (James et al, 2011), more on the evolving astrocyte story (White et al, 2011) and combinatorial interventions (Schnell et al, 2011, Garcia-Alias et al, 2011, Sun et al, 2011). Clinical trials are presently underway testing glibenclamide in TBI and stroke and research in animals suggests efficacy also in spinal cord injury; it may well be a compound that should be trialed in SCI sooner, rather than later (Simard et al, 2011; Simard et al, 2012). Riluzole continues to elicit interest for its neuroprotective properties as evidenced by a recent paper showing the drug increases the amount and activity of Heat Shock Factor 1, thereby increasing expression of heat shock proteins (Liu et al, 2011); interestingly this project received underwriting from the New Jersey Commission on Spinal Cord Injury.

In "Cellular Treatments for Spinal Cord Injury: The Time is Right for Clinical Trials" (Fehlings and Vawda, Neurotherapeutics 2011), the authors make the case that "the field of regenerative neuroscience should not be stalled at the animal model stage, but instead the clinical trials need to be focused, safe, and ethical, backed up by a robust, translationally relevant preclinical research strategy."

During the past several years, a number of clinical trials of potential spinal cord therapies have been announced or have commenced. These include, but are not limited to, the Novartis anti-Nogo antibody Phase I safety study (acute injury), stem cell trials led by Geron (acute) and StemCells Inc. (early chronic) and announcements from BioAxone BioSciences of plans to move forward with a placebo-controlled Cethrin Phase II b trial in 2012 and from the Miami Project/In Vivo Therapeutics to combine their (respective) Schwann cells and polymer scaffolding in a clinical trial.

On November 14, 2011, in a completely unexpected development, Geron announced it was halting its first-in-human safety study of its GRNOPC1 cells (ES-cell derived oligodendrocyte progenitors). Aside from the waves of disappointment the announcement sent through much of the spinal cord community, it was also a cautionary tale. After years of investment, hype and hope and hard work, the company said pursuit of the therapy was simply too expensive and it would focus instead on its potentially more financially rewarding cancer therapies. It is challenging to design robust spinal cord trials that will end with meaningful data; these studies are expensive and can be painstakingly slow. NACTN offers a strategic mechanism through which potential therapies can be rationally and safely tested and evaluated.

NACTN is the only established standing network for spinal cord injury clinical trials in North America. It was created in 2004 by the Christopher Reeve Foundation (CRF) and a consortium of university neurosurgical

departments. The U.S. Army Medical Research and Materiel Command of the Department of Defense has supported NACTN since 2006.

The Network's mission is to carry out clinical trials of the comparative effectiveness of new therapies for spinal cord injury using an established consortium of neurosurgery departments at university-affiliated medical center hospitals with medical, nursing and rehabilitation personnel who are skilled in the evaluation and management of SCI. NACTN is now regarded as a resource for the field at large, helping to set standards of care and best clinical practices. Importantly, the network has established rigorous procedures by which to select and conduct trials of therapy with minimal bias.

To-date, NACTN has developed data collection instruments to characterize the severity of the initial injury and the course of recovery and created a Data Management and Statistical Coordinating Center that has developed a database of the natural history of SCI and a Pharmacological Center. It has standardized data collection and reporting, and in a major accomplishment during this report period, has completed enrollment in its first clinical trial, a Phase 1 safety study of the neuroprotective drug Riluzole. Based on final data analysis, NACTN will likely move to a larger efficacy trial. At the same time, the NACTN Executive and Emerging Strategy Selection Committees are exploring other clinical trial options. Its Principal Investigators (PIs) are networking with relevant US and international clinical networks and funding agencies to leverage funding, infrastructure and expertise. NACTN PIs are authoring a series of papers which will be published in the summer of 2012 in a supplementary issue of the Journal of Neurosurgery- Spine, which is featuring the work of NACTN.

BODY: The following tasks were addressed during the contract period May 17, 2007 – December 31, 2011 and were incorporated into the Statements of Work for Contract #0361 (BAA-2006) and the (2008) Sternion and (2009) Budget Modifications.

1) Enroll patients with SCI to expand NACTN's statistical model of the functional outcomes of SCI that are stratified and characterized by neurological, physiological and radiological parameters. Goal: 400 patients throughout the network.

This goal has been exceeded with the enrollment of 524 SCI patients as of December 31, 2011. The clinical centers continue to consent and admit acutely injured patients into the registry.

2) Expansion of Phase I baseline assessment research protocols for hospitals joining NACTN, working with the United States Army Medical Research and Materiel Command (USAMRMC) Office of Research Protections (ORP), Human Research Protection Office (HRPO) and local IRBs

Standardized protocols were developed and Elizabeth Toups harmonized all the institutional IRB requirements with each other and with the ORP requirements for regulatory approvals. All NACTN sites have received the required institutional review board and DOD regulatory initial, annual Continuing Review and Informed Consent Form approvals for the NACTN data registry. NACTN clinical sites are actively recruiting.

3) Expansion of NACTN to include military, Veterans Administration and additional civilian hospitals

Military expansion was one of the initial goals of DOD contract #0361 but as we periodically reported during the award's Period of Performance, financial constraints and uncertainties about continued DOD support made it fiscally impossible to take action on this task. However, the award of a second contract, #0042, mitigated the immediate financial constraints and during 2011, Dr. Grossman laid the groundwork necessary to bring the San Antonio Military Medical Center (SAMMC) into the network. As we reported in October 2011, Lt. Col. Randall McCafferty, chief of the neurosurgical service at SAMMC had arranged a visit from the Coordinating Center to finalize plans for the neurosurgical service at SAMMC to join NACTN. Elizabeth Toups, MS, RN, CCRP, NACTN Project Manager, visited SAMMC on December 5, 2011; she toured the facilities, met with Dr. McCafferty and the new NACTN team (Robert Marsh, Maj, MD, PhD [NACTN PI], Rebecca Pitotti [Research Nurse Coordinator] and Shalece Kofford [Study Coordinator] and brought them up-to-date on NACTN's activities, future plans and policies and procedures. As noted below at #4, it is anticipated that SAMMC will be an important contributor to the WRNMMC projects and a particularly valuable addition to the network because as an acute care facility, it will be able to participate in NACTN-sponsored trials of acute therapies.

The Reeve Foundation is presently working with the Henry Jackson Foundation to facilitate the NACTN award contract (HJF will act as the Contractor for SAMMC, just as it does for WRNMMC). Dr. Marsh and his team have participated on the December and January NACTN-wide conference calls.

4) Characterize the differences between military and civilian injuries and the differences in their outcomes

The WRAMC Neurosurgery Service moved to the campus of the National Naval Medical Center on 17 August 2011; WRAMC closed permanently on 15 September 2011 and a merged facility, Walter Reed National Military Medical Center, is now fully established. The patient population and ability to enroll SCI patients is directly related to the current conflicts in which the military is involved. Due to the withdrawal of military personnel in Iraq and the stable/declining number of injuries currently from Afghanistan, we do not expect to see an increase in numbers.

The project, *Characterize the Biomechanical, Anatomical and Neurological Differences between Military and Civilian Injuries and Differences in their Outcomes*, has been initiated with enrollment of twenty WRAMC patients and a retrospective component was added to collect spinal cord injury and initial outcome data from WRAMC patients for the period 1 January 2003 to 23 March 2008. Data collected will be matched to the data collected in the prospective portion of the study. In preparation, efforts are currently in progress to address the IT issue of non-accessibility of WRAMC data at the new/merged facility; recent information about data access appears promising.

WRNMMC and the Data Management Center have discussed an analysis of WRNMMC penetrating injuries along with the civilian penetrating injuries that are currently in the database; 60% of WRNMMC NACTN subjects have penetrating injuries from gunshot wounds and blast injuries. WRNMMC has been in coordination with Landstuhl Regional Medical Center (LRMC) in Germany as the initial triage for spine injuries; we are rotating a neurosurgeon from WRNMMC at LRMC who is working with the LRMC spine surgeon on initial analysis of the pattern from penetrating injuries. LRMC has become a primary transition point for the management and collection of data. Injury patterns will be compared from the start of the conflicts in 2002 to present. A change in spine fracture patterns has been observed with the use of Mine Resistant Ambush Protected (MRAP) vehicles, specifically an increase in thoracolumbar fractures from blast impact associated with an increased incidence of neurological deficit. The issue of penetrating injuries in the military population is being addressed and will give context for the NACTN penetrating injury project.

It is anticipated that the addition of SAMMC to the network will mean that the data needed to begin characterizing the differences between military and civilian injuries and outcomes will reach critical mass forthwith. It is also expected that SAMMC will be able to contribute to the penetrating injuries study. Following execution of their 2012 research agreements, we will move to facilitate cooperation and collaboration on both tasks between Walter Reed and San Antonio.

5) Expand the Data Management Center at the University of Texas School of Public Health to incorporate the increased numbers of patients in the study

The Data Registry, a core function of the North American Clinical Trials Network (NACTN), serves two vital purposes. The first is to provide a statistical and scientific platform to develop the data, logistics and collaborations necessary to conduct Phase I through Phase III clinical trials of emerging neuroprotective and neuroregenerative therapies, particularly those that can be administered in the very early stages of injury and by early medical responders. A second and equally important purpose is to develop high quality, standardized, and validated acute care and follow-up data on a representative national sample of male and female adult patients who have suffered a spinal cord injury with neurological deficits. This acute care and follow-up data are an invaluable and unique resource needed to characterize the trajectory (natural history) of individuals who have suffered a spinal cord injury.

All data are collected prospectively starting at the time of admission to a NACTN clinical center. The registry data includes extensive demographic information, past medical history, pre-injury medication use, circumstances of injury, time of injury, and the time of arrival to the treating NACTN hospital. Further detail is elicited about the condition of the patient on arrival and includes a clinical evaluation, measurement of state of consciousness with the Glasgow Coma Scale (GCS) and of associated injuries with the Abbreviated Injury

Scale. The American Spinal Injury Association impairment scale (AIS) is scored on admission and at key times throughout the patients' hospital and post-hospital course. All examiners received training on performing the AIS examination and study procedures. Data are also collected on radiographic findings, non-operative and operative treatments, timing of treatments, and perioperative complications. Discharge AIS score, and the type of facility to which the patient was transferred are recorded in the discharge form. After acute care discharge, Long-term follow-up is scheduled at approximate intervals of six and twelve months after discharge. The follow-up registry protocol includes: the AIS Impairment Scale, and where appropriate, the Functional Independence Measure FIM™, the Spinal Cord Independence Measure (SCIM), and the Walking Index for Spinal Cord Injury (WISCI) evaluations.

During this contact period the goal was to enroll 400 patients in the Network. Currently there are nine clinical centers participating in the Network and as of December 31, 2011, a total of 524 patients have been enrolled into the NACTN SCI Registry.

Registry Data Acquisition Operations

An overview of the DMC data algorithms developed and flow of manual and computer processing is given in [Appendix A](#). The DMC has developed an efficient and secure data system for acquiring and sharing registry data with NACTN investigators and others approved for data access. Data are provided in the format requested by a user and are provided with either a de-identified data file or requested tabulations. In this reporting period data files and tabulations have been provided to NACTN investigators for research purposes. Registry tabulations were also provided to Dr. Michael Wang, University of Miami, to support an NIH-NINDS research application for a clinical trial designed to evaluate hypothermia for the treatment of acute traumatic spinal cord injury. The NACTN data protocol and Information about the structure and logistics of the Registry were also requested by Dr. Paul Jennings, Department of Epidemiology and Public Health, Monash University, Melbourne, Australia for inclusion in a world-wide survey of Spinal Cord Registries.

Tables in [Appendix B](#) provide a profile of SCI cases currently in the registry database. As of 12/31/2011, clinical coordinators at Network sites have screened 971 SCI patients for meeting eligibility criteria and informed consent to record prospective, standardized acute care treatment data and follow-up data for up to one-year after acute care discharge. Fifty-four percent of all patients screened met criteria and were enrolled (Table 1). Records for an additional 36 patients are currently pending review for inclusion in the database. The following text summarizes the current registry database information for 485 registry patients in early December of 2011.

The majority of registry cases are male (79%), white (76%), and the median age at injury is 44 years for all registry patients (Table 2).

Table 3 lists the circumstances of SCI injuries. The leading circumstances of injury were falls (37%) and motor vehicle accidents (31%). Recreation accidents including sports accounted for (11%). and diving was responsible for 58% of all sports injuries. Civilian assaults accounted for 26 (5%) of all SCI injuries.

Military personnel accounted for 11 (2%) of all SCI injuries. Of these 10 were SCI injuries transferred from Landstuhl (Germany) Regional Medical Center to Walter Reed Army Medical Center (WRAMC). Four of these ten cases were penetrating bullet wound injuries, four were classified as blast injuries, 1 the result of a helicopter crash, and 1 due to an accidental fall. Nine of the ten cases were transferred 3 to 9 days of injury and one case transferred 18 days after injury. The lone stateside case was a SCI injury due to surfing and this case was transferred to WRAMC 15 days after injury from a civilian hospital in Virginia Beach, VA.

Approximately 58% of all SCI patients arrived by EMS directly to a NACTN center from the scene of injury with a median arrival time of approximately 1 hour. Of patients transferred from intermediate hospitals the arrival time post-injury at a NACTN center was 9.3 hours.

The distribution of AIS severity of patients with a first AIS within 7 days of injury is given in Table 4; AIS A (31.1%), AIS B (11.3%), AIS C (12.2%), AIS D (24.5%), AIS E (7.4%). Approximately 5% of the 485 patients did not have initial AIS within 7 days of injury.

Of the 485 cases, 41% had no reported complications or intercurrent events during acute care whereas 59% had at least one mild, moderate or severe complication; 29% had four or more complications (Table 5). Of the total number of complications ascertained during acute care (1,376) and reported in Table 6, pulmonary, infections, hematologic, and cardiac complications accounted for 75% of all complications. The in-hospital acute care death rate for the 485 registry cases was 3.7%.

The vast majority of SCI injuries were blunt injuries or crushing injuries (95%), but 4% were penetrating SCI injuries, primarily bullet injuries. Of the 485 patients, 76% sustained cervical injuries and 18% thoracic injuries (Table 7).

Surgical types and corticosteroid treatments are summarized in Tables 8 and 9. 87% of all registry patients were surgically treated and 91% of patients evaluated as AIS A through AIS D within 7 days of injury were surgically treated. 50% of AIS E patients were surgically treated. .

Two-thirds of AIS A through AIS C patients received steroids.

Length of acute care hospitalization and discharge status is summarized in Table 10. For 459 SCI patients, approximately 44% had a length of hospital stay exceeding two weeks. For AIS A patients, the median hospital stay was approximately 19 days. More than two thirds of the SCI patients were discharged to either a rehabilitation hospital (68%) and 6% were transitioned to either long-term acute care or a nursing home. Forty-three patients were discharged as either partial or complete ventilator dependent. Rehabilitation was initiated for 81% of the patients prior to discharge from acute care.

Table 11 contrasts the AIS grades at admission to the AIS grades at hospital discharge for 365 SCI patients for whom complete data is currently available. Notable is that 88% of patients with a grade of AIS A at admission remained AIS A at discharge. Although there was improvement within each AIS grade, the improvement in AIS A through AIS C patients at the time of acute care discharge was modest.

Table 12 summarizes ambulation outcomes post-injury based on the SCIM (Spinal Cord Independence Measure) mobility scores obtained on 215 patients at 6 or 12 months post-injury. The mobility scores are reported by AIS at admission and differentiates between patients who are unable to walk or are on assistance while walking (SCIM scores 0-3) and those able to walk independently (SCIM scores 4-8). Overall 132 of the 215 (61%) of patients regained ambulation, but ambulation recovery is significantly associated with the AIS severity at admission.

Summary

An important milestone was achieved in the registry during the current reporting period. The registry now has over 500 cases of acute traumatic SCI and is now poised to become a national and international resource for SCI research.

6) Further validate quantitative measurements to assess neurological recovery, including the Graded Refined Assessment of Strength, Sensibility and Prehension (GRASSP) test and computerized measurement of the force generated by the isometric contraction of muscles (PRIME)

- **GRASSP Summary:** Attached at [Appendix C](#)
- **PRIME Summary:** Attached at [Appendix D](#)

7) Begin development and validation of sensitive, reproducible outcome measures for use in clinical trials – Neurological Outcomes Assessment Initiative (NOA)

During the course of this contract period and as reported in earlier quarterly and annual reports for W81XWH-07-1-0361 and W81XWH-10-2-0042, the Reeve Foundation has issued the following research awards to advance the work of the NOA Task Force:

- Peter Ellaway, PhD, Imperial College London for “Validation of the electrical perceptual threshold test as a quantitative assessment of cutaneous sensory function for spinal cord injury trials” (NOA1-2010(PE)). The final report from Dr. Ellaway is attached at Appendix E and a manuscript is being prepared for submission to the journal Spinal Cord.
- Andrei Krassioukov, MD, PhD, University of British Columbia, (NOA2-2010(AK)) and Susan Harkema, PhD, University of Louisville, (NOA3-2010(SH)) for “Natural progression and recovery of cardiovascular parameters following traumatic spinal cord injury”. The Foundation has authorized a one-year, no-cost extension on this contract through August 31, 2012. A report on their progress to-date is attached at Appendix F.
- Susan Harkema, PhD, University of Louisville for “Brain/Motor Control-EMG Measures” (NOA4-2010(SH)).

Dr. Harkema reports that a Functional NeuroPhysiological Assessment (FNPA) laboratory has been set up at Frazier Rehab. Research data has been analyzed as a result of a longitudinal study. The protocol has been refined and we have added new protocols. Standardized equipment with 32 EMG channels, using pre-amplified electrodes, which will reduce the noise – electrostatic and physical interference (i.e., cell phones, movement of wires), and software to increase the efficiency of acquisitions as well as the accuracy has also been developed. Presently, the BMC team is validating the new software and hardware and will begin collecting data on neurologically intact individuals. Data analyses and the acquisition protocol have been streamlined and standardized.

To-date, 154 evaluations have been performed. Utilizing the new process for evaluations, 90 research files have been fully analyzed, 10 are in progress and there are 8 files that cannot be analyzed. The team continues to collect data on research participants as they finish various stages of training and is beginning to implement the FNPA as a standard clinical tool in outpatient therapy at Frazier Rehab Institute.

A manuscript will be submitted to the Journal of Neurosurgery-Spine Supplemental NACTN Issue. Dr. Harkema is preparing an R01 grant for submission to the National Institutes of Health, to be submitted on February 5th.

- Michael Fehlings, MD, PhD, University Health Network (University of Toronto) for “The use of MRI characteristics to predict long-term functional and neurological outcomes after acute spinal cord injury” (NOA5-2011(MF)). A progress report is attached at Appendix G.

8) Expanded NACTN contributes to ongoing Surgical Treatment of Acute Spinal Cord Injury Study (STASCIS)

Michael F. Fehlings, MD, PhD was Co-Principal Investigator of the multicenter, international, prospective controlled study STASCIS (Surgical Trial in Acute Spinal Cord Injury Study: STASCIS) in adults aged 16-80 with cervical SCI, to evaluate the impact of early (<24 hours after injury) or late (≥24 hours after injury) decompressive surgery. The primary outcome was ordinal change in AIS grade at 6 months follow-up. Secondary outcomes included assessments of complications rates and mortality. Findings were that early decompressive surgery after cervical SCI can be performed safely and is associated with improved neurologic outcome. Furthermore, early surgery may result in reduced rates of major complications. Four NACTN sites (Toronto, Maryland, Thomas Jefferson and Virginia) took part in the study.

During the course of 2011 several projects based on original data from the Surgical Trial in Acute Spinal Cord Injury Study (STASCIS) have been undertaken. The three projects are described below, beginning with the primary STASCIS analysis. In addition, any publications, presentations or awards associated with these projects have been detailed.

#1) Early versus Delayed Decompression for Traumatic Cervical Spinal Cord Injury: Results of the Surgical Timing in Acute Spinal Cord Injury Study (STASCIS)

Study Objectives: There is convincing preclinical evidence that early decompression in the setting of spinal cord injury (SCI) improves neurologic outcomes. However, the effect of early surgical decompression in patients with acute SCI remains uncertain. Our objective was to evaluate the relative effectiveness of early (<24 hours after injury) versus late (≥24 hours after injury) decompressive surgery after traumatic cervical SCI.

Methods: We performed a multicenter, international, prospective cohort study (Surgical Timing in Acute Spinal Cord Injury Study: STASCIS) in adults aged 16-80 with cervical SCI. Enrolment occurred between 2002 and 2009 at 6 North American centers. The primary outcome was ordinal change in ASIA Impairment Scale (AIS) grade at 6 months follow-up. Secondary outcomes included assessments of complications rates and mortality.

Results: A total of 313 patients with acute cervical SCI were enrolled. Of these, 182 underwent early surgery, at a mean of 14.2(±5.4) hours, with the remaining 131 having late surgery, at a mean of 48.3(±29.3) hours. Of the 222 patients with follow-up available at 6 months post injury, 19.8% of patients undergoing early surgery showed a ≥2 grade improvement in AIS compared to 8.8% in the late decompression group (OR=2.57, 95% CI:1.11,5.97). In the multivariate analysis, adjusted for preoperative neurological status and steroid administration, the odds of at least a 2 grade AIS improvement were 2.8 times higher amongst those who underwent early surgery as compared to those who underwent late surgery (OR=2.83, 95% CI:1.10,7.28). During the 30 day post injury period, there was one mortality in both of the surgical groups. Complications occurred in 24.2% of early surgery patients and 30.5% of late surgery patients (p=0.21)

Conclusions: Decompression prior to 24 hours after SCI can be performed safely and is associated with improved neurologic outcome, defined as at least a 2 grade AIS improvement at 6 months follow-up.

Presentations:

This Analysis presented at:

The 2011 Congress of Neurological Surgeons in Chicago, IL. Oct 2011.

The 2011 Cervical Spine Research Society Meeting in Scottsdale, AZ. Dec 2011.

Awards:

Best Clinical Research Paper at 2011 Cervical Spine Research Society Meeting.

#2) The Impact of Facet Dislocation on Clinical Outcomes after Cervical Spinal Cord Injury: Results of a Multicenter North American Prospective Cohort Study

Study Objectives: Reports of dramatic neurological improvement in patients with Facet Dislocation (FD) and cervical SCI, treated with rapid reduction, have led to the hypothesis that this represents a subgroup of patients with significant recovery potential. However, without a large systematic comparative analysis, this hypothesis remains untested. Our main objective was to define differences in baseline characteristics and long-term clinical outcomes between cervical SCI patients with and without FD.

Methods: Patients were classified into FD and non-FD groups based on imaging investigations at admission. The primary outcome was change in ASIA motor score (AMS) at 1-year follow-up. Secondary outcome measures included ASIA Impairment Scale (AIS) grade conversion and Functional Independence Measure score at 1-year post injury, as well as length of acute hospitalization. Baseline characteristics and long-term outcomes were also compared between patients with unilateral and bilateral FD.

Results: Of 421 patients enrolled, 135(32.1%) had FD and 286(67.9%) had no FD. Patients in the FD group had a significantly worse presenting AIS grade and higher energy injury mechanisms (p<0.01). Bilateral FD patients had a greater severity of baseline neurological deficit compared to those with unilateral FD, as measured by AIS grade and AMS. The mean length of acute hospitalization was 41.2 days amongst FD patients and 30.0 amongst non-FD patients (p=0.04). At 1-year follow-up, FD patients experienced a mean AMS improvement of 18.0 points, whereas non-FD patients experienced an improvement of 27.9 points (p<0.01). In performing an adjusted analysis, with backwards elimination of predictors with a p-value>0.05, FD patients continued to demonstrate less AMS recovery as compared to the non-FD patients (p=0.04).

Conclusion: As compared to those without FD, cervical SCI patients with FD tended to present with a more severe degree of initial injury and displayed less potential for motor recovery at 1-year follow-up.

Presentations: Analysis presented at:

Global Spine Congress. Barcelona Spain. March 2011

American Association of Neurological Surgeon, Annual Meeting. Denver CO, April 2011.

#3) A Clinical Prediction Model for Long-Term Functional Outcome after Traumatic Spinal Cord Injury Based on Acute Clinical and Imaging Factors

Study Objectives: To improve the ability of clinicians to predict long-term outcome in the acute clinical setting and to aid in the classification of patients within clinical trials, we planned to create a clinical prediction rule which relates a combination of acute neurological exam and imaging findings, as well as demographic information, to functional outcome at 1 year post SCI. To validate this model internally, a bootstrap resampling procedure was used.

Methods: We performed a combined analysis of 2 prospective SCI datasets enrolling patients from North American trauma centers between 2002 and 2010. The cohort of interest included patients ≥ 16 years old with traumatic SCI and a standardized American Spinal Injury Association (ASIA) neurological examination performed within 3 days of injury. Functional Independence Measure (FIM) motor score at 1 year follow-up was the primary outcome. Functional independence (score ≥ 6 for each FIM-motor item at 1 year) was the secondary outcome.

Results: Of 729 patients, 376 met the inclusion/exclusion criteria. The mean FIM-motor score at 1 year was 62.9(± 28.6). Better functional status was predicted by less severe initial ASIA grade and by thoracolumbar level of injury as compared to a cervical level. In contrast, older age and MRI intra-medullary signal characteristics consistent with spinal cord edema or hemorrhage, predicted worse functional outcome. The linear model predicting FIM motor score demonstrated an R-square of 0.54 in the original dataset and 0.53 across 200 bootstrap validation replicates, with parameter estimates for each covariate across the bootstraps closely approximating estimates from the original dataset. Functional independence was achieved by 148 patients(39.4%). For the logistic model based on dichotomized functional independence, the area under receiver operator curve was 0.92, indicating excellent predictive discrimination.

Conclusion: We present the first prediction model that uses acute data to predict functional status at 1 year follow-up in patients with SCI. This model will have important clinical impact to guide decision making and to counsel patients and families.

Awards:

Synthes Spinal Cord Injury Resident Research Award, American Association of Neurological Surgeons. November 2011.

9) Contribute to a Phase II study of anti-Nogo antibody treatment for SCI (ATI533)

As reported at the start of contract #0361, the Reeve Foundation has supported development of the humanized anti-Nogo antibody since 1988 through awards to Martin Schwab, PhD, University of Zurich, initially through its Individual Research Grants program and since 1994, through its International Research Consortium on Spinal Cord Injury. Under the Consortium aegis, Schwab and his colleagues have begun to investigate combinatorial interventions using the anti-Nogo antibody and other interventions, for example, locomotor training (Maier et al, 2009) and chondroitinase and the NMDA-NR2d subunit (Schnell et al, 2011).

The Novartis CATI355 clinical trial, a Phase I safety study of the humanized anti-Nogo antibody was underway at the start of contract #0361. Since then, as updated in our quarterly and annual reports, NACTN investigators have had ongoing interactions with the ATI355 Novartis team – Dr. Grossman has met repeatedly with company representatives and has attended trial planning meetings in Switzerland. Dr. Grossman developed the IRB Informed Consent Form for the trial at centers to be used in the United States. Charles Tator, MD, PhD (NACTN co-PI, Toronto) is a member of the trial's Data Safety Monitoring Board. NACTN's Methodist Hospital and University of Toronto clinical centers had IRB approvals for the Phase I study. As we reported in October 2011, Dr. Klaus Kucher, Executive Director, Novartis TM Neuroscience, notified Dr.

Grossman a month earlier that the “Last Patient Last Visit” of the CAT1355A2102 trial was recently completed and that data cleaning was underway in order to reach database lock for full evaluation of the study.

In a January 16, 2012 email, Dr. Kucher advised that the clinical team is close to database lock and as soon as this important milestone has been reached, writing of the clinical study report will begin. He is planning to kick off evaluation of EM-SCI (European Multicenter Study about Spinal Cord Injury) data with a three-day meeting at Balgrist Hospital, Zurich, in early February with the goal of establishing a reliable stratification algorithm that would serve as basis for further studies.

10) Test the potential of Amnion-derived Multipotent Progenitor cells (AMPCs) to promote recovery after spinal cord injury (SCI)

On January 1, 2008, the Reeve Foundation issued an award to the University of California Irvine for a project headed by Aileen Anderson, PhD, “Efficacy of amnion derived multipotent progenitor cells (AMPCs) for acute spinal cord injury (SCI)”. The study was funded through a modification of the present award, W81XWJ-07-1-0361. Dr. Anderson, who is Scientific Director of the Foundation’s Animal Core Laboratory at UC Irvine, is well-known for her expertise in animal modeling and neurotransplantation and stem cell research. The final report on the contract was submitted to DOD on January 20, 2011. Since then, further studies have been ongoing:

P51.3 Project - Histology Stereology

Stereological analysis has been completed for fibronectin volume, NG2 volume, GFAP scar volume, and Lesion Core (GFAP negative Volume). Statistical analyses were conducted using one-tailed Students t-tests comparing Media vs. hAMPs. Analyses indicated no differences between the groups in either time point (Figure below). Given the observation of behavioral recovery with hAMP treatment on multiple metrics, the lack of a histological correlate is surprising. To further address alternative mechanisms of action, immunohistochemistry is currently underway to analyze the number of CC1 positive cells near the lesion site, to determine if hAMPs had an effect on the number of oligodendrocytes. CC1 cells will be quantified with the Optical Fractionator probe using MBF StereoInvestigator. After completion of this analysis and the parallel stereological metrics for P1.4 below, we will submit for publication.

P51.4 Project -Histology/Stereology

Final analyses in progress for publication; code has not been broken for data summary.

11) Conduct a phase I safety and pharmacokinetics trial of Riluzole, a sodium channel blocking agent with anti-glutaminergic activity, shown to have strong neuroprotective effect in experimental spinal cord injury

Riluzole Trial Update - The primary objective of NACTN is to conduct Phase I - III clinical trials of emerging neuroprotective and neuroregenerative therapies, particularly those that can be administered in the acute stages of injury. NACTN’s first trial is that of Riluzole, whose neuroprotective mechanisms of action includes block of slowly inactivating sodium (iNaP) channels, up-regulation of glutamate-1 transporter (GLT-1) in astrocytes and amplification of heat shock-1 (HSF-1) molecular chaperone. Patient inclusion criteria were: Age 18-70, Male and Female, C4-T12 injury, ASIA Impairment Scale scores A, B or C. Protocol: PO or NG administration of Riluzole within 12 hours of injury, 50 mg q12h for 14 days. The target enrollment of 36 SCI patients was carried out between 4/12/10 - 6/20/11. The last 6 month follow-up examination was completed in December. The goals and protocol requirements of the study were met. Tables in Appendix H provide a profile of patients enrolled in the Riluzole trial as of 12/31/2011. The patients enrolled in the trial were admitted to NACTN center hospitals within seven hours of injury. Riluzole was administered between 3.7 hours and 12.1 hours after injury. The majority of patients were male (83%), college educated (50%), and were employed at the time of injury (72%). Patients ranged in age from 18 to 69 years with a median age of 37 years. The ethnic distribution was White (64%), Black (28%), and Asian (8%). Motor vehicle accidents were the leading cause of injury (47%), followed by falls (25%), diving accidents (14%) and assault (6%). Pre-existing health problems were present in 28% of patients. Hypertension was the most prevalent co-morbidity. Cervical injuries predominated (81%); 19% were thoracic injuries. The distribution of ASIA Impairment Scale (AIS) severity of neurological deficit scores was: AIS A (n = 19, 53%), AIS B (n = 9, 25%), and AIS C (n = 8, 22 %).

Corticosteroids, commonly administered for treatment of SCI, were received by 35% of patients; 41% of AIS A patients received steroids. Surgical decompression of the spinal cord and stabilization of the spinal column were utilized in 33 of the 36 patients. Anterior plus posterior surgeries (47%) and posterior surgeries (32%) were the most common surgical approaches. The median time to surgery was 13.1 hours post-injury. The median time to surgery in a cohort of 128 comparable patients in the NACTN registry of SCI patients was 17.3 hours. Pharmacokinetic and pharmacokinetic analyses show that Riluzole peak and trough plasma levels were comparable to those reported in ALS patient receiving Riluzole treatment. Plasma concentrations on Day 14 were lower than on Day 3, resulting from a high clearance and change in volume distribution of Riluzole. To determine the safety of the administration of Riluzole, medical complications were tabulated and compared with those sustained by the historical control group. The incidence of severe complications was not significantly different between the Riluzole and the control group. No SAEs have been identified with probable links to Riluzole. No deaths have occurred in the safety trial.

Riluzole Treatment and Liver Enzyme Levels- It has been previously reported in the literature that prolonged use of riluzole induces elevated liver enzyme levels in ALS patients.) Spinal cord injury has been reported to produce a modest elevation of liver enzymes. The mechanism of this elevation is not known. Monitoring liver enzyme levels was a priority in this safety trial. Liver enzyme panels were obtained from each patient at baseline and days 3, 7, 10 and 14 of Riluzole treatment and at follow-up examinations. The liver panels included blood-level measurement of alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), and Bilirubin levels.

The Methodist Hospital Clinical Coordinating Center (TMH-CC) reviewed and standardized the liver enzyme panels from each clinical site. To date, complete verified panels are available for 33 of the 36 patients. Thus far, only one severe elevation of GGT has been recorded and this elevation was recorded on day 14 of Riluzole treatment. GGT elevations are not specific for liver dysfunction but are also associated with muscle dysfunction and other organ dysfunctions. One patient was withdrawn from Riluzole at day 7 of treatment with a moderately elevated GGT. The GGT level returned to baseline at the time of follow-up visit. Overall, the incidence of mild elevations liver enzymes was common, but moderate or severe elevations during treatment were infrequent.

Riluzole Pharmacology Analysis - the individual pharmacokinetic and population pharmacokinetic analyses of all 36 patients have been completed. The major finding is that Riluzole peak and trough concentrations on Day 14 were significantly lower than those on Day 3 for the patient population, resulting from a higher clearance (CL) and larger volume distribution (V) of Riluzole on Day 14 as compared those on Day 3.

Potential causes of lower plasma level of Riluzole on Day 14 compared to Day 3

1. Drug –drug interaction due to enzyme induction from concomitant medications
2. Change in hepatic blood flow: SCI may cause re-distribution of blood flow to the brain, heart and other highly perfused organs including the liver. (J Neurotrauma, 23:75-85, 2006)
3. Changes in intravascular volume and extracellular fluid volumes. However, there is no apparent fluid imbalance of Intake and Output during 14 days.
4. A decrease in blood concentration of albumin, to which Riluzole binds. Albumin may be decreased due to decreased protein synthesis after SCI. This would allow Riluzole to escape into the extracellular fluid.

The ASIA motor and sensory scores were compiled for 36 patients. Correlations are being made between PK and PD parameters with these scores, and with levels of liver enzymes.

Patient follow-up visits are underway with the “last patient last 6 month follow-up visit” due December, 2011. All 36 patients have completed baseline, 32 of 36 patients have completed 3 month follow-up; 28 of the 36 have completed 6 month follow-up and 2 are lost to follow-up. The 3 month, 6 month follow up log is attached, [Appendix I](#).

Manuscripts describing the planning of the Phase I study for the JNS-Spine Supplement and the pharmacology of Riluzole are attached as [Appendix J](#) and [Appendix K](#), respectively.

Rates of Complications in the Experimental Group as Compared to the NACTN SCI Data Registry –

1. Phase 1 Preliminary Findings –Pharmacological analysis: Particular care was made to track adverse events previously associated with riluzole administration in the ALS literature, particularly hepatotoxicity. Baseline blood work included alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma glutamyl transpeptidase (GGT), bilirubin, prothrombin time (PT) and international normalized ratio (INR). Therapeutic peak and trough plasma levels of Riluzole were achieved at day 3 and day 14 of Riluzole administration for all participants.
2. Safety: Throughout the course of this study, adverse events were carefully monitored for each participant. Data was recorded on a wide range of adverse events including infections, respiratory complications, cardiovascular events, deep vein thrombosis/pulmonary embolus, skin breakdown, and neuropathic pain. All serious adverse events were reported to the coordinating center and to the central medical monitor. There were no riluzole related serious adverse events (SAEs) among the 36 patients enrolled in the study. The rate of SCI related complications in the Riluzole group was similar to that in a control group of matched patients from the NACTN registry. No riluzole related serious adverse events (SAEs).
3. Neurological Outcome: Comparison of the ASIA Impairment Scores (AIS) on admission and at three month examinations, Riluzole treated patients who reached the 3 month follow-up, with a control group of matched patients from the NACTN registry show a trend toward greater improvement in the Riluzole treated patients. The number of patients is small and other factors such as very early surgical decompression and stabilization may be playing a role in the outcome of the Riluzole treated patients (although the historical control group had decompression and stabilization almost as early as the Riluzole treated group).

12) Organize and implement training for NACTN sites to insure standardized assessment of spinal cord injury using ASIA, SCIM, FIM and the WISCI-II scales with rigorous training in accordance with the standards set by the American Spinal Injury Association

Earlier DOD report submissions detailed NACTN-wide meetings whose goals were to educate NACTN personnel about the data registry and the Riluzole Phase I clinical study and to inculcate a sense of ownership in NACTN's goals, responsibility for NACTN's success and excitement about prospects for advancing therapies for spinal cord injury.

The first NACTN-wide meeting was held at The Methodist Hospital in February 2008 and was attended by Principal Investigators, Study Coordinators, the Data Management team and Dr. Diana Chow (Pharmacology Center at the University of Houston). The agenda focused on the Phase I Riluzole safety study, then in the planning stages, its protocol (inclusion/exclusion criteria, administration, data collection and transmission), the pharmacology/pharmacokinetics of Riluzole, the study's organization and logistics). Discussion was also devoted to a possible collaboration with the Neurological Emergencies Treatment Trials network; other potential funding opportunities; publications and upcoming training meetings.

Subsequently, two training meetings (for ASIA, FIM, SCIM, WISCI) were held at the NACTN clinical center at the University of Louisville/Frazier Rehab Institute, Louisville, KY on June 2 - June 3, 2008 and August 4 – August 5, 2008. They were led by Ralph Marino, MD (Project Director & Clinical Director, Regional Spinal Cord Injury Center of the Delaware Valley & Thomas Jefferson University Hospital (a NACTN clinical center) who was then chair of the Neurological Standards Committee for the American Spinal Injury Association; Mary Schmidt Read, PT, MS, Program Director of the Regional Spinal Cord Injury Center of the Delaware Valley as the Spinal Cord Injury Program Director and Research Coordinator at Magee Rehabilitation Hospital; and Steve Williams, MD, Chief and Chairman, Department of Physical and Rehabilitation Medicine, Boston Medical Center and director of the Foundation's NeuroRecovery Network Center at BMC. Dr. Williams was study monitor for the Phase I Riluzole trial.

NACTN personnel required to attend these meetings were:

- ASIA assessors for each NACTN center – it was mandatory that all centers send their assessors, those

study coordinators, physicians (or others) who were at that time or would later be testing patients for the data registry and/or riluzole study

- Other personnel NACTN PIs believed critical to the team.
- All NACTN PIs were encouraged to attend (virtually all did).

The August meeting also included a several-hour review of the Riluzole protocol, with all NACTN personnel in attendance.

A final Riluzole training/site initiation meeting was held at The Methodist Hospital January 14-15, 2009.

Agenda items included: an overview of the basic/preclinical research behind Riluzole and review of the clinical protocol; safety and SAE reporting, pharmacy procedures, clinical laboratory services; case report forms, data management process and monitoring and finally, presentations on the regulatory, sample-patient and investigator binders. As was the case with the earlier meetings, each site's NACTN team was represented at the meetings.

Beginning in 2010, as reported in earlier quarterly and final submissions, NACTN initiated monthly conference calls for (i) NACTN study coordinators – led by Elizabeth Toups, MS, RN, CCRP; (ii) Principal Investigators and coordinators, led by Dr. Grossman; and (iii) NACTN's Executive Committee. These regularly scheduled discussions are the glue which holds together NACTN's teams and they have facilitated standardization across all the sites. At its most recent call on January 18, 2012, the Executive Committee agreed to plan for another NACTN-wide meeting to finalize the Riluzole Phase IIb protocol (a draft has been written by Michael Fehlings, MD, PhD). This meeting will occur before the end of Q1 2012.

13) Further expand NACTN through ongoing collaborations with the European Multicenter Study about Spinal Cord Injury (EM-SCI) and through a new collaboration with the Canadian Spinal Cord Injury Translational Research Network (SCI-TRN), continued interactions with other clinical networks

- NACTN is collaborating with AOSpine International on a project to merge four spinal cord registry databases for the purposes of research: The four are NACTN, EM-SCI, STASCIS and the Rick Hansen Data Registry. The combined files are being developed to answer specific research questions in four areas related to (i) incomplete SCI, (ii) complications/intercurrent events, (iii) surgical timing and (iv) central cord injury. The number of SCI cases in such a merged database would be the largest sample of prospective SCI acute care and follow-up clinical case information ever assembled and would be capable of supporting research that would not otherwise be possible. The merged databases include the North American Clinical Trials Network (NACTN PI: Dr. Robert Grossman), the Rick Hansen Spinal Cord Injury Registry (RHSCIR PI: Dr. Marcel Dvorak), the Surgical Trial in Acute Spinal Cord Injury (STASCIS PI: Dr. Michael Fehlings), and the European Multicenter Study for Human Spinal Cord Injury (EM-SCI PI: Dr. Armin Curt). The NACTN Data Management Center (PI: Dr. Ralph Frankowski) completed a detailed questionnaire about the recording of NACTN registry data and provided AOSpine International with a copy of the current NACTN case report forms. On Dec 15, 2011, a meeting of the PIs was held in Davos to discuss the feasibility of the project and the decision was made to proceed with planning and logistics for merging these four large and complex clinical databases. Underway is the development of a common data-sharing and research agreement (Dr. Langer) to allow for the project to proceed. The current thinking is that AOSpine will contribute the infrastructure to perform the proposed database merge.
- On 12/20/2011, at the request of Dr. Naomi Kleitman, NINDS Program Director Repair and Plasticity, requested information about NACTN and NeuroRecovery Network (NRN) data collection methods for inclusion in the NINDS Common Data Elements (CDE) project. With assistance of NRN staff, copies of the NACTN Registry Forms, NRN Electronic Data Capture System, and a list of elements common to both NACTN and NRN were sent to Dr. Kleitman for inclusion in the CDE project. The NINDS CDE project goal is to collect existing data forms from SCI registries and related national and international SCI research projects to assess communalities and to develop a consensus on a Core Research Data elements and standardized definitions for SCI research. NACTN and NRN join other registries in this project, including the SCI Model Centers, EM-SCI and the Rick Hansen Registry; it is anticipated that data forms from the Proneuron and Sygen trials will also be incorporated in this NINDS project.

Once the CDE data forms collection phase is completed then the NINDS plan is to convene a group of SCI researchers, including NACTN and NRN investigators, to develop common data form templates and definitions for SCI research.

- As reported in the October 2011 quarterly report, NACTN database will be linked with that of the NeuroRecovery Network (NRN) through a program called CrossIQ. ITW is a medical records and data collection web application with a data center that is used by the NRN for data collection. It allows sites to have a single point of entry for their medical records and research collection, eliminating paper forms, providing error correction at the point of entry and reducing duplicate entry of data. CrossIQ integrates with ITW and enables tracking of patients across NACTN and NRN sites. This will enable new longitudinal types of analysis, a potentially powerful research tool. The programming required to support the NACTN database and integrate with the NeuroRecovery Network database has been completed. We have initiated the installment at the first two sites, Thomas Jefferson and the University of Louisville, with the expectation of having all sites incorporated by the end of 2012.
- As reported in our June 30th narrative, NACTN and EM-SCI are collaborating on a data-sharing project that is investigating a discrete research question: to determine in SCI patients who have received the current best standard of care treatment for their injury, the mean and standard deviation of ASIA scores for upper and lower muscles during the course of recovery. The goal is to describe the natural history of the outcome of spinal cord injuries at specific injury levels (e.g., C4, C5, etc.) to use as a historical control group in clinical trials of new therapies. Knowledge of the mean recovery of function and the variability are necessary for calculating how many patients must be enrolled in a trial to determine if a particular numerical improvement in muscle strength is statistically significant. Research on this project continues apace. It is probable that additional projects using the merged data will be initiated.

14) Write and submit a planning grant proposal to the National Institutes of Health (NIH) for the design of the phase IIb riluzole clinical trial

Following the suggestion of Dr. Naomi Kleitman, Program Director, Repair and Plasticity at the National Institute of Neurological Disorders and Stroke (NINDS), NACTN vigorously pursued collaboration with NETT (NIH's Neurological Emergencies Treatment Trials Network). Under the leadership of Michael Fehlings, MD, PhD, who knows many of the NETT leaders, NACTN investigators held several calls with NETT PIs, trying to establish common ground that would have facilitated collaboration. However, it became apparent that NETT does not have the neurosurgical/spinal cord injury expertise needed to conduct trials of SCI therapies and its investigators are not inclined to expand their repertoire at this time. We also aggressively pursued NIH funding. The first NACTN/NINDS meeting was held in November 2010, followed by a second on February 25, 2011. Drs. Grossman, Ralph Frankowski, Charles Tator, Susan Harkema and Susan Howley met with Dr. Storey Landis (Director, NINDS) and her team (Dr. Walter Koroshetz, Deputy Director; Dr. Paul Scott, Office of Science Policy & Planning; Dr. Bob Zalutsky, Senior Science Policy Advisor; Dr. Petra Kaufmann, Director Clinical Research; and Dr. Naomi Kleitman) to identify synergies between the two entities; our March 9th letter to Dr. Landis, attached as **Appendix L** is an accurate summary of the meeting outcomes. NINDS is philosophically averse to providing infrastructure support for disease-specific clinical trial networks but NACTN was encouraged to consider applying ad hoc for clinical trial support. At its January 18th 2012 conference call, the Executive Committee agreed to pursue this with Dr. Naomi Kleitman, per the outcome of the February 2011 meeting.

Additionally, Dr. Fehlings is exploring a collaboration with AO Spinal International, which is an international community of spine surgeons, orthopedic surgeons, neurosurgeons, academics, researchers and other spine care professionals dedicated to delivering knowledge, experience, and evidence to improve patient care and outcomes. AO Spine has recently identified traumatic spinal cord injury as one of four discrete areas of focus. AO Spine has set up Knowledge Forum Committees (AOKF) which correlate with the focus areas. The SCI Committee is chaired by Dr. Fehlings. Drs. Grossman and Aarabi from NACTN are two of the other four members of the committee.

15) Create NACTN committees to facilitate its research

An organizational paradigm shift occurred in NACTN during 2010. In response to 9/2007 PLR recommendations, NACTN and the Reeve Foundation wrote and in March 2010, formally adopted a Governance Manual to inform network activities, deliberations and decision-making. A network-wide reorganization led to the distribution of responsibilities across committees. NACTN is now led by an Executive Committee and Standing Committees include Publications, Data Management, NOA and Treatment Strategy Selection Committees. These committees meet regularly by telephone conference (the Executive Committee meets monthly) and minutes are taken and posted on the NACTN ftp site maintained by the Reeve Foundation.

In August 2011, the Reeve Foundation and NACTN's Executive Committee reviewed and revised the Governance Manual to reflect the Network's evolving needs. These included, but were not limited to development of a policy on Confidentiality to engender an environment of collegiality and trust that can facilitate the effective pursuit of NACTN's mission through open, honest and professional exchanges of ideas and the orderly and rigorous pursuit of NACTN-related activities. Significant changes to policies related to Requirements of Individual Sites, Informed Consent and Contracts and Reporting in order were made to infuse more rigor and accountability into NACTN's operations and activities.

- Executive Committee (Chair, Robert G. Grossman, MD; Ralph Frankowski, PhD, Michael Fehlings, MD, PhD and Susan Harkema, PhD) – provides governance and addresses long-term issues critical to the goals and objectives of NACTN. Monthly Executive Committee conference calls are held the third Wednesday of every month. Minutes of the October 2011 conference call are attached in [Appendix M](#).
- The Publications Committee (Chair, James Harrop, MD) facilitates dissemination of NACTN data via publications and/or other presentations and insures their integrity.

The primary focus of the Publications Committee, as noted in earlier reports, has been on the Journal of Neurosurgery – Spine Issue's invitation to NACTN to provide the content on spinal cord injury to be published in the summer of 2012. Technical and production support for this issue is being provided by AO Spine North America via Spectrum Research, Inc. January 30th was the deadline for submission of manuscripts. Papers are either systematic reviews (e.g. "Cell-based Therapies or primary data (e.g. "The GRASSP outcome measure for hand and upper extremity function").

Minutes of the most recent Publications Committee conference call (December 2, 2011) are attached at [Appendix N](#) and [Appendix O](#) is a final list of submitted manuscripts and authors.

- NOA (Chair, Susan Harkema, PhD) guides NACTN's development, testing and validation of sensitive and reliable motor, autonomic, sensory, pain and quality of life outcome measures to detect incremental improvements in patients (reference Section 7, above)
- The Treatment Strategy Selection Committee (Chair, Charles Tator, MD, PhD) is charged with soliciting and/or otherwise identifying potential new SCI therapeutics; reviewing the animal and preclinical data and formulating a recommendation to the Executive Committee as to whether or not NACTN should consider testing a particular intervention in clinical trial. As reported in mid-2011, this Committee expanded its membership to include Naomi Kleitman, PhD, Program Director Repair and Plasticity, NINDS (she represents NIH as "Federal Liaison" to NACTN) and James W. Fawcett, PhD, Cambridge University and a member of the Reeve Foundation's International Research Consortium on Spinal Cord Injury. Dr. Fawcett was invited to strengthen the basic science perspectives of this committee's deliberations
- The Data Management Committee (Chair, Ralph Frankowski, PhD) works closely with the Publications Committee to facilitate dissemination, publication and presentation of NACTN data and insure their integrity and to develop and monitor policies for data dissemination that comply

with IRB requirements for the protection of personal health information and access to publicly supported databases.

16) Administrative Core Activities

The functions of the NACTN Administrative Core are several-fold but they all are intended to insure uninterrupted fiscal and administrative support for the Coordinating Center and NACTN personnel and activities. CRF staff administers the award funds and the organizational aspects of NACTN and responsibilities include but are not necessarily limited to: (i) network funding; (ii) distribution of funds to NACTN sites via legally binding one-year contracts; (iii) fiscal integrity of network operations and activities; (iv) fulfilling all reporting obligations to DOD and any other funding agencies; (v) oversight of all NACTN activities to insure compliance with funding requirements and contract SOWs; (vi) providing ad hoc support to the Coordinating Center and/or other NACTN sites and personnel; (vii) networking nationally and internationally to insure NACTN's effectiveness as a resource to the field and represent its interests as appropriate.

During #0361 POP, the Administrative Core has been involved in the following:

1. Network expansion – as of May 14, 2007, there were five NACTN sites, The Methodist Hospital, University of Toronto, University of TX Houston Health Science Center, University of Virginia, Northwestern University/Rehabilitation Institute of Chicago and University of TX Houston School of Public Health (Data Management Center). Under #0361, the following changes have occurred: Northwestern University withdrew from the network and the following sites were added: WRNMMC, University of Louisville, University of Maryland, University of Miami, Thomas Jefferson University and University of Houston (Pharmacology Center). Through DOD contract W81XWH-10-2-0042, NACTN will be expanding to a second military hospital; effective January 1, 2012, San Antonio Military Medical Center will join the network.
2. Network funding – NACTN has been supported by two DOD contracts, #0361 and #0042 (POP July 17, 2010 – July 18, 2012). Efforts directed at seeking, implementing and reporting on these contracts have been detailed through #0361 POP quarterly and annual reports. The Administrative Core has also been closely involved in seeking to identify other, complimentary sources of funding, primarily through the National Institutes of Health (reference #14, above).

As reported in our 10-19-2011 #0036-#0042 combined quarterly report, NACTN has submitted a full application in response to the RFA from the Department of Defense Congressionally Directed Medical Research Programs Spinal Cord Injury Research Program. The proposal for the study, *"A Phase II Trial of Body Weight Support Locomotor Training in Gait Rehabilitation after Spinal Cord Injury: A Collaboration of NACTN and NRN,"* was submitted December 1, 2011. The application is attached at [Appendix P](#).

Dr. Susan Harkema and Gail Forrest, PhD, NRN Director at Kessler Rehabilitation, are collaborating on an RO1 grant application (due 2/5/2012) on GRASSP/Functional Neurophysiological Assessment / MRI Imaging.

NACTN will continue to pursue any and all federal and nonprofit organization funding opportunities that are appropriate.

More recently, NACTN has been exploring opportunities to interact with pharma and biotech companies in an effort to push translation forward and secure new revenue streams. As noted in an earlier report, NACTN's reputation is growing and it has become routine to entertain requests from companies and academic laboratories to explore the network's involvement in clinical studies. One of the most promising potential collaborations involves BioAxone, a Florida-registered company that is developing and commercializing Cethrin, a therapeutic protein, as a treatment for spinal cord injury. The Phase I/II outcomes, published in the Journal of Neurotrauma last year (Fehlings et al, 2011) and at that time, Lisa McKerracher, PhD, BioAxone's Chief Executive Officer, approached the Reeve Foundation to explore collaborative opportunities. In this instance, funding for both the company and NACTN is a challenge. Dr. McKerracher is working to raise capital to support testing the drug in a Phase IIb trial and NACTN is actively seeking continued support from DOD and other sources. That notwithstanding, discussions

between the principals are underway to define the nature of a NACTN/BioAxone collaboration which could involve one or more of these: (i) some or all NACTN sites join some/all of the Phase I/IIa non-NACTN sites for the IIb study; (ii) NACTN contributes to the clinical planning and trial design; (iii) Reeve Foundation provides patient resources to study subjects; and (iv) a financial relationship is created wherein the Reeve Foundation is repaid for in-kind and direct financial contributions (if any) to the Cethrin program. At this writing, the way forward is unclear but it is likely that NACTN will contribute to the BioAxone effort.

A second possible collaboration involves Acorda Therapeutics of Hawthorne, NY whose mission is to develop therapies that restore neurological function. (The original impetus for talks with Acorda came from Kenneth C. Curley, Neurotrauma Portfolio Manager, combat Casualty Care Directorate [RAD2] USAMRMC.) AC105 is a proprietary magnesium formulation licensed by Acorda in 2011 and it has impressive preclinical data behind it (demonstrating neuroprotective properties that have led to improved locomotor function in SCI and cognitive function in TBI. It has completed a Phase I study in healthy volunteers. Working through NACTN's Treatment Strategy Selection Committee, early exploratory discussions have been fruitful and Dr. Grossman and Susan Howley will visit Acorda headquarters on February 13th for extended discussion about Phase II resources, timing, funding and other related issues. As with the BioAxone relationship, there are funding challenges inherent in any AC105 trial but there are also potential fundraising opportunities.

3. NACTN organization: The Administrative Core took the lead on this important effort (reported in detail above at #15). Dr. Susan Harkema and Susan Howley drafted the first iteration of the Governance Manual, which was then reviewed by Dr. Grossman and improved upon. It established the policies and procedures by which NACTN functions and provided the roadmap for NACTN to transform into a Committee-driven organization. The Executive Committee is responsible for implementation of all adopted policies and procedures.

All NACTN committees, with the exception of the Executive Committee, meet at least quarterly or more often if need be. The Executive Committee convenes by phone regularly on the third Wednesday of every month. Earlier on that day, NACTN-wide conference calls include study coordinators (4:30EDT – 5PM) followed by Principal Investigators and coordinators (5EDT-5:30PM). These routine interactions have resulted in tangible improved communications, efficiencies (particularly in the conduct of the Riluzole study and data collection) and future planning. They are also facilitating creative brainstorming opportunities, some of which have given rise to new avenues of pursuit.

The Governance Manual is reviewed and updated on an annual basis and all PIs are required to acknowledge in writing their acceptance of the current policies and procedures. The (revised) August 2011 Governance Manual is attached at [Appendix Q](#) (#15 above).

17) Formulating Next Steps for NACTN

- To continue enrollment into the NACTN SCI data registry
- To continue to utilize NACTN's established consortium of hospitals, and coordinating, data management and pharmacological centers, to conduct SCI clinical trials and ensure the ability to enroll appropriate numbers of participants
- To continue NACTN's expansion in order to facilitate conducting two or more clinical trials simultaneously
- To define outcome measures by using combined NACTN, EM-SCI and STASCIS databases to provide a prior data set for the design of future clinical trials
- To expand on current NOA projects – validating quantitative outcome measures and incorporating the measures into future clinical trials – by identifying new grant opportunities

- To publish the final results of the Phase 1 safety trial of Riluzole
- To fully develop a Phase 2 Riluzole master protocol approved by the DOD and local IRB's
- To develop adaptive trial designs that are appropriate for cohorts in the range of 200-300 patients
- To work with investigators and pharma to evaluate and develop drug and cellular therapies for clinical trials.

18) Key Research Accomplishments

1. Establishment of an internationally recognized consortium of hospitals, a data management center and a pharmacological center to conduct trials of biological, cellular and surgical therapies for the treatment of spinal cord injury
2. Enrollment of 524 SCI patients in the NACTN data registry as of December 31, 2011 (#5 above)
3. Development and regulatory approvals of NACTN data registry standardized protocol, case report forms, Manual of Operation (MOO) and the capacity to provide data to users in the requested format with either a de-identified data file or tabulations (#5 above)
4. Expansion of NACTN to include Walter Reed Army Medical Center, San Antonio Military Medical Center, University of Houston, Louisville, Maryland and Miami and Thomas Jefferson University
5. NACTN-wide training meetings to achieve standardized data collection and reporting and use of ASIA and other outcome measure across all centers (#12 above)
6. Participation by two NACTN centers (The Methodist Hospital and University of Toronto) in the Novartis ATI355 Phase I clinical trial and the ongoing role of NACTN investigators (Drs. Grossman, Fehlings, Guest and Tator) as advisors to the Novartis ATI355 clinical team; if Novartis decides to proceed with a larger POC study, NACTN sites will participate (#9 above)
7. GRASSP (#6 above); available now to clinicians, investigators and academics (www.sci-grassp.org)
8. PRIME (#6 above)
9. STASCIS (#8 above) – the study addressed a critical and contentious question in acute SCI: the timing of decompression surgery. Two other questions (impact of facet dislocation on outcomes in cervical SCI and a long-term functional outcome clinical prediction model after traumatic SCI) were also addressed; STASCIS manuscript accepted for publication PLoS One; two other manuscripts submitted
10. NOA, the Neurological Outcomes Assessments Initiative, creation of an international Task Force to inform NOA activities which met in May and September 2009; five research contracts awarded (#7 above); first contract (electrical perceptual threshold test) concluded; results being readied for publication (#7 above)
11. Project exploring the potential of amnion-derived multipotent progenitor cells to promote recovery after spinal cord injury (final histology studies underway in anticipation of publication) (#10 above)
12. Completion of enrollment of 36 subjects in a Phase I safety study of the neuroprotective drug Riluzole (#11 above). There were no serious adverse effects related to the drug and a trend toward improved neurological outcomes was observed.
13. Development of a sensitive method of measuring Riluzole in plasma with analysis of the pharmacokinetics of Riluzole plasma levels.

19) Reportable Outcomes

- Product Line Review, Fort Detrick, MD, 9/11/2007 (#0361); feedback provided and implemented
- Product Line Review, Fort Detrick, MD, 9/13, 2011 (#0361, #0042); no feedback provided (Appendix R)
- NACTN-AO Spine North America supplement issue on NACTN and spinal cord injury in the Journal of Neurosurgery – Spine (#15 above)
- Bibliography (Appendix S)

Conclusion:

Effective with the 12/31/2011 termination of DOD contract W81XWH-07-1-0361, NACTN had addressed all the tasks enumerated in its original proposal. Completed successfully:

- #1 –Goal: Enrolling 400 acutely injured spinal cord injury patients into the NACTN data registry. 524 were enrolled effective 12/31/2011 and this task continues across all clinical centers.
- #2 – Harmonization of the Riluzole Phase I safety study research protocols across all NACTN centers (including USAMRMC, ORP, HROP and local IRBs). The “how-to” knowledge learned in launching and completing the Riluzole safety study will help NACTN achieve regulatory harmonization with greater speed efficiency in future multicenter trials.
- #3 – Military expansion was achieved with the addition of SAMMC at the end of 2011. Depending on financial resources, NACTN will continue to tap other military hospitals and to forge clinical research connections with the VA. The latter will likely be facilitated through NACTN’s collaborative relationship with the Reeve Foundation’s NeuroRecovery Network.
- #5 – NACTN’s Data Management Center successfully met increased data demands by maintaining a core staff throughout the POP (all part-time); as activities and/or data load increased, additional part-time staff was added on a short-term, ad hoc basis. It should be noted that during periods of high demand, the core staff increased their time and effort, at no additional cost to the grant.
- #8 - Publication of the results of the multicenter STASCIS study is expected to change standard of care for acutely injured spinal cord patients. As reported, several new projects have emerged from the STASCIS data and the NACTN registry database has been successfully merged with the University of Toronto Surgical Treatment of Acute Spinal Cord Injury (STASCIS) database.
- #10 - The final report for the Stemnion modification AMPC project was submitted January 20, 2011. However, Dr. Anderson continues analysis of data from two of the sub-projects and intends to submit her findings for peer-reviewed publication.
- #11 – NACTN completed enrollment in its first clinical trial, the Phase I safety study of the neuroprotective drug Riluzole. Based on final data analysis, it is likely the network will conduct a larger efficacy trial.
- #12 – Training and standardization were achieved, as reported, across all centers for the two NACTN studies, the data registry and the Riluzole Phase I trial.
- #13 – NACTN’s growing influence in the spinal cord field is evidenced, in part, by its increasing number of collaborations with other clinical networks. During the contract period, NACTN has interacted with, formed alliances with and/or undertaken projects with EM-SCI, STASTIS, the Reeve Foundation’s NeuroRecovery Network, AO Spine International, the Rick Hansen Institute, the NIH and NETT and ASIA/SCOPE. Obviously, these relationships (and others) will continue to unfold and expand in the future but NACTN is now a well-known and respected presence in the international spinal cord arena.
- #15 – The task of NACTN reorganization has been successfully achieved and importantly, a mechanism is in place to insure its continued governance and intellectual and scientific leadership.

Other tasks remain works-in-progress that continue to evolve over time:

- #4 – The military projects have been hampered by the unexpectedly low number of spinal cord patients enrolled in the data registry, Walter Reed’s 2011 move to the campus of the National Naval Medical Center and internal regulatory requirements. However, the successful emergence of WRNMMC and resolution of regulatory challenges, combined with SAMMC’s membership in NACTN, means the projects can be aggressively pursued.
- #6 – The development and validation of GRASSP and PRIME have been strategic and rigorous and both are on-track to become important assessment tools for use in the clinic and research.

- #7 – The NOA initiative includes one project that has been completed (findings being prepared for publication) and four others in progress. It is NACTN's intention to further expand NOA's efforts but obviously this will depend on available funding.
- #9 – The participation of NACTN centers in the Novartis anti-Nogo-A antibody clinical trial awaits a corporate decision to proceed to a larger study, pending final analysis of the safety study data. In the interim, NACTN investigators continue to interact with the ATI355 clinical team, as reported above.
- #14 – The actual nature of this task, originally envisioned as implementing a NACTN/NETT clinical trial collaboration, has dramatically changed, as reported above. NACTN is exploring any and all potential funding opportunities, including grant applications in response to relevant RFAs, biotech and pharma financial and in-kind support and partnerships with organizations with a spinal cord focus. At the federal level, the Reeve Foundation maintains strong ties to Congress, NIH (specifically NINDS) and other appropriate agencies (e.g., CDC). It is stating the obvious to say that this task will never be fully realized and that insuring a steady revenue stream for NACTN is of the highest priority.

Spinal cord research is a relatively new field but it didn't take its rightful place in neuroscience until the late 1980s – early 1990s, on the heels of seminal findings (David and Aguayo, 1981; Caroni and Schwab, 1988) which overturned existing dogma about central nervous system regeneration. Scientists have made rapid and robust progress at the bench during the past two decades and although there remains much basic science left to do, there is also consensus that the time is right to begin the delicate task of translating findings to the clinic. As with all diseases and disorders, spinal cord presents its own set of daunting challenges. But its intrinsic nature (the emotional, societal and financial tolls it extracts; the near-normal lifespan patients can expect; the physical and health ravages and rapid escalation of the aging process triggered by the injury) makes it especially devastating to each patient and his/her family. There is a compelling argument to be made in favor of beginning to rationally test the most promising interventions now, even though the expectation is that early results will be small and incremental.

The North American Clinical Trials Network is a unique response to and resource for the challenge of how best to identify and test promising therapies, insuring meaningful data and utmost patient safety. Embedded in NACTN's infrastructure is a sophisticated and unique patient data registry; policies, procedures and protocols that codify the network's activities and tangible outputs; the capacity to standardize discrete activities network-wide; and skilled spinal cord neurosurgical and nursing care and expertise. NACTN is a nexus of seasoned clinical and cutting-edge scientific knowledge: its investigators are leaders in spinal cord neurosurgery and biostatistics and its deliberations are informed by the newest clinical and basic research. NACTN represents the perfect antidote to the challenge of how to systematically and rationally identify the most promising experimental therapies and safely test them in a way that enriches knowledge in the field and moves it forward. The case for NACTN becomes even stronger when the calculus includes the understanding that these early therapies will likely yield small, difficult-to-identify benefits for the patients.

With DOD support continuing through July 2012 under contract #0042, NACTN is moving aggressively to solidify its financial prospects, finish those #0036 tasks still in progress and build upon the successes achieved during this Period of Performance. The Reeve Foundation and NACTN investigators are confident that the network will prevail, in spite of fiscal hurdles, the known challenges of clinical research and the particularly difficult nature of spinal cord injury. Failure is not an option.

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Appendices

Appendix A	Registry Data Flow
Appendix B	Registry Data Summary
Appendix C	GRASSP
Appendix D	PRIME
Appendix E	NOA – Ellaway
Appendix F	NOA - Krassioukov
Appendix G	NOA - Fehlings
Appendix H	Riluzole – Patient Profiles
Appendix I	Riluzole – Patient Follow-Up
Appendix J	Manuscript – Riluzole Phase I
Appendix K	Manuscript – Riluzole Pharmacology
Appendix L	NINDS Letter
Appendix M	Executive Committee Minutes
Appendix N	J Neurosurgery – Spine 2012 Supplement - Minutes
Appendix O	J Neurosurgery – Spine 2012 Supplement - Titles, Authors
Appendix P	CDMRP Proposal
Appendix Q	Governance Manual
Appendix R	PLR 9/13/2011
Appendix S	Bibliography

Final Report Format

1. Award No. W81XWH-07-1-0361
2. Report Date: December 31, 2011
3. Reporting period: May 14, 2007-December 31, 2011
4. Principal Investigator: Dr. Robert Grossman
5. Telephone No.: 713-441-3810
6. Award Organization: Christopher Reeve Foundation
7. Project Title: North American Clinical Trials Network for Treatment of Spinal Cord Injury
8. Current staff, role and percent effort of each on project. **CONTINUED ON NEXT PAGE**

STAFF MEMBER	Role	% EFFORT
Robert Grossman MD	PI-Main	20
Susan Howley	Admin	21.65
Peter Wilderotter	Admin	1.5
Edward Jobst	Admin	4.25
Anne Homa	Admin	9
Bruce Morgan thru 12/31/08	Admin	10
Elizabeth Toups RN	Study Coordinator	40

9. Contract expenditures to date (as applicable):

COST ELEMENTS	THIS QUARTER	CUMULATIVE
Personnel	24,839	2,929,637
Fringe Benefits	7,079	817,072
Supplies		57,052
Equipment		23,502
Travel		35,773
Other Direct Costs		607,608
Subtotal		4,470,644
Indirect Costs		
Fee	3,192	446,933
Total	35,110	4,917,577

10. Comments on administrative and logistical matters.
11. Use additional page(s), as necessary, to describe scientific progress for the quarter in terms of the tasks or objectives listed in the statement of work for this contract. Explain deviations where this isn't possible. Include data where possible.
12. Use additional page(s) to present a brief statement of plans or milestones for the next quarter.

8. Current staff, role and percent effort on project.

STAFF MEMBER	Role	% EFFORT
Michele Johnson, MD	PI	10
Martha Powner	Study Coordinator	60
Michael Fehlings MD PhD, Charles Tator, MD, PhD	PI	15
Yuriy Petrenko MD	Study Coordinator	60
Christopher Shaffrey MD	PI	20
Elizabeth Yount	Study Coordinator	60
Susan Harkema, PhD, Maxwell Boayke, MD	Co-PIs	15
Michael Durham	Study Coordinator	60
Bizhan Aarabi MD	PI	15
Christina Aldrich	Study Coordinator	60
James Guest, MD	PI	20
Qing He, MD	Study Coordinator	100
Marina Dididze MD	Scientific Trials Coordinator	25
James Harrop, MD	PI	20
Amanda Salvatore	Study Coordinator	100
Michael K. Rosner MD	PI	20
Vicki Miskovsky	Study Coordinator	75
Kim Clark	Nurse Clinician	75
Ralph Frankowski PhD	PI	2.3
Keith Bureau	Co PI	15
Hyvan Dang	Analyst	50
Joy De Los Reyes	Research Ass't	19
Nina Newton	Database Manager	50
	Support Specialist	23
	Grants	4
	Project Coordinator	4
Diana Chow	Co-PI	9.1
Yang Teng	Technician	50

W81XWH-07-1-0361
North American Clinical Trials Network
Personnel

Imperial College London [NOA1-2010(PE)]

Ms Maria Catley, Research Assistant – assisted PI in enrolling subjects, data collection and follow-ups.

The Methodist Hospital

Robert G. Grossman, MD, Lead Principal Investigator – responsibility for NACTN's multi-site clinical projects, including protocol design and development, biostatistical consultation and support, regulatory consultation and support, site management and project management for trial planning, start-up phase and study maintenance. He liaises closely with the Data Management Center at the University of Texas School of Public Health, Houston and the Pharmacological Center at the University of Houston, College of Pharmacy.

Elizabeth Toups, MS, RN, CCRP - NACTN project manager with responsibility for the day-to-day activities of NACTN's clinical projects including protocol development, submissions/regulatory approvals, organization of meetings, project monitoring/site management, communication between NACTN centers

Jerika Acosta, CRA – responsible for on-site monitoring visits to insure clinical trial protocol procedures are strictly followed

Tanisha Bernhardt - administrative support

Emmanuel Voado, MD – responsible for assisting in development/validation of PRIME

Thomas Jefferson University

James Harrop, MD, Principal Investigator – overall responsibility for Thomas Jefferson University's NACTN activities, including but not limited to enrolling subjects into the data registry and the Riluzole Phase I safety study and into future clinical trials. Chair of the NACTN Publications Committee.

Deborah August, Study Coordinator - responsible for recruiting and consenting subjects and follow-up

Amanda Salvatore, Study Coordinator - responsible for recruiting and consenting subjects and follow-up; no longer on the study

Ellen Simons, Study Coordinator - responsible for recruiting and consenting subjects and follow-up; no longer on the study

Phyllis Forcina, Nurse Coordinator – assisted lead Coordinator in recruiting and consenting subjects and follow-up; no longer on the study

University of California [Stemnion Modification]

Brian Cummings, Co-Principal Investigator – responsible for coordination/implementation of the cell transplants/ADCC injections and coded data maintenance.

C. deArmond, Laboratory Assistant level III – assisted with surgeries, behavioral data capture/analysis, MRI data analysis and supplemental histological analyses.

E. Partida, Laboratory Assistant level III – assisted with surgeries, behavioral data capture/analysis, MRI data analysis and supplemental histological analyses.

S. Bondi - administrative support.

University of Houston (Pharmacology Center)

Ms. Yang (Angela) Teng, Graduate Research Associate - responsibilities include performing (a) the quantification of riluzole in plasma samples of 36 patients (4 samples per patient, of total 144 samples), (b) pharmacokinetic analysis and modeling of riluzole in SCI patients for Day 3 and D14 and (c) pharmacokinetic/pharmacodynamic (PK/PD) correlations between PK parameters and riluzole efficacy in sensor/motion improvement, as well as the parameters and riluzole side effect on hepatic enzyme activity.

University of Louisville

Susan Harkema, Principal Investigator - overall responsibility for the University of Louisville's NACTN activities, including but not limited to enrolling subjects into the data registry and the Riluzole Phase I safety study and into future clinical trials. Chair of NACTN's Neurological Outcomes Assessments Committee.

Elizabeth McDowell, Study Nurse – responsible for recruiting and consenting subjects and follow-up

Michael Durham, Study Nurse - responsible for recruiting and consenting subjects and follow-up
Danny Bryant, Research Staff - responsible for data entry and management
David Alston – responsible for data entry and management
Anne Watson, Study Nurse – responsible for recruiting and consenting subjects and follow-up; no longer on the study
Renee Ford, Clinical Coordinator – provided assistance to the Study Nurse; no longer on the study
Christie Ferreira, Research Staff – responsible for recruiting and consenting subjects and follow-up; handled some data entry and management; no longer on the study
Andrea Willhite, Research Staff – responsible for data entry and management; no longer on the study
Christie Andi – responsible for data entry and management; no longer on the study

University of Louisville [NOA4-2010(SH)]

Sevda Aslan, PhD – responsible for development of software for data analysis.
Elizabeth McDowell (Study Nurse) - responsible for recruiting and consenting participants.

University of Louisville [NOA3-2010(SH)]

Sevda Aslan, PhD – responsible for conducting tests and analyzing data.
Michael Durham, Study Nurse - responsible for recruiting and consenting participants.

University of Maryland

Bizhan Aarabi, MD, Principal Investigator - overall responsibility for the University of Maryland's NACTN activities, including but not limited to enrolling subjects into the data registry and the Riluzole Phase I safety study and into future clinical trials.

Aldrich, Charlene (Senior Clinical Research Coordinator) - manages all regulatory and IRB updates and submissions, enrolls patients in the clinical trial, and completes follow up for patients enrolled.

Beam, Dana, Clinical Research Specialist - responsible for screening/enrolling patients, assisting with data collection/submission, scheduling appointments and completion of follow-up appointments.

Booker, Kalola, Epidemiologist Assistant III - responsible for screening/enrolling patients, assisting with data collection /submission, scheduling appointments and completion of follow-up appointments.

Dunlap, Madeline, Hourly Research Assistant - provided administrative support for the clinical trial. She is no longer with the Department; no current role in the administration of this study.

Lipka, Tammy, Hourly Research Assistant - provided administrative support for the clinical trial. She is no longer with the Department; no current role in the administration of this study.

McGlond, Andrea, Research Coordinator – was responsible for screening/ enrolling patients, assisting with data collection/submission, scheduling appointments and completion of follow-up appointments. She was replaced by Laura Yin.

Rosado-Diaz, Marla, Office Administrative Assistant - provides administrative support, including data entry and scheduling follow-up appointments.

Thomas Heather, Research Assistant - was responsible for regulatory processing, enrolling patients, and data processing. She is no longer with the Department; no current role in the administration of this study.

Yin, Laura, Clinical Research Coordinator - responsible for screening/enrolling patients, assisting with data collection/submission, scheduling appointments and the completion of follow-up appointments. She is no longer with the Department; no current role in the administration of this study.

University of Miami

James Guest, MD, Principal Investigator - overall responsibility for the University of Miami's NACTN activities, including but not limited to enrolling subjects into the data registry and the Riluzole Phase I safety study and into future clinical trials.

Marine Dididze, Associate Scientist, Study Coordinator – responsible for regulatory and IRB updates and submissions, enrolls patients in the clinical trial, and completes follow up for patients enrolled.

Qing He, Senior Research Associate 2 – assists Study Coordinator.

Christopher Gilbert, Research Support Coordinator – assists Study Coordinator.

Gizelda Casella, Associate Scientist, Study Coordinator – had responsibility for regulatory and IRB updates and submissions, enrolled patients in the clinical trial, and helped complete follow up for patients enrolled; no longer on the study.

University of Texas (Clinical Center)

Martha Powner, RN, MN, lead Study Coordinator – responsible for regulatory and IRB updates and submissions, patient enrollment in the clinical trial, and completed follow ups for patients enrolled.

Fusun Kiran, RN, Study Coordinator – assists lead Study Coordinator.

Lisa Schmitt, RN, BSN, Study Coordinator - assisted lead Study Coordinator; no longer on the study

Michelle Edelbrock, RN, MSN, Study Coordinator - assisted lead Study Coordinator; no longer on the study.

Jean Palmer, RN, MSN, Study Coordinator - assisted lead Study Coordinator; no longer on the study

T. Joshua Cao-Baker, RN, MD, Study Coordinator - assisted lead Study Coordinator; no longer on the study.

Maggie Gary, RN, Research Nurse – assisted lead Study Coordinator; no longer on the study.

Saroj Kumar, Study Coordinator - assisted lead Study Coordinator; no longer on the study.

Robert Funk, Study Coordinator - assisted lead Study Coordinator; no longer on the study.

Christopher Riley, Study Coordinator - assisted lead Study Coordinator; no longer on the study.

The following participated in NACTN research but were paid from other sources:

Georgene Hergenroeder, MHA, RN (CCRC) – assisted with regulatory, IRB and special problems

Adrian Smith, MD, 5th year Neurosurgery Resident)- assisted with enrolling for Riluzole

University of Texas (Data Management Center)

Keith D. Burau, PhD, Associate Professor of Biostatistics - responsible for design, development, implementation, and monitoring of all computer systems required for data acquisition, data sharing, and analysis of NACTN Registry and Riluzole clinical trial data.

Hyvan Dang, M.S., Programmer Analyst IV - responsible for development of the TeleForm optical recognition case report forms for the NACTN Registry and Riluzole clinical trial and responsible the implementation, monitoring, updating, archiving, and security of all DMC data and data systems.

Cara Newton, M.S., Research Associate, Database Manager - responsible for receipt/verification/ review of all data submitted to the DMC; responsible for training clinical coordinators in data collection protocols/monitoring each NACTN site for compliance with data protocols. Works with the Clinical Coordinating Center (Methodist Hospital) as necessary to develop and update standard operating procedures. Maintains physical files for all DMC data.

Joy de los Reyes, M.P.H., Research Assistant IV - performs electronic scanning/verification/entry of all TeleForm data for the NACTN registry /Riluzole clinical trial. Supports Database Manager in clinical site communications/distribution of routine data reports; supports the PI in the management of IRB requirements. Assists Clinical Coordinating Center (Methodist Hospital) as required.

Hui Peng, PhD, Graduate Research Assistant - developed computer programs for the secure transfer/ interface of Riluzole pharmacokinetic to the Pharmacology Core for research on the pharmacology/safety of Riluzole in SCI. Developed quality control/statistical computer programs for the analysis of Riluzole clinical trial data. Prepared data presentations as required by the Clinical Coordinating Center (Methodist Hospital).

Yi Cai, B.S., Graduate Research Assistant - under supervision developed computer programs for production of a variety of reports on the progress of the Riluzole clinical trial.

Lawrence Weiss, M.S., Programmer Analyst - developed SAS computer programs for data quality control and data retrieval algorithms for research/data sharing for the NACTN registry.

Gwen Baillargeon, M.S., Programmer Analyst - developed computer programs to automate monitoring of patient enrollment/editing procedures/data requests for each NACTN site.

Colleen Moore, Support Specialist - general secretarial tasks and staff communications.

University of Toronto

Yuliya Petrenko, Clinical Research Coordinator – responsible for screening/enrolling subjects into the research study; obtains Informed Consent, coordinates drug delivery timelines with IDS pharmacy (if necessary), collects required study data and monitors subject throughout the conduct of the study.

Yuriy Petrenko, Clinical Research Manager – handles REB approvals/renewal, ICF update(s), and maintains regulatory documentation and screens and enrolls subjects into the research study.

Amy Tran, Admin Assistant I/Clinical Research Study Assistant Nov 2007 – Dec 2010 – responsible for data entry of CRFs and scheduling of research subject follow-up visits.

Glenda Molina, Admin Assistant I Jan 2011 – Oct 2011 – responsible for data entry of CRFs and scheduling of research subject follow up visits.

Larissa Pashkievich, Admin Assistant I Oct 2011 – Dec 2011 – responsible for data entry of CRFs and scheduling of research subject follow-up visits.

Walter Reed Naval Military Medical Center

Kimberly Clark, PA-C – assist in identifying potential subjects, assessing capacity to consent, obtaining informed consent, performing neurologic assessments, collecting data.

Vicki Miskovsky, Study Coordinator – review/obtain informed consent, collect and submit data, insure local regulatory compliance.

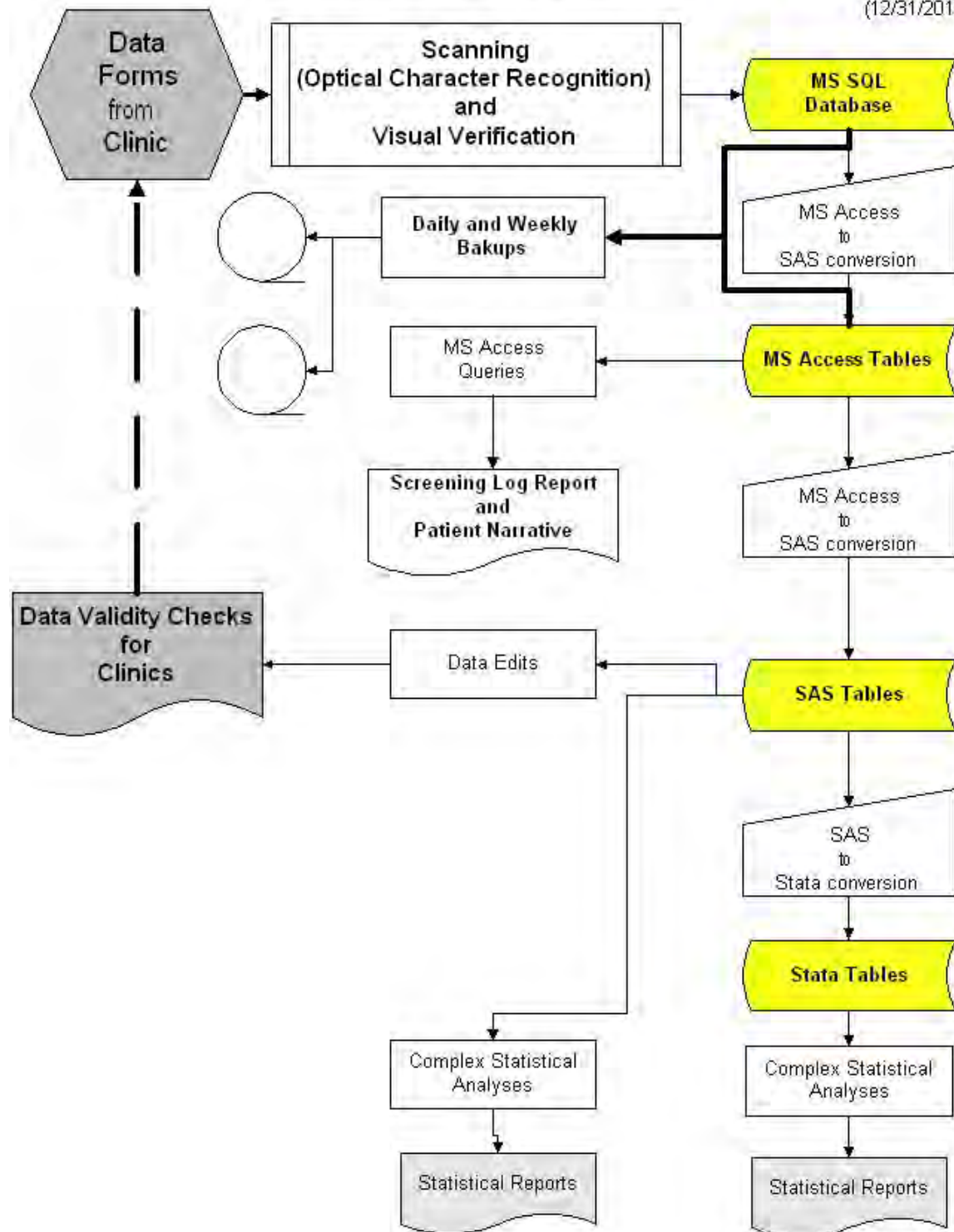
Thomas Maryniak, Study Coordinator - assist identifying potential subjects, assessing capacity to consent, obtaining informed consent, performing neurologic assessments, collecting data; no longer on the study.

Appendix A

NACTN Registry Data Flow

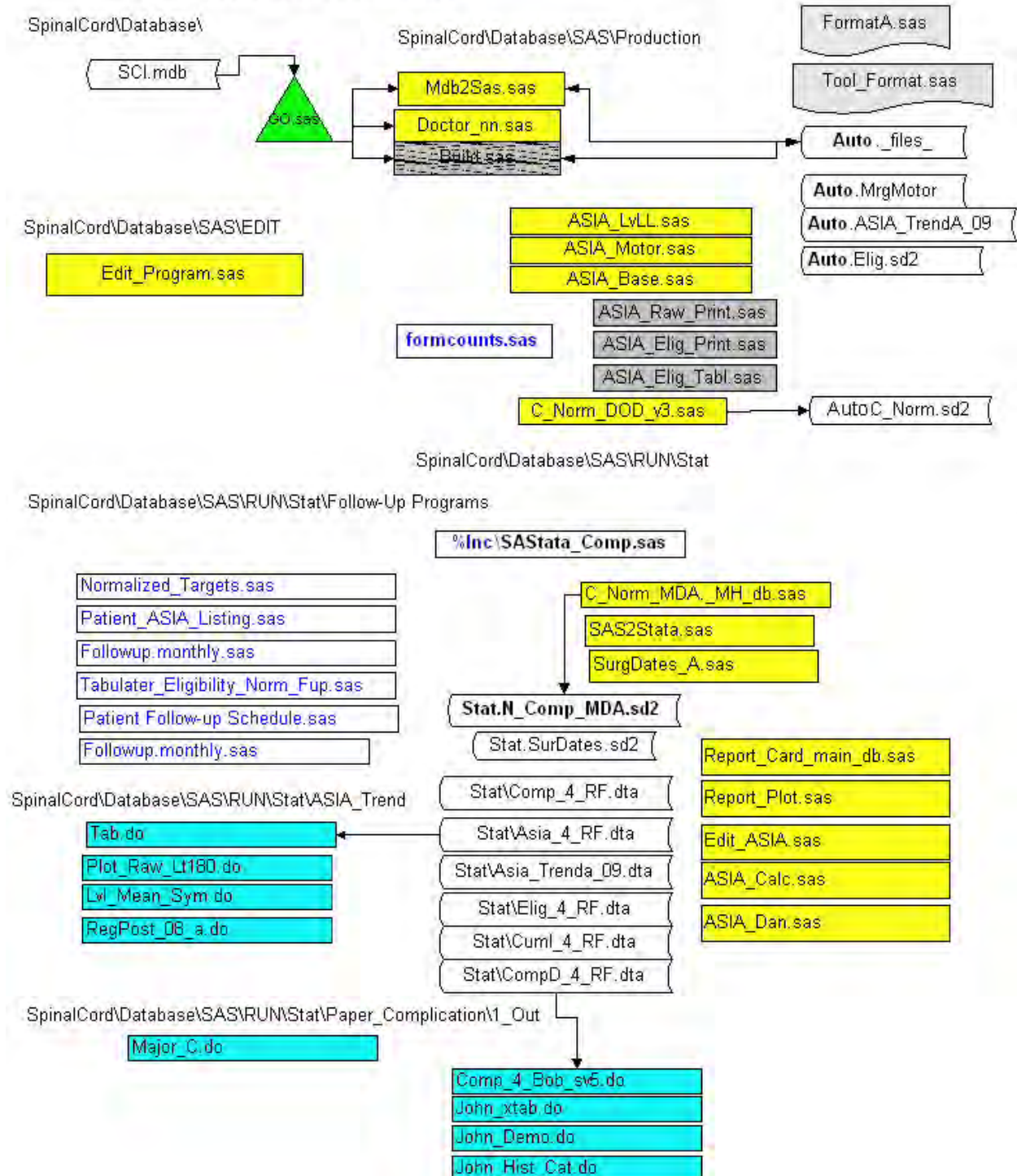
NACTN Registry Data Flow

(12/31/2010)



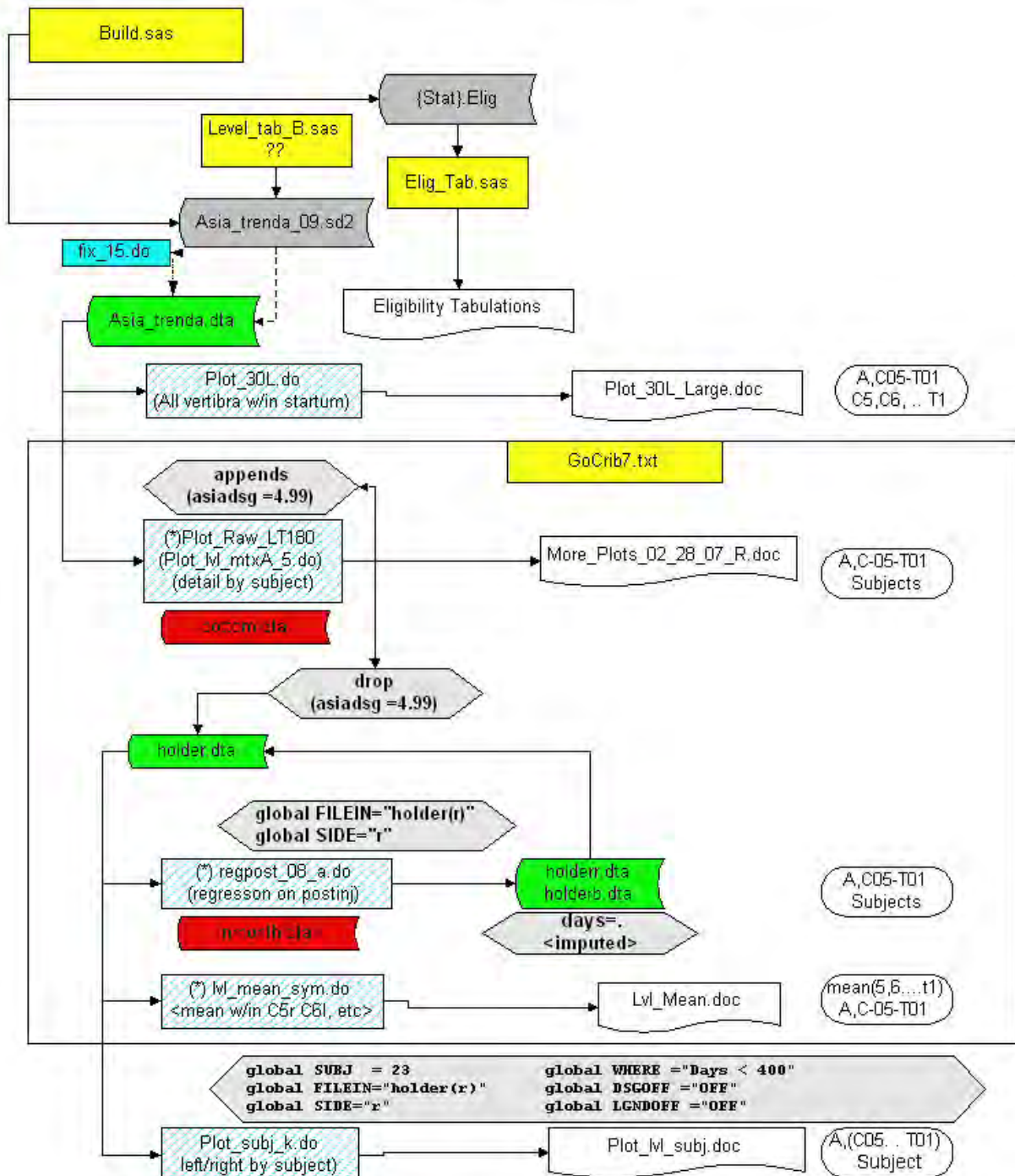
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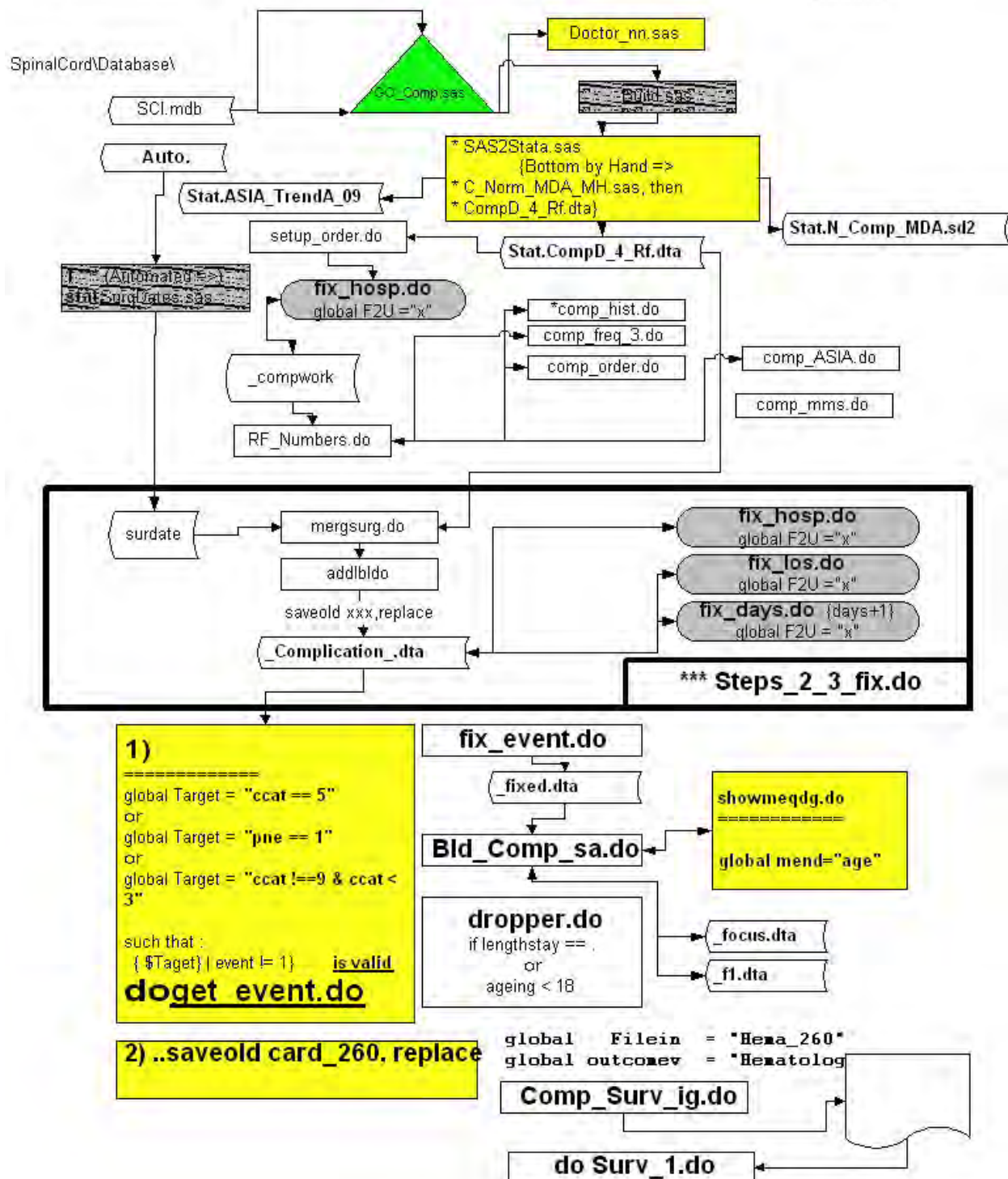
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(12/31/2010)

H:\DMG\SpinalCord\Database\SAS\RUN\Stat\ASIA_Trend\Go\ASIA_Go.vsd





Appendix B
North American Clinical Trials Network

SCI Data Registry Summary
12/31/2011

Table 1. Registry Screening and Enrollment

Registry Status	Number	Percent Total
Screened	971	-
Enrolled	524	54.0%
In Database	485	92.6%
Pending	36	6.9%

Table 2. Patient Demographics

Characteristic	Number (N=485)	Percent
Gender		
Male	387	79.8
Female	98	20.2
Age¹ (yrs)		
< 20	31	6.4
20-65	390	80.4
>65	64	13.2
Race		
White	363	74.8
Other	122	25.2

¹Median age at injury = 44 years of age

Table 3. Circumstances of Injury

Circumstance	Number (N=485)	Percent
Fall	181	37.3
MVA	151	31.1
Recreation	54	11.1
Motorcycle	42	8.7
Assault	26	5.4
Other	20	4.1
Military ¹	11	2.3

¹ See text for circumstance details

Table 4. Severity of SCI Neurological Deficit
Initial AIS Grade within 7 days of Injury

AIS Grade	Number	Percent
A	151	31.1
B	55	11.3
C	49	10.1
D	119	24.5
E	36	7.4
AIS unknown	75	15.5
TOTAL	485	100.0¹

¹ Percent total does not add to 100% due to rounding

Table 5. Injury Type and SCI Region

Characteristic	Number (N=485)	Percent
Injury Type		
Blunt	385	79.4
Crush	74	15.3
Penetrating	19	3.9
Other	7	1.4
Injury Region¹		
Cervical	367	75.7
Thoracic	88	18.1
Lumbar/Sacral	27	5.6
SCIWORA	3	0.6

¹Highest level reported when injury involved multiple levels

Table 6 Proportional Incidence of Complications¹ by AIS Severity
Initial severity within 7 days of injury

AIS Grade	Complication	No Complication	% Complication
A	126	25	83.4
B	35	20	63.6
C	20	29	40.8
D	37	82	31.1
E	13	23	36.1
AIS unknown	19	56	74.7
Total	287	198	59.2

¹ Patients with at least one mild, moderate or severe complication

Table 7. Acute Care Complications: Type, Frequency, and Incidence

Complication Type	Frequency N=1376 (%)	Incidence Rate (%) (N=485 SCI cases)
Pulmonary	348 (25.3)	36.7
Infection	285 (20.7)	33.2
Hematology	213 (15.5)	26.6
Cardiac	178 (12.9)	25.6
GI/GU	115 (8.4)	17.1
Skin	113 (8.2)	16.7
Neuropsychiatric	106 (7.7)	19.2
Death	18 (1.3)	3.7

Table 8. Surgeries by AIS Grade

	Number of Patients (N=485)				
AIS ¹ Severity	Posterior	Anterior	Both	None	TOTAL
A	76	23	42	10	151
B	26	14	11	4	55
C	24	13	8	4	49
D	41	46	17	15	119
E	14	3	1	18	36
AIS unknown	30	15	15	15	75
TOTAL	211	114	94	66	485

¹ First AIS obtained within 7 days of injury.

Table 9. Steroid Use by Severity of Neurological Deficit
Initial AIS Grade within 7 days of Injury

	Steroids ¹ (N=484)		
AIS Grade	Yes (%)	No (%)	N
A	56.8	43.2	169
B	62.3	37.7	61
C	57.1	42.9	60
D	47.6	52.4	128
E	12.2	87.8	41
AIS unknown	80.0	20.0	75

¹ One case (AIS A) where steroid use is unknown is excluded from this table.

Table 10. Hospital Stay and Acute Care Discharge

Hospital Length of Stay	Number (N=485)	Percent
< 8 days	128	26.4
8-14	141	29.1
15-21	79	16.3
> 21	137	28.2
Discharge Status	Number (N=485)	Percent
Rehab Hospital	338	68.6
Home Care	98	22.2
Nursing Home	16	3.5
Long-Term Care	15	2.0
In-Hospital Death	18	3.7

Table 11. AIS Severity Conversion
Admission versus Acute Care Discharge

	AIS² Discharge					
AIS¹ Admit	A	B	C	D	E	Total
A	120	11	5	0	0	136
B	1	39	11	4	0	55
C	1	1	33	14	0	49
D	0	0	4	105	10	119
E	0	0	0	0	36	36
Total	122	51	53	123	46	395

¹First AIS obtained within 7 days of injury² AIS obtained within 14 days of acute care discharge.

Table 12. Spinal Cord Independence Measure (SCIM)
Mobility Indoors

AIS Severity¹	Able to Walk Independently	Unable to Walk Independently	Total
AIS A	1 (1.3%)	77 (98.7%)	78
AIS B	2 (5.7%)	33 (94.3%)	35
AIS C	7 (22.6%)	24 (77.4%)	31
AIS D	48 (49.0%)	50 (51.0%)	98
AIS E	18 (100.0%)	0 (0%)	18
Total	76 (61%)	184 (39%)	260

¹ First AIS obtained within 7 days of injury

GRASSP Version 1.0 Report, January 2012:

Summary of Project: It had become clear to both the pharmaceutical industry and scientists in the field that approaches to measure and determine the efficacy of emerging therapies were lagging and a clinical outcome measure was needed that was both sensitive and responsive to change; one which could be used to track natural recovery and the response of individuals receiving treatment. These issues served as the rationale for the development of the Graded and Redefined Assessment of Strength Sensibility and Prehension, Version 1.0 (GRASSP). The International GRASSP Research and Design Team was brought together at a meeting held in Chicago in May of 2006 which specifically addressed the goal of development of a new measure. The GRASSP is a measurement strategy consisting of three domains (Sensation, Strength and Prehension) which evaluates subtle changes in sensorimotor impairment that are critical for functional independence. It has been designed to capture data after traumatic tetraplegia for any level at any point during recovery (acute, subacute, chronic). The GRASSP allows for the evaluation of subtle impairment changes in the upper limb which are important because small improvements can have a significant impact on functional independence, and subtle changes may be the only changes occurring in the development of emerging therapies.

1. Development of the GRASSP started with a conceptual framework; followed by testing of feasibility using a cross-section of individuals with chronic tetraplegia (n=30). Clinical utility was assessed with SCI clinicians (n=12) and the GRASSP was modified accordingly. Formal sensibility testing with the same clinicians established face and content validity of the GRASSP. (January to March 2007)
2. Part of the analysis conducted was regression analysis or modeling. Linear regression was used to establish the strength of the impairment components in the GRASSP to function as defined by the SCIM, and grasping tasks. The strength of the relationship of impairment components to functional components was used to exclude items and tests within the GRASSP. Subtests within the GRASSP were retained if the strength of association to one out of three levels of function existed. The three levels of function used to compare GRASSP sub scores are the SCIM total score (representative of global function), SCIM self-care sub score (representative of upper limb function) and the GRASSP quantitative prehension score (representative of hand function). Using the full dataset (n=72) collected at the first test session all sub-score totals were compared to three degrees of function with general linear modeling. The subtests and items within GRASSP Version 1.0 were based on the regression analysis (Table 1). (Kalsi-Ryan et al., 2009)

Table 1: Summary of GRASSP Version 1.0

Table 1: Summary of GRASSP, Version 1.0				
Subtests		Items	Origin of Test/ Method of Administration	Scoring
Domain – Sensation				
1. Dorsal Sensation	SWM tested across three dorsal surface locations for each hand. Points 1 to 3 are: C6–Dorsal Digit I Tip, C7-Dorsal Digit III Tip, C8-Dorsal Digit V Tip.	Conventional SWM mini-kit testing (Mackin et al., 2002). Grams of force are represented by numeric values ranging from 0 to 4. 3.61 – 4, 4.31 – 3, 4.56 – 2, 6.65 – 1, No Response - 0 Testing performed as described in instructions of SWM minikit and Mackin et al., 2002.	Each test location is scored from 0 to 4 and the three test locations for the dorsal side of each hand is summed to render a subtest total score between 0 and 12.	
2. Palmar Sensation	SWM tested across three palmar surface locations for each hand. C6–Palmar Digit I Tip, C7-Palmar Digit III Tip, C8-Palmar Digit V Tip		Each test location is scored from 0 to 4 and the three test locations for the palmar side of each hand is summed to render a subtest total score between 0 and 12.	
Domain – Strength				
3. Strength	Motor grading of 10 arm and hand muscles C5-Anterior Deltoid, Biceps, C6-Triceps, C7-Wrist Extensor, Opponens Policis, C8-Extensor Digitorum, DIII Finger Flexor, Flexor Policis Longus, T1-DV Finger Abductor, First Dorsal Interossei	Traditional motor grading is performed. Each muscle is tested with resistance through full range and given a muscle grade between 0 and 5. 0 – flaccid, 1 - flicker, 2 – full range gravity eliminated, 3 – full range against gravity, 4 – full range with moderate resistance, 5 – full range with maximal resistance. Specific details regarding stabilization points, resistance points and positioning for testing are available in the GRASSP manual. This testing was adapted from Daniels and Worthington, 1987.	Each muscle is graded from 0 to 5 and the ten grades for each side are summed to render a total strength score between 0 and 50 for each upper limb.	
Domain – Prehension				
4. Prehension Ability	Grades one's ability to generate three grasps. 1 Cylindrical Grasp 2 Lateral Key Pinch 3 Tip to Tip Pinch	Each grasp is graded by the assessor using specific components of grasp acquisition outlined in the GRASSP manual. In general the scoring ranges between 0 and 4. 0 represents no ability to use the wrist, fingers or thumb to perform a grasp and 4 represents the ability to keep the wrist in neutral and generate the grasp with full thumb and finger movement. This subtest was created by the GRASSP Research and Design Team.	Prehension Ability total score=12	
5. Prehension Performance	Performance of six prehension tasks, scored from 0 to 5. 1. Pour Water from a Bottle, 2. Open Jars, 3. Pick up and Turn a Key, 4. Transfer Nine Pegs Board to Board, 5. Pick Up 4 Coins and Place in Slot, 6. Screw Four Nuts onto Bolts	This test is adapted from the Sollerman Hand Function Test (Sollerman and Ejeskar, 1995). Each task is scored on a 0 to 5 scale (details of scoring available in the GRASSP Manual).	Prehension Performance total score=30	
The GRASSP Version 1.0 is a test kit with all of the standardized apparatus included along with a manual which details the instructions for administration with great detail. Each subtest (5) renders a subtest score for right and left. Subtest scores are used to characterize one's upper limb impairment.				

^a all testing is completed for right and left sides separately. SWM – Semmes Weinstein Monofilaments

3. Reliability and validity were established for the GRASSP with a cross sectional multi-centre/multi-national trial. The objectives of the study were to: 1) establish the inter rater and test retest reliability and 2) establish the construct and concurrent validity with the International Standards of Neurological Classification of Spinal Cord Injury (ISNCSCI), Spinal Cord Independence Measure II (SCIM) and the Capabilities of Upper Extremity Questionnaire (CUE). The study protocol included repeated administration of the GRASSP on a cross section of individuals with tetraplegia who were neurologically stable (n=72). ISNCSCI, CUE and SCIM assessments were also administered. Two assessors examined the individuals over a seven day period. Inter rater and test retest reliability for all subtests within the GRASSP were above the hypothesized value of ICC 0.80 (0.84-0.96 and 0.86-0.98 respectively). The GRASSP is approximately 50% more sensitive (construct validity) than the ISNCSCI when defining sensory and motor integrity of the upper limb; the subtests showed concurrence with the SCIM, SCIM self-care subscale and CUE. The strongest concurrence to impairment was with self-perception of function (CUE) (0.57-0.83, $p<0.0001$). The GRASSP was found to demonstrate reliability, construct validity and concurrent validity for use as a standardized upper limb impairment measure for individuals with tetraplegia. The ICC reliability values fell into the hypothesized range for acceptable reliability, therefore, the reliability for the subtests of the GRASSP are sufficient to deem the measure reliable for use between examiners and for repeated assessments by the same examiner.
January 2007- September 2010, Kalsi-Ryan et al. 2011).
4. Sample: The data used in this analysis includes a multi-centre/multi-national cross section of data. The total sample consisted of 72 individuals; the description of the sample is defined in Table 2. The analysis involves a number of different sub-analyses. All inter-rater reliability, validity, and modeling analyses involved the whole sample of 72. The test-retest reliability analysis only involved a portion of the sample (n=45) as this was the group of individuals that had three assessments completed. Sample and the location of where data was collected are described in Table 2.

Table 2: Description of Sample

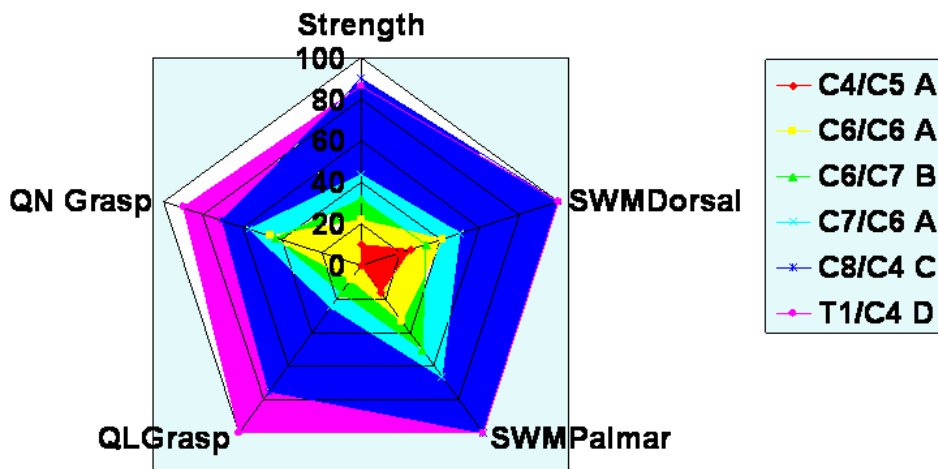
	Inter-rater Reliability	Test Retest Reliability	Validity	Modeling for Inclusion of Tests
North America				
1. Rehabilitation Institute of Chicago, Chicago USA	10	10	10	10
2. University of Toronto (TRI, UHN) Toronto Canada	15	15	15	15
3. Vancouver General Hospital & G.F. Strong, Vancouver Canada	10	10	10	10
4. Thomas Jefferson University, Philadelphia USA	10	10	10	10
Europe				
5. Balgrist University Hospital, Zurich Switzerland	9		9	9
6. Krakenhaus Hohe Worte , Bayreuth Germany	8		8	8
7. Traumacenter Murnau, Murnau Germany	10		10	10
Totals	72	45	72	72

5. Scoring of the GRASSP: Initial plans prior to analysis were to establish a clinical index or a global scoring system for all the sub tests in the GRASSP. This was not done as the significance of individual subtest scores within the GRASSP is where the most meaningful information lies. Therefore, the recommendation is for the scoring of the GRASSP to be presented in the following (Table 3) way in a table format and then plotted on a polar diagram Figure 1.

Table 3: Scoring of the GRASSP

GRASSP Sub Tests	Assessment One		Assessment Two	
	Right Score	Left Score	Right Score	Left Score
<i>Sensory</i>				
SWM Dorsal	/12	/12	/12	/12
SWM Palmar	/12	/12	/12	/12
<i>Motor</i>				
10 Muscles	/50	/50	/50	/50
<i>Functional</i>				
Prehension Ability	/12	/12	/12	/12
Prehension Performance	/12	/12	/12	/12

Figure 1: Polar Diagram of GRASSP Sub Scores



Superimposing consecutive assessments of the GRASSP in a polar diagram would allow a visual illustration of scores over time. The above figure is an example of six individuals from the cross-section of 72 to demonstrate different ratings. A diagram such as this would be generated for each hand separately.

- GRASSP Version 1.0 – The Product and Commercialization: Once the test and item inclusion was confirmed by the cross sectional study the process of reproducing the GRASSP Kit was the next stage. The version resulting from the cross sectional study has been labeled the GRASSP Version 1.0. This version of the measure has been copy written by all members of the International GRASSP Research and Design Team, with an inter-institutional agreement completed. The GRASSP is manufactured by a company named AXAL Inc. based in Richmond Hill, Ontario, Canada (D-U-N-S #246270097). The GRASSP website address is www.sci-grassp.org and the kit can be ordered online. The GRASSP Kit retails for \$800.00 CDN. Use of the GRASSP is open to all clinicians, researchers and academics, However, any sponsor or industry driven research does require a licensing agreement which is to be negotiated with the UHN Technology and Transfer Office in Toronto, Canada. All of this information is available on the website.
- Future Work: Currently and ongoing a longitudinal study using GRASSP is being conducted to establish the responsiveness of the test. This study is being conducted in Europe and Canada at the moment.

Dissemination:

Presentations:

1. Kalsi-Ryan S, Beaton D, Curt A, Duff S, Popovic M, Rudhe C, Fehlings MG, Verrier MC. Graded Redefined Assessment of Sensibility Strength and Prehension (GRASSP): Psychometric Development of an Upper Limb Impairment Measure for Individuals with Traumatic Tetraplegia. Top Spinal Cord Inj Rehabil, June 2011

Podium presentation: Sukhvinder Kalsi-Ryan

Meeting: ASIA/ISCoS Conference, Washington DC, June 2011

2. Steeves J, Lammertse D, Kramer, **Kalsi-Ryan S**, Jones L, Blight A, Anderson K. Outcome Measures for Acute/Sub-acute Cervical Sensorimotor Complete (AIS-A) Spinal Cord Injury during a Phase 2 Clinical. Workshop: ASIA/ISCoS Conference, June 2011. Washington DC, USA.

3. Kalsi-Ryan S, Kapadia N, Holmes J, Verrier M. Upper Limb Sensorimotor and Functional Assessment for Individuals with Tetraplegia - Graded Redefined Strength, Sensibility and Prehension (GRASSP). Workshop: National SCI Conference, October 2010. Niagara Falls, Canada

4. Sylvie Nadeau, Robert Forget, Dany Gagnon, and **Sukhvinder Kalsi-Ryan**. Sensory-motor assessment of individuals with spinal cord injury. Workshop: National SCI Conference, November 2008. Toronto, Canada

5. Kalsi-Ryan S, Duff S, Rudhe C, Curt A, Fehlings MG, Verrier MC. Reliability and Validity of the Graded and Redefined Assessment of Sensibility Strength and Prehension (GRASSP). 2008. *Journal of Spinal Cord Medicine* Vol. 31

Podium presentation: Sukhvinder Kalsi-Ryan

Meeting: Annual American Spinal Injury Association Meeting, San Diego, June 2008

6. Kalsi-Ryan S, Duff S, Rudhe C, Wuermser L, Curt A, Fehlings MG, Verrier MC. The GRASSP Protocol – The Value of Spinal Cord Injury (SCI) Research Networks to the Development of Outcome Measures. 2007. *Journal of Spinal Cord Medicine* Vol. 30(2): pp168

Poster presentation: Sukhvinder Kalsi-Ryan

Meeting: Annual American Spinal Injury Association Meeting, Tampa FL, June 2007.

Manuscripts:

1. Kalsi-Ryan S, Beaton D, Curt A, Duff S, Popovic MR, Rudhe C, Fehlings MG, Verrier MC. The Graded Redefined Assessment of Strength Sensibility and Prehension (GRASSP) – Reliability and Validity. Submitted to Journal of Neurotrauma 2011 Aug 12. [Epub ahead of print]

2. Kalsi-Ryan S, Curt A, Fehlings, MG and Verrier MC. Assessment of the Hand in Tetraplegia Using the Graded Redefined Assessment of Strength Sensibility and Prehension (GRASSP): Impairment versus Function. Top Spinal Cord Inj Rehabil (2009); 14(4):34-46.

3. Kalsi-Ryan S, Beaton D, Curt A, Duff S, Jiang D, Popovic MR, Rudhe C, Fehlings MG, Verrier MC. Defining the Role of Sensation, Strength and Prehension on Upper Limb Function in Cervical Spinal Cord Injury (SCI). Submitted to Neurorehabilitation and Neural Repair, under review. Manuscript #: NNR-11-1411.

4. Kalsi-Ryan S, Curt A, Verrier, MC and Fehlings MG. Filling the Clinical Measurement Gap in the Translation of Preclinical Models for the Upper Limb in Tetraplegia. Journal of Neurosurgery Spine, Focus NACTN Issue. Submitted.

OrthoIntrinsics PRIME ASIA Device Status Report – January 2012

PROGRESS SUMMARY:

Data capture:

- Improved the accuracy by 2000% to $\pm 0.05 \text{ lb}_f$ from $\pm 1 \text{ lb}_f$ (all readings displayed to 0.1 lb_f)
- Constructed new calibration apparatus and codified calibration procedure

Software:

- Improved Bluetooth functionality
 - Pairing between dynamometer and base control unit no longer depends on order of device activation
 - Data transfer rate between dynamometer and base control units improved
 - Additional checks placed to ensure data integrity during wireless transfer
- Introduced time values for all data points in patient records
- Implemented USB interface for exporting patient records to external computer
- Improved graphical user interface
 - Eliminated former bugs that could cause software to freeze
 - Enlarged buttons used to enter patient ID
- Added graphical icons and status text on dynamometer LCD display
- Economized power consumption for increase in battery life on both dynamometer and base control unit

Mechanical Changes:

- Designed new wrist strap for bicep/tricep to be adjustable, simpler to use, and easily disinfectable
- Designed new finger strap for intrinsics to be easily disinfectable
- Re-designed dynamometer to make wrist and finger straps easier to attach
- Added on/off switch to dynamometer

CALIBRATION PRODEDURES

I. Background Information

To achieve highly accurate data capture, PRIME utilizes strain gauge technology to measure minute material deformations caused by force acting on the PRIME dynamometer. The strain gauges work by affecting a circuit voltage that varies with the deformation. In electrical engineering terms, this is an “analog signal” that hardware can measure by means of an analog-to-digital converter (ADC), which produces a digital signal based on the circuit voltage. This digital signal is, in turn, interpreted by software and converted to the sample reading seen by the user. This process is illustrated below in Figure 1.

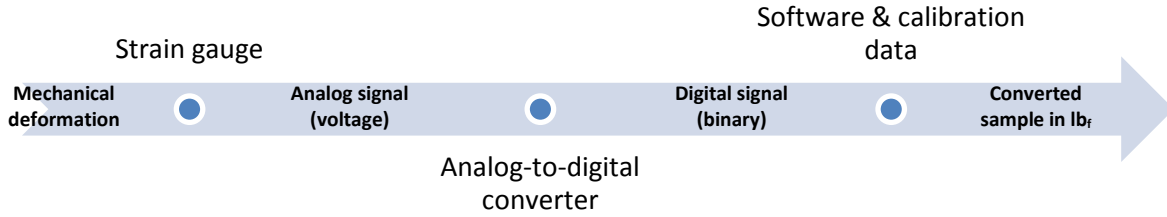


Figure 1: Data collection process

The difficulty of producing an accurate signal, then, lies in the conversion from material deformation to voltage (strain gauge hardware), and in the conversion from voltage to digital signal (ADC hardware). Of these two components, the strain gauges are by far the more accurate. Therefore, for all practical purposes, the expected error in the entire force-to-digital reading conversion process can be adequately described by the expected error from the ADC hardware alone. Error from the ADC depends on the maximum number of discrete values that the ADC can represent (over $2^{16.5}$, or 92,681, for all devices) and the fraction of those discrete values that are actually used. For example, a typical sensor on PRIME may produce an analog signal of +8.8 mV at 0 lb_f and a signal of +15.9 mV at 100 lb_f (though these specific values slightly between strain gauges). The analog input range for every PRIME ADC is ± 23.4 mV, so the resolution of the PRIME sensor above is given by:

$$\frac{100 \text{ lb}_f}{\text{Number of measurable values in } 100 \text{ lb}_f \text{ range}} = \frac{100 \text{ lb}_f}{2^{16.5} \times \left(\frac{15.9 \text{ mV} - 8.8 \text{ mV}}{23.4 \text{ mV} - (-23.4 \text{ mV})} \right)} = \frac{100 \text{ lb}_f}{14060.7} = 0.0071 \text{ lb}_f$$

Of course, to assert that resolution remains constant for any range of equal span (e.g., both for a range of 0-100 lb_f and for a range of 50-150 lb_f) implies that the value of the digital signal output from the ADC varies linearly with applied force. This is entirely the case with PRIME: the digital signal from the ADC varies directly and linearly with the analog signal to the ADC, and the circuit voltage from the strain gauge varies linearly with force input to the dynamometer. This is a consequence of the shape and mechanical properties of the material whose deformation the strain gauges measure (in the case of PRIME, a special aluminum bar housed in the dynamometer).

Accuracy of the entire system is verified individually for each of the two strain gauge sensors on every device.

II. Calibration with Heavy Weights

The process of calibration follows from the simple concept of mapping the unconverted digital signals produced by the PRIME dynamometer under a series of forces of known value, so that, in

turn, the force exerted by a patient can be accurately and precisely deduced from the resulting digital signal. To aid this process, a custom apparatus was used.

In essence, the apparatus restricts the movement of an upper platform to along the vertical axis. The dynamometer is oriented below the platform so that the intended axis of force application is also parallel to the vertical axis. Thus, as weights are loaded on the device, a known constant force is provided by gravity directly downward, along the same axis where a patient using the dynamometer exerts force.

The stepwise procedure for calibration is as follows:

1. The dynamometer is mounted in the apparatus below the upper platform such that one adjustable grip can make contact with the base of the platform, and the adjustable grip is pointing upward (Figure 2a)
2. The platform bearing the load lowers vertically along ball bearing slides until in contact with the adjustable grip that sits over the sensor to be calibrated (Figure 2b)
3. Weight is stacked above the moving platform to load apparatus (Figure 2c)
4. Weights (7 weights in total, each roughly 10 lbs) are sequentially applied and resulting digital signals recorded (Figure 2d)

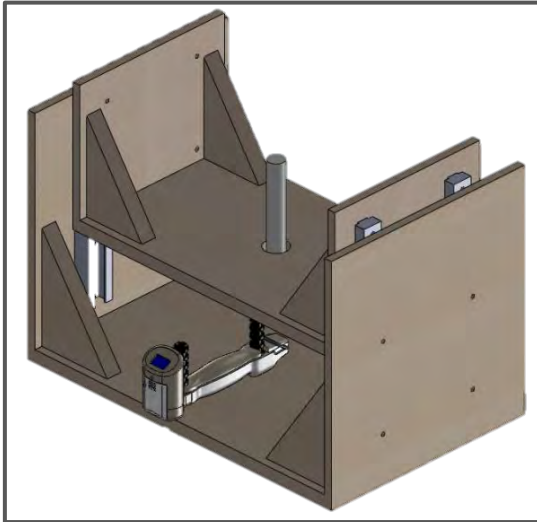


Figure 2a

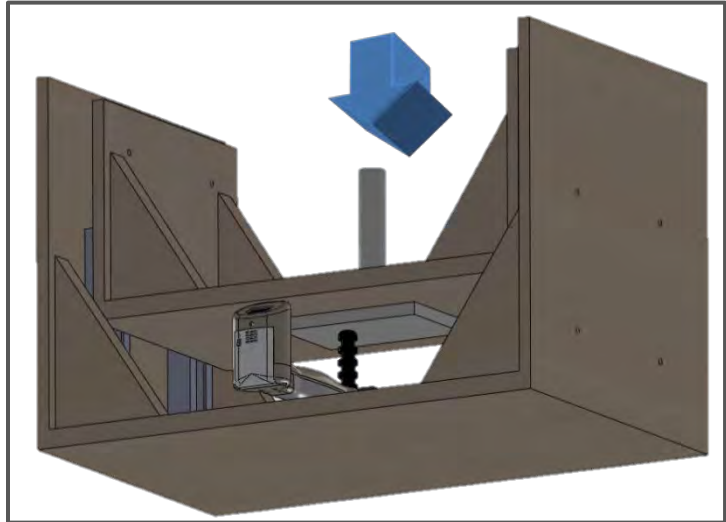
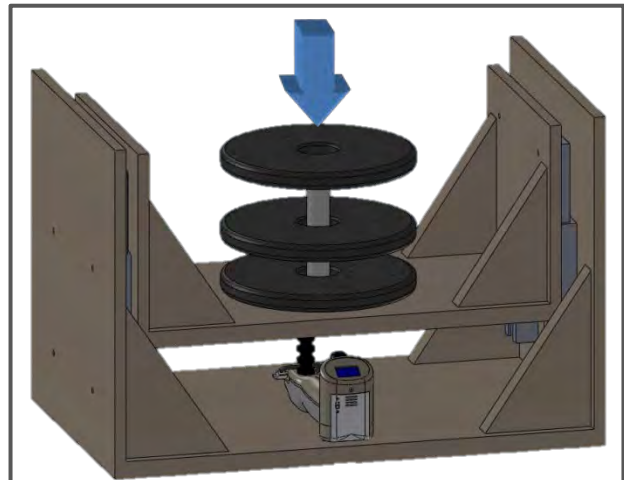
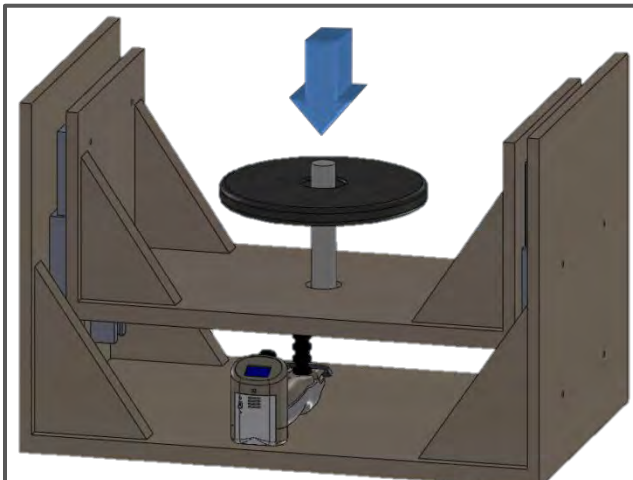


Figure 2b



***NOTE: All test procedures test applied force in compression. The physical properties that determine the linear-fit curve are valid both in tension and compression, and thus, the curve can be extrapolated to tensile forces away from the base unit strain bar case along the adjustable grip bar central axis.

III. Calibration with Small Weights

The calibration procedures involving small weights are similar to those used with heavy weights:

1. An attachment (Figure 4a) for holding small weights (Figure 4b) snaps onto the end of adjustable grip bar
2. The dynamometer is oriented so that the adjustable snap grips are pointing upwards, and the axis along which force is applied to the dynamometer is parallel with the vertical axis
3. Small weights of known mass (6 total, each about 2 lbs) are loaded onto the frame sequentially (Figure 4c)
4. Converted digital readings taken for each weight verify the accuracy of the calibration curve for small forces

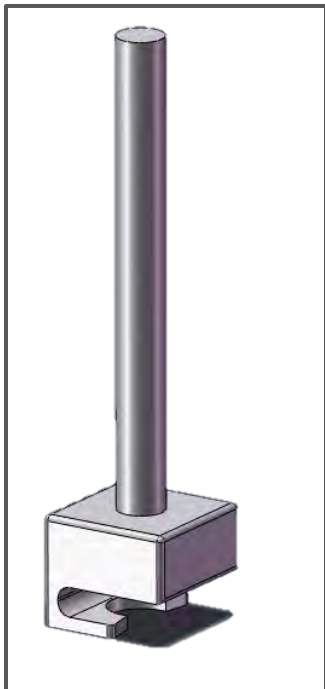


Figure 4a

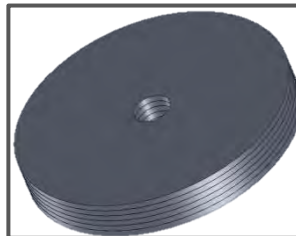


Figure 4b



Figure 4c

IV. Data Analysis

Data from each calibration procedure is used to construct linear-regression curves. The slopes of these curves are then incorporated into the dynamometer software in order to associate a given increase or decrease in measured voltage with the appropriate change in applied force. The offset of

each curve can be discarded, since the device dynamically sets the zero-value immediately preceding each test.

Figure 3 below depicts sample data. X-axis values represent the value of the unit-less digital signal, which Y-axis values are given in lb_f .

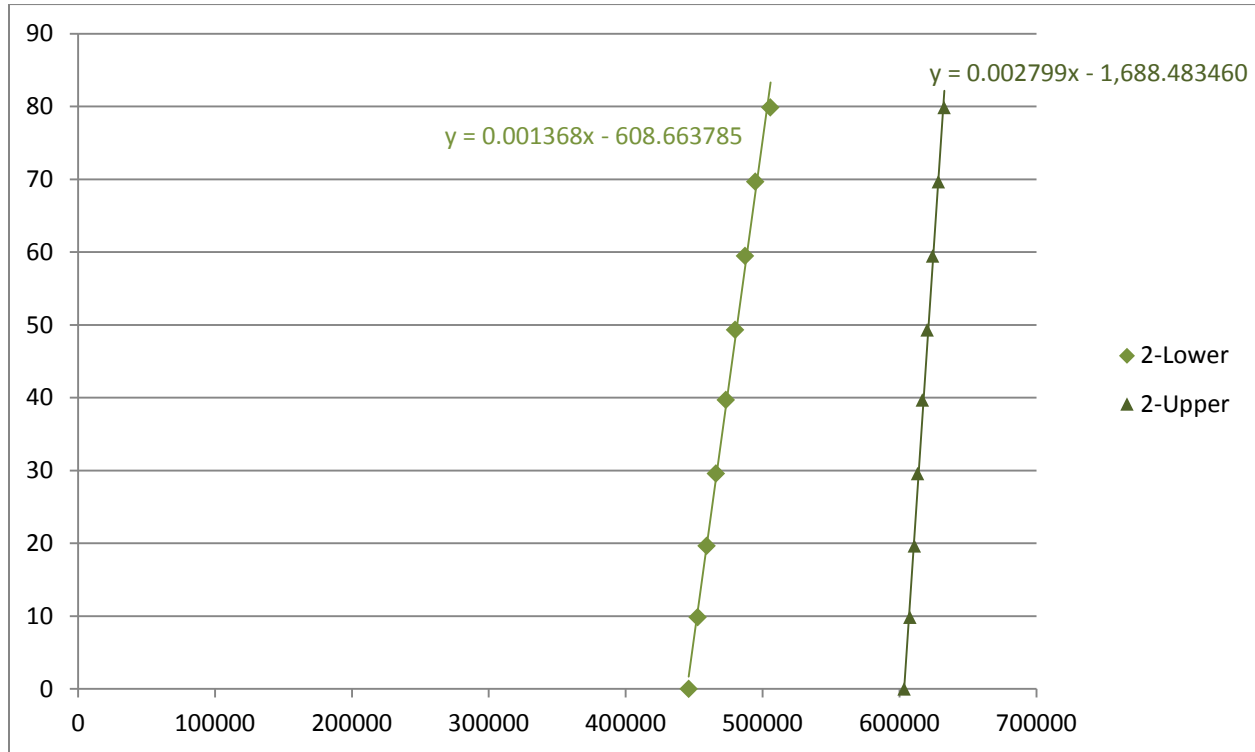


Figure 3: Calibration curves for upper and lower sensors on sample PRIME dynamometer

V. Verification of Accuracy with Voltage Dropout

An important aspect of the hardware involved in data acquisition is that the analog-to-digital converter (ADC), which converts an analog signal from the strain gauges to a digital signal that can then be matched to a calibration curve to determine the magnitude of an applied force in lb_f , depends on a reference signal of a specific voltage in order to make its conversion. It is crucial that this signal remains constant, and therefore, there is some concern that as supply voltage decreases (as will happen with any battery cell such as that used by the PRIME dynamometer), the ADC reference signal will also decrease in voltage and compromise the device accuracy.

The PRIME dynamometer includes certain hardware components that prevent this from happening. To demonstrate their effectiveness, all dynamometers are verified using the following simple procedure:

1. After calibration, the small weight verification procedure in Section IV above is carried out with a fresh set of batteries (input voltage ≈ 3.0 V).
2. The same calibration is carried out with a nearly-depleted set of batteries (input voltage ≈ 2.2 V).

The PRIME dynamometer software includes a battery life indicator that runs low when the battery is outside of the range where accuracy can be guaranteed. Note that continuing to use the device after the dynamometer indicates depleted batteries may result in inaccurate data, even if the device continues to stay on and operate under such conditions.

**Christopher Reeve Foundation
North American Clinical Trials Network (NACTN) - NOA**

FINAL REPORT ON CONTRACT NUMBER: NOA1-2010(PE)

PRINCIPAL INVESTIGATOR: PETER ELLAWAY, PHD, Imperial College, London, UK

Title: Validation of the electrical perceptual threshold test as a quantitative assessment of cutaneous sensory function for spinal cord injury trials

Background: The current gold standard for clinical assessment of sensory function in spinal cord injury (SCI) is the American Spinal Injuries Association (ASIA) Impairment Scale (AIS). There are limitations to this assessment in that (1) it uses an ordinal rather than a quantitative scale, (2) there is a strong component of subjectivity, and (3) evaluation of each dermatome is scored simply as either normal, absent or abnormal (including both heightened and lowered sensitivity). Improved outcome measures should allow both for improvements and worsening of a SCI in those undergoing clinical trials designed to promote recovery of function with a resolution down to a single vertebral level of the spinal cord. The Electrical Perceptual Threshold test (EPT) (Belci et al, 2004) meets these criteria in that it provides a quantitative and more objective measure of threshold for cutaneous sensory function for each dermatome. The method uses incrementing electrical stimulation and the method of limits to determine a threshold at a particular location on the skin. It has been validated against the AIS sensory grading in SCI (Ellaway et al, 2004; Savic et al, 2006) and has revealed good repeatability for inter and intra-rater trials both in SCI (King et al, 2009) and in control subjects (Leong et al, 2009). Validation has also been provided against dermatomal somatosensory evoked potentials in SCI (Kramer et al, 2009). This project set out to compare the reliability (repeatability) of the EPT against monofilaments (Semmes-Weinstein) in neurologically normal subjects.

Achievements: The proposal was to measure EPT and monofilament threshold for four dermatomes (C4, T1, T8 & L4) on both sides of the body in twenty male and twenty age-matched female, neurologically normal subjects. They would be studied on two occasions with an interval of at least one week to provide intra-rater repeatability measures. Correlations between EPT and monofilament readings would be established. These milestones and timelines have all been achieved. Interim results of the study have been presented at two International Scientific meetings^{1,2}. A full paper is in the final stages of preparation³ and will be submitted to a peer-reviewed journal (Spinal Cord).

Summary of the Study and Results

Study design: Prospective experimental.

Objectives: To determine and compare the reliability and repeatability of the electrical perceptual threshold (EPT) and Semmes-Weinstein monofilament (SWM) tests for cutaneous sensibility.

Methods: EPT and SWM tests were carried out on 40 neurologically normal healthy individuals (20 male, 20 female). One experienced examiner carried out all tests. Each individual was examined for EPT and SWM sensitivity at the American Spinal Injuries Association (ASIA) key point on four dermatomes (C4, T1, T6 and L4) on both sides of the body. The tests were repeated after an interval of approximately one week. Intra-rater reliability was determined using intra-class correlation coefficients (ICC). Repeatability was determined using the method of Bland and Altman (see Figure 2).

Results: There were no significant differences in the mean values of EPT or SWM between the two assessments for any dermatome (Figure 1). Significant differences in mean values for both EPT and SWM were observed between some dermatomes (Table 1). ICC ranged from 0.67 - 0.81 for the EPT and 0.46 - 0.61 for the SWM (Table 2). Higher ICC for the EPT compared to the SWM was again revealed when male and female subjects were assessed separately. EPT was lower for females for three of the four dermatomes tested. This was not the case for SWM thresholds, although a higher threshold for females was revealed for one dermatome (Figure 3). Correlation between EPT and SWM was weak or (largely) absent (Figure 4).

Conclusions: SWM has *poorer* reliability than EPT in normal subjects. The *lack of correlation* between the two measures indicates that they may be testing different cutaneous sensibilities. However, since both have the potential to add sensitivity and resolution to the standard clinical testing provided by the American Spinal Injuries Association (ASIA) Impairment Scale (AIS) it may be *advisable to include both tests* in any quantitative sensory assessment of SCI.

Future goals: The conclusion from this study suggests that further comparison of the repeatability of EPT and SWM, and the correlation between the measures, is indicated in a SCI population. It may well be that the wider range of sensibilities caused by injury in SCI subjects, compared to neurologically normal individuals, will result in a clearer indication as to whether the two tests are assessing different or the same sensory modalities. Furthermore, a contemporaneous study of repeatability of the two tests in SCI would confirm or otherwise reject the conclusion that the EPT has greater reliability than SWM.

Bibliography:

1. Ellaway PH. Electrical perceptual threshold: validity of a test for cutaneous sensation in the assessment of spinal cord injury. Abstract. Christopher and Dana Reeve Foundation. Spinal Cord Symposium: Bench to bedside. December 2010. Phoenix, USA
2. Peter Ellaway and Maria Catley. Electrical perceptual threshold and monofilaments: towards validation for a quantitative test of cutaneous sensation in spinal cord injury. Abstract. Annual Network Meeting of the International Spinal Research Trust. September 2011. London, UK
3. Peter H Ellaway and Maria Catley. Comparison of the electrical perceptual threshold and Semmes-Weinstein monofilament tests of cutaneous sensibility. 2012 In preparation. To be submitted as a full peer-reviewed paper to Spinal Cord.

List of personnel:

Ms Maria Catley – employed as Research Assistant

Figures and Tables:

Dermatomes	SWM				EPT			
	Assessment 1		Assessment 2		Assessment 1		Assessment 2	
	Diff of means	P	Diff of means	P	Diff of means	P	Diff of means	P
C4 v T1	0.34	<0.001	0.36	<0.001	0.12	insig	0.002	insig
C4 v T8	0.48	<0.001	0.41	<0.001	0.38	0.002	0.45	<0.001
C4 v L4	0.3	<0.001	0.18	insig	1.68	<0.001	1.78	<0.001
T1 v T8	0.13	insig	0.05	insig	0.51	<0.001	0.45	<0.001
T1 v L4	0.64	<0.001	0.55	<0.001	1.80	<0.001	1.71	<0.001
T8 v L4	0.78	<0.001	0.6	<0.001	1.29	<0.001	1.27	<0.001

Table 1. Post hoc multiple pair-wise comparisons (Bonferroni t-test) made following significant interactions revealed by two way repeated measures of analysis of variance (ANOVA) with the within-subject effects of assessment (first, second) and dermatome (C4, T1, T8 and L4). ANOVAs conducted independently for SWM and EPT measures.

Dermatome	Intra-Class Correlation	
	EPT	SWM
C4	0.67	0.46
T1	0.73	0.61
T8	0.74	0.55
L4	0.81	0.48

Table 2. Intra-class correlation coefficients (ICC) for repeated measures of EPT and SWM by the same rater on two occasions. ICCs for each dermatome include both left and right side measures on 40 subjects (20 male, 20 female).

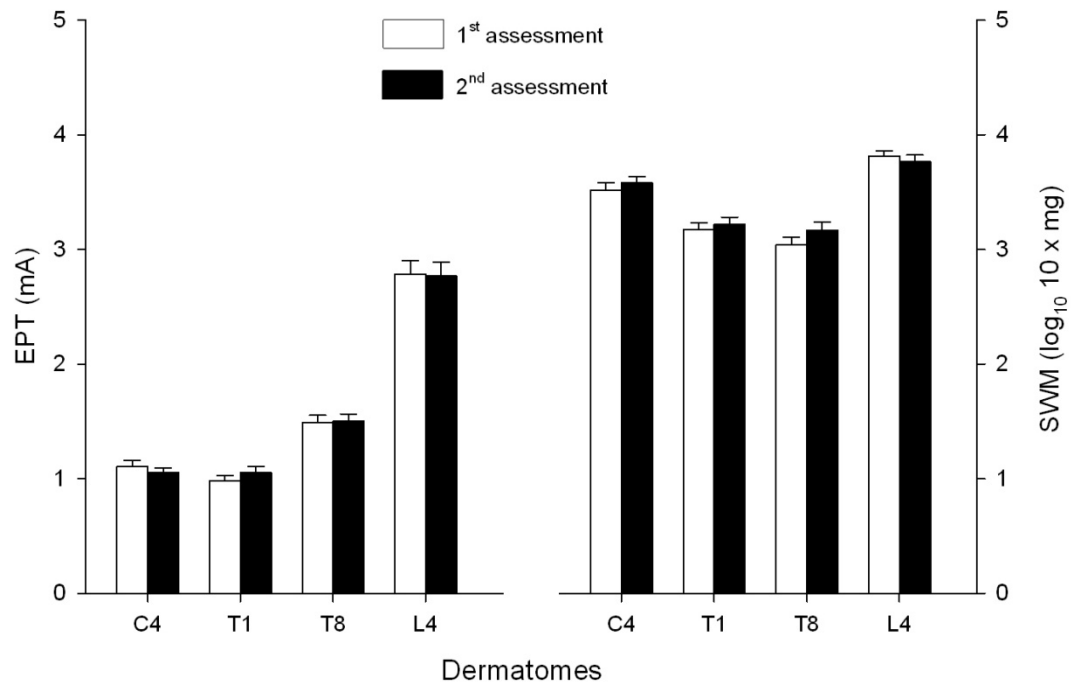


Figure 1. Mean (+SE) values for EPT (left) and SWM (right) thresholds for the first (open bars) and second (filled bars) assessments for the four dermatomes C4, T1, T8 and L4 for all 40 subjects.

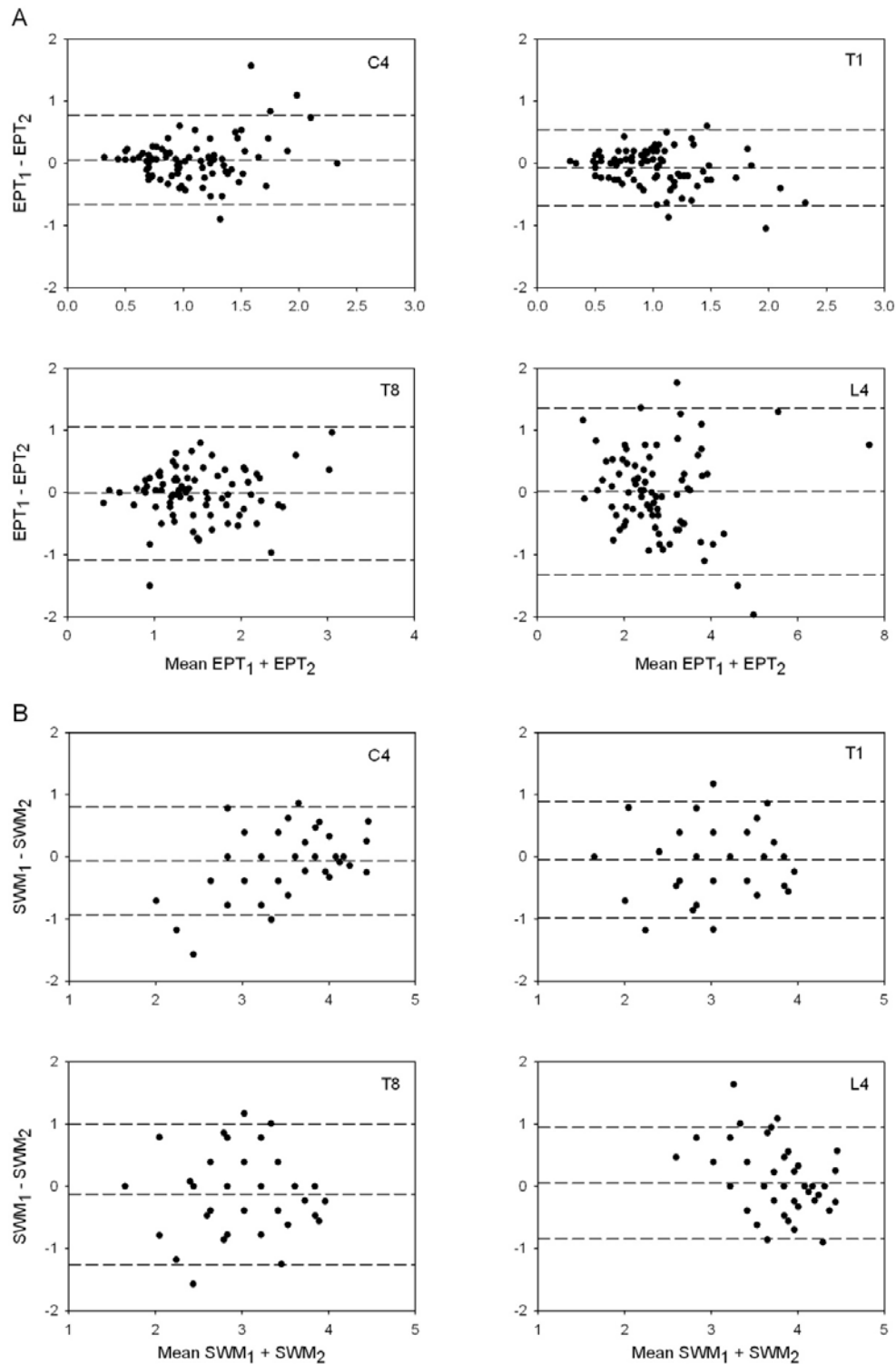


Figure 2. Bland and Altman plots for the difference between first and second (repeat) assessments against the mean value of the two assessments for EPT (above) and SWM (below) for each of the four dermatomes. Dashed lines represent mean (centre) and 95% limits (upper and lower) of the difference between assessments.

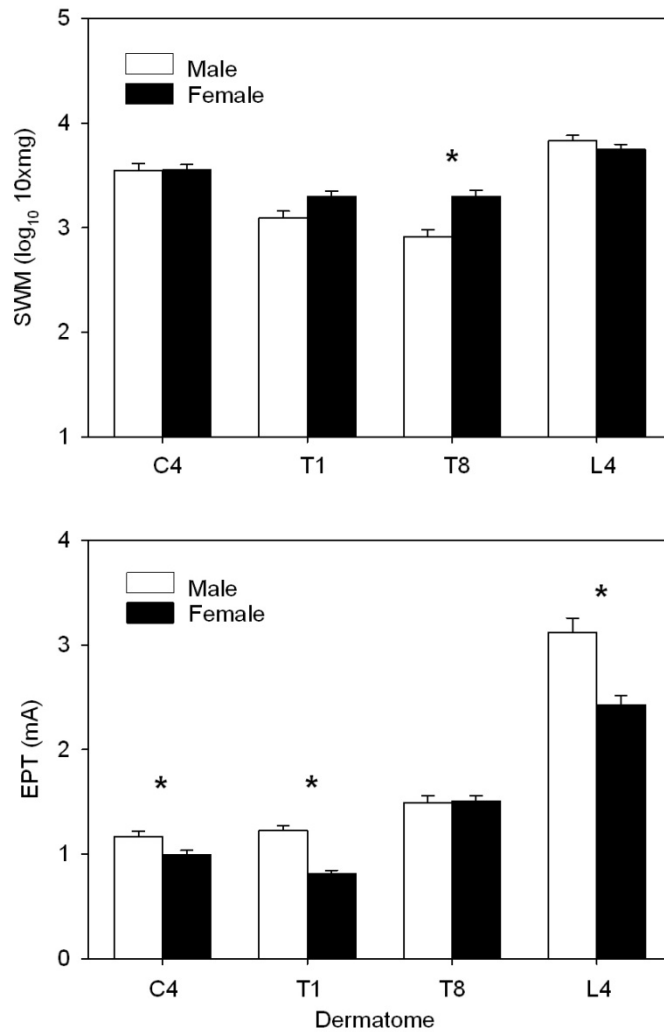


Figure 3. Mean (+SE) values for SWM (above) and EPT (below) thresholds for male (open bars) and female (filled bars) assessments for the four dermatomes C4, T1, T8 and L4. Significant differences ($P < 0.05$) between male and female subjects are marked with an asterisk.

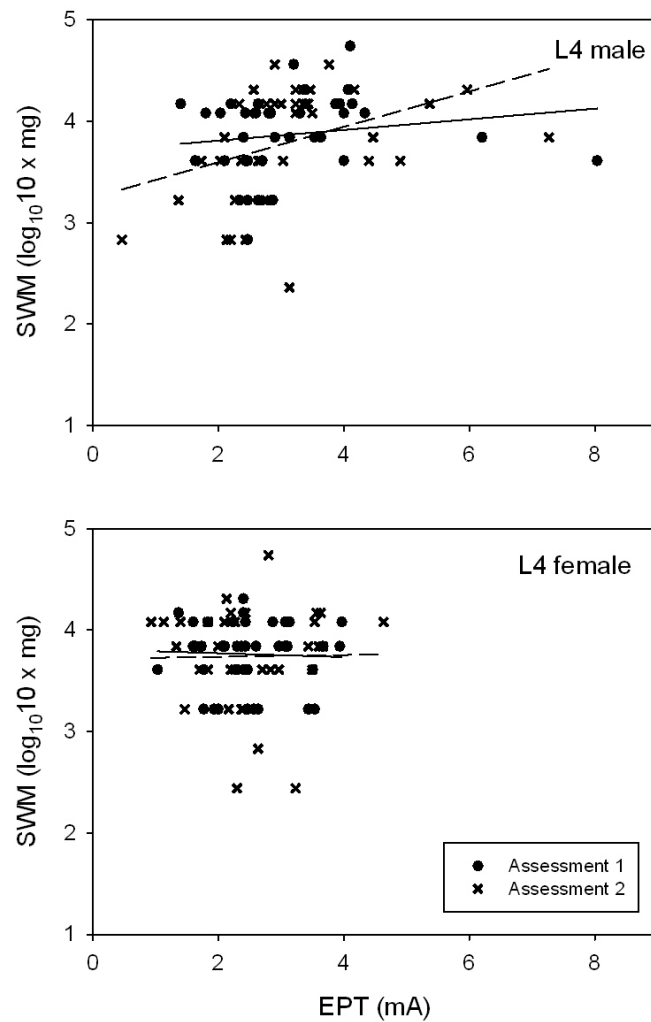


Figure 4. Regression analysis for SWM and EPT measures for the L4 dermatome for the first (closed circles, solid lines) and second (cross symbols, dashed lines) assessments for male (above) and female (below) subjects. Regression significant only for second assessment for male subjects ($r = 0.26$, $P = 0.02$).

FINAL REPORT

Title: Natural progression and recovery of cardiovascular parameters following traumatic spinal cord injury.
Contract: NOA2-2010(AK)
Principal Investigator: Andrei Krassioukov, MD, PhD, FRCPC
Funding period: September 1, 2010 to August 31, 2012
Report date: January 19, 2012

Background

Low arterial blood pressure (BP) and the presence of neurogenic shock (BP below 90 mmHg) after spinal cord injury (SCI) results in ischemia of the spinal cord, and is one of the major contributing factors to the cascade of secondary mechanisms involved in further damage of fragile neuronal tissue. However, only limited data from typically small groups of individuals with SCI are available on the prevention and/or development of cardiovascular abnormalities following acute SCI.

Objective

The purpose of this study was to investigate the acute and sub-acute changes in cardiovascular function following traumatic SCI, and determine whether these changes influence the process of neurological recovery. The aims of the study were as follows:

1. To establish a database with the natural progression and recovery of cardiovascular parameters in individuals with SCI.
2. To establish the effect of the changes in arterial blood pressure on potential neurological recovery following traumatic SCI.
3. To develop guidelines on the acute monitoring and management of cardiovascular parameters for individuals with SCI.

Methods

A retrospective review of ambulance service records and emergency room medical charts was conducted. Records for all patients with acute traumatic SCI admitted to Vancouver General Hospital between 2008 and 2010 were examined. The data retrieved included the following:

- Demographics (age, sex, education, ethnicity).
- Details of injury (time, date and mechanisms of injury, initial assessments on site)
- Surgeries (date and extent of preliminary and secondary spine/spinal cord procedures).
- American Spinal Injury Association Impairment Scale (AIS) and injury level (on admission, 7 days and 30 days post injury).
- Resuscitation (initiation of vasopressor therapy, fluid resuscitation, drugs, blood).

- Systolic and diastolic blood pressure, heart rate measurements (at the site of injury, upon admission to the emergency room, three times daily during the first 7 days, and every other day until 30 days post injury).

Major Findings

Patient Demographics:

A total of 227 charts were reviewed, but only 82 cases (36%) were selected for the study as these were admitted with acute traumatic SCI within 24 hours.

From this cohort of 82 cases, we collected comprehensive demographic, neurological, and cardiovascular data as outlined above.

In 34 patients we completed full extraction of data from the time of injury up to one month post admission, including vasopressor therapy, fluid resuscitation, hematological and other biochemical parameters crucial for the study.

The majority of these individual sustained cervical and upper thoracic SCI.

Baseline cardiovascular parameters:

In 34 reviewed patients, vasopressor or aggressive fluid resuscitation therapies were required on admission to the emergency department in 10 individuals (29%), the majority (90%) of whom sustained cervical complete (AIS A) SCI.

On average in this group, systolic blood pressure documented at initial assessment was approximately 76 mmHg. This level of blood pressure is consistent with neurogenic shock. The average length of pressor therapy was 10 days (ranging from 3 to 43 days).

In an additional 8 patients (24%), pressor therapy was started within the next 24 to 48 hours upon admission to the critical care unit. However, the reason for initiation of pressor therapy in this subgroup is less clear and further detailed analysis of the data is required.

Conclusions

- Approximately 30% of the cohort examined in the study exhibited neurogenic shock that required administration of pressor therapy and volume resuscitation.
- Although this group was homogenous with respect to level and completeness of injury, there was significant variation in length of requirement for pressor therapy. There is a possibility that the extent of damage to the spinal autonomic circuits varies significantly with SCI, which was reflected by the necessity of various durations of pressor therapy. Further studies are required to fully elucidate the need for inclusion of detailed autonomic assessments during the acute period of SCI.

- Furthermore, our study confirmed the importance of continuous monitoring of cardiovascular parameters, specifically arterial blood pressure and heart rate, in the acute phase of SCI.

It is important to recognize that initial treatment of cardiovascular instabilities due to neurogenic shock with vasopressors could be varied significantly from days to weeks, and will most likely depend on the severity of the destruction of the autonomic spinal pathways, examinations which are still not performed during initial admission to acute care facilities.

Successes

We have compiled a database which includes 227 cases of non-traumatic and traumatic SCI. Preliminary statistical analysis began in January 2012, the results from which will be submitted for presentation at the September 2012 International Spinal Cord Society annual scientific meeting in London, England (abstract deadline is February 3, 2012).

Challenges

As mentioned in our previous report, we faced enormous barriers in coordinating efforts between emergency room, trauma and neurosurgery/spine orthopedic services. Therefore, rather than performing a prospective evaluation of individuals admitted to acute care, a retrospective chart review was performed.

Personnel

Funds were used to support the part time salaries of Ms Melissa Pak (MSc, research coordinator), Dr. Jeff Dong Yan (MD, research associate) and Dr. Andrei Krassioukov (principal investigator). Two emergency resident physicians resident, Drs. Patrick Oxciano and Dayan Huang, also volunteered their time on the project. Their roles included coordinating access to health records through emergency medical services and acute care facilities, extensive chart review and compilation of patient data, as well as analysis of results. Meetings with the principal investigator were scheduled monthly, with additional meetings arranged when the need arose.

Abstracts/Publications

1. Dayan Huang, Patrick Oxciano, Dong Yan, Susan Harkema, and Andrei Krassioukov. Revisiting neurogenic shock. Blood pressure control in acute period of spinal cord injury. ISCoS Annual meeting London UK, Abstract, 2012 Submitted.
2. Dayan Huang, Patrick Oxciano, Dong Yan, Susan Harkema, and Andrei Krassioukov, Revisiting neurogenic shock. Blood pressure control in acute period of spinal cord injury. Spinal Cord. In preparation.

The use of MRI characteristics to predict long-term Functional and Neurological Outcome after Acute Spinal Cord Injury

Objectives

The **primary objective** of this study will be to evaluate the prognostic value of MRI characteristics obtained in the acute injury period in **predicting both neurologic and functional outcome at 6 months follow-up**. Our analyses will consider both quantitative and qualitative measures performed on the admission MR images of each patient enrolled within the NACTN database. In addition MRI variables will be combined with other clinical data elements to produce a comprehensive clinical-radiographic classification system predictive of outcome. Given the large amount of clinical and radiographic information available, this will represent the most comprehensive evaluation of the predictive capacity of MRI in the setting of SCI performed to date.

Methods

In order to gather the relevant data, MRI and CT source images (baseline and follow up) will be obtained for each patient from each of the NACTN sites under the following study protocols: NACTN registry, STASCIS trial and Phase I Riluzole study. Local ethics review boards have approved each of these studies and we anticipate an amendment will be necessary for the analysis of MR images. Images will be de-identified, coded based on the corresponding NACTN ID code and transported to a central location for review. Review will be completed independently by 2 radiologists evaluating the source images, and classifying them based on the variables discussed below, for each of patient. Any disagreements in variable classification for a given patient's MRI will be resolved by discussion.

The MRI predictor variables considered will include both qualitative characteristics and quantitative measurements.

The quantitative measures will be:

1. maximal canal compromise (MCC)
2. maximal spinal cord compression (MSCC)

For purposes of standardization, MCC will be calculated by comparing the AP canal diameter at the level of maximum injury with the AP canal diameter at nearest normal levels above and below on the mid-sagittal T1-weighted MRI (Table 1). Similarly, maximal spinal cord compression will be calculated by comparing the AP cord diameter at the level of maximum injury with the AP cord diameter at nearest normal levels above and below on the mid-sagittal T2-weighted MRI (Table 1). For both of these measurements, the result is a continuous variable (percentage out of 100) with a higher value implicating a more severe degree of canal compromise or cord compression. The reliability and validity of these measurements have been proven in previous publications of the Fehlings research group.

The qualitative MRI predictor variables will include the presence or absence of the following characteristics:

1. spinal cord transection
2. evidence of cord hemorrhage
3. cord swelling
4. cord compression
5. T2 hyperintensity
6. no signal change

In our recent publication (1) we have demonstrated that the presence of any one of these characteristics, along the spectrum listed here, affords a more sensitive and specific means of determining that any individual patient is less likely to recover. In other words, a person with cord hemorrhage is less likely to recover than a person with T2 hyperintensity. The proposed comparison of these qualitative MR characteristics to patient outcome at 6 months will represent the largest clinical series to date. Using clinical outcome as a gold standard, we will demonstrate the sensitivity and specificity of these MR characteristics on a group level (see reference 2 for example). Likelihood ratios will be used to communicate individual case examples. We hypothesize that qualitative MR characteristics will provide clinicians with a relatively straightforward means of augmenting the clinical examination to communicate information to patients and potentially to stratify patients into different arms of a clinical trial based on the severity of injury.

Work performed to date:

At present all of the hard copy DICOM MRI files have been collected from each of the 9 NACTN sites. We are presently in the process of analyzing the acute MR images on approximately 400 SCI patients. Three individuals including a neuro-radiologist and two neurosurgeons are independently evaluating all of the images to ensure reliability in image interpretation. The image interpretation portion of this project will be completed by March 2011 at which point we will commence the statistical analysis described above. We anticipate that a manuscript reflecting this analysis will be prepared by late spring of this year.

Maximal canal compromise %	Maximal cord compression %
$(1 - \frac{D_i}{D_a + D_b/2}) \times 100\%$	$(1 - \frac{d_i}{d_a + d_b/2}) \times 100\%$

Table 1

Standardized formulas for determining maximal canal compromise and maximal cord compression.

Modified from: Fehlings MG, Rao SC, Tator CH, et al. The Optimal Radiologic Method for Assessing Spinal Canal Compromise and Cord Compression in Patients with Cervical Spinal Cord Injury Part 2: Results of a multicenter study. Spine 1999;24:605-613.

Di= AP canal diameter at the level of maximal injury; Da= is the AP canal diameter at nearest normal level above level of injury; Db= is the AP diameter at nearest normal level below level of injury

di= AP diameter of the cord at the level of maximal injury; da= is the AP diameter of cord at nearest normal level above level of injury; db= is the AP diameter of the cord at nearest normal level below level of injury

References

- 1) Cadotte DW, Wilson JR, Mikulis D, et al. Magnetic Resonance Imaging as a diagnostic and prognostic tool in spinal cord injury. Expert Opinion on Medical Diagnostics. Accepted for publication January 2011.

Riluzole Safety Trial Review

December 31, 2012

Table 1. Riluzole Therapeutic Time Windows

Time Window	Minimum	25 th Percentile	Median	75 th Percentile	Maximum
Injury to NACTN Admission N=36	0.7 hrs	1.5 hrs	2.3 hrs	4.2 hrs	7.0 hrs
Injury to Riluzole Treatment N=34*	3.7 hrs	7.1 hrs	8.5 hrs	10.6 hrs	12.1 hrs

*Two cases pending verification of exact time to Riluzole treatment

Table 2. Gender and Ethnicity

Characteristic	N = 36 (percent)
<u>Gender</u>	
male	30 (83%)
female	6 (17%)
<u>Ethnicity</u>	
White	23 (64%)
Black	10 (28%)
Asian	3 (8%)

Table 3. Education and Employment

Characteristic	N = 36 (percent)
Education	
less than High School	4 (11%)
High School	11 (31%)
College or beyond	18 (50%)
Unknown	3 (8%)
Employment Status	
Currently Employed	26 (72%)
Unemployed	5 (14%)
Retired	3 (8%)
Unknown	2 (6%)

Table 4. Age at Injury

Age at Injury	Summary
N	36
Minimum	18 yrs
25 th Percentile	22 yrs
Median	37 yrs
75 th Percentile	55 yrs
Maximum	69 yrs

Table 5. Circumstances of Injury

Circumstance	N = 36 (percent)
Motor Vehicle Crash	17 (47%)
Fall	9 (25%)
Diving	5 (14%)
Assault	2 (8%)
Bicycle	2 (4%)
Motorcycle	1 (4%)

Table 6. Co-Morbidities of Riluzole patients

Co-Morbidity	N =36 (percent)
Yes	10 (28%)
No	26 (72%)
Type	Frequency
Hypertension only	4
Hypertension + Diabetes	1
Hypertension + Emphysema	1
Hypertension + Psychiatric	1
Hypertension + Diabetes + Psychiatric	1
Diabetes + Gastrointestinal	1
Psychiatric	1

Table 7. Injury level and AIS Severity

Injury Level	AIS A	AIS B	AITS C	Total
Cervical	12 (63%)	9 (100%)	8 (100%)	29 (81%)
Thoracic	7 (37%)	0	0	7 (19%)
Total	19 (100%)	9 (100%)	8 (100%	36(100%)
Percent AIS	53%	25%	22%	100%

Table 8. Severity by AIS Grade N = 36

	AIS A	AIS B	AIS C	Total (%)
Tetra IC	1 (5.3%)	7 (77.8%)	8 (100%)	16 (44.4%)
Tetra C	5 (26.3%)	1 (11.1%)	0	6 (16.7%)
Para IC	1 (5.3%)	1 (11.1%)	0	2 (5.6%)
Para C	12 (63.2%)	0	0	12 (33.3%)
Total (%)	19 (100%)	9 (100%)	8 (100%)	36 (100%)

Table 9. Steroid Use by AIS Grade

Steroid	AIS A	AIS B	AIS C	Total (%)
No	10 (59%)	7 (78%)	5 (63%)	22 { 65%}
Yes	7 (41%)	2 (22%)	3 (37%)	12 {35%}
Total	17 (100%)	9 (100%)	8 (100%)	34* (100%)

*Two cases pending verification of steroid use

Table 10. Surgeries By AIS Severity Grade

Surgery	AIS A	AIS B	AIS C	Total (%)
Posterior	5	2	4	11 (32%)
Anterior	2	0	2	4 (12%)
Both	9	6	1	16 (47%)
None	1	1	1	3 (9%)
Total	17	9	8	34 (100%)

Table 11. Time from Injury to Surgery Riluzole Patients N = 31 (3 patients had no surgery)

Time	Minimum	25 th Percentile	Median	75 th Percentile	Maximum
Injury to Surgery	6.4 hrs	9.0 hrs	13.1 hrs	20.8 hrs	213 hrs

Table 12. Time from Injury to Surgery; Historical NACTN Registry Control N = 128

Time	Minimum	25 th Percentile	Median	75 th Percentile	Maximum
Injury to Surgery	3.4 hrs	9.2 hrs	17.3 hrs	41.0 hrs	736 hrs

Table 13. Relative risk of severe complications for 31 Riluzole patients and a historical control of 137 NACTN AIS A, B, C Registry Patients

Complication	Riluzole Incidence N = 31	Registry Incidence N = 137	Risk Ratio Riluzole/ Registry	95% Confidence Interval	P-value
All Severe	9 (29.0%)	32 (23.4%)	1.24	(0.66, 2.33)	0.496
Pulmonary	4 (12.9%)	19 (13.9%)	0.93	(0.34, 2.54)	0.999
Cardiac	3 (9.68%)	9 (6.57%)	1.47	(0.42, 5.12)	0.465
Hematological	3 (9.68%)	2 (1.46%)	6.63	(1.15, 38.0)	0.044
GI/GU	2 (6.45%)	3 (2.19%)	2.95	(0.51, 16.9)	0.230
Infection	1 (3.22%)	12 (8.76%)	0.37	(0.50, 2.73)	0.466
Neurological	1 (3.22%)	3 (2.19%)	1.47	(0.16, 13.7)	0.561

Obs	Center	Patient ID	Injury Date	3-Mo-Due	3-Mo Complete	6-Mo-Due	6-Mo Complete	Comment
1	Maryland	R07-0001	04/12/2010	07/12/2010	07/20/2010	10/11/2010	10/24/2010	
2	Maryland	R07-0002	05/01/2010	07/31/2010	07/20/2010	10/30/2010	11/14/2010	
3	Maryland	R07-0003	05/08/2010	08/07/2010	08/17/2010	11/06/2010	Missing	Lost to FU
4	Maryland	R07-0004	05/31/2010	08/30/2010	09/11/2010	11/29/2010	01/11/2011	
5	Maryland	R07-0005	06/20/2010	09/19/2010	09/21/2010	12/19/2010	12/21/2010	
6	Maryland	R07-0006	07/03/2010	10/02/2010	10/12/2010	01/01/2011	01/08/2011	
7	Thomas_Jefferson	R10-0001	07/04/2010	10/03/2010	10/04/2010	01/02/2011	01/10/2011	
8	Maryland	R07-0007	07/08/2010	10/07/2010	10/19/2010	01/06/2011	01/14/2011	
9	Thomas_Jefferson	R10-0002	07/14/2010	10/13/2010	10/12/2010	01/12/2011	Missing	Lost to FU
10	Virginia	R05-0001	08/30/2010	11/29/2010	12/30/2010	02/28/2011	02/28/2011	
11	Virginia	R05-0002	09/02/2010	12/02/2010	12/23/2010	03/03/2011	04/07/2011	
12	Virginia	R05-0003	09/04/2010	12/04/2010	12/23/2010	03/05/2011	03/17/2011	12-month FU 9/19/11
13	Thomas_Jefferson	R10-0003	09/05/2010	12/05/2010	12/16/2010	03/06/2011	03/15/2011	
14	Thomas_Jefferson	R10-0004	09/07/2010	12/07/2010	12/16/2010	03/08/2011	03/03/2011	
15	Maryland	R07-0008	09/11/2010	12/11/2010	01/09/2011	03/12/2011	03/29/2011	
16	Thomas_Jefferson	R10-0005	09/11/2010	12/11/2010	12/28/2010	03/12/2011	03/07/2011	
17	Thomas_Jefferson	R10-0006	09/13/2010	12/13/2010	12/10/2010	03/14/2011	03/08/2011	
18	Virginia	R05-0004	09/22/2010	12/22/2010	Missing	03/23/2011	10/13/2011	Returned for 1 yr follow-up
19	Thomas_Jefferson	R10-0007	10/04/2010	01/03/2011	12/27/2010	04/04/2011	04/05/2011	
20	Hermann	R02-0001	10/04/2010	01/03/2011	12/15/2010	04/04/2011	04/05/2011	
21	Thomas_Jefferson	R10-0008	10/19/2010	01/18/2011	01/25/2011	04/19/2011	06/16/2011	
22	Kentucky	R06-0001	11/09/2010	02/08/2011	01/31/2011	05/10/2011	05/12/2011	
23	Thomas_Jefferson	R10-0009	12/08/2010	03/09/2011	03/03/2011	06/08/2011	06/20/2011	
24	Hermann	R02-0002	01/05/2011	04/06/2011	03/22/2011	07/06/2011	06/13/2011	Patient withdrawn - high liver enzymes. At 8 months liver enzymes returned to normal.
25	Maryland	R07-0009	01/23/2011	04/24/2011	04/19/2011	07/24/2011	07/20/2011	
26	Hermann	R02-0003	02/16/2011	05/18/2011	06/15/2011	08/17/2011	Missing	Patient cancelled appt. TIRR & UT
27	Maryland	R07-0010	02/16/2011	05/18/2011	05/19/2011	08/17/2011	Missing	Follow-up at discharge and 1 yr. completed. Located pt in Alaska
28	Kentucky	R06-0002	03/27/2011	06/26/2011	06/29/2011	09/25/2011	09/23/2011	
29	Thomas_Jefferson	R10-0010	04/05/2011	07/05/2011	Missing	10/04/2011	Missing	Pt still in rehab TJU communicating w rehab occupational therapist
30	Virginia	R05-0005	05/04/2011	08/03/2011	08/15/2011	11/02/2011	11/14/2011	
31	Toronto	R04-0001	05/31/2011	08/30/2011	09/13/2011	11/29/2011	12/06/2011	
32	Maryland	R07-0011	06/03/2011	09/02/2011	09/19/2011	12/02/2011	01/10/2012	
33	Kentucky	R06-0003	06/04/2011	09/03/2011	09/16/2011	12/03/2011	12/13/2011	
34	Thomas_Jefferson	R10-0011	06/12/2011	09/11/2011	09/09/2011	12/11/2011		
35	Thomas_Jefferson	R10-0012	06/18/2011	09/17/2011	Missing	12/17/2011		
36	Thomas_Jefferson	R10-0013	06/20/2011	09/19/2011	Missing	12/19/2011		

Riluzole for the Treatment of Acute Traumatic Spinal Cord Injury: Rationale for and Design of the NACTN Phase I Clinical Trial

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Abstract

In the immediate period after traumatic spinal cord injury (SCI) a variety of secondary injury mechanisms combine to gradually expand the initial lesion size, potentially leading to diminished neurological outcomes at long-term follow-up. Riluzole, a benzothiazole anticonvulsant drug, has been shown experimentally to mitigate aspects of this secondary injury cascade, specifically by preventing post-traumatic activation of neuronal sodium channels and thereby limiting the release of excitotoxic glutamate. Several preclinical SCI studies have associated riluzole administration with improved functional outcomes and increased neurologic tissue preservation. Currently, a phase I trial evaluating the safety and pharmacokinetic profile of riluzole in human SCI patients is being conducted by the North American Clinical Trials Network (NACTN) for Treatment of Spinal Cord Injury. The current review summarizes the existing preclinical and clinical literature on riluzole, provides a detailed description of the phase I trial and suggests potential opportunities for future investigation.

Key Words: Spinal Cord Injury; Riluzole; Clinical Trial; North American Clinical Trials Network

Introduction

Most therapeutic interventions that have been hypothesized to improve neurological outcomes after SCI fall into one of two broad categories with respect to mechanism of action. The first group of therapies aims to promote regeneration of neurological tissue within the spinal cord post injury. Such therapies include emerging drug treatments such as Cethrin, as well as stem cell implantation therapies¹⁻³. The second group of treatments, instead of generating new tissue, operate to protect viable spinal cord tissue early on after the injury by mitigating the evolution of secondary injury events. These therapies, which include methylprednisolone and GM-1 (Sygen), have been the subject of the largest clinical trials in SCI performed to date⁴⁻⁷. While treatments from both of the described categories have shown exceptional promise at the preclinical stages of investigation, none have proven to be uniformly effective in the treatment of human patients with SCI³.

Riluzole, a sodium channel blocking drug with putative neuroprotective properties gleaned from the preclinical literature, falls into the second group of therapies described above⁸. At present, a multicenter North American phase I trial, investigating the safety and pharmacokinetic profile of this agent, is underway. In this article we explore the relevant preclinical evidence evaluating riluzole in SCI, provide a detailed description of the trial underway, and outline potential options for future investigation.

Pathophysiology and Existing Preclinical/Clinical Evidence

Initiated by the primary spinal cord trauma, the evolution of secondary injury mechanisms begins within seconds and continues for several weeks⁹⁻¹¹. An important occurrence early on within this secondary injury cascade is the development of neuronal ionic imbalance, particularly increased intracellular sodium concentration, as a result of trauma-induced activation of voltage sensitive sodium channels^{12,13}. The increased intracellular sodium concentration leads to a concomitant rise in intracellular calcium levels, and also acts to stimulate intracellular acidosis and the development of cytotoxic edema¹⁴⁻¹⁶. The influx of sodium and calcium lead to an increased neuronal release of excitotoxic glutamate, resulting in excitatory mediated secondary injury and local cell death^{17,18}. One approach investigated to attenuate these specific injury events has been the delivery of pharmaceutical agents that block the constitutive neuronal sodium channel activation seen after SCI. A variety of sodium channel blocking compounds, including locally administered tetrodotoxin as well as systemically administered lidocaine and phenytoin, have shown to preserve neural tissue as well as improve behavioral outcomes in several preclinical animal models of SCI¹⁹⁻²¹. In spite of these promising findings, none of these compounds have been subject to systematic evaluation in the context of human SCI.

Riluzole is a sodium channel blocking benzothiazole anticonvulsant, which, like the agents described above, has demonstrated significant neuroprotective effects in preclinical SCI models

(Figure 1)^{22,23}. In a 2001 study by the Fehlings group, the effects of riluzole were compared to phenytoin, CNS5546A (a novel sodium channel blocking compound) and a control compound in rats with severe compression induced cervical SCI²⁴. At 6 weeks follow-up, while rats in all treatment groups demonstrated some degree of recovery, those in the riluzole treated group experienced a significantly larger degree of functional recovery as compared to the other treatment groups. Also in comparison to the other groups, the riluzole treated animals exhibited a significantly reduced area of tissue cavitation at the injury epicenter of injury on post-mortem histological analysis. Riluzole's neuroprotective effects are due to its combined ability to prevent sodium and calcium influx as well as to block the synaptic release of excitotoxic glutamate. However, in light of the relative paucity of synaptic connections within the spinal cord white matter, the axon sparing properties of riluzole are thought to be most related to its sodium channel blocking actions.

In the clinical realm, while riluzole has not been studied extensively in the context of SCI, it has been widely used in the treatment of the neurodegenerative disorder amyotrophic lateral sclerosis (ALS)²⁵⁻²⁸. A 2007 Cochrane review, summarizing the findings of 4 placebo controlled randomized trials, concluded that when given at a dose of 100 mg daily, riluzole is safe and improves median tracheostomy free survival by 2-3 months in patients with ALS²⁹. As regards adverse events, riluzole was well tolerated, with the exception that treated patients were 2.6 times more likely to experience an increase in serum alanine transaminase (ALT) as compared to patients treated with placebo²⁹. However, this effect was found to be uniformly reversible with cessation of riluzole therapy and was only reported after several months of medication administration. In light of this favorable safety and efficacy profile, riluzole has been FDA approved for patients with ALS, with administration typically commenced at the time of diagnosis and continued chronically.

Given its documented efficacy in preclinical SCI studies, as well as its safety in a human ALS population, riluzole appears an attractive candidate for evaluation in human patients with SCI. However, before proceeding with a comparative effectiveness study, it was felt prudent to first evaluate the safety and pharmacokinetic profile of this medication within an SCI specific population.

Phase I Clinical Trial for Riluzole in Traumatic SCI

Study Objectives and Design

Beginning in the spring of 2010, a phase I study was undertaken with the goal of developing the safety and pharmacokinetic profile of riluzole in patients with traumatic SCI. Secondary objectives were to compare neurological, functional and pain outcomes of the enrolled participants to outcomes of patients from the NACTN prospective SCI registry, matched for injury and demographic characteristics. This trial was designed as a prospective, single arm, open label multicenter study with a target enrollment of 36 participants. The sample size was based on NACTN registry incidence rates of adverse events ranging from 0.15 to 0.30. Using a

one-sided exact binomial test with a Type I error rate of 5%, a case series of 36 is expected to have at least 80% power to detect a doubling of a complication rate.

The safety endpoint follow-up period for the study is 6 months. However, neurologic, functional and pain outcomes will continue to be assessed at 12 months post injury.

Study Setting

The trial was undertaken by the North American Clinical Trials Network (NACTN) for Treatment of Spinal Cord Injury. NACTN is a collaborative network of 8 North American university affiliated departments of neurosurgery, a data management center and a pharmacological center (Table 1).

The study protocol was reviewed and approved by the U.S. Army Medical Research and Materiel Command, Office of Research Protections, Human Protection Office, and the Institutional Review Board of each participating site. This study is also listed in ClinicalTrials.Gov, a service of the U.S. National Institutes of Health.

Eligibility Criteria

Assessment of an individuals' study eligibility was made at hospital presentation by the site specific principal investigator or study coordinator according to inclusion/exclusion criteria listed below (Table 2).

Inclusion Criteria:

1) traumatic SCI and an ASIA impairment scale (AIS) grade of A, B or C; 2) neurologic level of injury from C4 to T12, 3) between the ages of 18 and 70 years; 4) able to receive riluzole within 12 hours of injury; and 5) able to cooperate in the completion of informed consent. AIS grade D patients were not included due to concerns about ceiling effects of the neurological and functional outcome measures.

Exclusion Criteria:

1) a history of pre-existent liver or kidney disease which would alter drug metabolism and elimination; 2) injuries arising from penetrating mechanisms; 3) a moderate or severe traumatic brain injury; 4) pregnant or nursing women; 5) a pre-existent neurologic or mental disorder which would preclude accurate evaluation and follow-up (i.e. Alzheimer's disease, Parkinson's Disease or Schizophrenia); 6) additional life threatening injuries, the management of which would delay drug administration past 12 hours post injury; 7) unable to receive medication via an oral or nasogastric route; and 8) a recent history of illicit drug or alcohol abuse.

Intervention details

Participants enrolled received riluzole 50 mg every 12 hours for a total of 14 days, with treatment initiated within 12 hours of injury. The 12 hour drug window, as well as the 2 week

duration of therapy, were chosen based on a desire to match the period of drug administration to the known period of sodium and glutamate induced secondary injury after SCI (several minutes after injury until 2 weeks after injury)³⁰. Riluzole was administered either orally or enterally through a nasogastric tube. When given orally, a single 50 mg tablet was given, however if an NG route was required, the 50 mg tablet was crushed and then dispersed in water prior to administration. Although riluzole is well-absorbed in the stomach and proximal intestine, co-administration of the drug with food can reduce absorption up to 20%. As a result, feeding, whether via an oral or NG route, was not permitted within 2 hours before, and was delayed until at least 1 hour after riluzole is given. Since riluzole undergoes hepatic metabolism, primarily by cytochrome 1A2, co-administration with other pharmacologic agents metabolized by this enzyme (such as quinolone antibiotics, amitriptyline and omeprazole) is prohibited to prevent variations in serum drug concentration.

Baseline Assessment

On admission to the study center the site principal investigator or designee performed a neurological examination in accordance with the American Spinal Injury Association (ASIA)/International Medical Society of Paraplegia(IMSOP) recommendations³¹. This examination established the baseline ASIA impairment scale (AIS) grade, ASIA motor score (AMS) and ASIA sensory score (AIS). Additional clinical information such as age, gender, Glasgow coma scale (GCS) score, injury mechanism information, the time of injury and past medical history, were also assessed and recorded. All personnel performing neurological assessments underwent a two day training course in performing ASIA examinations. Also at the time of initial assessment, a comprehensive set of trauma blood work was obtained including a pregnancy test and a serum liver panel as detailed below.

Outcome Data and Follow-up

Adverse Events:

Throughout the course of this study, adverse events were carefully monitored for each participant. Particular care was made to track adverse events previously associated with riluzole administration in the ALS literature, particularly hepatotoxicity. Baseline blood work included alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma glutamyl transpeptidase (GGT), bilirubin, prothrombin time (PT) and international normalized ratio (INR). Liver enzyme tests were repeated on days 3 and 14 after the start of riluzole. Data was recorded on a wide range of adverse events including infections, respiratory complications, cardiovascular events, deep vein thrombosis/pulmonary embolus, skin breakdown, and neuropathic pain. All serious adverse events were reported to the coordinating center and to the central medical monitor. There were no deaths among the 36 patients enrolled in the study.

Neurological, Functional and Pain Outcome Assessment:

ASIA impairment scale grade, ASIA motor score and ASIA sensory score are the primary neurological outcome measures utilized in this study. Spinal Cord Independence Measure

(SCIM) and Brief Pain Inventory (BPI) Short Form were used to assess functional status and pain outcomes respectively^{32,33}. Outcome measures are assessed at 6 weeks, 3 months, 6 months and 1 year post injury.

Follow-up data on adverse events as well as neurological, functional and pain outcomes will be compared between enrolled riluzole treated patients and non-riluzole treated patients enrolled in the NACTN prospective SCI registry in the final study analysis.

Collection of pharmacologic data:

Blood samples for determining the peak and trough serum riluzole concentrations were drawn on day 3 and day 14 of riluzole administration for all participants. Complete details of pharmacologic related data collection and analysis can be found in the pharmacologic review by Chow et al in this focus issue.

Progress Made to Date and Future Directions

As of January 2012, the target enrollment of 36 participants has been achieved. At present, complete analysis of the trial data is underway, and we anticipate that the final results will be available in the summer of 2012. Assuming that the safety profile of riluzole in SCI patients is confirmed, we will use the findings of this study to plan a phase II trial evaluating the effects of riluzole on long-term neurologic and functional outcomes. To this end, data from the current phase I trial will be used to determine an appropriate treatment effect size for future sample size calculations.

Conclusion

Initiated by the primary spinal cord trauma, a host of secondary pathological processes combine to expand the area of neurologic tissue injury after SCI. As part of this process, post-traumatic constitutive activation of neuronal voltage gated sodium channels leads to increased intracellular sodium and calcium concentrations with concomitant cellular swelling and increased release of excitotoxic glutamate. Riluzole, a sodium channel blocking anticonvulsant drug, has shown efficacy in preclinical SCI studies and has proven safe and effective in the treatment of human patients with ALS. To initiate the translation of this therapy to the clinic for SCI patients, we have undertaken an open label phase I trial to define the safety and pharmacokinetic profile of riluzole in this population. We look forward to publishing the final results of this study later this year.

Acknowledgements

The authors wish to acknowledge the support of the following agencies and granting bodies who contributed to the study: The Christopher and Dana Reeve Foundation and The United States Department of Defense.

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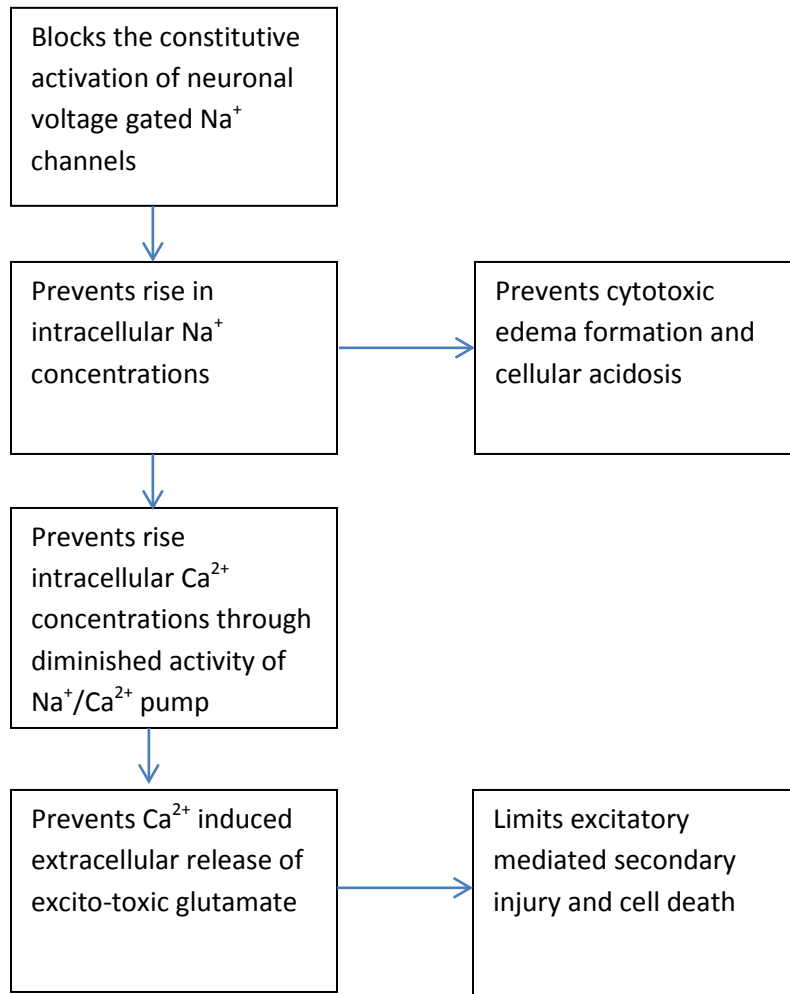
Table 1 Summary of Participating Centers in NACTN Phase 1 Riluzole Trial

Clinical Centers	The Methodist Hospital, Houston , Coordinating Center University of Toronto, Toronto University of Texas Health Science Center, Houston. University of Virginia, Charlottesville University of Louisville, Louisville University of Maryland, Baltimore University of Miami, Miami Thomas Jefferson University, Philadelphia
Data Management Center	University of Texas School of Public Health, Houston
Pharmacologic Center	University of Houston, College of Pharmacy, Houston

Table 2 Summary of Objectives and Inclusion/Exclusion criteria for Phase 1 Riluzole Trial

Study Objectives	Primary objective: To evaluate the safety and pharmacokinetic profile of riluzole in patients with traumatic SCI Secondary objective: Compare neurological, functional and pain outcomes of enrolled participants, to outcomes of matched patients from the NACTN SCI registry
Inclusion Criteria	1) Traumatic SCI and an AIS grade of A, B or C 2) A neurologic level of injury from C4 to C12 3) Between the ages of 18 and 70 years 4) Able to receive riluzole within 12 hours of injury 5) Able to cooperate in the completion of informed consent
Exclusion Criteria	1) Pre-existent liver or kidney disease 2) Injuries arising from penetrating mechanisms 3) Moderate or severe traumatic brain injury 4) Pregnant or nursing women 5) Those with a pre-existent neurologic or mental disorder which would preclude accurate evaluation and follow-up (i.e. Alzheimer's disease, Parkinson's Disease or Schizophrenia) 6) Life threatening injuries, the management of which would delay drug administration past 12 hours post injury 7) Unable to receive medication via an oral or nasogastric route; 8) Recent history of illicit drug or alcohol abuse.

Figure 1 Flow diagram summarizing the neuroprotective mechanisms of riluzole in SCI



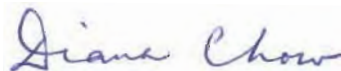
January 30, 2012

Dear Ms Shreve,

Please find attached the original article "Pharmacology of Riluzole in Acute Spinal Cord Injury", by Diana S-L. Chow, PhD, Yang Teng, BS, Elizabeth G. Toups, MS, RN, Bizhan Aarabi, MD, James S. Harrop, MD, Christopher I. Shaffrey, MD, Michele M. Johnson, MD, Maxwell Boakye, MD, Ralph Frankowski, PhD, Michael G. Fehlings MD, PhD and Robert G. Grossman, MD.

This article has not been published elsewhere. The authors report no conflict of interest concerning the materials or methods used in this study or findings specified in this paper.

Sincerely,



Diana Shu-Lian Chow, Ph.D.

Professor of Pharmaceutics

Director, Institute for Drug Education and Research

Pharmacology of Riluzole in Acute Spinal Cord Injury

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Key Words: Riluzole, Clinical Individual and Population Pharmacokinetics, Acute Spinal Cord Injury

Running Title: Pharmacology of Riluzole in Acute Spinal Cord Injury

Abstract

Objective: To characterize individual and population pharmacokinetics of riluzole in a phase 1 clinical trial of riluzole as a neuroprotective agent in patients with acute spinal cord injury.

Methods: Thirty-six SCI patients (ASIA Impairment Scale A-C, injured at spinal cord levels from C4-T12), enrolled in the phase I clinical trial sponsored by the North American Clinical Trial Network (NACTN), received 50 mg riluzole twice daily for 28 doses. The first dose was administered at 9.2 ± 2.7 hr (3.7 – 17.2 hr) post injury. Peak and trough plasma samples were collected on Day 3 and Day 14, two hr post-dose and within one hr pre-dose, respectively. Riluzole concentrations were quantified by HPLC assay. The data were analyzed for individual pharmacokinetics and population pharmacokinetics for basic structural and covariate models. The pharmacokinetics of riluzole were characterized by the peak concentration ($C_{\max}$), trough concentration ($C_{\min}$), systemic exposure (AUC_{0-12}), clearance (CL) and volume of distribution (V).

Results: The pharmacokinetics of riluzole ($C_{\max}$, $C_{\min}$, AUC_{0-12} , CL and V) changed during the acute and subacute phases of SCI and 14-day therapy, consistently observed in patients at all clinical sites. $C_{\max}$, $C_{\min}$, AUC_{0-12} (128.9 ng/ml, 45.6 ng/ml and 982.0 ng *hr/ml) were significantly higher on Day 3 than on Day 14 (76.5 ng/ml, 19.1 ng/ml and 521.0 ng *hr/ml, respectively), resulting from lower CL (49.5 versus 106.2 L/hr) and smaller V (557.1 versus 1297.9 L) on Day 14. No fluid imbalance or CYP1A2 induction was identified due to concomitant medications during the treatment course to account for such increases in V and CL, respectively. The reduced hepatic blood flow due to SCI may be associated with the lower CL on Day 3. The $t_{1/2}$ remained at 10.6-11.9 hr on Day 3 and Day 14.

Conclusion: This is the first report on clinical pharmacokinetics of riluzole in patients with SCI. The $C_{\max}$ and AUC_{0-12} achieved in SCI patients were lower than those in ALS patients on the same dose basis, due to a higher CL and larger V. Our findings further stress the impact of various phases of SCI on the absorption, distribution, metabolism and excretion of drugs particularly between Day 3 and Day 14 postinjury. For future clinical trials, the population pharmacokinetic model can be employed and the current blood sampling protocol is adequate to refine the SCI population-specific pharmacokinetics and for dosing regimen modification. Therapeutic drug monitoring and dosage adjustment are a rational approach for future optimization of riluzole therapy in SCI patients.

Introduction

Potential Neuroprotective Merit of Riluzole in Patients with Acute Spinal Cord Injury

Acute traumatic SCI results in a devastating loss of neurological function below the level of injury and adversely affects multiple systems within the body. The pathophysiology of SCI involves a primary mechanical insult to the spinal cord and activation of a delayed secondary cascade of events, which ultimately causes progressive degeneration of the spinal cord.

Whereas cell death from the mechanical injury is predominated by necrosis, secondary injury events trigger a continuum of necrotic and apoptotic cell death mechanisms. These secondary events include vascular abnormalities, ischemia-reperfusion injury, glutamate excitotoxicity and disturbances in ionic homeostasis, oxidative cell injury, and an extensive inflammatory response.

Clinical guidelines for the management of SCI have been established and widely accepted by physicians who treat patients with SCI¹. These guidelines include stabilization of the vertebrae, and cardiopulmonary and metabolic support of the patient. However, beyond supportive care there are no medical or surgical treatments that have been clearly demonstrated to improve functional outcome in human SCI. Clinical trials with methylprednisolone (NASCIS II and III)²⁻³, GM-1 ganglioside⁴, fampridine (4-aminopyridine)⁵⁻⁷, and lithium carbonate⁸⁻⁹ have provided suggestive but equivocal evidence of benefit.

In light of the overwhelming impact of SCI on the individual, new therapeutic interventions are urgently needed. Compelling evidence exists that riluzole, a sodium channel blocking agent with anti-glutamatergic activity, offers considerable promise for improving the outcome of SCI.

Molecular Mechanisms of Riluzole as Potential Neuroprotective Agent

Riluzole (Figure 1), a benzothiazole anticonvulsant Na⁺ channel blocker, received FDA approval in 1995 for the treatment in patients with amyotrophic lateral sclerosis (ALS), a progressive neurodegenerative disorder characterized by motoneuron and corticospinal tract degeneration¹⁰⁻¹². The standard regimen is of fixed oral doses of 50 mg BID.

There are potential merits of riluzole, as a Na⁺ channel blocker, to offer neuroprotective activity in primary immediate (≤ 2 hr) and early acute (≤ 48 hr) injury phases of SCI. SCI results in a deleterious accumulation of intracellular sodium [Na⁺]_i within neurons¹³; the resulting membrane depolarization associated with cellular inability to remove [Na⁺]_i favors further Na⁺ influx via non-inactivating Na⁺ channels. This in turn results in a reversal of function by Na⁺/Ca²⁺ exchangers allowing Ca²⁺ to be pumped into cells while Na⁺ is pumped out into the extracellular environment. Thus, an approach to prevent Ca²⁺/Na⁺ toxicity by Na⁺ channel blockers in the early phases of the injury is rational.

The neuroprotective effects of Na⁺ channel blockade are likely exerted on neurons and spinal cord axons to reduce intra-cellular increases in [Na⁺]_i and to reverse operation of axonal Na⁺/Ca²⁺ exchangers. In addition, Na⁺ channel blockade may preserve spinal cord white matter by preventing the disruption of the axonal Na⁺/H⁺ antiporter system, as shown in tetrodotoxin damage¹⁴ to maintain compound action potentials following acute compression in an *ex vivo* model of SCI¹⁵. Riluzole is also known to inhibit presynaptic Ca²⁺-dependent glutamate release¹⁶.

Studies have demonstrated that riluzole is neuroprotective and promotes functional neurological recovery in various species of animal models of brain and spinal cord ischemic and traumatic injury¹⁷⁻²⁰. Other authors have reported that the effects of riluzole are synergistic with those of methylprednisolone (MPSS), which is the only drug used in routine clinical practices to attenuate secondary injury effects after SCI²¹. In a recent study of prolonged administration of riluzole in Huntington's disease, no benefit was found in slowing disease progression but riluzole was well tolerated. Adverse effects were virtually similar in 357 patients treated with riluzole, compared to 180

placebo patients. Thirteen patients had elevation of liver enzymes and five patients discontinued treatment due to the elevation²².

Therefore, the use of riluzole as a therapy for SCI is potentially feasible. It is FDA approved agent for ALS²³ at a dose of 100 mg/day. Notably, riluzole is without potent neurotoxic and cardiotoxic adverse effects²⁴, even though potential hepatotoxicity has been noted²⁵. While riluzole is administered for the lifetime of the patient with ALS, the duration of therapy in the setting of spinal cord injury would not need to exceed 14 days, based on observations in preclinical animal models and given the anticipated duration of sodium and glutamate mediated secondary injury^{20, 26}.

Pharmacology of Riluzole-Pharmacokinetics

The pharmacology of riluzole includes the pharmacokinetics (absorption, distribution, metabolism and excretion) and pharmacodynamics (effects on improving motor and sensory scores, adverse effects in elevating hepatic enzymes) of the agent. This article is focused on the pharmacokinetics of riluzole. The pharmacokinetics of riluzole have been established in healthy subjects²⁶⁻²⁷, young and old, as well as in patients with ALS²⁸⁻²⁹ and pediatric patients with spinal muscular atrophy (SMA)³⁰. In humans, riluzole has been administered orally at a dose of 50 mg BID, or 50 mg QD in SMA patients³⁰. The half-life of riluzole is 12 hours. Most drugs reach steady state plasma concentrations in 4-5 half-lives and the same is assumed for riluzole at 48-60 hr post dose.

Riluzole is highly protein bound to serum albumin and lipoproteins, 96%, like phenytoin, and thus poses potential concerns on drug-drug interactions with other concomitant medications that compete for protein binding. In patients taking such concomitant medications, a higher concentration of free riluzole in the plasma, resulting from the competition, will be anticipated to exert a greater therapeutic activity.

Riluzole is metabolized in the liver by an enzyme of the cytochrome P (CYP) 450 family which has multiple CYP isozymes. Most of the drugs metabolizing enzymes are in the CYP 1, 2 & 3 families. Riluzole is specifically metabolized by CYP 1A2 subfamily extensively, with only 2% of the dose recovered unchanged in the urine. Smoking is known to induce CYP 1A2. In addition, the care of SCI patients may include the administration of MPSS which is a substrate and inducer of CYP 3A4 and 2C19, and may indirectly affect the hepatic clearance of riluzole. Therefore, smoking history and other concomitant medications of CYP 1A2 substrates, inhibitors or inducers may affect riluzole blood concentrations. The substrates of CYP1A2 include acetaminophen, caffeine, theophylline and warfarin. The inhibitors include tacrine (Cognex), omeprazole (Prilosec), quinolone antibiotics, erythromycin, and oral contraceptives. Co-administration of riluzole with these drugs can increase riluzole blood concentrations³⁰. The inducers, including carbamazepine, phenobarbital, phenytoin, St John's wort, ritonavir and smoking, can decrease riluzole blood concentrations.

The activity of the CYP 1A2 enzyme is lower in women than in men, as well as in the Japanese population, and possibly in other Asian populations (no data available). Presumably in these populations the activity of the drug would be greater, although no sex differences were noted in the ALS studies with riluzole.

The high intersubject variability of riluzole blood concentrations has been documented among ALS patients²⁸⁻²⁹ and SMA patients³⁰. Riluzole blood concentrations in patients with ALS are associated with the observed side effects and the symptom modifications of ALS²⁹.

The current phase 1 trial is the first characterization of riluzole pharmacokinetics in SCI. The dose employed in NACTN trial is the same as approved for ALS patients, 50 mg BID. One goal of the present study is to determine how SCI affects the pharmacokinetics of riluzole.

Alterations of Pharmacokinetics of Drugs in Spinal Cord Injury

The SCI population is heterogeneous, and possible changes in pharmacokinetics may depend on variables of injury characteristics (intensity, level and time elapsed after injury), pharmacological properties of the drug and the route of administration³¹⁻³². Based on the knowledge of SCI effects on the pharmacokinetics of drugs reported in the past 26 years (1985-2011)^{7, 32-42}, we may anticipate the following alterations of pharmacokinetics of riluzole in acute SCI patients from that in normal subjects:

Absorption: In SCI there may be reduced bioavailability (F) and prolonged peak time (t_{max}) of oral medications that are commonly prescribed for SCI patients, such as acetaminophen, theophylline⁴¹, dantrolene³⁷, carbamazepine³⁵, 4-aminopyridine⁷, cyclosporine A³⁸ and baclofen³⁹. The underlying causes are impaired gastric emptying and intestinal motility, as well as reduced microvascular gastrointestinal blood flow (MVBf)^{41, 43-45}. Moreover, it is also recognized that injury above T6 induces significant reduction in MVBf to GI and liver, more than that in injury below T6⁴⁶.

The oral absorption of riluzole may be affected similarly for the same pathophysiological causes.

In addition, riluzole is known a substrate of P-glycoprotein (Pgp), a transporter protein that is up-regulated, probably mediated by up-regulated proinflammatory cytokines TNF α and IL- β in SCI^(Grill and Dulin, personal communication, 2011). Consequently, the oral absorption may be further hampered with SCI.

Distribution: Distribution implies transporting the drug to tissues and ultimately to cells throughout the bloodstream. This process depends on several factors, including cardiac output, systemic macro- and micro-circulation, and drug-protein binding^{36, 47}.

Population-specific alterations in drug distribution kinetics are unavailable. However, SCI patients commonly present hypoalbuminemia that alters the plasma protein binding of highly bound drugs and results in increase of distribution, as known with ketamine⁴⁸, lorazepam⁴⁹, amikacin and cefotiam, ranging from 20% (amikacin) to 70% (cefotiam)⁴⁰.

Riluzole is a highly plasma protein binding drug (96% bound; $f_u=0.04$) and will be sensitive to a change of fraction unbound (f_u), since only the free drug molecules are transported to interstitial fluid.

Metabolism: The hepatic clearance (CL_H) related to drug metabolism decreases in SCI patients are reported with phenacetin³⁴, methylprednisolone⁵⁰ and cyclosporine A^{31, 38}. The underlying causes can be the reduced MVBf in liver⁵¹, enzyme synthesis or protein binding⁴⁷ and in combination.

In SCI subjects, reduction in the microvascular blood flow in the liver, spleen and skeletal muscle occurs at the acute phase of SCI and peaks at ~ 24 h after the injury (acute phase). The reduction is more pronounced after a high thoracic complete lesion than a low one. These alterations are likely due to a redirection of blood flow to maintain an adequate perfusion of the brain and heart⁵¹.

The decrease of hepatic blood flow (Q) due to SCI will reduce the hepatic metabolism clearance (CL_H) of drugs with high hepatic extraction ratio (high $E = CL_H/Q \geq 0.7$), such as phenacetin, methylprednisolone and cyclosporine A. In contrast, biotransformation of low-extraction drugs ($E \leq 0.3$), such as most non-steroidal anti-inflammatory drugs, does not depend on liver blood flow, but on liver intrinsic enzymatic activity (CL_{int})⁵²⁻⁵⁴ and plasma protein binding (f_u , fraction unbound)⁴⁷. The CL_H of drugs of intermediate hepatic extraction ratio ($0.7 > E > 0.3$), such as riluzole whose $E = 0.67$, will be affected by all the three factors, Q, CL_{int} and f_u .

Elimination (excretion): Decreased renal clearance (CL_R) and prolonged $t_{1/2}$ have been reported with amikacin⁵⁵, cefotiam, doxycycline, ketamine⁴⁸, diclofenac⁵⁶, vancomycin⁵⁷ and lorazepam⁴⁹, due to decrease in renal function. Riluzole is excreted unchanged in urine at only 2% of the dose, and urinary excretion may not be significantly affected by SCI.

Additional Considerations on Various Phases of SCI for Pharmacokinetic Alterations of Riluzole

A number of pathophysiological processes are triggered by the primary mechanical compressive-contusive-type injury leading to the prolonged secondary injury phase. The events of this secondary

injury process are divided temporally into multiple contiguous phases: the immediate, acute (early acute and subacute), intermediate, and chronic stages of SCI (Table I)⁵⁸.

Immediate phase (0-2 hours): The immediate phase begins at the time of injury, lasting for ~ 2 hours. The pathological changes include swelling of the spinal cord, disruption of the microvasculature and up regulation of the proinflammatory cytokines TNF α and IL- β .

Acute phase: The acute phase is the period in which the secondary injury processes become dominant. It is the SCI phase likely to be most amenable to neuroprotective interventions. The acute phase is divided into early acute and subacute stages.

Early acute phase (2-48 hours): The early acute phase of SCI can be considered to last from 2 to 48 hours following injury. This phase is characterized by continuing hemorrhage, increasing edema, and inflammation, and marks the onset of additional secondary injury processes including free radical production, ionic dysregulation, glutamate-mediated excitotoxicity, that contribute to further axonal injury and cell death. Vascular disruption, hemorrhage, and the resulting ischemia are central constituents of this secondary injury cascade.

Permeability of the BBB: In the uninjured CNS, the BBB functions as a highly selective filter limiting the transport of compounds both into and out of the CNS parenchyma. Following SCI there is a marked increase in BBB permeability due to both direct mechanical disruption by the primary injury and the effects on endothelial cells by numerous inflammatory mediators and other compounds. On the other hand, P-gp efflux transporter is also demonstrated to be up-regulated after SCI ^(Grill and Dulin, personal communication, 2011) that may result in high efflux of the drug out of CNS.

Inflammatory Mediators and the Cellular Immune Response: The early acute stage involves infiltration by inflammatory cells and continuing activation of resident microglia. The inflammatory process following SCI is highly complex and involves numerous cellular populations, including astrocytes, microglia, T cells, neutrophils, and invading monocytes. A multitude of noncellular mediators, including TNF α , interferons, and ILs also play important roles.

Cell Death and Demyelination: Cell death after SCI may occur by necrosis or apoptosis. Death of neurons at all stages of injury probably occurs mainly through necrosis although apoptosis has been observed in animal SCI.

Subacute phase (2 days to 2 weeks): The subacute phase is considered to last from ~ 2 days to 2 weeks following injury and importantly is the time period in which future cell-based therapeutic strategies are most likely to be applied. The phagocytic response is maximal during the subacute period.

Intermediate Phase (2 Weeks to 6 Months): The intermediate phase is characterized by the continued maturation of the astrocytic scar and by regenerative axonal sprouting.

Chronic phase (>6 months): The chronic phase begins ~ 6 months following injury and continues throughout the lifetime of the patient with SCI. The chronic phase is characterized by the maturation/ stabilization of the lesion including continued scar formation and the development of cysts and/or syrinxes. The process of Wallerian degeneration of injured or severed axons is ongoing and it may take years for severed axons and their cell bodies to be fully removed.

In the present phase 1 trial dosing of riluzole started within 12 hours post injury and was continued for 14 days through the early acute and subacute phases. Blood sampling for pharmacokinetic monitoring was on Day 3 and Day 14, both in the subacute phase. The pathophysiological conditions vary during the various phases of SCI and thus the pharmacokinetics (absorption, distribution, metabolism and renal excretion) of riluzole may be affected differently at different phases.

Riluzole Phase I Trial

A phase I trial of riluzole was conducted as a multi-site, single arm active treatment pilot study involving 36 patients. The primary aim of the trial was to obtain data on safety and pharmacokinetics (PK) of riluzole in patients who had sustained an acute traumatic SCI. Secondary objectives were to conduct exploratory analyses of functional outcomes for purposes of planning a subsequent phase 2 randomized study of the efficiency of Riluzole for the treatment of SCI.

Materials and Methods

1. Patient recruitment for riluzole clinical phase 1 trial at NACTN

Total thirty-six (36) SCI patients were enrolled at six sites, with the following inclusion and exclusion criteria:

1.1 Inclusion Criteria

- ✓ Age : ≥ 18 years and ≤ 70 years
- ✓ Written informed consent to participate in the study
- ✓ No other life-threatening injury
- ✓ Spinal cord injury at neurologic level from C4 to T12
- ✓ ASIA impairment scale (AIS) level A, B or C
- ✓ No cognitive impairment which would preclude an informed consent (including moderate or severe traumatic brain injury)
- ✓ Dosing time: less than 12 hours since injury

1.2 Exclusion Criteria

- ✓ Equal to or more than 12 hours since injury
- ✓ Hypersensitivity to riluzole or any of its components
- ✓ Unable to receive riluzole orally or via NG tube
- ✓ History of liver or kidney disease (e.g. Hepatitis A, B or C, Cirrhosis, etc.)
- ✓ A recent history of regular substance abuse (illicit drugs, alcohol)
- ✓ Unconscious
- ✓ Penetrating spinal cord injury
- ✓ Pregnancy as established by urine pregnancy test
- ✓ Is currently involved in another SCI research study
- ✓ Has a mental disorder or other illness, which in the view of the site investigator, would preclude accurate evaluation
- ✓ Unable to commit to the follow-up schedule
- ✓ Is a prisoner
- ✓ Unable to converse, read or write English at the elementary school level

2. Treatment with Riluzole (Rilutek®)

All enrolled patients (n=36) received riluzole (Rilutek®) according to the approved administration protocol, 50 mg by oral or nasogastric (NG) administration every 12 hours, starting within 12 hours of injury for 28 doses. On the 3rd and 14th days, plasma samples were collected one hour pre-dose and one or two hours post-dose for trough and peak concentrations, respectively. All other treatments were per standard of care. Administration of methylprednisolone (MPSS) was per site discretion.

3. Pharmacokinetic Evaluation

3.1 Specific Aims

To determine the individual peak and trough concentrations of riluzole on Day 3 and on Day 14

To derive individual pharmacokinetic parameters of half-life ($t_{1/2}$), systemic exposure ($AUC_{0 \rightarrow 12}$), volume of distribution (V) and clearance (CL) by one-compartment model, using WinNonlin v.3 (Pharsight) and population pharmacokinetics using NONMEM, v.7.2.0 (ICON Development Solutions) for basic structural and covariate models

3.2 Plasma sampling

Plasma blank control (5 ml) and two plasma samples for peak and trough concentrations on both Day 3 and Day 14 were collected by centrifugation of blood samples immediately at 2,700 g for 10 min, then stored at -80°C (or at least as low as -20°C) prior to the shipment with dry ice to Pharmacology Center of NACTN at University of Houston, College of Pharmacy at Texas Medical Center. The 5 specimen samples were labeled to conceal patient information.

Plasma, instead of serum, samples were collected, because it has been established that riluzole concentrations in plasma and serum are comparable at concentration < 500 ng/ml⁵⁹. With a standard drug regimen of 50 mg twice daily, riluzole serum concentrations are in the range of 20-250 ng/ml²⁸. The plasma samples retaining clotting factors will have less variability than serum samples.

3.3 HPLC assay of riluzole plasma concentrations

Validation of HPLC Assay for Riluzole Quantification

A specific, accurate and precise isocratic HPLC assay was developed and validated for the quantification of riluzole in small volumes (200 µl) of human plasma, using liquid-liquid extraction with ethyl acetate. Separation was on a C18 reversed-phase column with UV detection at 263 nm. The assay was linear from 7.8 to 1,000 ng/ml, with a lower limit of quantification (LLOQ) of 7.8 ng/ml. The mean recoveries of riluzole from human plasma samples ranged 72-85%. The accuracies and precisions were within 94-107% and less than 12.5% of variations, respectively (n=15). The assay was used to support the pharmacokinetic studies of riluzole as a neuroprotective therapy in the clinical phase I trial of 36 patients with SCI.

The HPLC chromatogram demonstrated that the riluzole peak with retention time of 9.0 min was well resolved from methylprednisolone (MPSS, 6.1 min), acetaminophen (2.1 min) and other potential concomitant medications (Figure 2).

Measurement of Riluzole in Plasma

Two hundred µl human plasma was mixed with 10 µl 5-methoxypsoralen (5-MOP, 10 µg/ml, internal standard). After addition of 1ml ethyl acetate, the mixture was vortexed and then centrifuged. Of the clear organic layer, about 1 ml was evaporated to dryness under a stream of air. The residue was reconstituted with the mobile phase, then mixed on a vortex and centrifuged. The clear supernatant samples were analyzed by the validated HPLC assay.

An isocratic HPLC assay was developed and validated for the quantification of riluzole in human plasma samples. The HPLC assay developed used a Waters system equipped with 717 plus auto-sampler, 515 HPLC pump and 2996 UV detector set at 263 nm. Baseline resolution was achieved on Waters Symmetry® C18 column (3.0×150 mm, 3.5 µm) with Symmetry® C18 guard column (2.1×10 mm, 3.5 µm), eluted at the flow rate of 0.45 ml/min, with the mobile phase of acetonitrile: methanol: 0.1 M ammonium acetate (3:2:5, v/v/v), adjusted with acetic acid to pH 6.5. The assay was linear from 7.8 to 1000 ng/ml, with a lower limit of quantification (LLOQ) of 7.8 ng/ml for human plasma samples. The plasma concentration range of riluzole in human who received 50 mg riluzole twice daily is from 20 ng/ml to 500 ng/ml⁵⁹. Our HPLC assay meets the requirements of detecting drug level in the nanogram range with LLOQ: 7.8 ng/ml.

3.4 Individual pharmacokinetic analysis

Individual pharmacokinetics were evaluated using two concentration-time data on each day (Day 3 and Day 14) to obtain the elimination rate constants (k), then using the following equations to estimate other parameters. AUC₀₋₁₂ and AUC_{0-∞} were calculated using the trapezoidal rule.

$$t_{1/2} = 0.693/k$$

$$AUC_{0-\infty} = AUC_{0-t} + C_t/k, \text{ when } C_{12} \text{ was the trough concentration calculated from the last sampling time}$$

$$CL = \text{Dose} / AUC_{0-\infty}$$

$$V = CL/k$$

3.5 Population pharmacokinetic (Pop PK) analysis

The Pop PK analysis for repeated measures was conducted via nonlinear mixed-effects modeling with a qualified installation of nonlinear mixed effects modeling software, NONMEM v 7.2.0. The Pop PK software is capable of analyzing clinical data with sparse samples, deviated sampling time and/or missing samples. Riluzole plasma concentration-time data were fitted by one compartment structural pharmacokinetic models with first-order absorption and elimination. The first-order conditional estimation method with η - ϵ interaction (FOCEI) was used for all model runs.

Data for the analysis were merged, formatted for the analyses with NONMEM VII (7.2.0), and saved as flat csv files, using the R software⁶⁴. Riluzole concentration observations that were below the analytical assay quantification limit or any values that were otherwise missing were excluded from the analysis.

Observed values of any time-dependent covariates were inserted chronologically in the population PK data set with linear interpolation for data records between observed time points

Model selection was guided by various goodness-of-fit criteria, including diagnostic scatter plots, plausibility of parameter estimates and precision of parameter estimates.

The basic pharmacokinetic parameters are clearance (CL), volume of distribution (V), and absorption constant (ka). The first-order elimination rate constant (k) was calculated as follows:

$$k = CL/V$$

Inter-individual variability in clearance and volume of distribution were modeled by the use of a proportional error model as follows:

$$CL_j = \widetilde{CL}_j \exp(\eta_{jCL})$$

$$V_j = \widetilde{V}_j \exp(\eta_{jV})$$

Where η_{jCL} represents the (proportional) difference between the true clearance of individual j (CL_j) and the typical value ($\widetilde{CL}_j$) predicted for the patient by the regression model, and η_{jV} represents the (proportional) difference between the true volume of distribution in individual j (V_j) and the typical value predicted for the patient by the regression model ($\widetilde{V}_j$). The random variables η_{jCL} and η_{jV} are distributed with means of zero and variances of ω_{CL}^2 and ω_V^2 , respectively. The variances ω_{CL}^2 and ω_V^2 represent the magnitude of inter-individual variability in clearance and volume of distribution, respectively, which are not explained by the regression models in this population.

Residual variability was modeled using an additive and proportional combined error model as follows:

$$C_{obsij} = C_{predij} \times (1 + \epsilon_{propij}) + \epsilon_{addij}$$

In which C_{obsij} and C_{predij} are the measured and predicted plasma riluzole concentrations, respectively, for individual j on occasion i, and random variable ϵ_{ij} denotes the residual intra-individual error, which is distributed with a mean of zero and a variance of σ^2 .

3.6 Covariate Model

Covariates considered for inclusion in the regression analysis included demographic factors (age, gender, race, and body weight), laboratory parameters (hepatic function, serum creatinine, creatinine clearance, albumin, and proteins), smoking status and concomitant medication. Covariate effects on volume of distribution were only considered after the final regression model was obtained for clearance.

The influence of each patient covariate on the clearance was individually assessed by univariate analysis. A full covariate regression model for clearance was subsequently derived by incorporating all significant covariates, and this was tested against restricted models by removing each covariate in turn to arrive at a final regression model. The regression relationship was modeled for continuous covariates, such as body weight (WT), as follows:

- Linear
 - $CL = CL_{pop} + \text{slope} * WT$
 - $CL = CL_{pop} + \text{slope} * (WT - WT_{pop})$ (Centered around population mean)
- Power

- $CL_i = CL_{pop} * WT_i^{\text{exponent}}$ (Allometric model: exponent=0.75)
 - $CL_i = CL_{pop} * (WT_i/WT_{pop})^{\text{exponent}}$ (Normalized by population mean)
 - Exponential
 - $CL_i = CL_{pop} * \exp(\text{slope} * WT_i)$
- and for dichotomous covariates, such as sex (as signed a value of 0 or 1), as follows:
- Power
 - $CL_i = CL_{pop} * \text{slope}^{\text{Sex}}$
 - Exponential
 - $CL_i = CL_{pop} * \exp(\text{slope} * \text{Sex})$

The change in the NONMEM objective function produced by the inclusion of a covariate term (asymptotically distributed as χ^2 with degrees of freedom equal to the number of parameters added to the model) was used to compare alternative models (likelihood ratio test). A change in objective function of at least 3.8, associated with a p value of <0.05 with one degree of freedom, was required for statistical significance at the initial covariate screening stage; this was increased to 7.8, associated with a p value of <0.005 with one degree of freedom, at subsequent stages (multivariate analysis).

3.7 Model Evaluation

The final population PK model was evaluated using a stratified nonparametric bootstrap and a predictive check. For the nonparametric bootstrap procedure, 1000 replicate data sets were generated by random re-sampling from the original data set with replacement, using the individual as the sampling unit. Population parameters for each data set were subsequently estimated using NONMEM, and empirical 95% CIs were constructed by observing the 2.5th and 97.5th quantiles of the resulting parameter distributions for all bootstrap runs.

For the predictive check, 100 Monte Carlo simulation replicates of the original data set were generated using the final population PK model, and the distribution of the median concentration (C_{med}) in the simulated data was compared with the distribution of the same characteristics in the observed data using exploratory graphics.

4. Plasma Protein Binding

In order to evaluate the extent of free (unbound) riluzole in human plasma, ultrafiltration was employed. Centrifree® YM-30 devices (Millipore Ireland Ltd.) were used. One ml human plasma samples were added into the ultrafiltration device and centrifuged at 1,000 g with fixed angle rotor. Ultrafiltrate (100 µl) from each subject was collected, and mixed with 5 µl 5-MOP (internal standard). The same extraction and reconstitute procedures previously described in [3.3](#) were followed. The clear supernatant samples were analyzed by the validated HPLC assay.

Results

Patient Demographics

Thirty-six (36) SCI patients were enrolled between April 12, 2010 to June 20, 2011 to receive 50 mg riluzole twice daily for 28 doses. The first dose was administered at 9.2 ± 2.7 hr (3.7-17.2 hr) post injury. Thirty-five (35) patients completed the 2-week regimen. One patient had riluzole administration stopped due to an elevation of liver enzyme levels. The basic demographics of the subjects with plasma samples available and evaluable for Day 3, Day 14 and both days are summarized in [Table 2](#). The ages of the patients were 39.4 ± 18.3 (18-69) years old, with body weights of 83.0 ± 16.9 kg and heights of 68.7 ± 4.2 inches. Among the 36 patients, 6 were female. One-third of the patients were smokers. The AIS scores of the patients were A (52.8%), B (25%) or C (22.2%). The highest neurological injury levels were C4-8(77.8%), T1-6 (13.9%) or T7-T12 (8.3%).

Distinct Alteration of Riluzole Pharmacokinetics in SCI Patients during Two-week Period Post Injury

The plasma profiles of riluzole on Day 3 and Day 14 were constructed for individual patients as represented by those of Subject R07-05 (Figure 3). The peak concentration (C_{max}) and trough concentration (C_{min}) were derived from the quantified samples. The C_{max} (Mean $\pm$ S.E.) achieved with the

50 mg BID dose varied significantly among subjects, 128.8 ± 13.8 (23.9-409.2) ng/ml (n=33) on Day 3, and 76.2 ± 13.7 (8.5-317.0) ng/ml (n=32) (Figure 4-a). The C_{min} were of large inter-subject variability as well, 45.6 ± 6.8 (8.4-183.8) ng/ml on Day 3 and 19.1 ± 2.5 (2.8-61.2) ng/ml on Day 14 (Figure 4-b). The declines of C_{max} and C_{min} on Day 14 from those of Day 3 were significant by nonparametric test ($p < 0.05$), and consistently observed in individual patients from all six sites. The extents of reduction were 68.6% and 56.5% for C_{max} and C_{min} , respectively.

The systemic exposures of riluzole from the treatment, AUC_{0-12} (truncated for each dosing interval of 12 hr) were calculated from individual plasma profiles using the trapezoidal rule. The AUC_{0-12} were 982.0 ± 111.2 ng hr/ml and 521.0 ± 87.3 ng hr/ml for Day 3 and Day 14, respectively, and exhibited the same trend of decline in C_{max} and C_{min} for Day 14 from Day 3 on the same dose basis (Figure 4-c).

The pharmacokinetic parameters of clearance (CL), volume of distribution (V) and biological half-life ($t_{1/2}$) were derived using standard pharmacokinetic equations in Materials and Methods, Section 3.4. The CL was 49.5 ± 7.8 (3.8-192.2) L/hr on Day 3, but significantly increased on Day 14 to 106.2 ± 19.8 (20.7-533.6) L/hr (Figure 5-a). The V was 557.1 ± 73.8 (120.8-2046.3) and 1297.9 ± 218.9 (129.8-5719.0) L for Day 3 and Day 14, respectively (Figure 5-b). The $t_{1/2}$ is affected by the alterations of CL and V independently, as $t_{1/2} = 0.693 V/CL$. As a result, the net effect on $t_{1/2}$ was nil, due to the increases in both CL and V offsetting each other with the comparable magnitudes. The $t_{1/2}$ remained as 10.6-11.9 hr on Day 3 and Day 14 (Table III). The C_{max} , AUC_{0-12} , CL, V and $t_{1/2}$ of riluzole on Day 3 were comparable to age-matched healthy subjects (Table III).

Therefore, the lower C_{max} , C_{min} and AUC_{0-12} observed on Day 14 as compared with those on Day 3 were resulted from the higher CL and larger V on Day 14.

Individual and Population Pharmacokinetic Parameters

The individual PK parameters were estimated using two concentration-time data on each day (Day 3 and Day 14) to obtain the elimination rate constant and other parameters using the equations described in Materials and Methods, Section 3.4, and compared with those from basic Pop PK model.

The basic population PK model was best represented by a one-compartment first-order absorption and elimination model that included inter-individual and intra-individual variability. The parameter estimates given by this model are summarized in Table IV. The absorption constant (k_a) proved to be difficult to estimate. Fixing k_a to values from 3 to 10 hr^{-1} did not influence the estimates of the other parameters, indicating that those values are equally probable, based on the available data. Therefore, k_a was fixed to 5 hr^{-1} .

The basic one-compartment pharmacokinetic model that incorporated inter-individual and intra-individual variability was retained for covariate model building. The covariates that we introduced into the clearance model did not significantly improve the fit of the basic model (objective function values, OFV > 3.8; $P < 0.05$). The covariates we tested included gender, body weight, smoking status, age and creatinine clearance. When added to the volume of distribution model, no covariate significantly improved the fit.

The riluzole population PK model evaluation results revealed that the final model provided a reliable description of the data with good precision of parameter estimates. The stratified nonparametric bootstrap procedure resulted in 95% CIs for population PK parameter estimates, which are presented in the Table IV.

The PK parameters obtained from individual estimation method and NONMEM population analysis were comparable for both Day 3 and Day 14 (Figure 6), which confirmed that the current sampling schedule (2 blood samples for peak and trough concentrations, respectively) was adequate to characterize the PK of riluzole for future clinical trial in SCI patients.

The riluzole pharmacokinetics in SCI was distinguished from those in amyotrophic lateral sclerosis (ALS) and pediatric spinal muscular atrophy (SMA). The C_{max} and $AUC_{0-\infty}$ were lower in SCI patients (128.8 ng/L and 827.8 ng*hr/ml on Day 3 and 76.5 ng/ml and 337.8 ng*hr/ml on Day 14) than those in patients of

ALS (231 ng/ml and 3409 ng*hr/ml) and SMA (371 ng/ml and 2257 ng*hr/ml). The decreased bioavailability (F) may be due to the reduced GI absorption in SCI. The CL and V in SCI population, 60.4 – 148 L/hr and 663-2080 L, were substantially higher than those in ALS subjects (25.9 L/hr and 361 L) and SMA patients (22.2 L and 299 L) (Table V).

Plasma Protein Binding

Retrospectively, ten patients' plasma samples were re-assayed for free fractions (fu) of riluzole. The fractions unbound were comparable between Day 3 and Day 14, $6.18 \pm 1.33\%$ and $9.57 \pm 3.08\%$, respectively, and could not be accounted for the significant larger V on Day 14.

Discussion

The riluzole pharmacokinetics in SCI were distinguished from those in amyotrophic lateral sclerosis (ALS) and pediatric spinal muscular atrophy (SMA). The C_{max} and $AUC_{0-\infty}$ in SCI patients on the same dose basis did not achieve the comparable levels as in ALS patients, but lower (128.8 ng/L and 827.8 ng*hr/ml on Day 3 and 76.5 ng/ml and 337.8 ng*hr/ml on Day 14) compared to those in patients of ALS (231 ng/ml and 3409 ng*hr/ml). The decreased bioavailability (F) in SCI may be due to the reduced GI absorption^{41, 43-45}. The CL and V in SCI population, 60.4-148 L/hr and 663-2080 L, were substantially higher than those in ALS subjects (25.9 L/hr and 361 L) (Table V).

The difference of CL between Day 3 and Day 14 post SCI may have the following potential causes:

- (1) Impaired hepatic metabolic clearance shortly after early acute phase (≤ 48 hr) on Day 3, due to the decreased hepatic microvascular blood flow and hepatocyte gene expression³⁴. The blood flow recovers gradually at subacute phase on Day 14. Riluzole is an intermediate to high hepatic extraction drug, whose hepatic metabolism decreases by lower hepatic blood flow, similar to MPSS and cyclosporine A.
- (2) Concomitant medications that are CYP 1A2 substrates, inducers or inhibitors would affect the riluzole metabolism by CYP 1A2. However, it was unlikely that any significant drug-drug interaction was accountable for the CL difference. After screening the medication chart of the patients, twenty-one (21) medications were identified, namely, acetaminophen, fentanyl, oxycodone, percocet, gabapentin, MPSS, morphine, aspirin, tramadol, pregabalin, lorazepam, diphenhydramine, propofol, methadone, hydromorphone, ibuprofen, lidocaine, MS contin, meperidine, Norco, vicodin. Nevertheless, among the first six medications that were used by more than 5 patients, only acetaminophen is a known substrate of CYP 1A2. Acetaminophen was used by six patients on both Day 3 and Day 14.

The difference of V between Day 3 and Day 14 may have the following potential causes:

- (1) Fluid imbalance during the first 14 days. However, no apparent net gain in body fluid on Day 14 was recognized, based on patients' fluid intake and output records.
- (2) Decreased protein binding of riluzole that would result in V increase on Day 14. Riluzole is 96% bound to plasma proteins, mainly to albumin and lipoproteins over the clinical concentration range. Retrospectively, ten patients' plasma samples were re-assayed for free fractions of riluzole. The fractions unbound were comparable between Day 3 and Day 14, $6.18 \pm 1.33\%$ and $9.57 \pm 3.08\%$, respectively, and could not account for the significantly larger V on Day 14.

The individual and population pharmacokinetic models were developed and validated with the observed concentrations, respectively. For future clinical trials, the population pharmacokinetic model can be employed. The current two blood sampling protocol is adequate to refine the SCI population-specific pharmacokinetics and for dosing regimen modification. Therapeutic drug monitoring and dosage adjustment based on the developed model are a rational approach for future optimization of riluzole therapy in SCI patients.

Conclusions

This is the first report of clinical pharmacokinetics of riluzole in patients with SCI. The $C_{\max}$ and AU C_{0-12} achieved in SCI patients were lower than those in ALS patients on the same dose basis, due to a higher CL and larger V. Our findings further stress the impact of various phases of SCI on the absorption, distribution, metabolism and excretion of drugs particularly between Day 3 and Day 14 post injury. For future clinical trials, the population pharmacokinetic model can be employed and the current two blood sampling protocol is adequate to refine the SCI population-specific pharmacokinetics and for dosing regimen modification. Therapeutic drug monitoring and dosage adjustment are a rational approach for future optimization of riluzole therapy in SCI patients.

Disclosure

Supported by the Telemedicine and Advanced Technology Research Center (TATRC), the U.S. Army Medical Research and Materiel Command (USAMRMC).

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following: Conception and design: Chow and Grossman. Acquisition of data: Toups, Aarabi, Harrop, Shaffrey, Johnson, Boakye, and Fehlings. Maintenance of database: Frankowski. Analysis and interpretation of data: Teng and Chow. Drafting the article: Chow and Teng. Critically revising the article: Grossman, Fehlings, Toups. Reviewed submitted version of manuscript: All authors. Approved the final version of the manuscript on behalf of all authors: Chow.

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Figure Legends

Figure 1 Chemical Structure and Physical-Chemical Properties of Riluzole

Figure 2 HPLC Chromatogram of Riluzole and Internal Standard (I.S.) for Samples with Concomitant Acetaminophen, Baclofen, Hydrocortisone, Methylprednisolone (MPSS) and Midazolam (Retention times: Baclofen+Acetaminophen, 2.1 min; Hydrocortisone, 4.3 min; MPSS, 6.1 min; I.S., 7.1 min; Riluzole, 9.0 min; Midazolam, 13.0 min).

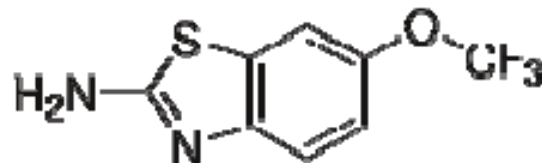
Figure 3 Authentic Pharmacokinetic Profile of Riluzole in Human Plasma Sample for Day 3 and Day 14 ((Open makers: calculated values; Solid makers: measured values).

Figure 4 Spaghetti Plots of (a) C_{max} , (b) C_{min} and (c) AUC_{0-12} on Day 3 and Day 14 (24 patients had both Day 3 and Day 14 data available and 35 patients had either Day 3 and Day 14 data).

Figure 5 Spaghetti Plots of (a) Clearance (CL) and (b) Volume of Distribution (V) on Day 3 and Day 14 (24 patients had both Day 3 and Day 14 data available and 35 patients had either Day 3 and Day 14 data).

Figure 6 Goodness Fit of Plots. Population Predicted and Individual Predicted Riluzole Concentrations (ng/ml) versus Observed Riluzole Concentrations on (a) Day 3 and (b) Day 14. The Line of Identity (solid black) is included as a Reference.

Figure 1



Physical-Chemical Properties:

Chemical name: 2-amino-6-(trifluoromethoxy) benzothiazole

Molecular mass: 234.2

Description: Riluzole is a white to slightly yellow powder

Solubility: Riluzole is highly soluble in dimethylformamide, dimethylsulfoxide (DMSO) and methanol, freely soluble in dichloromethane, sparingly soluble in 0.1 N HCl and very slightly soluble in water and in 0.1 N NaOH.

pKa: 3.8

Partition Coefficient: Octanol/Water is about 3000

Log P: 3.5

Melting Point: Between 117°C and 120°C.

Figure 2

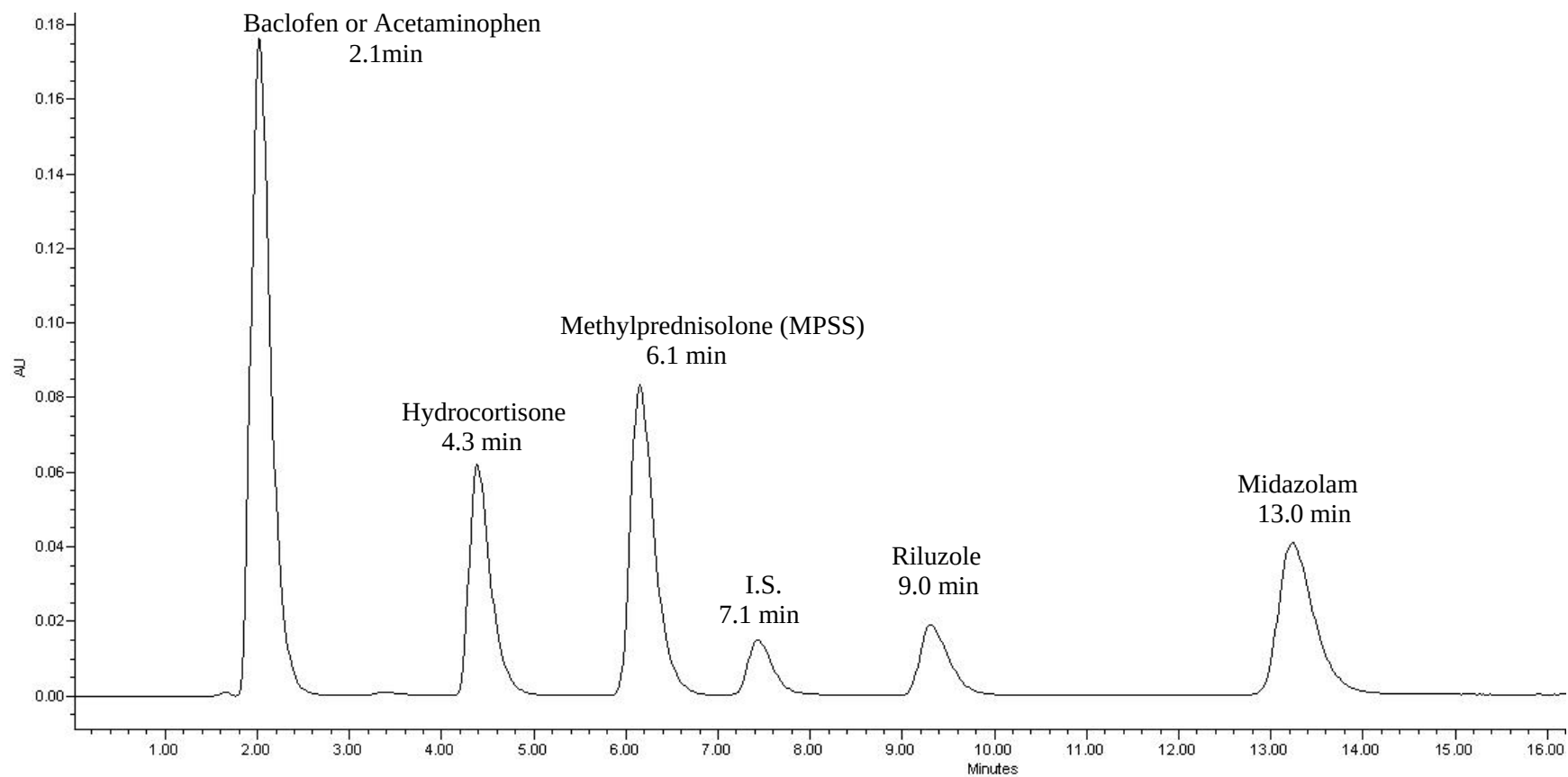


Figure 3

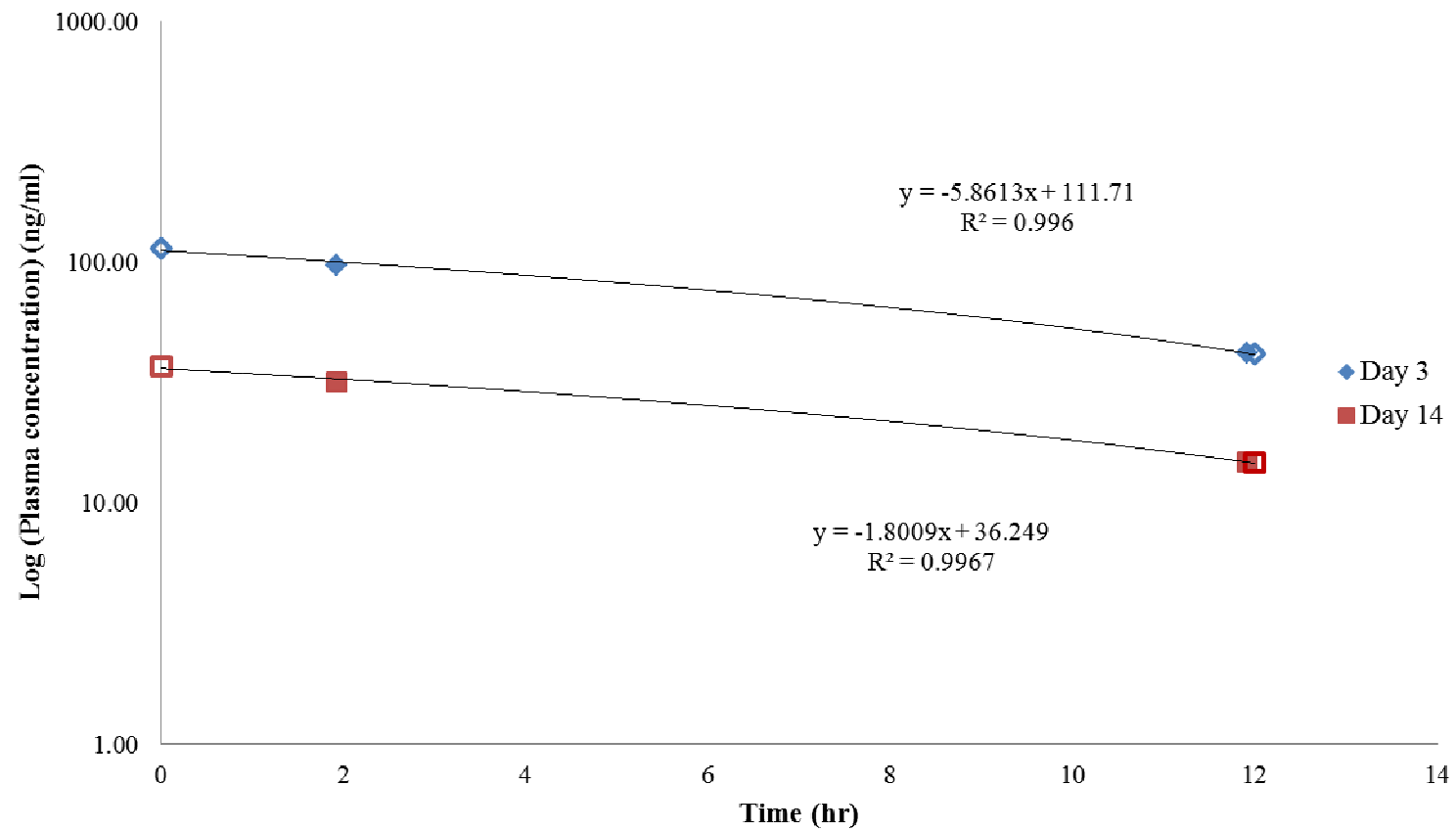


Figure 4

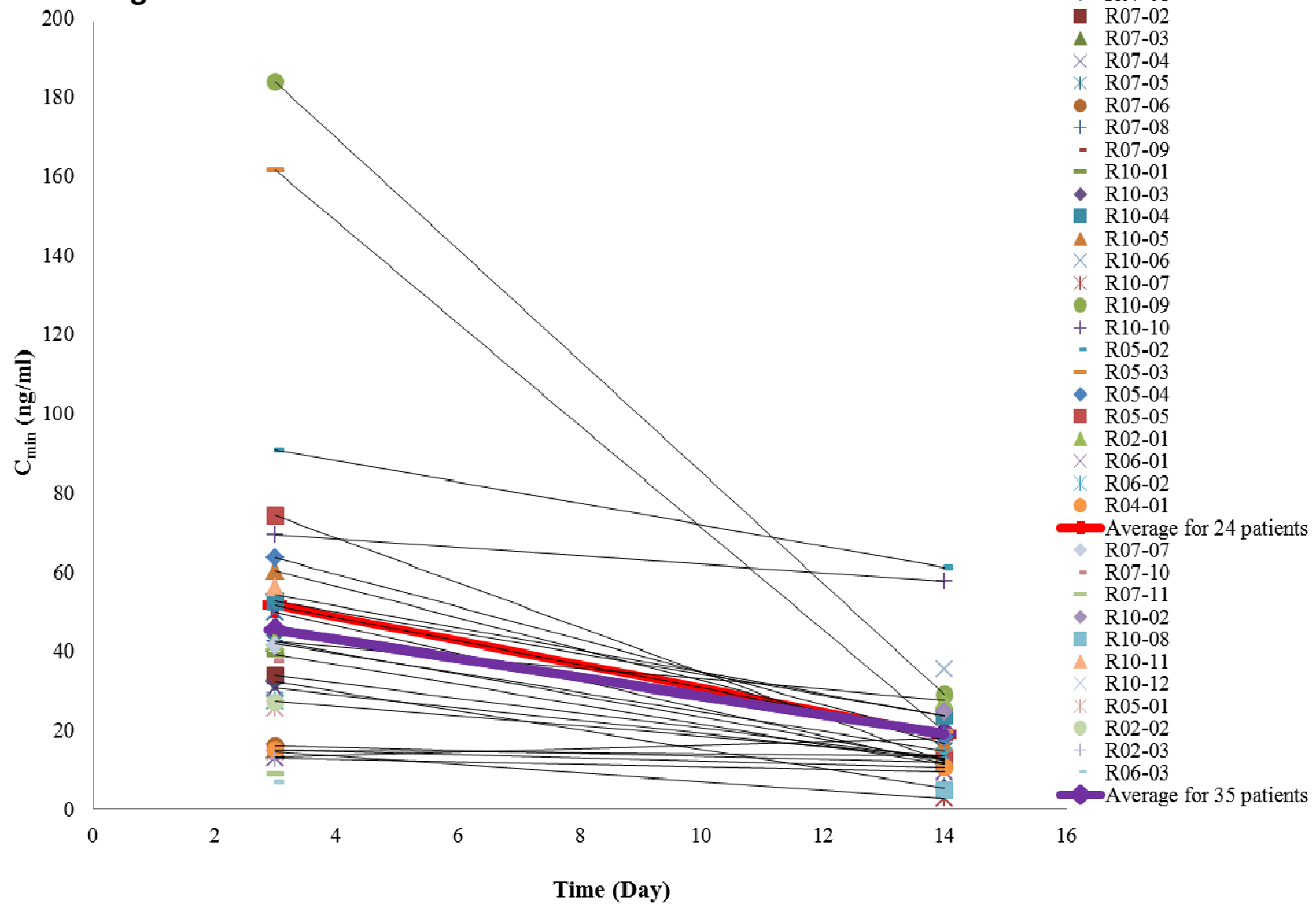
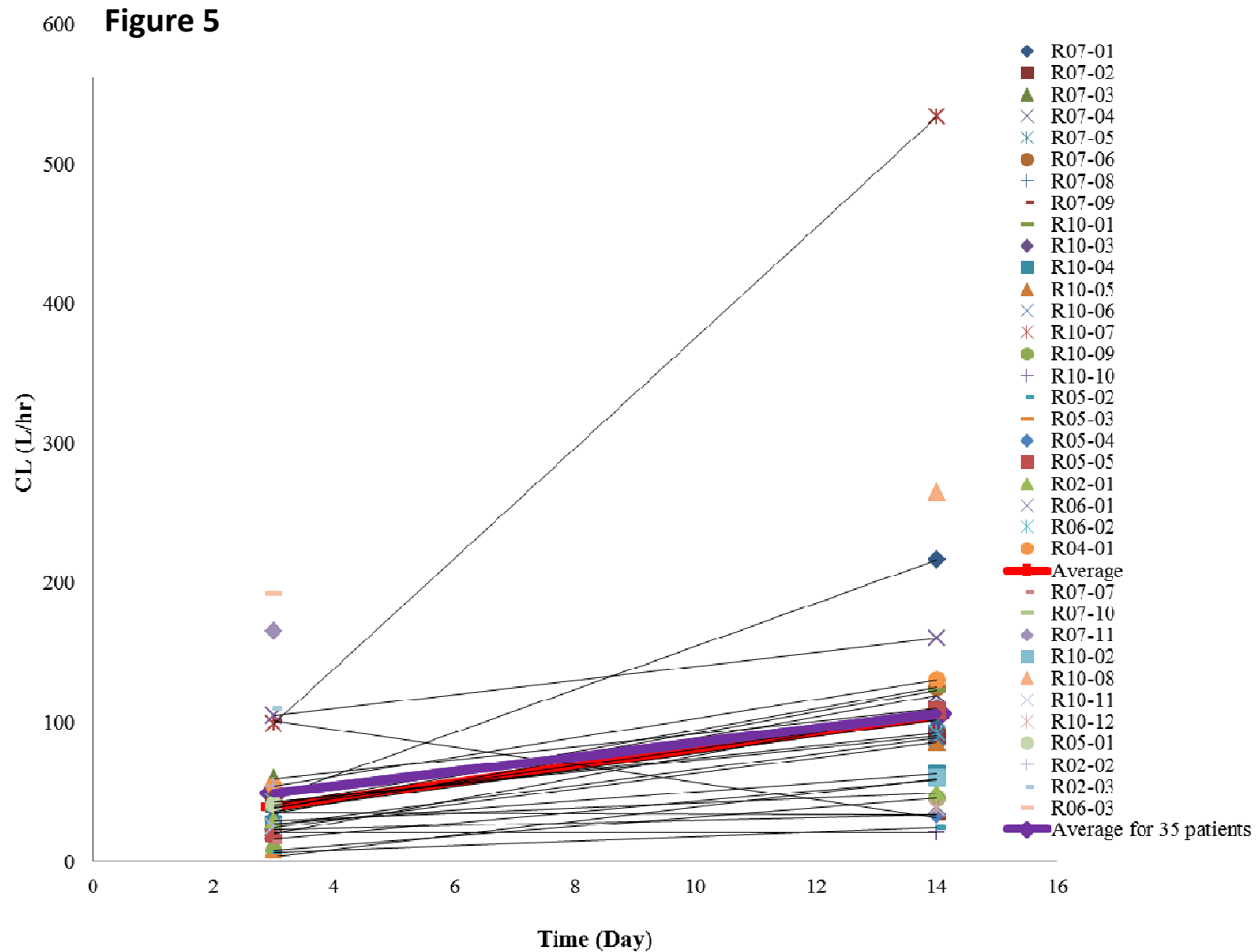
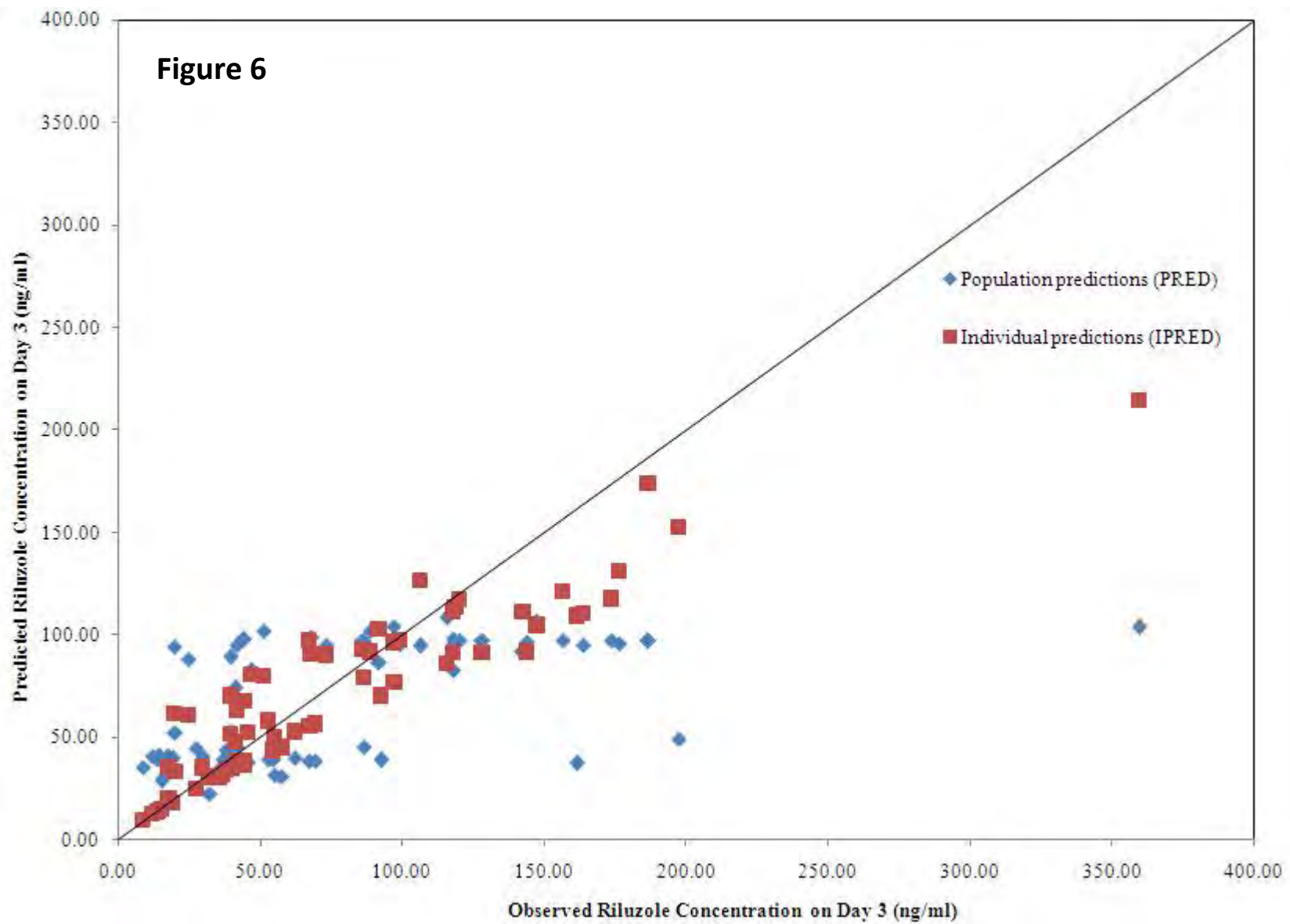


Figure 5





Tables for **Pharmacology of Riluzole in Acute Spinal Cord Injury**

Table I Spinal Cord Injury Phases and Key Pathological Events⁵⁸

Phase and Key Events	Time after SCI				
	≤ 2 hours	≤ 48 hours	≤ 14 days	≤ 6 months	≥ 6 months
Injury Phase	Primary Immediate	Early Acute	Secondary Subacute	Intermediate	Chronic/Late
Key Processes and Events	Primary mechanical injury Traumatic severing of axons Grey matter hemorrhage Hemorrhagic necrosis Microglial activation released factors: IL-1 β , TNF α , IL-6 & others	Vasogenic & cytotoxic edema ROS production: lipid peroxidation Glutamate-mediated excitotoxicity Continued hemorrhage & necrosis Neutrophil invasion Peak BBB permeability Early demyelination (oligodendrocyte death) Neuronal death Axonal swelling Systemic events (systemic shock, spinal shock, hypotension, hypoxia)	Macrophage infiltration Initiation of astroglial scar (reactive astrogliosis) BBB repair & resolution of edema	Continued formation of glial scar Cyst formation Lesion stabilization	Prolonged Wallerian degeneration Persistence of spared, demyelinated axons Potential structural & functional plasticity of spared spinal cord tissue
Therapeutic Aims	Neuroprotection	Neuroprotection Immune modulation Cell-based remyelination approaches Glial scar degradation		Glial scar degradation	Rehabilitation Neuroprostheses

Tables for **Pharmacology of Riluzole in Acute Spinal Cord Injury**

Table II Demographics of Patients

Patient covariate	Day 3	Day 14	Total
Number	33	32	36
Gender			
Men	28	26	30
Women	5	6	6
Smoking status			
Smoking	11	9	11
Non-smoking	22	23	25
Age (years)			
Mean $\pm$ SD	41.15 $\pm$ 18.21	39.63 $\pm$ 18.22	39.44 $\pm$ 18.34
Range	18-69	18-68	18-69
Weight (kg)			
Mean $\pm$ SD	81.22 $\pm$ 13.66	83.33 $\pm$ 17.79	83.01 $\pm$ 16.90
Range	55.69-113.4	55.69-113.4	55.69-113.4
Height (inch)			
Mean $\pm$ SD	68.55 $\pm$ 4.29	68.42 $\pm$ 4.33	68.69 $\pm$ 4.23
Range	62-75	62-75	62-75
AIS Impairment Score			
AIS A			19 (52.8%)
AIS B			9 (25.0%)
AIS C			8 (22.2%)
Spinal Cord Injury Level			
Cervical 04-08			28 (77.8%)
Thoracic 01-06			5 (13.9%)
Thoracic 07-12			3 (8.3%)

Tables for Pharmacology of Riluzole in Acute Spinal Cord Injury

Table III Pharmacokinetic Parameters of Riluzole in Spinal Cord Injured Patients and Healthy Volunteers²⁶⁻²⁷

Parameters	Spinal Cord Injured Patients Individual Estimation		Healthy Volunteers		
	Day 3	Day 14	White Subjects ⁽²⁶⁾	Young Subjects ⁽²⁶⁾	Elderly Subjects ⁽²⁷⁾
	Mean ± SE (RSE%)	Mean ± SE (RSE%)			
Dose	50 Bid	50 Bid	50 Bid	50 Bid	50 Bid
No.	32	27	12	18	18
Sex	28 M + 4 F	23 M +4 F	M	9 M+9 F	9 M+9 F
Age	41.15 ± 18.21	39.63 ± 18.22	18-40	18-30	70-82
C _{max} (ng/ml)	128.86 ± 14.03 (10.9%)	76.46 ± 15.04* (19.7%)	173 ± 72	244 ± 140	271 ± 122
AUC _{0-12 hr} (ng*hr/ml)	982.03 ± 111.18 (11.3%)	521.01 ± 87.32* (16.8%)	654 ± 280	869 ± 465	1029 ± 401
AUC _{0-∞} (ng*hr/ml)	2101.99 ± 441.09 (21.0%)	807.83 ± 111.26* (13.8%)			
CL/F (L/hr)	49.47 ± 7.77 (15.7%)	106.20 ± 19.80* (18.6%)		59.32 ± 29.66	71.35 ± 31.08
V _F (L)	557.06 ± 73.80 (13.2%)	1297.88 ± 218.92 * (16.9%)			
k (hr ⁻¹)	0.095 ± 0.009 (9.3%)	0.101 ± 0.010 (9.7%)			
t _{1/2} (hr)	11.91 ± 2.18 (18.3%)	10.61 ± 2.23 (21.0%)	14.7 ± 4.9	49.03 ± 10.93	40.30 ± 8.84

CL/F, apparent oral clearance; V_F, apparent volume of distribution; AUC_{0-∞}, the area under the curve; C_{max}, peak concentration; k, elimination rate constant; t_{1/2}, half life; RSE, relative standard error, the standard error divided by the mean and expressed as a percentage.

*Statistical difference between Day 3 and Day 14 using Nonparametric test (sign), p<0.05.

Tables for Pharmacology of Riluzole in Acute Spinal Cord Injury

Table IV Comparison of Population and Individual Estimated Pharmacokinetic Parameters of Riluzole for Day 3 and Day 14

Parameters	Population Pharmacokinetics				Individual Estimation	
	Day 3		Day 14		Day 3	Day 14
	Mean $\pm$ SE (RSE%)	Bootstrap 95% CI	Mean $\pm$ SE (RSE%)	Bootstrap 95% CI	Mean $\pm$ SE (RSE%)	Mean $\pm$ SE (RSE%)
No.	33	33	32	32	32	27
C _{max} (ng/ml)					128.86 $\pm$ 14.03 (10.9%)	76.46 $\pm$ 15.04** (19.7%)
AUC _{0-∞} (ng*hr/ml)	827.81		337.84		2101.99 $\pm$ 441.09 (21.0%)	807.83 $\pm$ 111.26** (13.8%)
CL/F (L/hr)	60.4 $\pm$ 6.24 (10.3%)	47.4 to 71.4	148 $\pm$ 25.5 (17.2%)	95.4 to 171	49.47 $\pm$ 7.77 (15.7%)	106.20 $\pm$ 19.80 (18.6%)
V _F (L)	663 $\pm$ 103 (16.3%)	391 to 715	2080 $\pm$ 947 (45.5%)	523 to 2780	557.06 $\pm$ 73.80 (13.2%)	1297.88 $\pm$ 218.92 ** (16.9%)
ka (hr ⁻¹)	5*	5*	5*	5*		
k (hr ⁻¹)	0.095		0.071		0.095 $\pm$ 0.009 (9.3%)	0.101 $\pm$ 0.010 (9.7%)
t _{1/2} (hr)	7.29		9.76		11.91 $\pm$ 2.18 (18.3%)	10.61 $\pm$ 2.23 (21.0%)
ωCL (%)	20.0% $\pm$ 8.13% (40.6%)	1.56 % to 27.4%	41.7% $\pm$ 23.6% (56.6%)	2.93% to 64.9%		
ωV (%)	0.13 % $\pm$ 0.11% (79.1%)	-0.009% to 0.3%	0.02% $\pm$ 0.01% (37.2%)	0.002% to 0.01%		
σProportional error (%)	11.8% $\pm$ 2.27% (19.2%)	8.68% to 20.1%	20.6% $\pm$ 5.19% (25.2%)	11.8% to 24.6%		
σAdditive error (ng/ml)	13.8 $\pm$ 11.9 (86.2%)	-63.4 to 124	2.43 $\pm$ 3.24 (133%)	-5.68 to 10.8		

CL/F, apparent oral clearance; V_F, apparent volume of distribution; Ka, absorption rate constant; AUC_{0-∞}, the area under the curve, calculated by Dose/CL/F; C_{max}, peak concentration; k, elimination rate constant; t_{1/2}, half life; RSE, relative standard error, the standard error divided by the mean and expressed as a percentage (%); ω, inter-individual variability; σ, residual variability.

*Fixed parameter. **Statistical difference between Day 3 and Day 14 using Nonparametric test (sign), p<0.05

Table V Comparison of Population Pharmacokinetic Parameters in Acute Spinal Cord Injury Patients (SCI) versus Patients with Amyotrophic Lateral Sclerosis (ALS)²⁸⁻²⁹ and Spinal Muscular Atrophy (SMA)³⁰

Parameters	PopPK in SCI Patients		ALS ⁽²⁸⁻²⁹⁾	SMA ⁽³⁰⁾
	Day 3	Day 14		
Dose	50 Bid	50 Bid	50 Bid	50 QD
No.	33	32	169 ²⁸ /179 ²⁹	13
Sex	28 M+5 F	26 M+6 F		4 M+9 F or 5 M+8 F
Age	41.15 ± 18.21	39.63 ± 18.22	55.0 ± 15.2 ²⁹	9-17
C _{max} (ng/ml)	128.86 ± 14.03* (10.9%)	76.46 ± 15.04* (19.7%)	231 ± 199 ²⁸	371 ± 224 (N)
AUC _{0-∞} (ng*hr/ml)	827.81	337.84	3409 ± 2864 (70 kg) ²⁸ 48.70 ± 40.94 (AUC/kg)	2257 ± 1601 (N) (0-24 hr)
CL/F (L/hr)	60.4 ± 6.24 (10.3%)	148 ± 25.5 (17.2%)	25.9 ± 14.72 51.4 (7.2%) ²⁹	22.15 (N)
V _F (L)	663 ± 103 (16.3%)	2080± 947 (45.5%)	361 (10.1%) ²⁹	299 ± 193 (C)
t _{1/2} (hr)	7.29	9.76	4.93	9.8 ± 4.6 (N)
T _{max} (hr)				1 (1-5) (N)

N: The parameters calculated by non-compartmental model; C: The parameters calculated by compartmental model.

*From individual estimation.



March 9, 2011

Story C. Landis, PhD
Director, NINDS
Building 31, Room 8A52
31 Center Drive, MSC 2540
Bethesda, MD 20892

Dear Dr. Landis:

Thank you for taking the time to meet with me and Ronnie Tepp and with Drs. Robert Grossman, Charles Tator, Susan Harkema and Ralph Frankowski to discuss ways the Foundation and NINDS can work together to advance the spinal cord research field and implement the Christopher & Dana Reeve Paralysis Act. We all very much appreciated the active engagement of you and your NINDS team.

We believe that NACTN offers NINDS the opportunity to support innovative translational projects that will move us toward our shared goal of identifying rational new therapies for people with spinal cord injury. We also believe that NACTN's exclusive focus on SCI makes it the best platform for testing promising SCI interventions for safety and efficacy. Our ability to strategically interact and link with the Foundation's NeuroRecovery Network and European and Canadian SCI clinical networks and to tap international expertise to develop more sensitive outcome measures leverages NACTN's strengths and potential achievements considerably.

We appreciate the challenges and inefficiencies posed for NINDS in creating ad hoc clinical networks focused on individual diseases and conditions. We also believe that the NINDS standing and in-development networks don't necessarily afford the best mechanisms for testing potential SCI therapies. That said, I believe you offered us a way forward that has the potential to marry the NINDS mission and funding mechanisms with NACTN's mission, infrastructure and resources. Per your encouragement, our PIs will take advantage of appropriate NINDS funding opportunities, counsel with NINDS personnel and submit proposals seeking support for discrete projects and/or clinical trials. As noted in our meeting last month, the Foundation intends to vigorously pursue continued DOD funding for the network's standing infrastructure.

We look forward to future opportunities for NACTN to successfully compete for NINDS support. There is no doubt that our common goals can be achieved more effectively by working together in partnership.

Sincerely,

A handwritten signature in black ink that reads "Susan P. Howley". The signature is written in a cursive, flowing style.

Susan Howley
Executive Vice President, Research

NACTN Executive Committee

Monthly Conference Call Minutes

Date: October 19th, 2011

Committee Members: Susan Howley (CDRF), Susan J Harkema (Louisville), Ralph Frankowski (Houston), Michael Fehlings (Toronto), Robert Grossman (Houston), Elizabeth Toups (Houston)

On Call : Howley, Harkema, Grossman, Frankowski, Fehlings, Toups, Kennedy

Next Meeting: November 16th, 2011

Topic	Discussion	Action Items
Governance Manual	PK – Governance Manual has been sent out. If everyone approves will start sending out Signature sheet. Approval received from all Committee members.	
Documents from Acorda AC105	RG – Any more discussion?	
Walter Reed Penetrating SCI Manuscript	RF – They have 18 cases now recruited for the registry and we have complete data on 11 of them. Now that Vicki has moved over, they will be completing the other cases shortly. We will have 18 penetrating injuries, plus probably an equivalent number from the civilian registry. The first thing would be to talk to the lead author on that.	
NACTN Budget	SHowley –We are in the second year of our DOD award and there is nothing happening in Washington in terms of next year’s budget. There is a million dollars in the appropriations committee for NACTN. What happens with that when things begin to move down there is anybody’s guess. There is no RFA for us to be applying to for continued funding. We are going to move on a couple of fronts. Basically when you look at our budget, in theory we have enough money to keep the June to May sites fully funded in their current contract. What that does, however, leave us very little money for anything else. One thing I’m watching very carefully is we have a handful of centers carrying forward huge amounts of money. I think we are probably going to be forced to pull back that money and redistribute it so that everybody gets a full grant year next year. Year 2 formally ends on July 17, 2012. If you recall the money we are working	

Topic	Discussion	Action Items
	from now is a 2-year grant that came out of TATRC's 2010 surplus. There is no doubt we are an important program within TATRC. I don't know if they are sitting on reserve funds. One of the things that really excites me about Susie's proposal is if we can get Walter Reed engaged this would be terrific. If there were any way at all to include Walter Reed in some of the clinical trial planning, that would be great. SAMMC is a mixed bag. We've got in the Year 2 budget for two new military sites, but I really need to recycle that to the current NACTN sites. If SAMMC comes in, that is terrific from a military perspective, but it reduces that by . We are going to start really working the numbers. I am going to try and re-engage Ken Curley and Colonel Friedel and get them to see the realities of what we are dealing with. SJH – I think Ken would be really excited to hear what we want to do with the NRN site. SHowley – If we can get SAMMC on board and engage Walter Reed at a level they have not been engaged in so far, these are things we can use to our advantage. If any of you have any thoughts, let me know. SJH – As we put together this DOD budget, if we can unload some of the core money, maybe that will help as well. Maybe you could help on the budget. SHowley – Grossman, Fehlings, Frankowski, Michele Johnson and Chris Shaffrey are on a calendar year contract, and I can come up with pretty much full funding for all of you for a full year – through 2012. The centers that are on the June-May funding cycle, they are a little more problematic. They are fully funded through May 2012 and I will probably have enough money, particularly if I pull back unexpended, uncommitted funds, to keep them going for another 6 months, but not much longer. SHowley – Have to move on the publications now. Michael, if you can have someone send me a couple lines from the predictions paper, I will include it in my upcoming report.	SHowley – Work with SJH on DOD budget. MF – Will send a copy of Predictions Abstract.

Topic	Discussion	Action Items
	RG – One of the things we talked about was working with Naomi and the clinical trials group, but I think to do that we need to have the preliminary Phase 1 data completed.	
Other Business	Next meeting Wednesday, November 16 th , 2011.	

North American Clinical Trials Network/AO Spine North America Focus Issue on Spinal Cord Injury

Minutes (12/2/2011)

1. Introduction

- Dr. Fehlings did a roll call
- Dr. Norvell did a quick review of project progress

2. Update to manuscripts

- Each PI or representative did a review of their manuscript objectives and status. The majority of papers are well underway and should not have a problem meeting the deadlines. There are a few that are larger in scope that have yet to reach a final set of objectives and search criteria potentially delaying their completion. Estimates of time can be made in near future once a final number of articles is estimated.
- Spectrum had at least one representative for each paper on the phone call. These investigators will update their personal notes and be in contact with their co-authors to continue making progress. Details of every paper will not be included in these minutes.

- Two articles were dropped:

<i>Early surgical intervention for SCI – outcomes in patients with facet dislocation [this will be submitted to another journal]</i>

<i>Outcomes of spinal cord injury – AIS analyses</i>

- We now have 18 papers (including the introduction and methods paper). *See final page of minutes for updated article list.*
- The following systematic reviews still need a final agreement on objectives and inclusion/exclusion criteria for Spectrum to begin its systematic search:

<i>Evaluation of therapies and incorporation into clinical trials – Pharmacologic</i>

<i>Evaluation of therapies and incorporation into clinical trials – Cell based therapies</i>

<i>Unique treatments for thoracolumbar SCI</i>

3. Action Items

- Spectrum collaborators will follow-up with author groups on next steps and progress. Those authors who still need literature searches need to request these in detail ASAP so that Spectrum has time to complete these in time to meet final manuscript deadlines.
- Authors with primary data papers should send their drafts to their Spectrum collaborator for review prior to going through peer review.
- Summary of papers on pharmaco and cell based therapies:
Pharmacologic-based therapies:
Primary action items:
 - Finalize the scope and methodology of the article.
 - Robin will write a short methods section detailing the processes we will use (including inclusion/exclusion) for both key questions. Disseminate this to the group for approval asap.
 - Determine the extent to which the authors want to come up with their own grading system or make suggestions for additions to Kwon's criteria (to be discussed in subsequent phase/papers) since we're not going to be able to do a modified Delphi approach.
 - Determine how much of a focus should be placed on discussing the preclinical studies in light of previous/current clinical trials. Do we need to abstract clinical studies?

Cell-based therapies: Dr. Fehlings and Dr. Harrop were going to discuss the scope of this paper. The project is on hold until we hear back from them.

Primary action items: finalize the scope and methodology of the article.

- o Finalize key questions.
- o Finalize PICO table.
- o Finalize cell type(s) to be included
- o Finalize general strategy.

4. Timeline review

Deadline for submission of final manuscript: January 15, 2012

Reviews due back by: February 1, 2012

Revised papers due: February 15, 2012

Planned pub date: Spring 2012

Appendix. Working article titles, type of article, and tentative authors.

	Tentative Article Title	Article type	Authors	Spectrum Investigator
	Editor		Michael Fehlings	
	Co-editors		Robert Grossman; Christopher Shaffrey; Jens Chapman; James Guest; James Harrop; Charles Tator; Paul Arnold; Alexander Vaccaro; Bizhan Aarabi	
1	Introduction	Editorial	Michael Fehlings and other co-editors	None
2	Methods paper for systematic review & primary data	Summary	Dan Norvell, Dettori, Michael Fehlings, et al	Dr. Norvell
3	Development of the NACTN clinical trial network	Systematic Review	Robert Grossman, Ralph Frankowski, others	Dr. Hashimoto
4	Demographics of SCI patients	Systematic Review	Ralph Frankowski	Dr. Norvell
5	Delineation of New Therapies for Treatment in SCI	Systematic Review	James Guest et al	Dr. Norvell
6	The Phase I Riluzole Trial	Primary data/methods	Michael Fehlings, Robert Grossman, Ralph Frankowski, other Riluzole investigators: Diana Chow	Dr. Norvell
7	Pharmacology of Riluzole in SCI	Primary data	Diana Chow, Angela Teng, Elizabeth Toups, Bizhan Aarabi, James Harrop, Christopher Shaffrey, Michele Johnson, Maxwell Boayke, Ralph Frankowski, Michael Fehlings, Robert Grossman	Dr. Norvell
8	Evaluation of therapies and incorporation into clinical trials – Pharmacologic	Systematic Review	Charles Tator, Michael Fehlings, others—on the Therapeutics Committee: James Harrop, James Guest, Bizhan Aarabi, Robert Grossman	Dr. Hashimoto
9	Evaluation of therapies and incorporation into clinical trials – Cell based therapies	Systematic Review	James Harrop, James Guest, Michael Fehlings, Charles Tator, Jens Chapman	Dr. Hashimoto
10	QoL outcomes after spinal cord injury	Systematic Review	Max Boakye	Dr. Skelly
11	Unique treatments for thoracolumbar SCI	Systematic Review	Jens Chapman	Dr. Skelly
12	Predictors of pulmonary function -	Primary data	Bizhan Aarabi	Dr. Dettori
13	Quantitative outcomes assessments for spinal cord injury-NOA	Systematic Review	Susan Harkema/Maxwell Boakye, Peter Ellway	Dr. Skelly
14	The GRASSP outcome measure for hand and upper extremity function	Primary data	Sukhvinder Kalsi-Ryan	Dr. Dettori

15	Neurological complications and age/gender/race on outcomes	Primary data	Anoushka Singh, Sukhvinder Kalsi-Ryan, Jefferson Wilson, Michael Fehlings, Ralph Frankowski, Maxwell Boayke, Robert Grossman, Paul Arnold	Dr. Norvell
16	Predictive Factors for recovery after cervical spinal cord injury	Systematic Review	Jefferson Wilson, Michael Fehlings, Alexander Vaccaro	Dr. Dettori
17	Imaging and outcomes	Primary data	Jeff Wilson, David Cadotte, James Guest, Michael Fehlings	Dr. Dettori
18	Spinal cord fMRI	Systematic Review	David Cadotte	Dr. Dettori

	Tentative Article Title	Article type	Authors full name	Spectrum Investigator
	Editor		Michael Fehlings	
	Co-editors		Robert Grossman; Christopher Shaffrey; Jens Chapman; James Guest; James Harrop; Charles Tator; Paul Arnold; Alexander Vaccaro	
1	Introduction	Editorial	Michael Fehlings and other co-editors	All
2	North American Clinical Trials Network (NACTN) for Treatment of Spinal Cord Injury: Goals and Progress	Review	Robert Grossman , Ralph Frankowski, others	Dr. Norvell
3	Filling the Clinical Measurement Gap in the Translation of Preclinical Models for the Upper Limb in Tetraplegia	Systematic Review	James Guest et al	Dr. Norvell
4	Riluzole for the Treatment of Acute Traumatic Spinal Cord Injury: Rationale for and Design of the NACTN Phase I Clinical Trial	Primary data/methods	Michael Fehlings , Robert Grossman, Ralph Frankowski, other Riluzole investigators: Diana Chow; Branko Kopjar	Dr. Norvell
5	Pharmacology of Riluzole in Acute Spinal Cord Injury (ASCI)	Primary data	Diana Chow , Angela Teng, Elizabeth Toups, Bizhan Aarabi, James Harrop, Christopher Shaffrey, Michele Johnson, Maxwell Boakye, Ralph Frankowski, Michael Fehlings, Robert Grossman	Dr. Norvell
6	Review of Neuroprotection through Pharmacotherapy for Human Spinal Cord Injury Trials	Systematic Review	Charles Tator , Michael Fehlings, others—on the Therapeutics Committee: James Harrop, James Guest, Bizhan Aarabi, Robert Grossman	Dr. Hashimoto
7	Evaluation of Clinical Experience of Cell Based Therapies in SCI: A Systematic Review	Systematic Review	James Harrop , James Guest, Michael Fehlings, Charles Tator, Jens Chapman	Dr. Hashimoto
8	Quality of Life in Persons with SCI: Comparisons with Other Populations	Systematic Review	Max Boakye	Dr. Skelly
9	Acute Spinal Cord Injury: Systematic Review of Prognosis for Thoracic Injury	Systematic Review	Jens Chapman , Rick Bransford	Dr. Skelly
10	Predictors of Pulmonary Complications in Blunt Traumatic Spinal Cord Injury	Primary data	Bizhan Aarabi	Dr. Dettori
11	Quantitative Testing: Overview of Reliability and Predictive Validity	Systematic Review	Susan Harkema /Maxwell Boakye, Peter Ellaway	Dr. Skelly
12	The GRASSP Outcome Measure for Hand and Upper Extremity Function	Primary data	Sukhvinder Kalsi-Ryan	Dr. Dettori

13	A Clinical Prediction Model for Acute Inpatient Complications after Traumatic Cervical Spinal Cord Injury: A Sub-analysis from the Surgical Timing in Acute Spinal Cord Injury Study (STASCIS)	Primary data	Anoushka Singh , Sukhvinder Kalsi-Ryan, Jefferson Wilson, Michael Fehlings, Ralph, Max, Bob Grossman, Paul Arnold	Dr. Norvell
14	Clinical Predictors of Neurologic Outcome, Functional Status and Survival after Traumatic Spinal Cord Injury: A Systematic Review	Systematic Review	Jefferson Wilson , Michael Fehlings, Alexander Vaccaro	Dr. Dettori
15	A Systematic Review of Spinal fMRI	Systematic Review	David Cadotte	Dr. Dettori
16	Electrophysiological Assessment of SCI	Primary data	Maxwell Boakye / Susan Harkema	Dr. Dettori

Descriptive Title: A Phase II Trial of Body Weight Support Locomotor Training in Gait Rehabilitation After Spinal Cord Injury: A Collaboration of NACTN and NRN

Submission Title: SC110036

Opportunity ID: W81XWH-11-SCIRP-CTA-R

Opportunity Title: DoD Spinal Cord Injury Clinical Trial Award - Rehabilitation

Agency Name: Dept. of the Army -- USAMRAA

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RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE – Project Director/Principal Investigator					
Prefix:	Dr.	First Name:	Robert	Middle Name:	
Last Name:	Grossman			Suffix:	
Position/Title:	Chairman	Department:	Neurosurgery		
Organization Name:	TMHS (The Methodist Hospital System)		Division:		
Street 1:	6560 Fannin, Suite 944				
Street 2:					
City:	Houston	County/Parish:			
State:	TX: Texas		Province:		
Country:	USA: UNITED STATES		Zip / Postal Code:	77030	
Phone Number:	713/441-3800	Fax Number:	713-793-1004		
E-Mail:	rgrossman@tmhs.org				
Credential, e.g., agency login	RGROSSMAN				
Project Role:	PD/PI	Other Project Role Category:			
Degree Type:	MD				
Degree Year:	1957				
Attach Biographical Sketch	Biosketch_Grossman.pdf				
Attach Current & Pending Support	Support_Grossman.pdf				

ADDITIONAL SENIOR/KEY PERSON PROFILE(S)

Additional Biographical Sketch(es)

Additional Current and Pending Support(s)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME Grossman, Robert George, M.D.	POSITION TITLE Professor and Chairman, Department of Neurosurgery Co-Director, The Methodist Hospital Neurological Institute		
eRA COMMONS USER NAME (credential, e.g., agency login) rgrossman			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	MM/YY	FIELD OF STUDY
Swarthmore College, Swarthmore, Pennsylvania	BA	1949-1953	Mathematics & Natural Science
College of Physicians & Surgeons of Columbia University, New York, New York	MD	1953-1957	Medicine
University of Rochester, NY	Surgical Internship	1957-1958	General Surgery
Walter Reed Army Institute of Research Washington, DC	Capt MC US Army	1958-1960	Neurophysiology, Neuroanatomy
Neurological Institute of New York	Residency	1960-1963	Neurosurgery

A. Positions and Employment

1963-1969 Assistant to Associate Professor, Division of Neurological Surgery, The University of Texas Southwestern Medical School, Dallas, TX
 1969-1973 Associate to Professor of Neurological Surgery, Department of Neurological Surgery, Albert Einstein College of Medicine, Bronx, NY
 1973-1980 Professor of Surgery and Chief of the Division of Neurological Surgery, The University of Texas Medical Branch, Galveston, TX
 1980-2005 Professor and Chairman, Dept. of Neurosurgery, Baylor College of Medicine, Houston, TX
 1980-present Chairman, Department of Neurosurgery, The Methodist Hospital, Houston, TX
 2005-present Co-Director, Neurological Institute, The Methodist Hospital, Houston, TX

B. Public Advisory Boards, USPHS

1970-1974 Neurology "B" Study Section, National Institutes of Health
 1972-1973 Chairman, Neurology "B" Study Section, National Institutes of Health
 1979-1986 Neurological Disorders Program Advisory Committee, National Institutes of Health
 1989-1993 Board of Scientific Counselors, National Institute of Neurological Disorders and Stroke
 1991-1993 Chairman, Board of Scientific Counselors, NINDS
 1993-1996 National Advisory Council, National Institute of Neurological Disorders and Stroke

C. Editorial Board Memberships

1982-1989 Editorial Board, Journal of Neurosurgery
 1987-1989 Chairman, Editorial Board, Journal of Neurosurgery
 2002-2009 Editorial Board, Neurosurgery
 2009-present Editorial Board, World Neurosurgery

D. Offices in Neurosurgical Societies

1977-1978 Secretary, Society of University Neurosurgeons
 1978-1979 Vice President, Society of University Neurosurgeons
 1979-1980 President, Society of University Neurosurgeons
 1984-1990 Director, American Board of Neurological Surgery

1988-1989 Vice Chairman, American Board of Neurological Surgery
1989-1990 Chairman, American Board of Neurological Surgery
1990-present Advisory Council, American Board of Neurological Surgery
1994-1995 President, Society of Neurological Surgeons

E. Honors

2007 Cushing Medal, American Association of Neurological Surgeons for service to Neurosurgery

F. Selected Peer-reviewed Publications Relevant to SCI Trials(Selected from 159 publications)

1. Bracken MB, Collins WF, Freeman DF, Shepard MJ, Wagner FW, Siltan RM, Hellenbrand KG, Ranschoff J, Hunt WE, Perot PL, **Grossman RG**, Green BA, Eisenberg HM, Rifkinson N, Goodman JH, Meagher JN, Fischer B, Clifton GL, Flamm ES, Rawe SE: Efficacy of methylprednisolone in acute spinal cord injury. *JAMA* 251:45-52, 1984.
2. Bracken MB, Shepard MJ, Hellenbrand KG, Collins WF, Leo LS, Freeman DF, Wagner FC, Flamm ES, Eisenberg HM, Goodman JH, Perot Jr PL, Green BA, **Grossman RG**, Meagher JN, Young W, Fischer B, Clifton GL, Hunt WE, Rifkinson N: Methylprednisolone and neurological function 1 year after spinal cord injury: Results of the National Acute Spinal Cord Injury Study. *J Neurosurg* 63:704-713, 1985.
3. Bartlett P, Blight A, Dietz V, Dobkin B, Fawcett J, Fehlings M, Grossman RG, Guest J, Kleitman N, Lammertse D, Privat A, Steeves J, Tuszynski M: Development of SCI Clinical Trials Guidelines. www.icord.org/ICCP.html, 2006.
4. Courtine G, Bunge MB, Fawcett JW, **Grossman RG**, Kaas JH, Lemon R, Maier I, Martin J, Nudo RJ, Ramon-Cueto A, Rouiller EM, Schnell L, Wannier T, Schwab ME, Edgerton VR: Can experiments in nonhuman primates expedite the translation of treatments for spinal cord injury in humans? *Nature Medicine* 13:561-566, 2007.
5. Fawcett JW, Curt A, Steeves JD, Coleman WP, Tuszynski MH, Lammertse D, Bartlett PF, Blight AR, Dietz V, Ditunno J, Dobkin BH, Havton LA, Ellaway PH, Fehlings MG, Privat A, **Grossman R**, Guest JD, Kleitman N, Nakamura M, Gaviria M, Short D: Guidelines for the conduct of clinical trials for spinal cord injury as developed by the ICCP panel: spontaneous recovery after spinal cord injury and statistical power needed for therapeutic clinical trials. *Spinal Cord* Mar;45:190-205, 2007.
6. Steeves JD, Lammertse D, Curt A, Fawcett JW, Tuszynski MH, Citunno JF, Ellaway PH, Fehlings MG, Guest JD, Kleitman N, Bartlett PF, Blight AR, Dietz V, Dobkin BH, **Grossman R**, Short D, Nakamura M, Coleman WP, Gaviria M, Privat A; International Campaign for Cures of Spinal Cord Injury Paralysis: Guidelines for the conduct of clinical trials for spinal cord injury (SCI) as developed by the ICCP panel: clinical trial outcome measures. *Spinal Cord* Mar; 45:206-21, 2007.
7. Tuszynski MH, Steeves JD, Fawcett JW, Lammertse D, Kalichman M, Rask C, Curt A, Ditunno JF, Fehlings MG, Guest JD, Ellaway PH, Kleitman N, Bartlett PF, Blight AR, Dietz V, Dobkin BH, **Grossman R**, Privat A: International Campaign for Cures of Spinal Cord Injury Paralysis: Guidelines for the conduct of clinical trials for spinal cord injury as developed by the ICCP Panel: clinical trial inclusion/exclusion criteria and ethics. *Spinal Cord* Mar;45:222-31, 2007.
8. Blight A, Curt A, Ditunno JF, Dobkin B, Ellaway P, Fawcett J, Fehlings M, **Grossman RG**, Lammertse DP, Privat A, Steeves J, Tuszynski M, Kalichman M, Guest JD: Position statement on the sale of unproven cellular therapies for spinal cord injury: the international campaign for cures of spinal cord injury paralysis. *Spinal Cord* 47:713-4, 2009.
9. Harkema S, Gerasimenko Y, Hodes J, Burdick J, Angeli C, Chen Y, Ferreira C, Willhite A, **Grossman RG**, Rejc E, Edgerton R. Effect of epidural stimulation of the lumbosacral spinal cord on voluntary movement, standing and assisted stepping after motor complete paraplegia: a case study. *Lancet* 2011; 377:1938-1947.

G. Research Support

Department of Defense – Telemedicine and Advanced Technology Research Center (TATRC)

U.S. Army Medical Research and Materiel Command (MRMC)

Grant from the Department of Defense to the Christopher Reeve Foundation

Principal Investigator: Robert G. Grossman, MD

Building Infrastructure to Accelerate Transfer of Basic Research in Spinal Cord Injury (SCI) to Clinical Practice: North American Clinical Trials Network (NACTN) for Treatment of Spinal Cord Injury

July 19, 2010 – August 18, 2012

CURRENT AND PENDING

Robert G. Grossman, MD

Current Support

BAA W81XWH-10-2-0042

Building Infrastructure to Accelerate transfer of basic research in spinal Cord Injury to clinical Practice: The North American clinical Trials Network for Treatment of Spinal Cord Injury Telemedicine and Advanced Technology Research Center (TATRC),
U. S. Army Medical Research and Materiel Command (USMRMC)
Department of Defense to the Christopher Reeve Foundation
Principal Investigator: Grossman
Research Period: July 19, 2010 – 12/31/2012

The goal of this study is to incorporate the infrastructure and expertise to conduct clinical trials of new therapies for spinal cord injury

BAA W81XWH-07-1-0361

North American Clinical Trials Network for Treatment of Spinal Cord Injury
Telemedicine and Advanced Technology Research Center (TATRC),
U. S. Army Medical Research and Materiel Command (USMRMC)
Department of Defense to the Christopher Reeve Foundation
Principal Investigator: Grossman
Research Period: 05/014/07-12/31/12

The major goal of this project is to achieve clinical trials capable of indicating effectiveness of promising Spinal Cord Injury (SCI) therapies while ensuring patient safety. NACTN has created a network of hospitals that enrolls sufficient numbers of patients, defines and adheres to standard protocols and provides the infrastructure and highly skilled personnel to conduct trials of therapy for SCI.

- Specific Aim is to bring promising therapies from Spinal Cord Injury from the laboratory to clinical trials in a manner that will provide incontrovertible evidence of effectiveness, with maximum safety to patients undergoing treatment.

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Senior/Key Person					
Prefix:	Mrs.	First Name:	Elizabeth	Middle Name:	Gardiner
Last Name:	Toups	Suffix:			
Position/Title:	Academic Clinical Research Manager		Department:	Neurosurgery	
Organization Name:	TMHS (The Methodist Hospital System)			Division:	
Street 1:	6560 Fannin, Suite 944				
Street 2:					
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State:	TX: Texas		Province:		
Country:	USA: UNITED STATES			Zip / Postal Code:	77382
Phone Number:	713-441-3897		Fax Number:	713-793-1004	
E-Mail:	etoups@tmhs.org				
Credential, e.g., agency login					
Project Role:	Other (Specify)		Other Project Role Category:	Project Manager	
Attach Biographical Sketch	Biosketch_Toups.pdf				
Attach Current & Pending Support	Support_Toups.pdf				

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME Elizabeth G. Toups		POSITION TITLE Clinical Trials Manager, Department of Neurosurgery, The Methodist Hospital Neurological Institute	
eRA COMMONS USER NAME (credential, e.g., agency login)			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	MM/YY	FIELD OF STUDY
Northeastern Louisiana University, Louisiana	B.S.	1976-1986	Nursing
Texas Women's University, Houston, Texas	M.S. (Dual Degree)	1991-1995	Nursing and Healthcare Administration

A. Personal Statement

As a clinical coordinator on this study, I am well positioned to support this project. I assisted in the development of an international multi-center clinical trials network with similar goals in mind. I have assisted in the development and clinical research operations including trial coordination and management of network projects for the past 6 years. In my current role, I provide leadership for clinical research operations and provide expertise and support in protocol training, budgeting, regulatory compliance and standard operating procedures. I have successfully implemented network and other departmental projects in a timely manner. My interest is in improving the outcome of patients of spinal cord injury.

B. Positions and Employment

1980-1982	Registered Nurse, Cardiovascular ICU, St. Luke's Hospital, Houston, Texas
1982-1983	Med Staff Agency, Critical Care Registered Nurse, the Methodist Hospital, Ben Taub Hospital, Bellaire Hospital, Clearlake Hospital, Doctor's Hospital, Home Healthcare, Private Duty, Houston Texas
1983-1990	Registered Nurse, Cardiovascular Intensive Care Unit, The Methodist Hospital, Houston, Texas
1991-2002	Clinical Research Nurse II, Baylor College of Medicine, Department of Neurosurgery, Houston, Texas
2003-2004	Adjunct Instructor, Department of Nursing, North Harris College, Houston, Texas
2005-2009	Sr. Research Coordinator, Department of Neurosurgery, The Methodist Hospital Neurological Research Institute, Houston, Texas
2009-2010	Clinical Research Manager, Department of Neurosurgery, The Methodist Hospital Neurological Research Institute, Houston, Texas
2010-2011	Clinical Trials Manager, Department of Neurosurgery, The Methodist Hospital Neurological Research Institute, Houston, Texas

Other Experience and Professional Memberships

1994-2002	Clinical Research Nurse II, Baylor College of Medicine

- 2005 - 2009 Double blind randomized trial of the anti-progestational agent mifepristone in the treatment of unresectable meningioma, Phase III
Sr. Research Coordinator, Department of Neurosurgery, The Methodist Hospital Coordinating Center and clinical site for North American Clinical Trials Network (NACTN) for Treatment of Spinal Cord Injury
- 2006 - 2009 Sr. Research Coordinator, Quantitative Measurement of Muscle Strength and Movement
- 2007 - 2009 Sr. Research Coordinator, An Atlas of the Cytoarchitecture of the Human Spinal Cord
- 2009 - Present Project Manager, The Methodist Hospital Coordinating Center (TMHCC) and clinical site for a Multi-site Research Program
- 2009 - Present Sub-Investigator, The Institute of Research and Rehabilitation (TIRR)
A Reliability Study of the Quantitative Motor Assessment device (QMAD) in Spinal Cord Injury
- 2009 - Present Co-Investigator, The Methodist Hospital
Quantitative Measurement of Muscle Strength and Movement
- 2009 - Present Co-Investigator, The Methodist Hospital
An Atlas of the Cytoarchitecture of the Human Spinal Cord
- 2009 - Present Co-Investigator, The Methodist Hospital
Quantitative Measurement of Muscle Strength and Movement
- 2007 - Present Society of Clinical Research Associates (SOCRA)
- 2007 - Present Association of Clinical research Professionals (ACRP)

Certification

2009 Certified Clinical Research Professional (CCRP), SOCRA

C. Selected Peer-reviewed Publications

Grossman RG, Frankowski RF, Burau KD, Toups E, Johnson MM, Fehlings MG, Shaffrey CI, Harkema SJ, Hodes JE, Arabi B, Rosner MK, Guest JD, Harrop JS: Incidence and Severity of Acute Complications after Spinal Cord Injury. Submitted for publication In: Journal of Neurotrauma.

Grossman RG, **Toups E**, Frankowski R, Burau K, Howley S, for the NACTN Investigators, NACTN: Building a Clinical Trials Network for Spinal Cord Injury. In: *Essentials of Spinal Cord Injury*; Thieme (in press).

Krauss JL, Toups EG, Jankovic J, Grossman RG: Symptomatic and functional outcome of surgical treatment of cervical dystonia. J Neurosurgery psychiatry 63(5):642-648, 1997.

D. Research Support

Ongoing Research Support

BAA W81XWH-10-2-0042 Grossman (PI) 07//19/10 – 12/31/12
Building Infrastructure to Accelerate Transfer of Basic Research in Spinal Cord Injury to Clinical Practice: the North American Clinical Trials Network for Treatment of Spinal Cord Injury
Telemedicine and Advanced Technology Research Center (TATRC),
U.S. Army Medical Research and Materiel Command (USMRMC)
Department of Defense to the Christopher Reeve Foundation
The goal of this study is to incorporate the infrastructure and expertise to conduct clinical trials of new therapies for spinal cord injury.
Role: Project Manager

BAA W81XWH-07-1-0361 Grossman (PI) 05/14/07 – 05//14/09
North American Clinical Trials Network for Treatment of Spinal Cord Injury
Telemedicine and Advanced Technology Research Center (TATRC),

Program Director/Principal Investigator: Grossman, Robert George

U.S. Army Medical Research and Materiel Command (USMRMC)

Department of Defense to the Christopher Reeve Foundation

The goal of this project is to establish an infrastructure of university-affiliated departments of neurological surgery in North America engaged in clinical trials of new therapy for the treatment of spinal cord injury.

Role: Sr. Research Coordinator

Completed Research

Southwest Oncology Group Grossman (PI)

03/15/95 – 5/15/2000

Double Blind Randomized Trial of the Anti-Progestational Agent Mifepristone in the Treatment of Unresectable Meningioma, Phase III.

The goal of the study is to determine if mifepristone will prevent progression on benign aggressive

Role: Clinical Research Nurse II

CURRENT AND PENDING

Elizabeth G. Toups, MS, RN, CCRP

Current Support

BAA W81XWH-10-2-0042

Building Infrastructure to Accelerate transfer of basic research in spinal Cord Injury to clinical Practice: The North American clinical Trials Network for Treatment of Spinal Cord Injury
Telemedicine and Advanced Technology Research Center (TATRC),
U. S. Army Medical Research and Materiel Command (USMRMC)
Department of Defense to the Christopher Reeve Foundation
Principal Investigator: Grossman
Research Period: July 19, 2010 – 12/31/2012

The goal of this study is to incorporate the infrastructure and expertise to conduct clinical trials of new therapies for spinal cord injury

BAA W81XWH-07-1-0361

North American Clinical Trials Network for Treatment of Spinal Cord Injury
Telemedicine and Advanced Technology Research Center (TATRC),
U. S. Army Medical Research and Materiel Command (USMRMC)
Department of Defense to the Christopher Reeve Foundation
Principal Investigator: Grossman
Research Period: 05/014/07-12/31/12

The major goal of this project is to achieve clinical trials capable of indicating effectiveness of promising Spinal Cord Injury (SCI) therapies while ensuring patient safety. NACTN has created a network of hospitals that enrolls sufficient numbers of patients, defines and adheres to standard protocols and provides the infrastructure and highly skilled personnel to conduct trials of therapy for SCI.

- Specific Aim is to bring promising therapies form Spinal Cord Injury from the laboratory to clinical trials in a manner that will provide incontrovertible evidence of effectiveness, with maximum safety to patients undergoing treatment.

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Senior/Key Person			
Prefix:	First Name:	Julia	Middle Name:
Last Name:	Benoit		Suffix:
Position/Title:	Doctoral Candidate	Department:	Biostatistics
Organization Name:	Univ of Texas Health Sci Ctr School of Public Health	Division:	
Street 1:	1200 Herman Pressler St		
Street 2:	RAS Bldg E803D		
City:	Houston	County:	
State:	TX: Texas	Province:	
Country:	USA: UNITED STATES	Zip / Postal Code:	77030
Phone Number:	713-500-9558	Fax Number:	713-500-9530
E-Mail:	julia.s.benoit@uth.tmc.edu		
Credential, e.g., agency login	jsbenoit		
Project Role:	Other (Specify)	Other Project Role Category:	Nested New Investigator
Attach Biographical Sketch	Biosketch_Benoit.pdf		
Attach Current & Pending Support	Support_Benoit.pdf		

BIOGRAPHICAL SKETCH

NAME Julia Sanders Benoit	POSITION TITLE Doctoral candidate in biostatistics
eRA COMMONS USER NAME (credential, e.g., agency login) JSBENOIT	

EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)

INSTITUTION AND LOCATION	DEGREE (if applicable)	YEAR(s)	FIELD OF STUDY
McNeese State University, Lake Charles, LA	BS	1998-2003	Mathematics
University of Texas Health Science Center-School of Public Health, Houston, TX	M.S.	2003-2006	Biostatistics
University of Texas Health Science Center-School of Public Health, Houston, TX	Ph.D.	2007-present	Biostatistics

A. Personal Statement

While attending graduate school at the University of Texas Health Science Center at Houston, School of Public Health, I was on a Training Program in Biostatistics at UTHSCH-SPH (T32), funded by NIH, which gave me the opportunity to focus solely on my doctoral studies, where I took courses in Biostatistics, Epidemiology, and Occupational and Environmental Health Sciences as well as research ethics. It also allowed me the opportunities to engage in various research projects. These experiences have guided me in narrowing my research focus. I currently work on a brain trauma injury clinical trial that enrolls patients from two local hospitals. Working day to day with clinical trial biostatisticians, participating in phone calls with the PI, attending Data Safety and Monitoring Board (DSMB) meetings, handling statistical and ethical issues, and learning about the outcomes of severely injured patients have substantially helped build on the coursework I have taken in clinical trials, public health related ethics courses, and many biostatistics courses.

My dissertation research focuses on modeling longitudinal outcome data which may potentially be misclassified that can describe the dynamic characteristics of change over time in disease severity and allows for possible misclassification of stage of disease based on at least two latent variables. Using this model we will be able to estimate the probability of misclassification and to find the determinants of disease stage changes.

The opportunity to become a nested new investigator on a multi-site spinal cord injury clinical trial is a perfect fit for me. Although I have gained invaluable experience working with in a brain trauma injury clinical trial, I am ready to be challenged further with multiple sites, learning more about the regulatory aspect of clinical trials, all the while finding another way to apply my dissertation topic in public health.

My Biostatistics training thus far has given me a solid foundation to independently contribute to the development of statistical methodology in longitudinal studies and apply this method in many public health fields to improve the understanding of outcomes or processes that may be difficult to observe. I have worked diligently over the last several years to accomplish my goals, and I look forward to capitalizing on my prior skills and experiences during my previous training and work experience, enabling me to maximize my contribution to clinical trial public health research.

B. Positions and Honors

Positions and Employment

2010-present	Graduate Research Assistant, Division of Biostatistics, University of Health Science Center at Houston, School of Public Health, Houston, TX.
2007-present	Graduate student, Division of Biostatistics, University of Texas Health Science Center at Houston, School of Public Health, Houston, TX
2006-2007	Statistician, Michael & Susan Dell Center for Advancement of Healthy Living, University of Texas Health Science Center (Houston) School of Public Health, Houston, TX
2003-2006	Graduate student, Division of Biostatistics, University of Texas Health Science Center at Houston, School of Public Health, Houston, TX

Other Experience and Professional Memberships

Fall 2003	Teaching Assistant Biometry 1725 : Intermediate Biometric Methods I
Fall 2004	Teaching Assistant Biometry 1726: Intermediate Biometric Methods II
2004	Re search Assistant, M.D. Anderson Cancer Center, Houston, TX
2005-2006	Research Assistant, Michael & Susan Dell Center for Advancement of Healthy Living, University of Texas Health Science Center (Houston) School of Public Health, Houston, TX

2005-present Member, American Statistical Association

Honors

2007-Present Training Program in Biostatistics at UTHSCH-SPH funded by NIH
2004 Can cer Prevention Training Fellowship, M.D. Anderson Cancer Center, Houston, TX
1998-2002 H.C. Drew Academic Scholarship, McNeese State University, Lake Charles, LA

C. Publications

Hoelscher DM, Kelder SH, Pérez A, Day RS, **Benoit JS**, Frankowski RF, Walker JL, and Lee ES. "Changes in the Regional Prevalence of Child Obesity in 4th, 8th, and 11th Grade Students in Texas From 2000–2002 to 2004–2005". Obesity (2009) doi:10.1038/oby.2009.305

D. Current and Pending Support

Current Support

3P01NS5038660-10S1 PI: C. Robertson, Baylor College of Medicine 05/01/10-11/31/12 Graduate Assistant (50%)
NIH-NINDS UTSPH PI: B. Tilley Baylor College of Medicine Sub-contract
Effects of Erythropoietin on Vascular Dysfunction and Anemia in Traumatic Brain Injury

Pending Support

None

Current and Pending Support

Julia Benoit

Current Support

3P01NS5038660-10S1

Effects of Erythropoietin on Vascular Dysfunction and Anemia in Traumatic Brain Injury

Principal Investigator: C. Robertson, Baylor College of Medicine

Project Period: 05/01/10-11/31/12

Graduate Assistant (50%)

NIH-NINDS

UTSPH PI: B. Tilley Baylor College of Medicine Sub-contract

Pending Support

None

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Senior/Key Person			
Prefix:	Dr.	First Name: Susan	Middle Name: J
Last Name:	Harkema	Suffix:	
Position/Title:	Prof & Rehab Research Director	Department:	Neurosurgery
Organization Name:	University of Louisville/Frazier Rehab Inst.	Division:	
Street 1:	220 Abraham Flexner Way		
Street 2:	Suite 220		
City:	Louisville	County:	
State:	KY: Kentucky	Province:	
Country:	USA: UNITED STATES	Zip / Postal Code:	40202-3826
Phone Number:	505-581-8747	Fax Number:	502-582-7605
E-Mail:	susan.harkema@jhsmh.org		
Credential, e.g., agency login		harkema2	
Project Role:	Co-Investigator	Other Project Role Category:	
Attach Biographical Sketch	Biosketch_Harkema.pdf		
Attach Current & Pending Support	Support_Harkema.pdf		

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME Susan J. Harkema, PhD	POSITION TITLE Professor		
eRA COMMONS USER NAME (credential, e.g., agency login) harkema2			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	MM/YY	FIELD OF STUDY
Michigan State University, East Lansing, MI	BS	1987	Physiology
Michigan State University, East Lansing, MI	PhD	1993	Physiology
University of California, Los Angeles, CA	Postdoctoral	1993-95	Neurophysiology

A. Personal Statement

I am a Professor of Neurological Surgery and hold the Endowed Owsley B. Frazier Chair in Neurological Rehabilitation. I also serve as the Director of the Christopher and Dana Reeve Foundation NeuroRecovery Network. I have 12 years experience studying recovery of function and health in individuals with spinal cord injury. I have maintained an NIH funded research program since 1998 in neuroplasticity after human spinal cord injury and served as the Director of a NIH funded program project grant from 1998 – 2008. I am currently funded by grants from the NIH NCRR and NIBIB, the DOA, the Christopher and Dana Reeve Foundation, the Paralyzed Veterans Administration, and the Craig H. Neilsen Foundation. I have, and plan to continue, collaborations with other industry leaders both at the University of Louisville and on an international scale.

B. Positions and Honors

Positions and Employment

1995 – 1998	Assistant Research Neurologist, Department of Neurology and Brain Research Institute, University of California, Los Angeles
1998 – 2005	Assistant Professor in Residence, Department of Neurology and Brain Research Institute, University of California, Los Angeles
2005 – 2010	Associate Professor and Rehabilitation Research Director, Department of Neurological Surgery, University of Louisville, Kentucky
2005 – present	Owsley B. Frazier Chair in Neurological Rehabilitation, University of Louisville
2005 – present	Rehabilitation Research Director, Kentucky Spinal Cord Injury Research Center, University of Louisville
2005 – present	Director of Research, Frazier Rehab Institute, Louisville, Kentucky
2010 – present	Professor and Rehabilitation Research Director, Department of Neurological Surgery, University of Louisville, Kentucky

Other Experience and Professional Memberships

2004 – present	Director, Christopher & Dana Reeve Foundation NeuroRecovery Network
American Congress of Rehabilitation Medicine	American Spinal Injury Association
Society for Neuroscience	Society of Neurotrauma

Honors and Awards

2000	G. Heiner Sell Memorial Lectureship, American Spinal Cord Injury Association
2006	Louis E. Alley Memorial Lectureship, University of Iowa
2007	Women 4 Women Academic Honoree, University of Louisville
2007	SCI Hall of Fame Achievement in Research Quality of Life Award from the National Spinal Cord Injury Association
2007	Kentucky Spinal Cord Injury Research Center's Doctors' Ball Excellence in Research Award
2008	Estabrook Award from the Kessler Medical Rehabilitation Research and Education Corp
2009	Reeve-Irvine Research Medal from the Reeve-Irvine Research Center
2011	Rick Hansen Difference Maker Award from the Rick Hansen Foundation
2011	Popular Mechanics Breakthrough Award, Popular Mechanics Breakthrough Conference

C. Selected Peer-reviewed Publications (selected from 43 publications)

1. Harkema, SJ. (2008) Plasticity of interneural networks of the functionally isolated human spinal cord. *Brain Res Rev.* Jan;57(1):255-64.
2. Knikou M, Angeli C, Ferreira C, Harkema S. (2008) Soleus H-Reflex modulation during body weight support treadmill walking in spinal cord intact and injured subjects. *Exp Brain Res* Nov;193(3):397-407.
3. Forrest GF, Sisto SA, Barbeau H, Kirshblum S, Wilen J, Bond Q, Bentson S, Harkema S. (2008) Neuromotor and Musculoskeletal Responses to Locomotor Training for an Individual with Chronic Motor Complete, ASIA-B Spinal Cord Injury. *J Spinal Cord Med* 31(5):509-21.
4. Harkema SJ, Ferreira CK, van den Brand RJ, Krassioukov AV. (2008) Improvements in orthostatic instability with stand locomotor training in individuals with spinal cord injury. *J Neurotrauma* 2008 Dec;25(12):1467-75.
5. Datta S, Lorenz DJ, Morrison S, Ardolino E, Harkema SJ. (2009) A Multivariate Examination of Temporal Changes in Berg Balance Scale Items for Patients with ASIA Impairment Scale C and D Spinal Cord Injuries. *Arch Phys Med Rehabil* July;90(7):1208-1217.
6. Knikou M, Angeli C, Ferreira C, Harkema SJ. (2009) Flexion reflex modulation during stepping in human spinal cord injury. *Exp Brain Res* July;196(3):341-351.
7. Knikou M, Angeli C, Ferreira C, Harkema S. (2009) Soleus H-reflex gain, threshold, and amplitude as function of body posture and load in spinal cord intact and injured subjects. *Int J Neurosci* 119(11): 2056-2073.
8. Dy CJ, Gerasimenko YP, Edgerton VR, Dyhre-Poulsen P, Courtine G, and Harkema SJ. (2010) Phase dependent modulation of percutaneously elicited multisegmental muscle responses after spinal cord injury. *J Neurophysiol.* May; 103(5):2808-20.
9. McKay WB, Ovechkin AV, Vitaz TW, Terson De Paleville D, Harkema SJ. (2011) Long-lasting Involuntary Motor Activity in Acute Spinal Cord Injury. *Spinal Cord* Jan;49(1):87-93.
10. Galvez JA, Budovitch A, Harkema SJ, Reinkensmeyer DJ. (2011) Trainee variability during step training after spinal cord injury: Implications for robotic gait training device design. *J Rehabil Res Dev.* 48(2):147-60.
11. McKay WB, Ovechkin AV, Vitas TW, Terson De Paleville D, Harkema SJ. (2011) Neurophysiological Characterization of Motor Recovery in Acute Spinal Cord Injury. *Spinal Cord.* Mar;49(3):421-9.
12. Anderson KD, Acuff ME, Arp BG, Backus D, Chuna S, Fisher K, Fjerstad JE, Graves DE, Greenwald K, Groah SL, Harkema SJ, et al. (2011) United States (US) multi-center study to assess the validity and reliability of the Spinal Cord Independence Measure (SCIM III). *Spinal Cord.* Aug;49(8):880-5
13. Harkema S, Gerasimenko Y, Hodes J, Burdick J, Angeli C, Chen Y, Ferreira C, Willhite A, Rejc E, Edgerton VR. (2011) Epidural spinal stimulation enables independent standing and assisted stepping in a paraplegic human. *Lancet.* Jun 4;377(9781):1938-47.
14. Harkema SJ, Schmidt-Read M, Behrman AL, Bratta A, Sisto SA, Edgerton VR. Establishing the NeuroRecovery Network: Multi-site rehabilitation centers that provide activity-based therapies and assessments for neurologic disorders. *Archives of Physical Medicine and Rehabilitation.* In press.
15. Harkema SJ, Schmidt-Read M, Lorenz D, Edgerton VR, Behrman AL. Balance and ambulation improvements in individuals with chronic incomplete spinal cord injury using Locomotor Training-based rehabilitation. *Archives of Physical Medicine and Rehabilitation.* In press.

D. Research Support.

Ongoing Research Support

NRN-2008

Harkema (PI)

10/1/04-11/14/12

Center for Disease Control/Christopher & Dana Reeve Foundation

Development of NeuroRecovery Network (NRN) for functional, health and quality of life improvements after neurologic injury

The major goal of this project is to develop specialized centers that provide standardized activity-based therapy care based on current scientific and clinical evidence for people with spinal cord injury and other selected neurological disorders.

CTN4	Harkema (PI)	6/1/07-5/31/12
Department of Defense/Christopher & Dana Reeve Foundation		
North American Clinical Trials Network (NACTN)		
The major goal of this project is to achieve clinical trials capable of indicating effectiveness of promising spinal cord injury (SCI) therapies (i.e. Riluzole phase I study) while ensuring patient safety.		
R01 EB007615	Edgerton (PI), Harkema (Co-I)	9/1/08-8/31/13
National Institute of Health (NIBIB)		
Spinal epidural electrode array to facilitate standing and stepping after SCI		
The major goal of this research is to investigate the combined effects of stand and step (loco motor) training with electrical stimulation of the spinal cord in individuals who have had a complete SCI.		
NOA3-2010(SH)(6)	Harkema (PI)	10/1/10-9/30/12
Department of Defense/Christopher & Dana Reeve Foundation		
Natural progression and recovery of cardiovascular parameters following traumatic spinal cord injury		
The major goal of this project is to establish a data base with the natural progression and recovery of cardiovascular parameters in individuals with SCI; to establish the effect of the changes in arterial blood pressure on potential neurological recovery following traumatic SCI, and to develop guidelines on the acute monitoring and management of cardiovascular parameters for individuals with SCI.		
SC090246	Behrman (PI) Harkema (Co-I)	10/1/10-9/30/13
Department of Defense/University of Florida		
A new measure of neurological and behavioral recovery after SCI		
The major goal of this project is to Assess the responsiveness of the Phase System for evaluating recovery from SCI over the period of 1) in-patient rehabilitation (sub-acute SCI) receiving usual care and 2) outpatient rehabilitation (chronic SCI) while receiving an intense, activity-based therapy.		
	Harkema (PI)	12/01/10-11/30/11
Department of Defense/Christopher & Dana Reeve Foundation		
Brain Motor Control Assessment		
The major goal of this research is to cultivate an objective neurophysiological measurement tool that assesses motor and sensory neural recovery in individuals with SCI for use in multi-center clinical trials.		
357-01	Harkema (Co-I)	7/1/2011-6/30/2013
Kessler Foundation, Inc		
An activity-dependent rehabilitation model to improve bone and muscle for sub acute to chronic SCI: Intensive standing training with electrical stimulation.		
The major goal of this project is to examine the effectiveness of stand training with electrical stimulation to induce positive changes in bone.		
1P30RR031159-01	Harkema (PI – Core F)	4/1/11-3/31/16
National Institutes of Health (NCRR)		
Mechanisms of plasticity and repair after SCI		
This grant will support our Centers of Biomedical Research Excellence (COBRE) Core Facilities and extend their availability to other members of the University of Louisville neuroscience community. Dr. Harkema is the Director of the Human Translational Studies core.		
ES1-2011(SH)	Harkema (PI)	4/15/11-3/31/13
Christopher & Dana Reeve Foundation		
Facilitation of Standing and Stepping following SCI with Epidural Stimulation		
The major goal of this research is to investigate the combined effects of stand and step (locomotor) training with electrical stimulation of the spinal cord in individuals who have had a complete SCI.		
UF11142	Harkema (Co-I)	9/30/2010-10/29/2012
University of Florida		
Exercise dependent modulation of neurourological health following spinal cord injury		
The major goal is to test new methods to control voiding function in persons with spinal cord injuries (SCIs) to meet an important clinical need.		

H133N110007	Harkema (Co-I)	
US Dept. of Education		
Frazier Rehab & Neuroscience Spinal Cord Injury Model System (FRNSCIMS)		
The major goal of this research is to provide an integrated multidisciplinary system of rehabilitation care specifically designed to meet the needs of individuals with SCI.		
17R47982	Krassioukov (PI) Harkema (Co-I)	6/1/10-5/31/12
Paralyzed Veterans Administration/The University of British Columbia		
Autonomic Dysreflexia, and Health Care Practitioners' Knowledge		
The major goal of this study is to evaluate health care practitioner's prior knowledge of autonomic dysreflexia.		
<u>Completed Research Support (selected from 18 completed research grants)</u>		
5-14	Harkema (PI)	1/15/05-1/14/11
KY Spinal Cord & Head Injury Research Trust		
Cine Flow MRI in Human Spinal Cord Injury		
The major goal of this project is to determine whether CSF flow velocity is related to neurological & functional improvement in acute and chronic SCI, and to determine if C-MR provides an objective measure of quantitative functional continuity of the spinal cord. Also determine if current surgical interventions adequately decompress the spinal cord allowing restoration of normal flow post-operatively.		
R01 NS049954-05	Harkema (PI)	09/15/04-04/30/10
National Institute of Health (NINDS)		
Novel imaging and physiological evaluation of human SCI		
The major goal of this project is early application of novel, non-invasive imaging & electrophysiological techniques to predict functional outcome after spinal cord injury.		
R01 NS 049209	Harkema (PI)	4/1/05-3/31/10
National Institute of Health (NINDS)		
Plasticity of human spinal neural networks after injury		
The major goal of this project is to study clonus during manual stretch of the plantar flexors, standing and stepping in order to assess whether repetitive afferent input can alter the functional interneuronal organization of the human spinal cord.		
5-7	Harkema (PI)	1/15/06-1/14/10
Kentucky Spinal Cord Head & Injury Research Board		
Recovery of cardiovascular function after human spinal cord injury		
The major goal of this project is to evaluate the mechanisms involved in regulation of cardiovascular function in response to locomotor training in individuals with cervical and upper thoracic SCI.		
07B-30630SCR-E-0	Forrest (PI), Harkema (Co-I)	11/15/06-12/31/09
NJ Commission on Spinal Cord Research		
Standing retraining combined with functional electrical stimulation in incomplete SCI		
The major goals of this project are to address whether standing and FES will provide a greater level of neuromuscular and bone improvements compared to standing alone or FES alone and further enhance the responses of the neuromuscular and skeletal system of the lower limbs, to levels of limb loading and limb kinematics to modify motor output, increase muscle volume (MV) muscle torque around the joint, and locomotor capacity.		
UBC #17R69086	Krassioukov (PI), Harkema (Co-I)	7/1/08-6/30/10
ICORD		
Autonomic standards for the evaluation of individuals with SCI		
The major goal of this research is to provide a battery of test for clinicians and scientists working with individuals with SCI that can reliably and validly assess autonomic dysfunction in this population.		

OTHER SUPPORT
HARKEMA, SJ

ACTIVE

NRN-2008 Harkema Christopher Reeve Foundation Development of NeuroRecovery Network (NRN) for functional, health and quality of life improvements after neurologic injury The major goal of this project is to develop specialized centers that provide standardized activity-based rehabilitation care based on current scientific and clinical evidence for people with spinal cord injury and other selected neurological disorders.	10/05/04-11/14/11	2.40 calendar
CTN4 Harkema Christopher Reeve Foundation North American Clinical Trials Network The major goal of this project is to achieve clinical trials capable of indicating effectiveness of promising Spinal Cord Injury (SCI) therapies while ensuring patient safety. NACTN has created a network of hospitals that enrolls sufficient numbers of patients, defines and adheres to standard protocols and provides the infrastructure and highly skilled personnel to conduct trials of therapy for SCI.	06/01/07-05/31/12	1.20 calendar
R01 EB007615 Edgerton (PI) Harkema (Co-I) NIH NIBIB Spinal epidural electrode array to facilitate standing & stepping after SCI The major goal of this research is to investigate the combined effects of stand and step (loco motor) training with electrical stimulation of the spinal cord in individuals who have had a complete SCI.	09/01/08-08/31/13	1.80 calendar
NOA3-2010(SH) (6) Harkema Christopher & Dana Reeve Foundation Natural progression and recovery of cardiovascular parameters following traumatic spinal cord injury The major goal of this project is to establish a data base with the natural progression and recovery of cardiovascular parameters in individuals with SCI; to establish the effect of the changes in arterial blood pressure on potential neurological recovery following traumatic SCI, and to develop guidelines on the acute monitoring and management of cardiovascular parameters for individuals with SCI.	09/01/2010 – 08/31/2012	0.12 calendar
SC090246 Behrman (PI) Harkema (Co-I) University of Florida A new measure of neurological and behavioral recovery after SCI The major goal of this project is to Assess the responsiveness of the Phase System for evaluating recovery from SCI over the period of 1) in-patient rehabilitation (sub-acute SCI) receiving usual care and 2) outpatient rehabilitation (chronic SCI) while receiving an intense, activity-based therapy.	09/30/2010-08/31/2013	0.12 Calendar
NOA4-2010(SH) Harkema Christopher Reeve Foundation Brain Motor Control Assessment The major goal of this research is to cultivate an objective neurophysiological measurement tool that assesses motor and sensory neural recovery in individuals with SCI for use in multi-center clinical trials	10/01/2010-09/30/2011	0.12 calendar
ES1-2010(SH) Harkema Christopher & Dana Reeve Foundation Epidural Stimulation Project Facilitation of Standing and Stepping following SCI with Epidural Stimulation. The major goal of this research is to investigate the combined effects of stand and step (locomotor) training with electrical stimulation of the spinal cord in individuals who have had a complete SCI.	04/01/2011-03/31/2013	3.0 calendar

Hubscher (PI) Harkema (Co-I) Department of the Army Exercise-dependent modulation of neuromuscular health following spinal cord injury The major goal is to test new methods to control voiding function in persons with spinal cord injuries (SCIs) to meet an important clinical need.	08/15/2011-08/14/2014	0.60 calendar
1P30RR031159-01 (Whittemore) (Harkema Core Director) NIH NCRR Mechanisms of plasticity and repair after SCI This grant will support our Centers of Biomedical Research Excellence (COBRE) Core Facilities and extend their availability to other members of the University of Louisville neuroscience community. Dr. Harkema is the Director of the Human Translational Studies Core.	06/01/10-05/30/15	0.60 calendar
#357-01 Forrest (PI) Harkema (Co-I) Kessler Foundation, Inc An activity-dependent rehabilitation model to improve bone and muscle for subacute to chronic SCI: Intensive standing training with electrical stimulation The major goal is to examine the effectiveness of stand training with electrical stimulation to induce positive change in bone.	01/01/2011-12/31/2013	0.24 calendar
17R47982 Krassioukov (PI) Harkema (Co-I) The University of British Columbia Autonomic dysreflexia and health care practitioners' knowledge Introduce an educational tool (the ABC's of AD course) to health care practitioners to improve the early diagnosis and appropriate management of life threatening autonomic dysreflexia.	06/01/2010-05/31/2012	0.12 calendar
Graves (PI) Harkema (Co-I) NIDRR Spinal Cord Injury Model System The major goal of this project is to establish a Model System of spinal cord medicine to provide integrated multidisciplinary system of rehabilitation care specifically designed to meet the needs of individuals with spinal cord injury.	10/01/2011-09/30/2016	0.60 calendar
<u>PENDING</u>		
Edgerton (PI) Harkema (Co-I) NIH NIBIB Supplement Spinal epidural electrode array to facilitate standing & stepping after SCI The major goal of this research is to investigate the combined effects of stand and step (locomotor) training with electrical stimulation of the spinal cord in individuals who have had a complete SCI.	07/01/2011-08/31/2012	0.36 calendar
Harkema (PI) Boakye (Co-I) KSCHIRT Neurophysiological assessment of residual supraspinal input after human spinal cord injury The major goal of this project is to develop quantitative, sensitive tools to measure neuroplasticity in the human after injury to detect change preceding functional changes.	02/01/2012-01/31/2015	0.60 calendar

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Senior/Key Person			
Prefix:	Dr.	First Name:	Keith
		Middle Name:	D
Last Name:	Bureau	Suffix:	
Position/Title:	Assoc. Prof of Biostatistics	Department:	
Organization Name:	Univ of Texas School of Public Health	Division:	
Street 1:	1200 Herman Presler		
Street 2:	Data Management Center		
City:	Houston	County:	
State:	TX: Texas	Province:	
Country:	USA: UNITED STATES	Zip / Postal Code:	77030-3900
Phone Number:	713-500-9472	Fax Number:	713-500-9442
E-Mail:	keith.c.bureau@uth.tmc.edu		
Credential, e.g., agency login		kbureau	
Project Role:	Co-Investigator	Other Project Role Category:	
Attach Biographical Sketch	Biosketch_Bureau.pdf		
Attach Current & Pending Support	Support_Bureau.pdf		

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME Burau, Keith D.	POSITION TITLE Associate Professor of Biostatistics		
eRA COMMONS USER NAME (credential, e.g., agency login) kburau			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	MM/YY	FIELD OF STUDY
Southwest Minnesota State University	B.A.	1973	Biology and Health
University of Minnesota	M.S.	1975	Biometry and HIS
University of Minnesota	Ph.D.	1980	Biometry and HIS

A. Personal Statement

Dr Burau has over 30 years of experience managing very large data files, including VCG analyses, 7-day/24 hour uterine activity analyses, occupational cohort analyses, SEER registry and more recently Medicare data bases. He has been Co-PI, since 2004, for the North American Clinical Trial Network (NACTN), an ongoing registry of Spinal Cord Injury data, and is currently the primary data systems architect and analyst for a Phase I study of the safety of Riluzole following acute SCI. He is also a Co-investigator in a Phase III clinical trial of Parkinson Disease. He has supervised data processing efforts for over 25 years and has taught graduate school courses in SAS data management for approximately 15 years. He has extensive experience with clinical trial data management systems and analysis programs, in particular Stata and SAS. His data management and statistical analysis experience provides a strong contribution to this grant application. Dr. Burau will be the PI of the Biostatistical Center and will coordinate and oversee all data analyses required in the grant.

B. Positions and Honors

Positions and Employment

1975-1978 NIEHS Fellowship, University of Minnesota, Department of Biometry and Health Information Systems
1978-1980 Applications Programmer, University of Minnesota
1980-1983 Programmer Analyst III, The University of Texas, School of Public Health
1983-2002 Assistant Professor of Biometry, The University of Texas, School of Public Health, Houston, TX
2002- Associate Professor of Biometry, The University of Texas, School of Public Health, Houston, TX

Other Experience and Professional Memberships

1980- Membership, American Association for the Advancement of Science
1983- Membership, American Statistical Association
1983- Membership, American Association of University Professors

Honors

1994-2000 Excellence in Scholarship Incentive Award, UTSPH.
2001-2003 Excellence in Research Incentive Award, UTSPH.
2003 Nominee for Faculty Mentoring Award, Committee on the Status of Women, UTSPH.
2003-2004 Excellence in Scholarship Incentive Award, UTSPH.
2004 Alumni Achievement Award, Southwest Minnesota State University
2007-2010 Excellence in Teaching Incentive Award, UTSPH.

C. Selected Peer-reviewed Publications (Selected from 55 peer-reviewed publications)

Brown LM, Mason TJ, Pickle LW, Stewart PA, Buffler PA, Burau KD, Ziegler RG and Fraumeni JF Jr, 1988. Occupational risk factors for laryngeal cancer on the Texas Gulf Coast. Cancer Res 48:1960-1964.

Buffler PA, Cooper SP, Stinnet S, Contant C, Shirts S, Hardy R, Agu V, Gehen B, Burau KD, 1988. Air pollution and lung cancer mortality in Harris County, Texas 1979-1981. Am J Epidemiol 128:683-699.

Moore TR, Iams JD, Creasy RK, BURAU KD, Davidson AL, 1994. Diurnal and gestational patterns of uterine activity in normal human pregnancy. Obstet Gynecol 83:517-523.

Cooper SP, Labarthe D, Downs T, Burau KD, Whitehead L, Vernon S, Spitz M, New B, Sigurdson A, 1997. Cancer mortality among petroleum refinery and chemical manufacturing workers in Texas. J Environ Pathol Toxicol Oncol 16:1-14.

Cooper SP, Sigurdson A, Labarthe D, Whitehead L, Downs T, Burau KD, Vernon SW, Spitz M, New B, 1998. Assessing the burden of cancer in Texas using vital statistics data. South Med J 91:173-181.

Burau KD, Huang B, Whitehead LW, Delclos GM and Downs TD, 1998. A system linking occupation history questionnaire data and magnetic field monitoring data. J Expo Anal Environ Epidemiology 8:231-252.

Hoque A, Sigurdson AJ, Burau KD, Humphrey HB, Hess KR, Sweeney AM, 1998. Cancer among a Michigan cohort exposed to polybrominated biphenyls in 1973. Epidemiology. 9:373-378.

Sweeney AM, Symanski E, Burau KD, Kim Y, Humphrey HEB, Smith MA, 2001. Changes in serum PBB and PCB levels over time among women of varying ages at exposure. Environ Res 86:128-139.

Okcu MF, Goodman KJ, Carozza SE, Weiss NS, Burau KD, Bleyer WA, Cooper SP, 2002. Birth weight, ethnicity and occurrence of cancer in children: a population-based, incident case-control study in the state of Texas, USA. Cancer Causes Control 13:595-602.

Du XL, Chan W, Giordano S, Geraci JM, Delclos GL, Burau KD, Fang S, 2005 Variation in modes of chemotherapy for breast cancer and association with hospitalization for chemotherapy-related toxicity. Cancer 104:913-24.

White A**, Liu CC**, Xia R**, BURAU KD, Cormier JN, Chan W, Du XL, 2008. Racial disparities and treatment trends in a large cohort of elderly African American and Caucasians with colorectal cancer, 1991 to 2002. Cancer 11:3400-9..

Wang M**, BURAU KD, Fang S, Wang H, 2008. Ethnic variations in diagnosis, treatment, socioeconomic status and survival in elderly patients with non-hodgkin's lymphoma, cancer. Cancer 113:321-41.

Hardy D, Liu CC**, Xia R**, Cormier JN, Chan W, BURAU K, Du XL, 2009. Racial disparities and treatment trends in a large cohort of elderly black and white patients with non-small cell lung cancer. Cancer 115: 2199-211.

Nurgalieva Z, Xia R**, Liu CC**, BURAU KD, Hardy D**, Du XL, 2009. Risk of chemotherapy- induced peripheral neuropathy in large population-based cohorts of elderly patients with breast, ovarian and lung cancer: Am J Ther 17: 148-58.

Du XL, Xia R, BURAU K, Liu CC. Cardiac toxicity associated with anthracycline-containing chemotherapy in older women with breast cancer, 2009. Cancer 115: 5849-51.

D. Research Support:

Current Support:

5R01HS016743-04 PI: Du 4/1/2007 - 3/31/2012 1.20 Cal. months (10%)

AHRQ

Postmarketing Surveillance of Toxicities Associated with Cancer Chemotherapy

This project analyzes the updated SEER-Medicare data for women diagnosed with breast and ovarian cancer, and for men and women diagnosed with colorectal and lung cancer from 1992 to 2002 in the eleven SEER areas across the United States.

5U01NS043127-11 PI: Tilley 7/1/2009 - 11/30/2011 6.00 Cal. months (50%)

NIH

Parkinson's Disease Clinical Trial: Statistical Center

Dr. Tilley provides expertise in clinical trials and statistical analysis of the long-term trial of Creatine (LS-1), the phase II futility trial of pioglitazone (FS-Zone), and the recently completed FS-1 and FSTOO futility studies. She provides general expertise in the recruitment and retention of participants to the Clinical Coordinating Center. Investigators develop and characterize outcome measures and review articles on innovative outcome measures such as UPSIT, MOCA, etc., for their validity and appropriateness for inclusion as secondary or exploratory measures. One primary aim is to develop innovative statistical approaches, and develop procedures for monitoring quality control and participant safety and conduct analysis of the data.

CTN7-2011 (RF) PI: Frankowski 1/1/2010 - 12/31/2011 1.92 Cal. months (16%)

CRF

North American Clinical Trial Network for the Treatment of Spinal Cord Injury

The goal of the project is to bring promising therapies for spinal cord injury from the laboratory to clinical trials in a manner that will provide evidence of effectiveness, with maximum safety to patients undergoing treatment. There are two components; a spinal cord injury acute care registry and a phase I safety trial of Riluzole that involves nine North American Clinical Centers and a Biostatistical and Data Coordinating Center located in the University of Texas School of Public Health..

Pending Support:

1/1/2012 - 12/31/2014 1.20 Cal. months (10%)

PI: Du

ACS /

Role of Health Insurance in Cancer, Screening, Treatment & Survival in Texas

This project will study how the lack of health insurance and low income relate to the receipt of screening for cancer and the receipt of recommended therapy in Texas. We will identify patients (without personal identifiers) diagnosed with breast and colorectal cancer at age 40 or older between 2001 and 2009 from the Texas Cancer Registry.

Current Research Support

Current Support: 4/1/2007 - 3/31/2012 1.20 Cal. months (10%)

5R01HS016743-04 PI:

Du

AHRQ

Postmarketing Surveillance of Toxicities Associated with Cancer Chemotherapy

This project analyzes the updated SEER-Medicare data for women diagnosed with breast and ovarian cancer, and for men and women diagnosed with colorectal and lung cancer from 1992 to 2002 in the eleven SEER areas across the United States.

5U01NS043127-11 PI: 7/1/2009 - 11/30/2011 6.00 Cal. months (50%)

Tilley

NIH

Parkinson's Disease Clinical Trial: Statistical Center

Dr. Tilley provides expertise in clinical trials and statistical analysis of the long-term trial of Creatine (LS-1), the phase II futility trial of pioglitazone (FS-Zone), and the recently completed FS-1 and FSTOO futility studies. She provides general expertise in the recruitment and retention of participants to the Clinical Coordinating Center. Investigators develop and characterize outcome measures and review articles on innovative outcome measures such as UPSIT, MOCA, etc., for their validity and appropriateness for inclusion as secondary or exploratory measures. One primary aim is to develop innovative statistical approaches, and develop procedures for monitoring quality control and participant safety and conduct analysis of the data.

CTN7-2011 (RF) PI: 1/1/2010 - 12/31/2011 1.92 Cal. months (16%)

Frankowski

CRF

North American Clinical Trial Network for the Treatment of Spinal Cord Injury

The goal of the project is to bring promising therapies for spinal cord injury from the laboratory to clinical trials in a manner that will provide evidence of effectiveness, with maximum safety to patients undergoing treatment. There are two components; a spinal cord injury acute care registry and a phase I safety trial of Riluzole that involves nine North American Clinical Centers and a Biostatistical and Data Coordinating Center located in the University of Texas School of Public Health..

Pending Support:

PI: Du 1/1/2012 - 12/31/2014 1.20 Cal. months (10%)

ACS /

Role of Health Insurance in Cancer, Screening, Treatment & Survival in Texas

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RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Senior/Key Person			
Prefix:	Dr.	First Name:	Bizhan
Last Name:	Aarabi	Middle Name:	
Position/Title:	Professor	Department:	Neurosurgery
Organization Name:	University of Maryland	Division:	
Street 1:	22 South Greene Street		
Street 2:	S12D		
City:	Baltimore	County:	
State:	MD: Maryland	Province:	
Country:	USA: UNITED STATES	Zip / Postal Code:	21201-1508
Phone Number:	410-328-3162	Fax Number:	
E-Mail:	baarabi@smail.umaryland.edu		
Credential, e.g., agency login		baarabi	
Project Role:	Other (Specify)	Other Project Role Category:	Site Investigator
Attach Biographical Sketch	Biosketch_Aarabi.pdf		
Attach Current & Pending Support	Support_Aarabi.pdf		

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME Bizhan Aarabi, MD	POSITION TITLE Professor, University of Maryland, Department of Neurosurgery Director of Neurotrauma, R. Adams Cowley Shock		
eRA COMMONS USER NAME (credential, e.g., agency login) baarabi			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	MM/YY	FIELD OF STUDY
Shiraz University School of Arts & Sciences, Shiraz, Iran	Premed	1965-1967	Premed
Shiraz University Medical School, Shiraz, Iran	M.D.	1967-1973	Medicine
Cook County Hospital, Chicago, IL	Internship	1973-1974	Internship
The Johns Hopkins Hospital, Baltimore, MD	Neurosurgery	1974-1979	Residency

As the director of Neuro trauma at the Department of Neurosurgery and at the Shock Trauma Center I have had the opportunity to investigate traumatic cervical spinal cord injuries through multiple grants. I have worked extensively on acute traumatic central cord syndrome and the participated in studies focused on the timing of spinal cord decompression following trauma. Please see the biblio.

B. Positions and Honors. List in chronological order previous positions, concluding with your present position. List any honors. Include present membership on any Federal Government public advisory committee.

POSITIONS

1979 -1990	Associate Professor, Neurosurgery Shiraz University of Medical Sciences
1990 – 1995	Professor and Chairman, Neurosurgery Division Shiraz University of Medical Sciences
8/89, 7/90, 5/92	Visiting Professorship, Neurosurgery Section University of Nebraska Medical Center
1995 - 2000	Associate Professor, Neurosurgery Section University of Nebraska Medical Center
3/2000 - Present	Director of Neurotrauma R Adams Cowley Shock Trauma Center
5/2001 - Present	Associate Professor, Department of Neurosurgery University of Maryland School of Medicine
7/2008 - Present	Professor, Department of Neurosurgery University of Maryland School of Medicine

HONORS

1973	Pahlavi University Medical Award (Valedictorian)
1987	First Prize Award for "Traumatic aneurysms due to missile head wounds"
2001-2004,	R Adams Cowley Shock Trauma Center Hero Award
2006-2007, 2010	

C. Selected Peer-reviewed Publications.

1. **Aarabi B**, Chesler D, Maulucci C, Blacklock T and Alexander M: Dynamic of subdural hygroma following decompressive craniectomy: a comparative study. *Neurosurg Focus*, June 2009.
2. **Aarabi B**, Simard M: Traumatic brain injury. *Curr Opin Crit Care* 15(6):548-553, 2009.
3. Kahraman S, Dutton RP, Hu P, Xiao Y, **Aarabi B**, Stein DM, Scalea TM: Automated Measurement of "Pressure Times Time Dose" of Intracranial hypertension best predicts outcome after severe traumatic brain injury. *J Trauma* 69 July (1): 110-118, 2009.
4. Stein DM, Menaker J, McQuillan K, Handley C, **Aarabi B**, Scalea TM: Risk factors for organ dysfunction and failure in patients with acute traumatic cervical spinal cord injury. *Neurocritical Care* Aug 13 (1):29-39, 2010.
5. Lenehan B, Fisher CG, Vaccaro A, Fehlings M, **Aarabi B**, Dvorak MF: The urgency of surgical decompression in acute central cord injuries with spondylosis and without instability. *Spine* (Phila Pa 1976). 2010 Oct 1;35(21 Suppl):S180-6.PMID: 20881460.
6. Fehlings MG, Rabin D, Sears W, Cadotte DW, **Aarabi B**: Current practice in the timing of surgical intervention in spinal cord injury. *Spine* (Phila Pa 1976). 2010 Oct 1;35(21 Suppl):S166.
7. Furlan JC, Kailaya-Vasan A, **Aarabi B**, Fehlings MG: A Novel Approach to Quantitatively Assess Posttraumatic Cervical Spinal Canal Compromise and Spinal Cord Compression: A Multicenter Responsiveness Study. *Spine* (Phila Pa 1976). 2010 Dec 29.
8. **Aarabi B**, Alexander M, Mirvis SE, Shanmuganathan K, Chesler D, Maulucci C, Iguchi M, Aresco C, Blacklock T. Predictors of outcome in acute traumatic central cord syndrome due to spinal stenosis. *J Neurosurg Spine*. 2011 Jan;14(1):122-30.
9. Dutton RP, Prior K, Cohen R, Wade C, Sewell J, Fouche Y, Stein D, **Aarabi B**, Scalea TM. Diagnosing mild traumatic brain injury: where are we now? *J.Trauma*. 2011 Mar;70 (3):554-9.
10. Stein DM, Kufera JA, Lindell A, Murdock KR, Menaker J, Bochicchio GV, **Aarabi B**, Scalea TM. Association of CSF Biomarkers and Secondary Insults Following Severe Traumatic Brain Injury. *Neurocrit Care*. 2011 Apr 14(2):200-7.
11. Furlan JC, Kailaya-Vasan A, **Aarabi B**, Fehlings MG. A novel approach to quantitatively assess post-traumatic cervical spinal canal compromise and spinal cord compression: a multicenter responsiveness study. *Spine*. 2011 May 1;36(10): 784-93.
12. Stein DM, Lindell A, Murdock KR, Kufera JA, Menaker J, Keledjian K, Bochicchio GV, **Aarabi B**, Scalea TM. Relationship of serum and cerebrospinal fluid biomarkers with intracranial hypertension and cerebral hypoperfusion after severe traumatic brain injury. *J. Trauma*. 2011 May; 70(5):1096-103.
13. Bono CM, Schoenfeld A, Gupta G, Harrop JS, Anderson P, Patel AA, Dimar J, **Aarabi B**, Dailey A, Vaccaro AR, Gahr R, Shaffrey C, Anderson DG, Rampersaud R. Reliability and Reproducibility of Subaxial Cervical Injury Description System: A Standardized Nomenclature Schema. *Spine*. 2011 August 1;36(17):E1140-E1144.
14. Stein BM, Hu PF, Brenner M, Sheth KN, Liu KH, Xiong W, **Aarabi B**, Scalea TM. Brief episodes of intracranial hypertension and cerebral hypoperfusion are associated with poor functional outcome after severe traumatic brain injury. *J. Trauma*. 2011 Aug;71(2):L364-74.

15. Cheran S, Shanmuganathan K, Zhuo J, Mirvis SE, **Aarabi B**, Alexander MT, Gullapalli RP. Correlation of MR Diffusion Tensor Imaging Parameters with ASIA Motor Scores in Hemorrhagic Acute Spinal Cord Injury. *J.Neurotrauma*. 2011 August 29. PMID: 21875333 [Epub ahead of print]

D. Research Support. List both selected ongoing and completed (during the last three years) research projects (Federal or non-Federal support). Begin with the projects that are most relevant to the research proposed in this application. Briefly indicate the overall goals of the projects and responsibilities of the senior/key person identified

07/2005- 07/2013	Principal Investigator (3%) "North American Clinical Trials Network (NACTN) for Treatment of Spinal Cord Injury" Christopher and Dana Reese Foundation NCT00178724; CTN1-2004(RG); W81XWH-07-1/0361
07/2007- 12/2012	Co-Investigator (15%) PI: H.M. Eisenberg "Citicoline Brain Injury Treatment Trial (CORBIT)" Eunice Kennedy Shriver National Institute of Child and Health and Human Development @NIH NCT00545662; BA-HD042, HD042687-04, HD042738-05, HD042678-03, HD042653-05, HD042689-05, HD042736-04, HD 042686-01A1, HD042652-04, HD042823-05
04/2010- 08/2012	Principal Investigator (3%) "Safety and Pharmacokinetics of Riluzole in Patients With Traumatic Acute Spinal Cord Injury" Christopher and Dana Reeve Foundation and The Department of Defense ID #HP-40687; IND 79,600; NCT00876889
2011-2013	Co-Investigator PI: H.M. Eisenberg "Glyburide: A Randomized, Placebo-Controlled Treatment Study of Glyburide in Ischemic Stroke" Department of Defense/USA MPMC Contract#W81XWH-08-2-0159
2011-2012	Co-Investigator PI: H.M. Eisenberg "Serum Biomarkers: Correlation between biomarkers, MR imaging, and six month ASIA exam in spinal cord injury patients" Department of Defense ID# 10492195

CURRENT AND PENDING

Bizhan Aarabi, MD

Current Support

BAA W81XWH-10-2-0042

Building Infrastructure to Accelerate transfer of basic research in spinal Cord Injury to clinical Practice: The North American clinical Trials Network for Treatment of Spinal Cord Injury Telemedicine and Advanced Technology Research Center (TATRC),
U. S. Army Medical Research and Materiel Command (USMRMC)
Department of Defense to the Christopher Reeve Foundation
Principal Investigator: Aarabi
Research Period: June 11, 2010 – May 31, 2012

The goal of this study is to incorporate the infrastructure and expertise to conduct clinical trials of new therapies for spinal cord injury

BAA W81XWH-07-1-0361

North American Clinical Trials Network for Treatment of Spinal Cord Injury
Telemedicine and Advanced Technology Research Center (TATRC),
U. S. Army Medical Research and Materiel Command (USMRMC)
Department of Defense to the Christopher Reeve Foundation
Principal Investigator: Aarabi
Research Period: June 01, 2011- May 31, 2012

The major goal of this project is to achieve clinical trials capable of indicating effectiveness of promising Spinal Cord Injury (SCI) therapies while ensuring patient safety. NACTN has created a network of hospitals that enrolls sufficient numbers of patients, defines and adheres to standard protocols and provides the infrastructure and highly skilled personnel to conduct trials of therapy for SCI.

- Specific Aim is to bring promising therapies form Spinal Cord Injury from the laboratory to clinical trials in a manner that will provide incontrovertible evidence of effectiveness, with maximum safety to patients undergoing treatment.

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Senior/Key Person			
Prefix:	First Name:	Rhonda	Middle Name:
Last Name:	Abbott		Suffix:
Position/Title:	Dir. Therapy Services	Department:	Therapy Services
Organization Name:	The Institute for Rehabilitation & Research	Division:	
Street 1:	1333 Moursund		
Street 2:	A-222		
City:	Houston	County:	
State:	TX: Texas	Province:	
Country:	USA: UNITED STATES	Zip / Postal Code:	77030
Phone Number:	713-797-5718	Fax Number:	
E-Mail:	rhonda.abbott@memorialhermann.org		
Credential, e.g., agency login			
Project Role:	Other (Specify)	Other Project Role Category:	Site Investigator
Attach Biographical Sketch	Biosketch_Abbott.pdf		
Attach Current & Pending Support	Support_Abbott.pdf		

BIOGRAPHICAL SKETCH

Provide the following information for ALL key personnel.

For Post-doctoral Fellowships, a separate biosketch for the Mentor/Sponsor is required as well as a biosketch for the Fellow.

NAME: Rhonda Abbott, PT	POSITION TITLE: Director of Therapy Services Director of Clinical Programs		
EDUCATION/TRAINING - Begin with baccalaureate or other initial professional education, such as nursing. Include postdoctoral training and residency training if applicable.			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	YEAR(s) (MM/YYYY)	FIELD OF STUDY
Texas A&M University, College Station, Texas Texas Woman's University	BS MS	1998 2001	Biomedical Science Physical Therapy

Current Duties – Provide a brief description of the duties performed under the Position Title listed above.

Leader for 120 personnel department encompassing all therapy staff including: Music Therapy, Therapeutic Recreation, Occupational Therapy, Physical Therapy, Speech Language Pathology, and Patient Escort services. Provide oversight for staffing, team development, budget, equipment purchases, orientation, performance, goal setting and measurement. As Director of Clinical Programs, provide oversight and leadership to the Brain Injury and Stroke, Spinal Cord Injury (SCI), and Specialty Rehabilitation Programs which includes outcome review, program development, family and patient education programs, and research collaboration. Lead our Weekend Program development.

Personal Statement - Briefly describe why your experience and qualifications make you well-suited for your role with the proposed project.

I have been employed at TIRR for all 10 years of my therapy career and began as a Physical Therapist on our SCI unit. During that time, I participated in one of the earliest Locomotor Training courses as this treatment modality was being developed. Following this training, I returned to TIRR and developed team training, orientation, and patient treatment plans using the body weight support treadmill system. I treated patients frequently using this intervention and also taught clinicians and students to be able to implement the strategies as well. Upon promotion to Supervisor for the SCI PT team, we continued to develop our program with Locomotor Training and pursued involvement in the CDRF NRN program based on our past experiences. I have been involved in this program since the inception of it at TIRR and have participated in annual meetings in the capacity of Finance Administrator as well.

Date	Positions/Honors – List in chronological order previous positions, concluding with present position.
2001	Physical Therapist
2004	Supervisor, SCI PT team
2007	Manager of SCI OT and PT team
2008	Director of Therapy Services, Director of Clinical Programs

Date	Selected Peer-Reviewed Publications - Please list in chronological order beginning with the most recent publications.

Date	Research Support - <i>Please provide your last five years of funding as well as all current funding.</i>
2006-2011	Christopher & Dana Reeve Foundation <i>CDRF NeuroRecovery Network</i>
1972-2011	NIDRR <i>Spinal Cord Injury Model System</i>

Research Support

2006-2011	Christopher & Dana Reeve Foundation <i>CDRF NeuroRecovery Network</i>
1972-2011	NIDRR <i>Spinal Cord Injury Model System</i>

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Senior/Key Person			
Prefix:	First Name:	Kimberly	Middle Name: N
Last Name:	Atkinson	Suffix:	
Position/Title:	Dir., Spinal Cord Medicine Program	Department:	Frazier NeurRecovery Network
Organization Name:	Frazier Rehab Institute	Division:	
Street 1:	220 Abraham Flexner Way		
Street 2:			
City:	Louisville	County:	
State:	KY: Kentucky	Province:	
Country:	USA: UNITED STATES	Zip / Postal Code:	50202-3826
Phone Number:	502-582-7658	Fax Number:	
E-Mail:	kimberly.atkinson@jhsmh.org		
Credential, e.g., agency login			
Project Role:	Other (Specify)	Other Project Role Category:	Site Investigator
Attach Biographical Sketch	Biosketch_Atkinson.pdf		
Attach Current & Pending Support	Support_Atkinson.pdf		

BIOGRAPHICAL SKETCH

Provide the following information for ALL key personnel.

For Post-doctoral Fellowships, a separate biosketch for the Mentor/Sponsor is required as well as a biosketch for the Fellow.
DO NOT EXCEED FOUR (4) PAGES.

NAME: Kimberly N Atkinson, PT, MPT, NCS	POSITION TITLE: Director, Spinal Cord Medicine Program Director, Frazier NeuroRecovery Network Center

EDUCATION/TRAINING - Begin with baccalaureate or other initial professional education, such as nursing. Include postdoctoral training and residency training if applicable.

INSTITUTION AND LOCATION	DEGREE (if applicable)	YEAR(s) (MM/YYYY)	FIELD OF STUDY
Texas A&M University, College Station, TX	BS	1999	Microbiology
University of Texas Southwestern Medical Center, Dallas, TX	MPT	2002	Physical Therapy

Current Duties – Provide a brief description of the duties performed under the Position Title listed above.

As Director of Frazier’s Spinal Cord Medicine Program, responsibilities include budgeting, personnel management, operations and strategic development of the outpatient spinal cord injury therapy services (PT, OT and SLP) and the Assistive Technology Resource Center (including w/c seating and mobility clinic, augmentative communication, and adaptive computer access). As well as, program growth and development for the inpatient Spinal Cord Medicine Programs at Frazier for continuum of care improvement.

NeuroRecovery Network (NRN) Center Director- manage the IRB submissions and revision for collaborative grants sought out through NRN partnerships, facilitate the implementation of protocols into the clinical setting, and collaborate with other center Directors to identify future network activities.

Personal Statement - Briefly describe why your experience and qualifications make you well-suited for your role with the proposed project.

As collaborating Director with other NRN sites, I have the experience and support of the Network to perform the roles described within the grant application.

Date	Positions/Honors – List in chronological order previous positions, concluding with present position.
Positions	
2002 – 2003	HealthSouth Rehabilitation Hospital, Humble, TX – Staff physical therapist
2003 – 2010	TIRR Memorial Hermann Hospital, Houston, TX – Spinal cord injury program staff physical therapist, PT III
2008 – 2010	TIRR Memorial Hermann Hospital, Houston, TX – Physical Therapist III, Center Coordinator for Clinical Education, Program Director for Neurologic Physical Therapy Residency Program
2010 – present	Frazier Rehab Institute, Louisville, KY – Director, Spinal Cord Medicine Program
Honors	
2008	TIRR Memorial Hermann Employee of the year nominee

Date	Selected Peer-Reviewed Publications - <i>Please list in chronological order beginning with the most recent publications.</i>

Date	Research Support - <i>Please provide your last five years of funding as well as all current funding.</i>
2006-2011	Christopher & Dana Reeve Foundation <i>CDRF NeuroRecovery Network</i>
10/1/11- 9/30/16	US Dept. of Education <i>Frazier Rehab & Neuroscience Spinal Cord Injury Model System (FRNSCIMS)</i>

Kimberly N Atkinson

Research Support

2006-2011

Christopher & Dana Reeve Foundation
CDRF NeuroRecovery Network

10/1/11- 9/30/16

US Dept. of Education
*Frazier Rehab & Neuroscience Spinal Cord Injury Model System
(FRNSCIMS)*

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Senior/Key Person			
Prefix:	Dr.	First Name:	Maxwell
Last Name:	Boakye	Middle Name:	
Position/Title:	Associate Professor	Department:	Neurosurgery
Organization Name:	Other Employer	Division:	
Street 1:	University of Louisville		
Street 2:	220 Abraham Flexner Way		
City:	Louisville	County:	
State:	KY: Kentucky	Province:	
Country:	USA: UNITED STATES	Zip / Postal Code:	40202-3826
Phone Number:	502-540-3694	Fax Number:	
E-Mail:	max.boakye@louisville.edu		
Credential, e.g., agency login			
Project Role:	Other (Specify)	Other Project Role Category:	Site Investigator
Attach Biographical Sketch	Biosketch_Boakye.pdf		
Attach Current & Pending Support	Support_Boakye.pdf		

BIOGRAPHICAL SKETCH

NAME Maxwell Boakye	POSITION TITLE Associate Professor		
eRA COMMONS USER NAME (credential, e.g., agency login) Maxwell.Boakye			
EDUCATION/TRAINING			
INSTITUTION AND LOCATION	DEGREE (if applicable)	MM/YY	FIELD OF STUDY
Rutgers University, Newark, NJ	BA	1989	Mathematics and Physics
Cornell University Medical College, New York, NY	MD	1995	Medicine
Upstate Medical University, Syracuse, NY	Residency	1995-2002	Neurological Surgery
Emory Healthcare, Atlanta, GA	Fellowship	2002-2003	Spinal Neurosurgery
Memorial Sloan Kettering Cancer Center, New York, NY	Fellowship	2003	Spinal Oncology
Johns Hopkins Bloomberg School of Public Health	MPH	12/2011	Outcomes and Health services research

A. Personal Statement

As a neurosurgeon, I have devoted my clinical and research career to taking care of patients with spinal disorders and spinal cord injury patients and performing outcomes and health services research. I have extensive experience with Outcomes Research and was Director of the Outcomes research lab at Stanford University and the Palo Alto VA from 2003-2010. I have completed the American College of Surgeons surgical outcomes research course and the Harvard school of public health outcomes research course and have completed 57 credits of 80 credits MPH program with focus on epidemiology, biostatistics, comparative effectiveness and outcomes research at Johns Hopkins Bloomberg School of Public Health. I will complete requirements for my MPH degree in December 2011. I am currently the director of spinal Neurological Surgery at the University of Louisville and the Nelson Endowed Chair in outcomes and translational research. I am Principal Investigator of a VA cooperative studies trial comparing laminectomy and X-stop for lumbar stenosis treatment which is in final developmental phase, and university of Louisville site director of the North American Clinical trials network (NACTN). I have published extensively with data from a variety of administrative databases including the Nationwide Inpatient Sample (NIS) databases, state inpatient and VA NSQIP databases. I am also developer and manager of department-wide Neurosurgery outcomes research registry at the Center for Advanced neurosurgery at the University of Louisville and principal investigator of University of Louisville pilot site for the American Association of Neurological surgeons national outcomes registry.

B. Positions and Honors

1992	Howard Hughes – National Institutes of Health Research Scholar, Laboratory of Surgical Neurology, National Institutes of Health (NIH)
1992 - 1994	Howard Hughes – National Institutes of Health Research Scholar, Laboratory of Adaptive Systems, National Institutes of Health (NIH)
2003 - 2010	Assistant Professor, Department of Neurosurgery, Stanford University, Palo Alto, CA
2003 - 2010	Attending Neurosurgeon, Surgical Service, VA Palo Alto Health Care System, Palo Alto, CA

2004 - 2010 Director, Neural Plasticity Lab, Stanford University/VA Palo Alto Health Care System, Palo Alto, CA

2004 - 2010 Director, Outcomes research Lab, Stanford University/VA Palo Alto Health Care System, Palo Alto, CA

2011 - Present Associate Professor, Center for Advanced Neurosurgery, University of Louisville

2011 - Present Director, Spinal Neurological Surgery, University of Louisville, Frazier Rehab Hospital, Louisville, KY

2011 - Present Nelson Endowed Chair, Outcomes and translational research, center for Advanced Neurosurgery, university of Louisville, KY

Honors:

1989 Phi Beta Kappa

1989 Recipient, Betty Skuse Thompson Physics Honors Prize, Rutgers University

1992-1994 Howard Hughes – National Institutes of Health Research Scholar

1994-1995 Recipient, Howard Hughes Medical Institute Continued Fellowship Support Award,

1995 Recipient, Outstanding Research Prize, Cornell Medical College

1996 Best Surgical Intern, Medical Students Choice, Upstate Medical University

2004 Young Clinician Investigator Award (Declined), American Association of Neurological Surgeons (AANS), National Research Educational Foundation (NREF)

2005 Stanford University Center of Excellence Faculty Award

2007 Stanford School of Medicine Dean's Faculty Fellow

2007-2008 America's Top Surgeons, Consumer's research Council of America

C. Selected Peer-reviewed Publications

1. Patil CG, Lad SP, Santarelli J, **Boakye M**. National Inpatient Complications and Outcomes After Surgery For Spinal Metastasis from 1993-2002. *Cancer*. 2007; Aug 1;110(3):625-30.
2. **Boakye M**, Mummaneni P, Hai d R, Rodt s G. Anterior cervical spine fusion using polyetheretherketone (PEEK) cage and bone morphogenetic protein (BMP). *Journal of Neurosurgery, Spine* 2005;2(5):521-525.
3. **Boakye M**, Ho C, Patil CG, Santarelli J, Lad SP. Cervical Spondylotic Myelopathy: National Inpatient Complications and Outcomes After Spinal Fusion from 1993-2002. [Neurosurgery](#). 2008 Feb;62(2):455-61; discussion 461-2
4. **Boakye M**, Patil CG, Santarelli J, Ho C, Tian W, Lad SP. Laminectomy and fusion after spinal cord injury: national inpatient complications and outcomes. [J Neurotrauma](#). 2008 Mar;25(3):173-83
5. Patil CG, Patil TS, Lad SP, **Boakye M**. Complications and Outcomes after Spinal Cord Tumor Resection in the United States from 1993-2002. [Spinal Cord](#). 2008 May;46(5):375-9. Epub 2007 Dec 11
6. **Boakye M**, Patil CG, Ho C, Lad SP. Cervical corpectomy: complications and outcomes. [Neurosurgery](#). 2008 Oct;63(4 Suppl 2):295-301; discussion 301-2
7. Patil CG, Santarelli J, Lad SP, Ho C, Tian W, **Boakye M**. Inpatient complications, mortality, and discharge disposition after surgical correction of idiopathic scoliosis: a national perspective. [Spine J](#). 2008 Nov-Dec;8(6):904-10. Epub 2008 Mar 20
8. Lad SP, Patil CG, Berta S, Santarelli JG, Ho C, **Boakye M** National trends in spinal fusion for cervical spondylotic myelopathy [Surg Neurol](#). 2009 Jan;71(1):66-9; discussion 69. Epub 2008 Jun 2
9. Lad SP, Patil CG, Lad EM, Hayden MG, **Boakye M**. National trends in vertebral augmentation procedures for the treatment of vertebral compression fractures. [Surg Neurol](#). 2009 May;71(5):580-4; discussion 584-5. Epub 2008 Jun 2
10. Lad SP, **Boakye M** A socioeconomic survey of spinal cord stimulation (SCS) surgery, Accepted, *Neuromodulation*, 2010
11. Li G, Patil C, Lad SP, **Boakye M**. Effects of Age and Comorbidities on Complication Rates and Adverse Outcomes after Lumbar Laminectomy in Elderly Patients *Spine*. *Spine (Phila Pa 1976)*. 2008 May 15;33(11):1250-5
12. Veeravagu A, Patil CG, Lad SP, **Boakye M** Risk factors for postoperative spinal wound infections after spinal decompression and fusion surgeries [Spine \(Phila Pa 1976\)](#). 2009 Aug 1;34(17):1869-72

13. Kalanithi PS, Patil CG, **Boakye M** National complication rates and disposition after posterior lumbar fusion for acquired spondylolisthesis [Spine \(Phila Pa 1976\)](#). 2009 Aug 15;34(18):1963-9
14. Kalanithi PS, **Boakye M** Traumatic Epidural Hematoma: Trends in National Mortality and Cost from 1993-2006, AANS Neurosurgeon Bulletin, Vol 19:2, 29-33, 2010
15. Lad SP, Patil CG, **Boakye M**. Trends in median, ulnar, radial, and brachial plexus injuries in the United States, Neurosurgery 66(5):953-960, 2010
16. Robert T. Arrigo, Paul Kalanithi, Ivan Cheng, Todd Alamin, Eugene J. Carragee, Stefan A. Mindea, Jongsoo Park, **Maxwell Boakye** Predictors of Survival following Surgical Treatment of Spinal Metastasis, Accepted Neurosurgery 2010
17. Robert T. Arrigo, Paul Kalanithi, **Maxwell Boakye** Is Cauda Equina Syndrome being Treated within the Recommended Timeframe?, Accepted, Neurosurgery, 2010
18. Lad SP, **Boakye M** Trends in the use of bone morphogenetic protein (BMP) as a substitute to autologous iliac crest bone grafting for spinal fusion procedures in the United States. Accepted, Spine, 2010
19. Robert T. Arrigo, Paul Kalanithi, Ivan Cheng, Todd Alamin, Eugene J. Carragee, Stefan A. Mindea, **Maxwell Boakye**, Jongsoo Park Charlson Score is a Robust Predictor of 30-Day Complications following Spinal Metastasis Surgery, Accepted, Spine 2010
20. Lad SP, **Boakye M** Socioeconomic trends in hospitalization for multiple sclerosis, Neuroepidemiology, 35(2):93-99, 2010

D. Research support

Ongoing Research Support

Grant Title: BDNF Polymorphism and TBS on Practice Dependent Plasticity in Lower Limb

Funding Source: VA RRD Merit

Duration: [7/1/10](#) - [6/30/13](#)

Grant: #F7208R

PI: Maxwell Boakye, MD

Completed Research Support

Grant Title: Differential Plasticity of Sensory and Motor Cortical Systems in Patients with Spinal Cord Injury

Funding Source: VA RRD Merit

Duration: [3/31/10](#) - [4/1/11](#)

Grant: #B6020

PI: Maxwell Boakye, MD

Grant Title: Spinal Plasticity after Central Nervous System Lesions

Funding Source: ICA FRANCE-STANFORD CENTER FOR INTERDISCIPLINARY STUDIES

Grant #: PTA # 1118826-100-GHBJA

Duration: [9/1/08](#) - [7/30/2009](#)

PI: Maxwell Boakye, MD

Grant Title: "Differential Plasticity of Sensory and Motor Cortical Systems in Patients with Spinal Cord Injury"

Funding Source: American Heart Association Beginning Grant-In-Aid Award

Grant: 0465013Y

Duration: [7/1/2004](#)-[6/30/2006](#)

E. PI: Maxwell Boakye, MD

Research support
Boakye, M.

Ongoing Research Support

Grant Title: BDNF Polymorphism and TBS on Practice Dependent Plasticity in Lower Limb

Funding Source: VA RRD Merit

Duration: 7/1/10 - 6/30/13

Grant: #F7208R

PI: Maxwell Boakye, MD

Grant Title: Differential Plasticity of Sensory and Motor Cortical Systems in Patients with Spinal Cord Injury

Funding Source: VA RRD Merit

Duration: 3/31/10 - 4/1/11

Grant: #B6020

PI: Maxwell Boakye, MD

Completed Research Support

Grant Title: Spinal Plasticity after Central Nervous System Lesions

Funding Source: ICA FRANCE-STANFORD CENTER FOR INTERDISCIPLINARY STUDIES

Grant #: PTA # 1118826-100-GHBJA

Duration: 9/1/08 - 7/30/2009

PI: Maxwell Boakye, MD

Grant Title: "Differential Plasticity of Sensory and Motor Cortical Systems in Patients with Spinal Cord Injury"

Funding Source: American Heart Association Beginning Grant-In-Aid Award

Grant: 0465013Y

Duration: 7/1/2004-6/30/2006

A. PI: Maxwell Boakye, MD

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Senior/Key Person			
Prefix:	Dr.	First Name: Michael	Middle Name:
Last Name:	Fehlings		Suffix:
Position/Title:	Medical Director, Krembil Neuroscience Prog.	Department:	Neurosurgery
Organization Name:	University of Toronto	Division:	
Street 1:	Toronto Western Hospital		
Street 2:	399 Bathurst St. W-449		
City:	Toronto	County:	
State:		Province:	ON
Country:	CAN: CANADA	Zip / Postal Code:	MST-2S8
Phone Number:	416-603-5627	Fax Number:	
E-Mail:	michael.fehlings@uhn.on.ca		
Credential, e.g., agency login		MFEHLINGS	
Project Role:	Other (Specify)	Other Project Role Category:	Site Investigator
Attach Biographical Sketch	Biosketch_Fehlings.pdf		
Attach Current & Pending Support	Support_Fehlings.pdf		

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.

Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME Fehlings, Michael George	POSITION TITLE		
eRA COMMONS USER NAME MFEHLINGS	Medical Director, Krembil Neuroscience Program		
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	YEAR(s)	FIELD OF STUDY
University of Toronto	M.D.	1983	Medicine
University of Toronto	Ph.D.	1989	Neuroscience
University of Toronto	F.R.C.S.C.	1990	Neurosurgery
NYU Medical Center	PDF	1992	Spinal Cord Injury

A. Personal Statement

I am the Medical Director of the Krembil Neuroscience Center, Head of the Spinal Program at the Toronto Western Hospital and a Professor of Neurosurgery at the University of Toronto. I hold the Krembil Chair in Neural Repair and Regeneration, am a Senior Scientist in the Division of Genetics and Development at the Toronto Western Research Institute, a Scientist at the McEwen Centre for Regenerative Medicine and a McLaughlin Scholar in Molecular Medicine. I combine an active clinical practice in complex spinal surgery with a translationally oriented research program focused on discovering novel treatments for spinal cord injury. I also lead a multi-disciplinary team of researchers which is examining the application of stem cells, nanotechnology and tissue engineering for spinal cord repair and regeneration. I am also a principal investigator in the Christopher and Dana Reeve Foundation North American Clinical Trials Network, am co-chair of the internationally renowned Spine Trauma Study Group and lead several international clinical research efforts through the AOSpine.

B. Positions and Honors**Positions and Employment**

1992-1997 Assistant Professor, Department of Surgery, University of Toronto, Toronto, ON
 1997-2000 Associate Professor, Department of Surgery, University of Toronto, Toronto, ON
 1994-present Director, Spinal Program, Toronto Western Hospital, Toronto, ON
 1997-present Senior Scientist, Toronto Western Research Institute, Toronto, ON
 1999-present Research Director, Division of Neurosurgery, University of Toronto, Toronto, ON
 2000-present Professor, Department of Surgery, University of Toronto, Toronto, ON
 2001-present Medical Director, Krembil Neuroscience Program, University Health Network, Toronto, ON
 2001-present Krembil Chair in Neural Repair and Regeneration, University Health Network, Toronto, ON
 2008-present Director, University of Toronto Neuroscience Program, University of Toronto, Toronto, ON
 2008-present Co-Director, University of Toronto Spine Program, University of Toronto, Toronto, ON

Selected Other Experience and Professional Memberships

1988-present Deputy Editor-in-Chief, Spine
 2006-2010 Chair, Joint Section of Neurotrauma & Critical Care, American Association of Neurological Surgeons
 2007-present Member, CIHR Team Grants A Scientific Review Panel
 2007-present Chair, Medal Award in Surgery Committee, Royal College of Physicians and Surgeons
 2007-present Chairman, AOSI Outcome & Clinical Research Committee, AOSpine International
 2008-2010 Chairman, Journal of Neurosurgery: Spine
 2009-present Associate Editor, Neurosurgery
 2010-present Deputy Editor Clinical Sciences, Evidence-Based Spine-Care Journal
 2010-present President-Elect, Cervical Spine Research Society
 2010-present Associate Director, Board of Directors, NeuroDevNet
 2010-present Director, International Research Development, Rick Hansen Institute

Honors

- 1996 Royal College of Physicians and Surgeons of Canada Gold Medal Award in Surgery
- 2001 Larson Award from the AANS/CNS
- 2003 Wightman-Berris Award for Individual Teaching Excellence, University of Toronto
- 2005 Cited in the Who's Who in Medical Sciences Education
- 2007 Lister Award for sustained excellence in research activities, Dept of Surgery, University of Toronto
- 2008 Wightman-Berris Award for Individual Teaching Excellence, University of Toronto
- 2009 Leon Wiltse Award for excellence in leadership and/or clinical research in spine care, North American Spine Society
- 2009 Olivecrona Award for important contributions in spinal cord injury research, Karolinska Institute, Stockholm Sweden

C. Selected Peer-Reviewed Publications (from Lifetime Total of 360; in chronological order)

h-index = 46, Total Number of Citations = 8,118 (based on Scopus)

1. Bracken MB, Shepard MJ, Holford TR, Leo-Summers L, Aldrich EF, Fazl M, Fehlings MG, Herr DL, Hitchon PW, Nockels RP, Pascale V, Perot PL, Piepmeier J, Sonntag V, Wagner F, Wilberger J, Winn HR, Young W. Administration of methylprednisolone for 24 or 48 hours or tirilazad mesylate for 48 hours in the treatment of acute spinal cord injury: Results of the third National Acute Spinal Cord Injury randomized controlled trial. JAMA 1997;277(20):1597-1604. PMID: 9168289
2. Bracken MB, Shepard MJ, Holford TR, Leo-Summers L, Aldrich EF, Fazl M, Fehlings MG, Herr DL, Hitchon PW, Nockels RP, Pascale V, Perot PL, Piepmeier J, Sonntag V, Wagner F, Wilberger J, Winn HR, Young W. Methylprednisolone or tirilazad mesylate administration after acute spinal cord injury: 1 year follow-up. Results of the third National Acute Spinal Cord Injury randomized controlled trial. J Neurosurg 1998;89(5):699-706. PMID: 9817404
3. Fehlings MG, Rao S, Tator C, Skaf G, Arnold P, Benzel E, Dickman C, Cuddy B, Green B, Hitchon P, Northrup B, Sonntag V, Wagner F, Wilberger J. The optimal radiological method to assess spinal canal compromise and cord compression in patients with cervical spinal cord injury. Part II: Results of a multicenter study. Spine 1999;24(14):605-613. PMID: 10101829
4. Anderson DK, Beattie M, Blesch A, Bresnahan J, Bunge M, Dietrich D, Dietz V, Dobkin B, Fawcett J, Fehlings M, Fischer I, Grossman R, Guest J, Hagg H, Hall ED, Houle J, Kleitman N, McDonald J, Murray M, Privat A, Reier P, Steeves J, Steward O, Tetzlaff W, Tuszynski MH, Waxman SG, Whittemore S, Wolpaw J, Young W, Zheng B. Editorial: Recommended guidelines for studies of human subjects with spinal cord injury. Spinal Cord 2005;43(8):453-8. PMID: 15824756
5. Fawcett JW, Curt A, Steeves JD, Coleman WP, Tuszynski MH, Lammertse D, Bartlett PF, Blight AR, Dietz V, Ditunno J, Dobkin BH, Havton LA, Ellaway PH, Fehlings MG, Privat A, Grossman R, Guest JD, Kleitman N, Nakamura M, Gaviria M, Short D. Guidelines for the conduct of clinical trials for spinal cord injury as developed by the ICCP panel: spontaneous recovery after spinal cord injury and statistical power needed for therapeutic clinical trials. Spinal Cord 2007;45(3):190-205. PMID: 17179973
6. Steeves JD, Lammertse D, Curt A, Fawcett JW, Tuszynski MH, Ditunno JF, Ellaway PH, Fehlings MG, Guest JD, Kleitman N, Bartlett PF, Blight AR, Dietz V, Dobkin BH, Grossman R, Short D, Nakamura M, Coleman WP, Gaviria M, Privat A. Guidelines for the conduct of clinical trials for spinal cord injury (SCI) as developed by the ICCP panel: clinical trial outcome measures. Spinal Cord 2007;45(3):206-21. PMID: 17179972
7. Hawryluk GWJ, Rowland JW, Fehlings MG. Protection and repair of the injured spinal cord: A review of completed, ongoing and planned clinical trials for acute spinal cord injury. Neurosurg Focus 2008;25(5):E14. PMID: 18980474
8. Kalsi-Ryan S, Curt A, Fehlings MG, Verrier MC. Assessment of the hand in tetraplegia using the Graded Redefined Assessment of Strength, Sensibility and Prehension (GRASSP): Impairment versus function. Top Spinal Cord Inj Rehabil 2009;14(4):34-46.
9. Wilson J, Fehlings MG. Emerging approaches to the surgical management of acute traumatic spinal cord injury. Neurotherapeutics. 2011;8(2):187-94. PMID: 21373951

10. Furlan JC, Noonan V, Cadotte DW, Fehlings MG. Timing of decompressive surgery of spinal cord after traumatic spinal cord injury: An evidence-based examination of pre-clinical and clinical studies. J Neurotrauma. 2011;28(8):1371-99. PMID: 20001726
11. Kalsi-Ryan S, Beaton D, Curt A, Duff S, Popovic M, Rudhe C, Fehlings M, Verrier M. The Graded Redefined Assessment of Strength Sensibility and Prehension (GRASSP) - Reliability and validity. J Neurotrauma (2011), doi: 10.1089/neu.2010.1504. PMID: 21568688

D. Research Support

Selected Ongoing Research Support

NetworksCentres of Excellence NeuroDevelopment Network (NeuroDevNet) A Canadian NCE dedicated to helping children overcome neurodevelopmental disorders by accelerating the pace of understanding disorders of brain development and to implement solutions that improve the lives of affected children and families. Role: Co-investigator	Goldowitz (PI)	12/31/09 -12/31/14
Krembil Foundation Spinal Cord Injury New Emerging Team (SCI-NET) Regenerative Medicine Project To support a new team with increased breadth in skills and expertise related to stem cell regenerative medicine, nanotechnology, tissue engineering, neurosurgical skills, rehabilitation and neural plasticity, as well as magnetic resonance imaging (MRI). Role: PI	Fehlings (PI)	06/01/11 - 05/30/14
National Institutes of Health (1R01NS052741-01A2) Regulation and function of kallikreins in spinal cord injury and repair To determine the dynamics and cellular specificity of expression of all 15 kallikreins in human and murine traumatic spinal cord injury. Role: Co-investigator	Scarisbrick (PI)	04/01/08 - 03/31/13
Canadian Institutes of Health Research (MOP-97852) Neuroprotective approaches to enhance recovery in cervical spondylotic myelopathy Transplantation of NPCs (rodent or human) in combination with growth factors, neuroprotective/anti-inflammatory strategies and approaches to target key inhibitory molecules in the glial scar, to promote functionally significant remyelination after severe SCI. Role: PI	Fehlings (PI)	10/01/09 - 09/30/12
Canadian Institutes of Health Research (NHG-99090) Investigation of induced pluripotent stem cells, derived by novel, non-viral transposition reprogramming, as a regenerative strategy for spinal cord remyelination Use of an improved method of generating induced pluripotent stem (iPS) cells using skin fibroblast cells as the source material to generate neural stem cells to regenerate myelin after SCI. Role: PI	Fehlings (PI)	10/01/09 - 09/30/12
McEwen Centre for Regenerative Medicine iPS derived neural stem cells and bioengineered strategies to treat chronic spinal cord injury To evaluate the combined therapeutic effects of a novel bioengineered drug delivery strategy (HAMC) to deliver growth factors and iPS cell-derived neural stem cells in animal models of chronic spinal cord injury, Role: PI	Fehlings (PI)	07/05/10 - 07/04/12
Physicians' Services Incorporated Foundation (10Q2119) A bioengineered approach to enhance recovery following severe traumatic spinal cord injury. To study if the subarachnoid delivery of hyaluronan and methyl cellulose (HAMC) will reduce cyst formation, attenuate glial scarring, promote sparing of neural tissue, enhance recovery of locomotor function and reduce neuropathic pain after severe SCI which is complicated by post traumatic syringomyelia. Role: PI	Fehlings (PI)	07/01/10 - 06/30/12

Canadian Institutes of Health Research (MOP-82782) Fehlings (PI) 04/01/07 - 03/31/12
Investigation and treatment of traumatic axonal dysfunction after spinal cord injury
Transplantation of NPCs (rodent or human) in combination with growth factors, neuroprotective/anti-inflammatory strategies and approaches to target key inhibitory molecules in the glial scar, to promote functionally significant remyelination after severe SCI.
Role: PI

Christopher Reeve Foundation (CTN7-2011 F-T) Fehlings (PI) 01/01/11 - 12/31/11
North American Clinical Trials Network for the Treatment of Spinal Cord Injury.
Establishment of a network of clinical centers treating SCI patients from the acute phase of injury through rehabilitation to provide control and experimental groups for trials of new therapy for SCI.
Role: PI

Selected Completed Research Support

Heart and Stroke Foundation (T 6328) Fehlings (PI) 07/01/08 - 06/30/11
The ischemic axon: cross-talk with myelin in K⁺ channel terms.
To identify the mechanisms by which the ischemic oligodendrocyte signals through the internodal myelin to cause dysfunction in axons.
Role: PI

Christopher Reeve Foundation (KB1-0807-2) Karimi (PI) 01/01/09 - 12/31/10
A combinatorial strategy to optimize neural repair and plasticity after chronic spinal cord injury
The combined strategy will involve transplantation of adult neural stem cells, promotion of neural stem cell survival, approaches to block the inhibitory components of the glial scar and intensive rehabilitation therapy.
Role: Co-investigator

Christopher Reeve Foundation (CTN6-2010 F-T) Fehlings (PI) 01/01/10 - 12/31/10
North American Clinical Trials Network for the Treatment of Spinal Cord Injury.
Establishment of a network of clinical centers treating SCI patients from the acute phase of injury through rehabilitation to provide control and experimental groups for trials of new therapy for SCI.
Role: PI

Craig H. Neilsen Foundation Karimi (PI) 09/01/08 - 08/31/10
Combinatorial therapeutic approaches to promote repair mechanisms mediated by endogenous neural stem/progenitor cells after spinal cord injury
To potentiate the repair capabilities of endogenous NPCs in the adult injured spinal cord by a multifaceted therapeutic approach including growth factor treatments, pharmacological approaches to attenuate the inhibitory properties of the glial scar and physical rehabilitation.
Role: Co-investigator

Canadian Institutes of Health Research (KWS-99421) Fehlings (PI) 09/01/09 - 08/31/10
Global Blueprint Stakeholders Conference for Stem Cell Translation
To provide a vehicle to engage key international stakeholders -- including scientists, NGO's, policy makers and industry -- to gain consensus regarding best practices for the translation and knowledge mobilization of stem cells for spinal cord injury.
Role: PI

Canadian Institutes of Health Research (RMF-72552) Fehlings (PI) 10/01/04 - 09/30/09
Regenerative medicine strategies for spinal cord injury repair: Integration of stem cell biology, nanotechnology, bioengineering approaches and neurosurgical application
A new emerging team integrating the application of cell-adhesive tubular constructs and neural stem cells for spinal cord repair and regeneration with novel bio-engineered drug delivery systems for the optimization of cell survival after SCI.
Role: PI

Sources of current funding:

Michael G. Fehlings

1. **Title:** NeuroDevelopment Network (NeuroDevNet)
Funding Source: Networks of Centres of Excellence
Grant Number:
Support Period: 12/31/09-12/31/14
2. **Title:** Regulation and function of kallikreins in spinal cord injury and repair
Funding Source: National Institutes of Health
Grant Number: 1R01NS052741-01A2
Support Period: 04/01/08-03/31/13
3. **Title:** The living myelin sheath: functional organization and role in dynamic modulation of axonal function in CNS
Funding Source: Natural Science and Engineering Research Council of Canada
Grant Number: 313400
Support Period: 04/01/08-03/31/13
4. **Title:** Building the UHN Advanced Therapeutics Research Platform
Funding Source: Canada Foundation for Innovation
Grant Number:
Support Period: 11/01/08-10/31/12
5. **Title:** Neuroprotective approaches to enhance recovery in cervical spondylotic myelopathy
Funding Source: Canadian Institutes of Health Research
Grant Number: MOP-97852
Support Period: 10/01/09-09/30/12
6. **Title:** Investigation of induced pluripotent stem cells, derived by novel, non-viral transposition reprogramming, as a regenerative strategy for spinal cord remyelination
Funding Source: Canadian Institutes of Health Research
Grant Number: NHG-99090
Support Period: 10/01/09-09/30/12
7. **Title:** Psychometric testing of a new scale measuring medical outcomes of dysphagia (MOD) in adult patients with swallowing disorders secondary to head and neck cancer
Funding Source: Canadian Cancer Society Research Institute
Grant Number: 020190
Support Period: 07/01/09-06/30/12
8. **Title:** A bioengineered approach to enhance recovery following severe traumatic spinal cord injury
Funding Source: Physicians' Services Incorporated Foundation
Grant Number: 10Q2119
Support Period: 07/01/10 - 06/30/12
9. **Title:** iPS derived neural stem cells and bioengineered strategies to treat chronic spinal cord

Sources of current funding:

Michael G. Fehlings

injury

Funding Source: McEwen Centre for Molecular Medicine

Grant Number: n/a

Support Period: 07/01/10 - 06/30/12

10. **Title:** Investigation of human piggyback induced pluripotent stem cells for repair and regeneration of the injured cervical spinal cord

Funding Source: Wing for Life Spinal Cord Research Foundation

Grant Number: WFL-CA-003/11

Support Period: 07/01/11 - 06/30/12

11. **Title:** Investigation and treatment of traumatic axonal dysfunction after spinal cord injury

Funding Source: Canadian Institutes of Health Research

Grant Number: MOP-82782

Support Period: 04/01/07-03/31/12

12. **Title:** Psychometric testing of a new scale measuring medical outcomes of dysphagia (MOD) in adult patients with swallowing disorders secondary to stroke, cervical spine abnormalities and head and neck cancer

Funding Source: Canadian Institutes of Health Research

Grant Number: MOP-93685

Support Period: 04/01/09-03/31/12

13. **Title:** North American Clinical Trials Network for the Treatment of Spinal Cord Injury

Funding Source: Christopher Reeve Foundation

Grant Number: CTN7-2011 (F/T)

Support Period: 01/01/11-12/31/11

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Senior/Key Person			
Prefix:	Dr.	First Name:	James
		Middle Name:	D
Last Name:	Guest	Suffix:	
Position/Title:		Department:	
Organization Name:	University of Miami	Division:	
Street 1:	1095 NW 14th Terrace		
Street 2:			
City:	Miami	County:	
State:	FL: Florida	Province:	
Country:	USA: UNITED STATES	Zip / Postal Code:	33136-1060
Phone Number:	305-575-7059	Fax Number:	
E-Mail:	jguest@med.miami.edu		
Credential, e.g., agency login			
Project Role:	Other (Specify)	Other Project Role Category:	Site Investigator
Attach Biographical Sketch	Biosketch_Guest.pdf		
Attach Current & Pending Support	Support_Guest.pdf		

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME James D. Guest	POSITION TITLE Associate Professor of Neurological Surgery at the University of Miami and the Miami Project to Cure Paralysis		
eRA COMMONS USER NAME (credential, e.g., agency login) jguest			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	MM/YY	FIELD OF STUDY
University of Alberta, Edmonton, Alberta, Canada	BA	Graduated 6/83	Economics and Political Science, Asian studies
University of Alberta, Edmonton, Alberta, Canada	BSc	Graduated 6/85	Chemistry and Biology
University of Alberta, Edmonton, Alberta, Canada	MD	Graduated 6/12/89	Medicine
University of British Columbia, Vancouver, BC, Canada	Residency	7/90 to 6/98	Neurosurgery
University of Miami, Miami, Florida, USA	PhD	6/93- 6/98	Neuroscience
Barrow Neurosurgical Institute, Phoenix, AZ	Fellowship	7/98 to 6/99	Spinal Neurosurgery

A. Personal Statement

The current primary focus of the Guest lab is on the transplantation of autologous glial cells to repair spinal cord injuries. This focus was established during PhD training with the thesis "The potential for human Schwann cell grafts to influence spinal cord regeneration in the nude rat" The ability of transplanted glia including Schwann cells and olfactory ensheathing glia to ensheath, remyelinate, induce sprouting of axons and lead to changes in neurological recovery have the main questions under investigation. Our secondary focus is on neuroprotection and we have conducted studies of hypothermia in the past. We utilize several types of animal models with an emphasis on solving translational questions related to human clinical application. We have developed expertise in the use of large animal models including Yucatan minipigs and primates. We also emphasize minimally-invasive surgical lesion-making and transplantation techniques. Sophisticated outcome assessment techniques have been developed to evaluate transplant effects in both the acute and chronic state of injury. These include kinematic assessment of hand function and gait, electrophysiologic study of conduction across lesion sites, and sensory testing. Other areas of research include studies of human post-mortem spinal cord tissue, intraoperative human spinal cord conduction studies, and research design for human clinical trials. Clinical practice has been in the domain of spinal surgery with emphases on chronic spinal cord injury, spine and spinal cord pain problems, and the use of minimally-invasive techniques.

B. Positions and Honors

Positions and Employment

7/98-6/99	Attending Neurosurgeon and Spine Fellow to Volker Sonntag, MD St. Joseph's Hospital, Phoenix, AZ
7/98-6/99.	Attending Neurosurgeon Scottsdale Memorial North Hospital, Scottsdale, AZ
7/99-12/01	Attending Neurosurgeon West Palm Beach VA Medical Center. West Palm Beach, FL
7/99-Present	Attending Neurosurgeon Miami VA Medical Center. Miami, FL, Jackson Memorial Hospital, Miami, FL.
8/99 –11/2005	Assistant Professor, Neurosurgery

University of Miami and the Miami Project to Cure Paralysis. Miami, Florida
 11/2005- present Associate Professor, Neurosurgery
 University of Miami and the Miami Project to Cure Paralysis. Miami, Florida
 5/2004- present Neuroscience Graduate Program, University of Miami, Florida.
 6/2008-present Special Government Employee, FDA, CBER

Honors and Awards

Dr. H.E Weinlos Award in Medicine. 1989.
 Rick Hansen Man in Motion Foundation Fellowship 1994.
 Research Fellowship of the Research Foundation of the American Assoc. of Neurological Surgeons. 1994-96.
 K.G. McKenzie award in basic neuroscience research. 1995.
 WB and MH Chung Lectureship, Best Resident Research Presentation. University of British Columbia. 1997.
 Award of Academic Merit, University of Miami Graduate School. 1999.
 Outstanding Scientists of the 21st Century, International Biographical Center.2008.
 Marquis. Who's Who in America, 2009.
 Robson Award, International Spinal Research Trust, 2009.
 Meritorious Service Award. American Spinal Injury Association, 2011.

C. Peer-reviewed Publications. Last 3 years.

1. A Grading System To Evaluate Objectively the Strength of Pre-Clinical Data of Acute Neuroprotective Therapies for Clinical Translation in Spinal Cord Injury B Kwon, E Okon, E Tsai, M Beattie, J Bresnahan, D Magnuson, P Reier, D McTigue, P Popovich, A Blight, M Oudega, **J Guest**, L Weaver, M Fehlings, W Tetlaff. J Neurotrauma 28: 1525-1543, 2011.
2. Grossman RG, Frankowski RF, Burau KD, Toup EG, Crommett JW, Johnson MM, Fehlings MJ, Tator CH, Shaffrey CI, Harkema SJ, Hodes JE, Aarabi B, Rosner MK, **Guest JD**, Harrop JS. Incidence and Severity of Acute Complications after Spinal Cord Injury. J Neurotrauma, 2011 (under final review).
3. J Steeves, J Kramer, J Fawcett, J Cragg, D Lammertse, A Blight, RMarino, J Ditunno, Jr., W Coleman, F Geisler, **J Guest**, L Jones, S Burns, M Schubert, H van Hedel. Armin Curt for the EM-SCI Study Group Extent of spontaneous motor recovery after traumatic cervical sensorimotor complete spinal cord injury. Spinal Cord (49):257-265, 2011.
4. **Guest JD**, Benavides F, Padgett K, Mendez E, Tovar D. Technical aspects of spinal cord injections for cell transplantation. Clinical and translational considerations. Brain Res Bull. 84(4-5):267-79, 2011.
5. J Zariffa, J Kramer, J Fawcett, D Lammertse, A Blight, **J Guest**, L Jones, S Burns, and M Schubert, M Bolliger, A Curt for the EM-SCI Study Group, J Steeves. Characterization of neurological recovery following traumatic sensorimotor complete thoracic spinal cord injury. Spinal Cord 49(3):463-71, 2011.
6. Kim KN, **Guest JD**, Oh JS, Pennant WA, Yoon do H, Ha Y. Effect of primate bone marrow stromal cells on survival and neurite outgrowth. Neuroreport 21(13):877-81, 2010.
7. Kwon BK, Okon EB, Tsai E, Beattie MS, Bresnahan J, Magnuson DS, Reier PJ, McTigue DM, Popovich P, Oudega M, Blight AR, **Guest JD**, Weaver L, Fehlings M, Tetzlaff WA. Grading System to Objectively Evaluate the Strength of Preclinical Data of Acute Neuroprotective Therapies for Clinical Translation in Spinal Cord Injury. J Neurotrauma, 2010 (Epub ahead of print).
8. **Guest JD**, Anderson K. Hopes and Illusions. A comment on Stem Cell Tourism and the Power of Hope by Charles E Murdoch and Christopher Thomas Scott. Ameri. J. Bioethics 10(5) 46-48, 2010.
9. O Nesic, **JD Guest**, D Zivadinovic, Ponnada A. Narayana, JJ. Herrera, RJ. Grill, VU.L. Mokkapati, BB. Gelman Julieann Lee Aquaporins in spinal cord injury. The Janus face of AQP4. Neurosci. 168:4, 1019-1035, 2010.
10. A Blight A,Curt A,Ditunno J, Dobkin B, Ellaway P, Fawcett J, Fehlings M, Grossman R, Lammertse D, Privat A, Steeves J, Tuszyński M, Kalichman M, **Guest, JD**. Position statement on the sale of unproven cellular therapies for spinal cord injury The International Campaign for Cures of Spinal Cord Injury Paralysis. Spinal Cord 47(5) 427-428, 2009.
11. Benglis, D.M., **Guest JD**, M.Y. Wang, Clinical feasibility of minimally invasive cervical laminoplasty. Neurosurg. Focus 25(2): p. E3, 2008.
12. **Guest JD**, Herrera L, Margitich I, Oliveria M, Marcillo A, Casas CE. Xenografts of expanded primate olfactory ensheathing glia support transient behavioral recovery that is independent of serotonergic or corticospinal axonal regeneration in nude rats following spinal. Exp. Neurol. 212(2) 261-274, 2008.

D. Research Support

Ongoing Research Support

1. **Sponsor:** North American Clinical Trials Network
Topic: Database and Riluzole study
Site Principal Investigator

2008-2011
2. **Sponsor** International Spinal Research Trust
Topic. Comparison of Schwann cells and Skin-derived precursor cells for repair of demyelination in the primate corticospinal tract.
Principal Investigator
3. **Sponsor.** US Department of Defense
Topic. SC090411P2 Schwann cell (SC) implantation for SCI repair: optimization of dosing, long-term cell persistence and the evaluation of toxicity and tumorigenicity.
Co-Investigator

Completed Research Support (most relevant)

Sponsor: International Spinal Research Trust
Topic: Generation and testing of human ensheathing glia for spinal cord transplantation.
(Shared with P Wood, MB Bunge, NK Kleitman)
2004-2005: no-cost extension after original end date with no additional funds granted.
Grant #: NET002
Sponsor: US Army Medical Research
Topic: Neuroprotection, The effects of various levels of epidural perfusion hypothermia on spinal cord blood flow. (Contract # W81XWH-05-1-0061)
Nov 2004-Nov 2005

Percent Effort: 30%
UM Account #: 66098M
Sponsor: Ralph Wilson Medical Research Foundation
Topic: Autologous Transplantation of primate ensheathing glia into the transected medullary pyramid of the primate.
2001-2002

CURRENT & PENDING SUPPORT

Guest, James D.

ACTIVE

- **Title:** Safety and Pharmacokinetics of Riluzole in Patients with Traumatic Acute SCI
- **Time commitments:** 20% effort (PI)
- **Supporting Agency:** Christopher Reeve Foundation
- **Name and address of the Funding Agency's Procuring Contracting/Grants Officer:** Susan P. Howley, Executive Vice President, Research - 636 Morris Turnpike, Ste. 3A - Short Hills, NJ 07078
- **Performance period:** 06/01/11 – 05/31/12
-
- **Brief description of the project's goals:** The primary goal of this study is to develop acute care safety and pharmacokinetic profiles of riluzole in patients who have sustained a traumatic spinal cord injury. Secondary objectives are to conduct exploratory analyses of functional outcomes for purposes of planning a subsequent Phase II b – Phase III randomized study of the efficiency of Riluzole for the treatment of acute spinal cord injury.
- **List of specific aims:**
 1. To evaluate the safety and preliminary efficacy of riluzole in patients with acute spinal cord injury.
 2. To collect information about efficacy outcomes in SCI subjects treated with riluzole.
 3. To obtain information about pharmacokinetics and pharmacodynamics of riluzole and relate that information to toxicity and efficacy outcomes.
-
- **Title:** Schwann Cell (SC) Implantation for SCI Repair: Optimization of Dosing, Long-Term Cell Persistence, and the Evaluation of Toxicity and Tumorigenicity
- **Time commitments:** 15% effort (PI)
- **Supporting Agency:** USA Med Research Acq Activity
- **Name and address of the Funding Agency's Procuring Contracting/Grants Officer:** Kathy Robinson, Contract Specialist, USA Med Research Acq Activity, 820 Chandler St., Fort Detrick, MD 21702-5014
- **Performance period:** 09/15/2010 – 10/14/2013
-
- **Title:** Autologous Transplantation of Schwann Cells & Skin-Derived Schwann Cell Presursors to Repair the Chronically Damaged Primate Corticospinal Tract
- **Time commitments:** 6% effort (PI)
- **Supporting Agency:** International Spinal Research Trust
- **Name and address of the Funding Agency's Procuring Contracting/Grants Officer:** 8a Bramley Business Centre, Station Road, Bramley, Guildford, Surrey GU5 0AZ, UK
- **Performance period:** 03/01/2010 – 02/28/2013
-

Overlap

None

PENDING

None

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Senior/Key Person			
Prefix:	First Name: James	Middle Name: S	
Last Name: Harrop		Suffix:	
Position/Title:	Department:		
Organization Name: Thomas Jefferson University	Division:		
Street 1: 909 Walnut St.			
Street 2: Suite 300			
City: Philadelphia	County:		
State: PA: Pennsylvania	Province:		
Country: USA: UNITED STATES	Zip / Postal Code: 19107-5211		
Phone Number: 215-955-7959	Fax Number:		
E-Mail: james.harrop@jhefferson.edu			
Credential, e.g., agency login			
Project Role:	Other (Specify)	Other Project Role Category:	Site Investigator
Attach Biographical Sketch	Biosketch_Harrop.pdf		
Attach Current & Pending Support	Support_Harrop.pdf		

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME James S Harrop, MD, FACS	POSITION TITLE Associate Professor		
eRA COMMONS USER NAME (credential, e.g., agency login)			

EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	MM/YY	FIELD OF STUDY
Cleveland Clinic Spinal Disorders Fellowship		2001-2002	
Thomas Jefferson University Hospital		1996-2001	
Neurosurgery Program			
Thomas Jefferson University Hospital Surgical Internship		1995-1996	
Jefferson Medical College (Philadelphia, PA)	MD	1991-1995	
University of Connecticut (Farmington, CT)		1990-1991	
Bowdoin College (Brunswick, ME)	AB	1986-1990	

A. Positions and Honors

Positions and Employment

2001-2002 Clinical Instructor, Cleveland Clinic

2001-2007 Thomas Jefferson University, Assistant Professor of Neurological Surgery

2001-Present Trauma Director, Department of Neurosurgery

2002-Present Neurosurgical Director, Delaware Valley Spinal Cord Injury Center

2004-2006 Acting Director, Division of Spine and Peripheral Nerve Surgery

2005-2007 Thomas Jefferson University, Assistant Professor of Orthopedics

2005-Present Magee Rehabilitation Hospital

2005-Present Director, Neurosurgery Spine & Spinal Disorders Fellowship

2006-Present Clinical Director, Department of Neurosurgery – Gibbon

2006-Present Director, Division of Spine and Peripheral Nerve Surgery

2007-Present Director, Medical Student Education 3rd & 4th Year

2007-Present Thomas Jefferson University, Associate Professor of Orthopedics

2007-Present Thomas Jefferson University, Associate Professor of Neurological Surgery

2009-Present Frankford Hospital

Other Experience and Professional Memberships

1993-Present Alpha Omega Alpha Honor Society

1995-Present American Association of Neurological Surgeons

1993-Present American Medical Association

1995-Present Congress of Neurological Surgeons

Member, CNS Education Committee

Member, CNS Scientific Program Committee

2007-Present Congress of Neurological Surgeons

Vice Chair, CNS Publication Committee

Vice Chair, Practical Course Education (CNSU Spine Dean)

1999-Present Pennsylvania Neurosurgical Society

2001-Present North American Spine Society

2009-Present NASS, Performance Measure Advisory Committee

2004-Present Pennsylvania Medical Society

2004-Present Philadelphia County Medical Society

2004-Present American Spinal Injury Association; Chair, Spine Committee

2007-Present Cervical Spine Research Society; Member, Board of Directors

2009-Present Cervical Spine Research Society; Member, Research Committee
 2009-Present Cervical Spine Research Society; Member Nominating Committee
 2008-Present Scoliosis Research Society
 2009-Present 2010 DSPN Scientific Program Planning Meeting

Honors

President of JMC Student Council
 Jefferson Medical College Student Council Representative
 Bowdoin College Board of Trustees Student Representative
 Eagle Scout (Boy Scouts of America)
 The Hope Award (A Step Toward Hope), 2007

C. Selected Peer-reviewed Publications (Selected from 125 peer-reviewed publications)

1. Rihn JA, Kane J, Joshi A, Albert TJ, Vaccaro AR, Harrop J, Anderson DG, Hilibrand AS. Gastroesophageal reflux following anterior cervical surgery: A controlled, prospective analysis. *Spine*, 2011, Epub ahead of print.
2. Anderson DG, Patel A, Maltenfort M, Vaccaro AR, Ratliff J, Hilibrand A, Harrop JS, Sharan AD, Ponnappan RK, Rihn J, Albert TJ. Lumbar decompression using a traditional midline approach vs. a tubular retractor system: comparison of patient-based clinical outcomes. *Spine*, 2011, E320-5.
3. Harrop JS, Naroji S, Maltenfort MG, Ratliff JK, Tjoumakaris SI, Frank B, Anderson DG, Albert T, Vaccaro AR. Neurologic improvement after thoracic, thoracolumbar and lumbar spinal cord (conus medullaris) injuries.
4. Harrop JS, Hart R, Anderson PA. Optimal treatment for odontoid fractures in the elderly. *Spine*, 2010, 35: S219-S227.
5. Dailey A, Harrop JS, France JC. High-energy contact sports and cervical spine neuropraxia injuries: what are the criteria for return to participation? *Spine*, 2010, 35: S193-S201.
6. Smith HE, Kerr SM, Fehlings MG, Chapman J, Maltenfort M, Zavlasky J, Harris E, Albert TJ, Harrop J, Hilibrand AS, Anderson DG, Vaccaro AR. Trends in epidemiology and management of Type II odontoid fractures: 20-year experience at a model system spine injury tertiary referral center. *Journal of Spine Disorders and Techniques*, 2010, Epub ahead of print.
7. Saldia NS, Harrop JS. The compromise between motion preservation and arthrodesis. *Spine Journal*, 2010, 10: 815-816.
8. Teufack SG, Singh H, Harrop J, Ratliff J. Dorsal epidural intervertebral disk herniation with atypical radiographic findings: case report and literature review. *Journal of Spinal Cord Medicine*, 2010, 33: 268-271.
9. Campbell PG, Malone J, Yadla S, Maltenfort MG, Harrop JS, Sharan AD, Ratliff JK. Early complications related to approach in thoracic and lumbar spine surgery: a single-center prospective study. *World Neurosurgery*, 2010, 73: 395-401.
10. Yadla S, Malone J, Campbell PG, Maltenfort MG, Harrop JS, Sharan AD, Ratliff JK. Early complications in spine surgery and relation to preoperative diagnosis: a single-center prospective study. *Journal of Neurosurgery Spine*, 2010, 13: 360-366.
11. Fisher CG, Dipaola CP, Ryken TC, Bilsky MH, Shaffrey CI, Berven SH, Harrop JS, Fehlings MG, Boriani S, Chou D, Schmidt MH, Polly DW, Biagini R, Burch S, Dekutoski MB, Ganju A, Gerszten PC, Gokaslan ZL, Groff MW, Liebsch NJ, Mendel E, Okuno SH, Patel S, Rhines LD, Rose PS, Sciubba DM, Sundaresan N, Tomita K, Varga PP, Vialle LR, Vrionis FD, Yamada Y, Fourney DR. A novel classification system for spinal instability in neoplastic disease: an evidence-based approach and expert consensus from the Spine Oncology Study Group. *Spine*, 2010, Epub ahead of print.
12. Ding T, Maltenfort M, Smith H, Ratliff J, Vaccaro A, Anderson DG, Harrop J. Correlation of C2 fractures and vertebral artery injury. *Spine*, 2010, 35:E520-E524.
13. Bono CM, Schoenfeld AJ, Anderson PA, Harrop JS, France J, Vaccaro AR, Dvorak M, Fehlings M. Observer variability of radiographic measurements of C2 (axis) fractures. *Spine*, 2010: 1206-1210.
14. Yadla S, Malone J, Campbell PG, Maltenfort MG, Harrop JS, Sharan AD, Vaccaro AR, Ratliff JK. Obesity and spine surgery: reassessment based on a prospective evaluation of perioperative

complications in elective degenerative thoracolumbar procedures. Spine Journal, 2010, Epub ahead of print.

15. Singh H, Harrop JS, Schiffmacher P, Rosen M, Evans J. Ventral surgical approaches to cranio-vertebral junction chordomas. Neurosurgery, 2010, 66:96-103.
16. Smith HE, Fehlings M, Chapman J, Maltenfort M, Zaslavsky J, Harris E, Albert T, Harrop J, Hilibrand A, Anderson DG, Vaccaro A. Trends in epidemiology and management of Type II odontoid fractures: 20 year experience at a model system spine injury tertiary referral center. Journal of Spinal Disorders and Techniques, in press.
17. Rihn JA, Fisher C, Harrop J, Morrison W, Yang N, Vaccaro AR. Assessment of the posterior ligamentous complex following acute cervical spine trauma: A prospective comparison of preoperative MRI and intraoperative findings. Journal of Bone and Joint Surgery, 2010: 583-589.
18. Nasser R, Yadla S, Maltenfort MG, Harrop JS, Anderson DG, Vaccaro AR, Sharan AS, Ratliff JK. Complications in spine surgery: a literature review. Journal of Neurosurgery Spine, 2010, 13:144-157.

D. Research Support

Ongoing Research Support

Christopher & Dana Reeve Foundation Harrop (PI) 06/01/10-05/31/12

North American Clinical Trial Network (NACTN) for Treatment of Spinal Cord Injury

The goal of this project is to create a database to record how people get spinal cord injuries, how they respond to standard treatment, and what happens to those people over the course of the following year.

Christopher & Dana Reeve Foundation Harrop (PI) 06/01/10-05/31/12

Safety & Pharmacokinetics of Riluzole in Patients with Traumatic Acute Spinal Cord Injury (CTN3-2011 JH)

The primary aim of this study is to develop acute care safety and pharmacokinetic profiles of riluzole in patients who have sustained a traumatic spinal cord injury. Secondary objectives are to conduct exploratory analyses of functional outcomes for purposes of planning a subsequent Phase II b – Phase II randomized study of the efficiency of Riluzole for the treatment of acute spinal cord injury.

DePuy Biologics Harrop (PI) 06/30/06-06/12/12

A Prospective, Multicenter, Randomized Study Comparing the use of HEALOS to Autograft in a Transforaminal Lumbar Interbody Fusion (TLIF) Approach

The goal of this project is to compare the safety and effectiveness of HEALOS to standard of care bone graft when used with a Leopard cage, in promoting bone growth in subjects undergoing spinal fusion surgery.

Cerapedics, Inc Harrop (PI) 08/27/08-05/31/12

An Assessment of P-15 Bone Putty in Anterior Cervical Fusions with Instrumentation Investigational Plan

The goal of this project is to evaluate P-15 bone putty (investigational device) is not inferior in effectiveness and safety to local autologous bone (control device) when applied in instrumented anterior cervical discectomy and fusion (ACDF) with use of a structural allograft ring in patients with degenerative cervical disc disease.

Spinecore, Inc. Harrop (PI) 03/26/04-12/31/50

FlexiCore Intervertebral Disc for the Treatment of Discogenic Pain Associated with Degenerative Disc Disease

The goal of this project is to compare the safety and effectiveness of the FlexiCore Intervertebral Disc to circumferential spinal fusion surgery in the treatment of discogenic pain unresponsive to conservative treatment associated with degenerative disc disease (DDD) at a single level in the lumbosacral spine (L1-S1)

Smith & Nephew, Inc. Harrop (PI) 06/01/10-05/31/13

A Prospective, Multi-center, Double-blind, Randomized, Placebo Controlled Pivotal Study of Ultrasound Therapy as Adjunctive Therapy for Increasing Posterolateral Fusion Success Following Single Level Posterior Instrumented Lumbar Surgery (Protocol Ex-Spine 0907)

The major goal of this project is to assess the primary efficacy outcome during the EXO_SPINE cohort of the study measured by comparing the 12-month fusion success rate for the investigation treatment as compared to the control treatment.

Geron Corporation

Harrop (PI)

12/02/10-11/30/13

A Phase I Safety Study of GRNOPC1 in Patients with Neurologically Complete, Subacute, Spinal Cord Injury (CP35A07) and Long Term Follow Up of Subjects who Received GRNOPC1 (CP35A008)

The major goal of this project is to evaluate the safety of GRNPC1 administered at a single time-point between 7 and 14 days post surgery, inclusive, to patient with neurologically complete spinal cord injuries (SCI) and to evaluate neurological function following administration of GRNOPC1.

James S. Harrop, MD

Current Research Support

1. Christopher & Dana Reeve Foundation Harrop (PI) 06/01/10-05/31/12
North American Clinical Trial Network (NACTN) for Treatment of Spinal Cord Injury.
The goal of this project is to create a database to record how people get spinal cord injuries, how they respond to standard treatment, and what happens to those people over the course of the following year.
2. Christopher & Dana Reeve Foundation Harrop (PI) 06/01/10-05/31/12 Safety & Pharmacokinetics of Riluzole in Patients with Traumatic Acute Spinal Cord Injury (CTN3-2011 JH). The primary aim of this study is to develop acute care safety and pharmacokinetic profiles of riluzole in patients who have sustained a traumatic spinal cord injury. Secondary objectives are to conduct exploratory analyses of functional outcomes for purposes of planning a subsequent Phase II b – Phase II randomized study of the efficiency of Riluzole for the treatment of acute spinal cord injury.
3. DePuy Biologics Harrop (PI) 06/30/06-06/12/12
A Prospective, Multicenter, Randomized Study Comparing the use of HEALOS to Autograft in a Transforaminal Lumbar Interbody Fusion (TLIF) Approach The goal of this project is to compare the safety and effectiveness of HEALOS to standard of care bone graft when used with a Leopard cage, in promoting bone growth in subjects undergoing spinal fusion surgery.
4. Cerapedics, Inc Harrop (PI) 08/27/08-05/31/12 An Assessment of P-15 Bone Putty in Anterior Cervical Fusions with Instrumentation Investigational Plan The goal of this project is to evaluate P-15 bone putty (investigational device) is not inferior in effectiveness and safety to local autologous bone (control device) when applied in instrumented anterior cervical discectomy and fusion (ACDF) with use of a structural allograft ring in patients with degenerative cervical disc disease.
5. Spinecore, Inc. Harrop (PI) 03/26/04-12/31/50 FlexiCore Intervertebral Disc for the Treatment of Discogenic Pain Associated with Degenerative Disc Disease The goal of this project is to compare the safety and effectiveness of the FlexiCore Intervertebral Disc to circumferential spinal fusion surgery in the treatment of discogenic pain unresponsive to conservative treatment associated with degenerative disc disease (DDD) at a single level in the lumbosacral spine (L1-S1) Smith & Nephew, Inc. Harrop (PI) 06/01/10-05/31/13 PHS 398/2590 (Rev. 06/09) Page
6. A Prospective, Multi-center, Double-blind, Randomized, Placebo Controlled Pivotal Study of Ultrasound Therapy as Adjunctive Therapy for Increasing Posterolateral Fusion Success Following Single Level Posterior Instrumented Lumbar Surgery (Protocol Ex-Spine 0907) The major goal of this project is to assess the primary efficacy outcome during the EXO_SPINE cohort of the study measured by comparing the 12-month fusion success rate for the investigation treatment as compared to the control treatment.

7. Geron Corporation Harrop (PI) 12/02/10-11/30/13 A Phase I Safety Study of GRNOPC1 in Patients with Neurologically Complete, Subacute, Spinal Cord Injury (CP35A07) and Long Term Follow Up of Subjects who Received GRNOPC1 (CP35A008) The major goal of this project is to evaluate the safety of GRNPC1 administered at a single time-point between 7 and 14 days post surgery, inclusive, to patient with neurologically complete spinal cord injuries (SCI) and to evaluate neurological function following administration of GRNOPC1.

Pending Support

None

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Senior/Key Person			
Prefix:	Dr.	First Name: Michele	Middle Name: M
Last Name:	Johnson	Suffix:	
Position/Title:	Department:		
Organization Name:	University of Texas Health Science Center	Division:	
Street 1:	Memorial Hermann Plaza Bldg.		
Street 2:	6400 Fannin St., Ste. 2800		
City:	Houston	County:	
State:	TX: Texas	Province:	
Country:	USA: UNITED STATES	Zip / Postal Code:	77030-2761
Phone Number:	713-704-7100	Fax Number:	713-704-7125
E-Mail:	michele.m.johnson@uth.tmc.edu		
Credential, e.g., agency login			
Project Role:	Other (Specify)	Other Project Role Category:	Site Investigator
Attach Biographical Sketch	Biosketch_Johnson.pdf		
Attach Current & Pending Support	Support_Johnson.pdf		

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Senior/Key Person			
Prefix:	First Name:	Mary	Middle Name:
Last Name:	Schmidt Read		Suffix:
Position/Title:	Spinal Cord Program Director	Department:	
Organization Name:	Magee Rehabilitation Hospital	Division:	
Street 1:	1513 Race Street		
Street 2:			
City:	Philadelphia	County:	
State:	PA: Pennsylvania	Province:	
Country:	USA: UNITED STATES	Zip / Postal Code:	19101-1125
Phone Number:	215-587-3151	Fax Number:	
E-Mail:	mschmidt@mageerehab.org		
Credential, e.g., agency login			
Project Role:	Other (Specify)	Other Project Role Category:	Site Investigator
Attach Biographical Sketch	Biosketch_SchmidtRead.pdf		
Attach Current & Pending Support	Support_SchmidtRead.pdf		

BIOGRAPHICAL SKETCH

Provide the following information for ALL key personnel.

For Post-doctoral Fellowships, a separate biosketch for the Mentor/Sponsor is required as well as a biosketch for the Fellow.

DO NOT EXCEED FOUR (4) PAGES.

NAME: Mary Schmidt Read, PT, DPT, MS	POSITION TITLE: Spinal Cord Injury Program Director and Coordinator of Research		
EDUCATION/TRAINING - Begin with baccalaureate or other initial professional education, such as nursing. Include postdoctoral training and residency training if applicable.			
INSTITUTION AND LOCATION	DEGREE (if applicable)	YEAR(s) (MM/YYYY)	FIELD OF STUDY
University of Maryland	BS	1973	Science, Phys Ed
University of Pennsylvania	Certificate	1977	Physical Therapy
Temple University	MS	1983	Master's Degree
Temple University	DPT	2007	Doctor of Phys Therapy

Date	Positions/Honors – List in chronological order previous positions, concluding with present position.
Positions	
1977 – 1978	Hospital of University of Pennsylvania, part-time physical therapist
1977 – 1979	Our Lady of Lourdes Rehabilitation Center, full-time physical therapist
1977 – 1987	Private Home Care Physical Therapist in Penna and New Jersey
1978 – 1979	Community Health & Nursing Services of Camden Cty, part-time physical therapist
1979 – 1981	Moss Rehabilitation Hospital, Group Facilitator, Sexual Attitude Reassessment seminars
1979 – 1991	Various positions at Magee Rehabilitation Hospital, serving different capacities in Physical Therapy service, including staff level, Clinical Specialist in Spinal Cord Injury, SCI Supervisor, and part-time contract work
1983 – 1991	Assistant Professor and Academic Clinical Coordinator, Hahnemann University, Graduate School, Program in Physical Therapy; Also served this program as Adjunct Asst Professor from 1991 – 1997
1984 – 1987	Adjunct Clinical Instructor, Beaver College
1985 – 1986	Temple Sports Medicine Clinic, physical therapist
1991 – 1998	Director of Physical Therapy, Magee Rehabilitation Hospital
1997 – present	Spinal Cord Injury Program Director, Magee Rehabilitation Hospital
2002 – present	Research Coordinator, Magee Rehabilitation Hospital
2004 – present	Site Director, NeuroRecovery Network, Magee Rehabilitation Hospital
2004 – present	Chair, Institutional Review Board, Magee Rehabilitation
2006 – present	Member, Board of Directors, Adam Taliaferro Charitable Foundation
2009 – present	Member various committees for American Spinal Injury Association, including International Standards Committee, Education Committee, Rehab Standards Committee
2010 – present	Co-Network Director, NeuroRecovery Network, Christopher & Dana Reeve Foundation
Honors	
1995	Recipient, Pennsylvania Physical Therapy Association Service Award
2005	Keynote speaker, Drexel University Physical Therapy Graduation

Date	Selected Peer-Reviewed Publications - Please list in chronological order beginning with the most recent publications.
2010	Oyster M, Karmarkar A, Patrick M, Schmidt-Read M, Nicolini L, Boninger M (2010) Investigation of Factors Associated with manual Wheelchair Mobility in Individuals with Spinal Cord Injury, <i>Arch Phys Med and Rehab</i> ; accepted, pending publication.

2010	Waring, W et al (2010) 2009 Review and Revisions of the International Standards for Neurological Classification of Spinal Cord Injury, <i>J Spinal Cord Medicine</i> ; accepted, pending publication.
2010	Marino R, Scivoletto G, Patrick M, Tamburella F, Schmidt-Read M, Burns A, Hauck W. Ditunno J (2010) Walking Index for Spinal Cord Injury version 2 (WISCI II) with repeatability of the 10-m walk time, <i>Am J Phys Med Rehabil</i> ; 89:7-15.
2010	Ardolino, Watson, Behrman, Harkema, Schmidt-Read (2010) Book Chapter: Spinal Cord Injury Locomotor Training, <i>Improving Functional Outcomes in Physical Rehabilitation</i> , FA Davis.
2008	Jackson AB, Cernel CT, Ditunno JF, Read MS, Boninger ML, Schmeler MR, Williams SR, Donovan WH (2008) Outcome measures for gait and ambulation in the spinal cord injury population. <i>J Spinal Cord Medicine</i> ; 31(5):487-99.
2008	Schmidt Read, Sisto, Ditunno (2008) Standardized Ambulation Assessments Following Spinal Cord Injury. <i>Top Spinal Cord Inj Rehabil</i> ; 14(1):39-60.
1998	Staas, Formal, Gershkoff, Hirschwald, Schmidt, Schultz & Smith (1998) Spinal Cord Injury and Spinal Cord Medicine, <i>Rehabilitation Medicine: Principles & Practice</i> , 2 nd Ed., 3 rd Ed.
1991	Cioschi, Goodman, Petrillo, Schmidt & Wooden (1991) Lifetime Care Management: Spinal Cord Injury, <i>Continuing Care</i> . August/Sept.
1989	Wilhite MR, Schmidt ME (1989) Management of the Disabled: A Three Part Curriculum Plan to Promote Community Reintegration; <i>Journal of Physical Therapy Education</i> ; Section on Education APTA.

Date	Research Support - Please provide your last five years of funding as well as all current funding.
2004 – 2012	Center for Disease Control/Christopher & Dana Reeve Foundation <i>Development of NeuroRecovery Network (NRN) for functional, health and quality of life improvements after neurologic injury</i>
2006 – 2011	NIDRR (National Institute of Disability Rehabilitation and Research) <i>SCI Model System of Care</i>
2010 – 2012	Craig H. Neilsen Foundation <i>Musculoskeletal and Cardiovascular Effects of Two Functional Electrical Stimulation Cycling Paradigms</i>
2010 -	Geron Corporation <i>A Phase 1 Safety Study of GRNOPC1 in patients with neurologically complete, subacute, spinal cord injury</i>

Research support

2004 – 2012	Center for Disease Control/Christopher & Dana Reeve Foundation <i>Development of NeuroRecovery Network (NRN) for functional, health and quality of life improvements after neurologic injury</i>
2006 – 2011	NIDRR (National Institute of Disability Rehabilitation and Research) <i>SCI Model System of Care</i>
2010 – 2012	Craig H. Neilsen Foundation <i>Musculoskeletal and Cardiovascular Effects of Two Functional Electrical Stimulation Cycling Paradigms</i>
2010 -	Geron Corporation <i>A Phase 1 Safety Study of GRNOPC1 in patients with neurologically complete, subacute, spinal cord injury</i>

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Senior/Key Person			
Prefix:	Dr.	First Name: Christopher	Middle Name: I
Last Name:	Shaffrey		Suffix:
Position/Title:		Department:	
Organization Name:	University of Virginia	Division:	
Street 1:	PO Box 800212		
Street 2:			
City:	Charlottesville	County:	
State:	VA: Virginia	Province:	
Country:	USA: UNITED STATES	Zip / Postal Code:	22908-0212
Phone Number:	434-243-9714	Fax Number:	
E-Mail:	CIS8Z@virginia.edu		
Credential, e.g., agency login			
Project Role:	Other (Specify)	Other Project Role Category:	Site Investigator
Attach Biographical Sketch	Biosketch_Shaffrey.pdf		
Attach Current & Pending Support	Support_Shaffrey.pdf		

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME Christopher I. Shaffrey, MD	POSITION TITLE Harrison Distinguished Teaching Professor Department of Neurological and Orthopaedic Surgery		
eRA COMMONS USER NAME (credential, e.g., agency login)			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	MM/YY	FIELD OF STUDY
The Citadel The University of Virginia	BS MD	8/78 – 5/82 8/82 – 5/86	Biology Medicine
Naval Hospital San Diego The University of Virginia The University of Virginia University of Virginia	Internship Residency Residency Spine Fellowship	7/86-6/87 7/87-6/94 7/88-6/92 7/94-6/95	General Surgery Neurosurgery Orthopaedic Surgery Fellowship in Adult and Pediatric Complex Spinal Surgery

A. Personal Statement

Dr. Shaffrey has an active research interest in spinal surgery, particularly in numerous multicenter outcome research studies of pediatric and adult scoliosis, spinal trauma and tumors involving the spinal column. Over the past 10 years, he has been particularly involved in clinical outcome studies in adult spinal deformity and spinal cord injury. He has been a funded principal investigator in numerous grants and clinical trials.

He served on the Editorial Boards of Journal of Neurosurgery, Neurosurgery, Spine and Journal of Spinal Disorders. Dr. Shaffrey has greater than 100 peer-reviewed publications, greater than 500 national and international presentations and served as editor for several textbooks on spinal surgery.

During his career in medicine, Dr. Shaffrey has won numerous awards for clinical medicine. He has had numerous positions within organized neurosurgery and spinal surgery. He has been the scientific program chair, annual meeting chair and the chair for the AANS/CNS Joint Section on Disorders of the Spine and Peripheral Nerves. He has served as the Morbidity and Mortality Committee Chair and is currently on the Board of Directors for the Scoliosis Research Society. He is the current chair of the IMAST committee. He is currently on the Board of Directors for the AANS. He is a Director for the American Board of Neurological Surgery.

B. Positions and Honors

Positions and Employment (past 10 years)

- 1999-2003: Associate Professor of Neurological Surgery, University of Washington School of Medicine, Seattle, WA
- 2000-2003: Adjunct Associate Professor of Orthopaedics and Sports Medicine, University of Washington School of Medicine, Seattle, WA
- 2003-2008: Professor of Neurological Surgery, University of Virginia School of Medicine, Charlottesville, VA
- 2003-2008: Adjunct Professor of Orthopaedic Surgery, University of Virginia School of Medicine, Charlottesville, VA
- 2008-Present: Harrison Distinguished Teaching Professor of Neurological Surgery and Orthopaedic Surgery, University of Virginia School of Medicine, Charlottesville, VA

Other Experience and Professional Memberships

AANS/CNS Joint Section on Disorders of the Spine and Peripheral Nerves
American Academy of Orthopaedic Surgeons
American Academy of Neurological Surgery
American Association of Orthopaedic Surgeons
American Association of Neurological Surgeons
American College of Surgeons
American Orthopaedic Association
Cervical Spine Research Society
Congress of Neurological Surgeons
North American Spine Society
Scoliosis Research Society
The Society of Neurological Surgeons

Honors

2010 – 2012: The Best Doctors in America

2001 – 2011: Castle Connolly's America's Top Doctors

Oct 2001: Counsel of State Neurosurgical Societies Young Neurosurgeons Award, "Economic Analysis rhBMP-2 vs. Autogenous Iliac Crest Bone Graft for One Level Spinal Fusions

C. Selected Peer-reviewed Publications

1. Schwab F, Ungar B, Blondel B, Buchowski J, Coe J, Deinlein D, Dewald C, Mehdi H, Shaffrey C, Tribus C, Lafage V. SRS-Schwab Adult Spinal Deformity Classification: A Validation Study. *Spine* (Phila Pa 1976). 2011 Oct 29. [Epub ahead of print]
2. Smith JS, Bess S, Shaffrey CI, Burton DC, Hart RA, Hostin R, Klineberg E And The International Spine Study Group. Dynamic Changes of the Pelvis and Spine Are Key to Predicting Postoperative Sagittal Alignment Following Pedicle Subtraction Osteotomy: A Critical Analysis of Preoperative Planning Techniques. *Spine* (Phila Pa 1976). 2011 Oct 21[Epub ahead of print].
3. Williams BJ, Smith JS, Fu KM, Hamilton DK, Polly DW Jr, Ames CP, Berven SH, Perra JH, Knapp DR Jr, McCarthy RE, Shaffrey CI. Does BMP increase the incidence of perioperative complications in spinal fusion? A comparison of 55,862 cases of spinal fusion with and without BMP. *Spine* (Phila Pa 1976). 2011 Sep 15;36(20):1685-1691.
4. Lafage V, Bharucha NJ, Schwab F, Hart RA, Burton D, Boachie-Adjei O, Smith JS, Hostin R, Shaffrey C, Gupta M, Akbarnia BA, Bess S. Multicenter validation of a formula predicting postoperative spinopelvic alignment. *J Neurosurg Spine*. 2011 Sep 23. [Epub ahead of print].
5. Reames DL, Smith JS, Fu KM, Polly DW Jr, Ames CP, Berven SH, Perra JH, Glassman SD, McCarthy RE, Knapp RD Jr, Heary R, Shaffrey CI; Scoliosis Research Society Morbidity and Mortality Committee. Complications in the Surgical Treatment of 19,360 Cases of Pediatric Scoliosis: A Review of the Scoliosis Research Society Database. *Spine* (Phila Pa 1976). 2011 Aug 15;36(18):1484-1491.
6. Lafage V, Smith JS, Bess S, Schwab FJ, Ames CP, Klineberg E, Arlet V, Hostin R, Burton DC, Shaffrey CI; The International Spine Study Group. Sagittal spino-pelvic alignment failures following three column thoracic osteotomy for adult spinal deformity. *Eur Spine J*. 2011 Aug 12. [Epub ahead of print]
7. Fu KM, Rhagavan P, Shaffrey CI, Chernavsky DR, Smith JS. Prevalence, Severity and Impact of Foraminal and Canal Stenosis among Adults with Degenerative Scoliosis. *Neurosurgery*. 2011 Jun 24. [Epub ahead of print]
8. Lafage V, Ames C, Schwab F, Klineberg E, Akbarnia B, Smith J, Boachie Adjei O, Burton, D, Hart R, Hostin R, Shaffrey C, Wood K, Bess S, International Spine Study Group. Changes in Thoracic Kyphosis Negatively Impact Sagittal Alignment Following Lumbar Pedicle Subtraction Osteotomy.: A comprehensive radiographic Analysis.*Spine* (Phila Pa 1976). 2011 Jun 13. [Epub ahead of print]
9. Smith JS, Sansur CA, Donaldson WF III, Perra JH, Mudiya R, Choma TJ, Zeller RD, Knapp DR, Noordeen HH, Berven SH, Goytan MJ, Boachie-Adjei O, Shaffrey CI. Short-term morbidity and mortality associated with correction of thoracolumbar fixed sagittal plan deformity. A report of the Scoliosis Research Society Morbidity and Mortality Committee. *Spine* 36(12):958-964, 2011.

10. Smith JS, Shaffrey CI, Glassman S, Berven S, Hamill C, Horton W, Ondra S, Schwab F, Sansur CA, Bridwell K. Risk-benefit assessment of surgery for adult scoliosis: an analysis based on patient age. *Spine* 36(10):817-824, 2011.
11. Smith JS, Shaffrey CI, Sansur CA, Berven SH, Broadstone PA, Choma TJ, Goytan MJ, Noordeen HH, Knapp DR, Hart RA, Donaldson, WF III, Polly D, Perra JH, Boachie-Adjei O. Rates of infection following spine surgery based on 108,419 procedures: a report from the Scoliosis Research Society Morbidity and Mortality Committee. *Spine* 36(7):556-563, 2011.
12. Sansur CA, Smith JS, Coe J, Glassman SD, Berven SH, Polly DW Jr, Perra JH, Boachie-Adjei O, Shaffrey CI. Scoliosis Research Society morbidity and mortality of adult scoliosis. *Spine* 36(9):593-597, 2011.
13. Fu KM, Smith JS, Shaffrey CI, Perra JH, Polly DW Jr, Berven SH, McCarthy R. Correlation of higher preoperative American Society of Anesthesiology grade and increased morbidity and mortality rates in patients undergoing spine surgery. *J Neurosurg Spine* 14:470-474, 2011.
14. Smith JS, Fu KM, Polly DW Jr, Sansur CA, Berven SH, Broadstone PA, Choma TJ, Goytan MJ, Noordeen HH, Knapp DR, Hart RA, Donaldson, WF III, Perra JH, Boachie-Adjei O, Shaffrey CI. Complication rates of three common spine procedures and rates of thromboembolism following spine surgery based on 108,419 cases: a report from the Scoliosis Research Society Morbidity and Mortality Committee. *Spine* 35(24):2140-9, 2010.
15. Fu KM, Smith JS, Polly DW Jr, Perra JH, Sansur CA, Berven SH, Broadstone PA, Choma TJ, Goytan MJ, Noordeen HH, Knapp DR, Hart RA, Zeller RD, Donaldson, WF III, Boachie-Adjei O, Shaffrey CI. Morbidity and mortality in the surgical treatment of 10,329 adults with degenerative lumbar stenosis. *J Neurosurg Spine* 12(5):443-6, 2010.
16. Fu KM, Smith JS, Sansur CA, Shaffrey CI. Standardized measures of health status and disability and the decision to pursue operative treatment in elderly patients with degenerative scoliosis. *Neurosurgery* 66(1):42-7, 2010.
17. Smith JS, Shaffrey CI, Berven S, Glassman S, Hamill C, Horton W, Ondra S, Schwab F, Fu KM, Bridwell K. Operative versus conservative treatment of leg pain in adults with scoliosis: A retrospective review of a prospective multicenter database with two-year follow-up. *Spine* 34(16):1693-8, 2009.
18. Smith JS, Shaffrey CI, Berven S, Glassman S, Hamill C, Horton W, Ondra S, Schwab F, Shainline M, Fu KG, Bridwell K. Improvement of back pain with operative and nonoperative treatment in adults with scoliosis. *Neurosurgery* 65(1):86-94, 2009.
19. Smith JS, Fu KM, Urban P, Shaffrey CI. Neurological findings in adults with scoliosis: Incidences and correlations with operative versus conservative management. *J Neurosurg Spine* 9:326-331, 2008.
20. Smith JS, Abel M, Shaffrey CI, Ames CP. Decision making in pediatric deformity. *Neurosurgery* 63(3 Suppl):54-68, 2008.

D. Research Support

1. Jul 2009 – Jun 2014 134532 – GO10989 - Title of Project: Adult Deformity Outcomes Study
Sponsor: Washington University
PI: Shaffrey, C. I.
Period: 5/20/04 - 12/8/12
Title of Project: A Multi-Center Prospective Study of Quality of Life in Adult Scoliosis
NIHPI: Shaffrey, C.I.
2. Aug 2007 – Aug 2013 126318 – GI12014 – Title of Project: A Mult-Center, Prospective, Randomized Controlled Trial Comparing Arthroplasty to Anterior Cervical Discectomy and Fusion for the Treatment of Cervical Degenerative Disc Disease
Sponsor: Depuy
PI: Shaffrey, C.I.
3. Jul 2008 – Jul 2013 132576 - GI12651 – Title of Project: Multi-Center Prospective Evaluation of Operative Versus Nonoperative Treatment for Adult Spinal Deformity: Differentiating Clinical and Radiographic Features and Evaluation of Treatment Outcomes
4. Jan 2008 – Jan 2011 132575 – GI12650 – Title of Project: Mult-Center Retrospective Evaluation of Complications Following Adult Spinal Surgery: Working Towards a Risk Scoring System for Adult Spinal Deformity
Sponsor: Children's Specialists Foundation, Inc.

PI: Shaffrey, C. I.

5. Dec 2007 – Dec 2010 130528 - GI12494 -- ISSG Retrospective Studies

Sponsor: Depuy AcroMed, Inc.

PI: Shaffrey, C. I.

6. Mar 06 – Aug 2010 125923 - GI11991 -- Funding Source: AOSpine North America

Title of Project: 12276 An Assessment of Surgical Techniques for Treating Cervical Spondylotic Myelopathy

CURRENT AND PENDING

Christopher I. Shaffrey, MD

Current Support

Sponsor: AO Spine North America

Principle Investigator: Shaffrey, Christopher

Project Period: 8/1/11-7/31/13

Total Award:

Fellowship Funding to support spine fellow 2011-2013

Sponsor: Neurosurgery Research & Education Foundation

Adult Spine Fellowship 2011-2012

Principle Investigator: Shaffrey, Christopher

Project Period: 7/1/11-6/30/12

Total Award:

Fellowship funding to support Adult Spine Fellow 2011-2012

Sponsor: Children's Specialists Foundation, Inc.

Principle Investigator: Shaffrey, Christopher

Project Period: 7/1/08-9/1/13

Total Award:

Multi-Center Prospective Evaluation of Operative Versus Nonoperative Treatment for Adult Spinal Deformity: Differentiating Clinical and Radiographic Features and Evaluation of Treatment Outcomes.

Sponsor: Children's Specialists Foundation, Inc.

Principle Investigator: Shaffrey, Christopher

Project Period: 7/1/08-Current

Total Award:

Multi-Center Retrospective Evaluation of Complications Following Adult Spinal Surgery: Working Towards a Risk Scoring System for Adult Spinal Deformity.

Sponsor: Washington University

Principle Investigator: Shaffrey, Christopher

Project Period: 09/01/09-Current

Total Award:

A Multi-centered Prospective Study of Quality of Life in Adult Scoliosis.

Sponsor: Christopher & Dana Reeve Foundation

Principle Investigator: Shaffrey, Christopher

Project Period: 1/1/11-12/31/11

Total Award:

North American Clinical Trials Network

Sponsor: Depuy Acromed, Inc.

Principle Investigator: Shaffrey, Christopher

Project Period: 08/09/06-08/08/13

Total Award:

A Multi-Center, Prospective, Randomized, Controlled Trial Comparing Cervical Arthroplasty to Anterior Cervical Discectomy and Fusion for the Treatment of Cervical Degenerative Disc Disease

Pending Support

AO Spine International

Evaluation of Neurologic Complications Associated with Surgical Correction of Adult Spinal Deformity

Project Period: 9/28/11-12/28/13

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Senior/Key Person			
Prefix:	First Name: Steve	Middle Name:	
Last Name: Williams		Suffix:	
Position/Title: Medical Monitor	Department: Chief, Rehabilitation Medicine		
Organization Name: Boston Medical Center	Division:		
Street 1: 732 Harrison Avenue, Suite 511			
Street 2:			
City: Boston	County:		
State: MA: Massachusetts	Province:		
Country: USA: UNITED STATES	Zip / Postal Code: 02118		
Phone Number: 617-638-7911	Fax Number: 617-638-7313		
E-Mail: steve.williams@bmc.org			
Credential, e.g., agency login			
Project Role: Other (Specify)	Other Project Role Category:	Medical Monitor	
Attach Biographical Sketch	Biosketch_Williams.pdf		
Attach Current & Pending Support	Support_Williams.pdf		

BIOGRAPHICAL SKETCH

Provide the following information for ALL key personnel.

For Post-doctoral Fellowships, a separate biosketch for the Mentor/Sponsor is required as well as a biosketch for the Fellow.

DO NOT EXCEED FOUR (4) PAGES.

NAME: Steve Williams, MD	POSITION TITLE: Chairman, Department of Rehabilitation Medicine Chief, Rehabilitation Services		
EDUCATION/TRAINING - Begin with baccalaureate or other initial professional education, such as nursing. Include postdoctoral training and residency training if applicable.			
INSTITUTION AND LOCATION	DEGREE (if applicable)	YEAR(s) (MM/YYYY)	FIELD OF STUDY
University of Virginia Charlottesville, VA	BA	1982-1986	History, Art History
Medical College of Virginia, School of Dentistry Richmond, VA		1986-1989	Dentistry
Eastern Virginia Medical School Norfolk, VA	MD	1990-1994	Medicine
Children's Hospital of the King's Daughter, Norfolk, VA		1994-1995	Internship Pediatrics
Boston University Boston, MA		1995-1997	Rehabilitation Medicine Residency
New York University School of Medicine The Rusk Institute for Rehabilitation Medicine New York, NY		1997-1998	Rehabilitation Medicine Residency

Current Duties – Provide a brief description of the duties performed under the Position Title listed above.

Responsible for all administrative duties for the department of Rehabilitation Medicine at Boston University School of Medicine. Responsibility for all clinical Rehabilitation services at Boston Medical Center.
Principal Investigator, New England Regional Spinal Cord Injury Center, NIDRR
Principal Investigator, Boston Medical Center NeuroRecovery Network, CDRF and CDC

Personal Statement - Briefly describe why your experience and qualifications make you well-suited for your role with the proposed project.

Steve Williams, MD is the Chief and Chairman of the Department of Rehabilitation Medicine at Boston University Medical School/Boston Medical Center.

He is board certified in Physical Medicine & Rehabilitation and subspecialty certified in Spinal Cord Medicine. Dr. Williams holds the faculty rank of Associate Professor of Rehabilitation Medicine. He is the Principal Investigator of the New England Regional Spinal Cord Injury Center's Spinal Cord Injury Model Systems Grant from the National Institute's on Disability and Rehabilitation Research (NIDRR). In addition he holds grants from the Center for Disease Control and Prevention (CDC) focusing on the prevention of secondary effects from paralysis and a grant from the Christopher and Dana Reeve Foundation (CDRF) to study body weight supported Locomotor Training as part of the CDRF's NeuroRecovery Network. Dr. Williams' specialized interests include activity based therapies and functional recovery, prevention of the secondary effects of paralysis, consumer education and advocacy and emerging technologies in rehabilitation.

Date	Positions/Honors – <i>List in chronological order previous positions, concluding with present position.</i>
November 2011	Massachusetts Medical Law Report: Rx for Excellence in Medicine, hero of The Medical Community Award
May 2011	Boston University School of Medicine: Leonard P. Tow Humanism in Medicine Faculty Award
September 2006	Massachusetts Governor's Award for Community Service and Education to the Spinal Cord Injury Community of Massachusetts
1997	American Medical Association/Glaxo-Wellcome National Resident Award for Outstanding Community Service
1997	American Medical Association/Glaxo-Wellcome National Resident Award for Outstanding Leadership

Date	Selected Peer-Reviewed Publications - <i>Please list in chronological order beginning with the most recent publications.</i>
2011	Houlihan BV, Jette A, Paasche-orlow M, Wierbicky J, Zazula J, Cuevas P, Williams S. A Telerehabilitation Intervention for Persons with Spinal Cord Dysfunction American Journal of Physical Medicine & Rehabilitation
2010	Yang, Z, Kun Y, Williams, S, Lew H. An Unusual Cause of Abdominal Pain in a Patient with Severe Traumatic Brain Injury (TBI): Intussusception of the Jejunum American Journal of Physical Medicine & Rehabilitation
2010	McClure, L.A., Boninger, M.L., Oyster M.L., Williams, S., Houlihan B., Lieberman J.A., Cooper, R. Wheelchair Breakdowns, Consequences and Impact on People with Traumatic Spinal Cord Injury Archives of Physical Medicine & Rehabilitation
2009	Goodman, N, Jette, A, Houlihan, B, Williams, S. Computer & Internet Use by Individuals Post Traumatic Spinal Cord Injury Archives of Physical Medicine & Rehabilitation 2008; 89(8): 1492-98.
2008	Morse, L., Nguyen, H., Jain, N., Williams, S., Tun, C., Battaglino, R., Stashenko P., Garshick, E. Age and Motor Score Predict Osteoprotegerin level in Chronic SCI Journal of Musculoskeletal Neuronal Interactions 2008; 8(1): 50-57.

Date	Research Support - <i>Please provide your last five years of funding as well as all current funding.</i>
2011-2016	NIDRR Model Spinal Cord Systems Grant
2006-2011	NIDRR Model Spinal Cord Systems Grant
2006-2011	Christopher and Dana Reeve Foundation through a Cooperative Agreement with the CDC NeuroRecovery Network
2007-2010	CDC Telehealth R-01 Grant

Research Support

2011-2016	NIDRR Model Spinal Cord Systems Grant
2006-2011	NIDRR Model Spinal Cord Systems Grant
2006-2011	Christopher and Dana Reeve Foundation through a Cooperative Agreement with the CDC NeuroRecovery Network
2007-2010	CDC Telehealth R-01 Grant

Project/Performance Site Locations(s)

Project/Performance Site Primary Location

☐ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: The Methodist Hospital Research Institute
DUNS Number: 1856410520000
Street 1: 6670 Bertner Ave., R2-216
Street 2:
City: Houston,
State: TX: Texas
Province:
Country: USA: UNITED STATES
ZIP / Postal Code: 77030

County: Harris

Project/Performance Site Congressional District: TX-009

Project/Performance Site Location 1

☐ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: Univ of Maryland, Baltimore
DUNS Number: 1884359110000
Street 1: 620 W. Lexington St.
Street 2: 4th Floor
City: Baltimore
State: MD: Maryland
Province:
Country: USA: UNITED STATES
ZIP / Postal Code: 21201-1508

County:

Project/Performance Site Congressional District: MD-007

Project/Performance Site Location 2

☐ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: University of Virginia
DUNS Number: 0653915260000
Street 1: PO Box 800212
Street 2:
City: Charlottesville
State: VA: Virginia
Province:
Country: USA: UNITED STATES
ZIP / Postal Code: 22908-0212

County: Albemarle

Project/Performance Site Congressional District: VA-005

Project/Performance Site Location 3

☐ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: University of Texas School of Public Health
DUNS Number: 8007715940000
Street 1: PO Box 20036
Street 2:
City: Houston
State: TX: Texas
Province:
Country: USA: UNITED STATES
ZIP / Postal Code: 77225-0036

County:

Project/Performance Site Congressional District: TX-009

Project/Performance Site Location 4

☐ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: The Institute for Rehabilitation and Research (TIIR)
DUNS Number: 0741738730000
Street 1: 1333 Mouusund
Street 2: A-222
City: Houston
State: TX: Texas
Province:
Country: USA: UNITED STATES
ZIP / Postal Code: 77030-3408

County:

Project/Performance Site Congressional District: TX-007

Project/Performance Site Location 5

☐ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: University of Texas Health Science Center
DUNS Number: 8007715940000
Street 1: 6400 Fannin St.
Street 2: Suite 2800
City: Houston
State: TX: Texas
Province:
Country: USA: UNITED STATES
ZIP / Postal Code: 77030-2761

County:

Project/Performance Site Congressional District: TX-007

Project/Performance Site Location 6

☐ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: Frazier Rehab Institute
DUNS Number: 130410780000
Street 1: 220 Abraham Flexner Way
Street 2:
City: Louisville
State: KY: Kentucky
Province:
Country: USA: UNITED STATES
ZIP / Postal Code: 40202-3826

County:

Project/Performance Site Congressional District: KY-003

Project/Performance Site Location 7

☐ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: University of Louisville
DUNS Number: 0575888570000
Street 1: Med Center One
Street 2: Ste 315
City: Louisville
State: KY: Kentucky
Province:
Country: USA: UNITED STATES
ZIP / Postal Code: 40202

County: 501 E. Broadway

Project/Performance Site Congressional District: KY-003

Project/Performance Site Location 8

☐ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: University of Miami
DUNS Number: 0527809180000
Street 1: 1095 NW 14th Terrace
Street 2:
City: Miami
State: FL: Florida
Province:
Country: USA: UNITED STATES
ZIP / Postal Code: 33136-1060

County: Miami-Dade

Project/Performance Site Congressional District: FL-021

Project/Performance Site Location 9

☐ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: Magee Rehabilitation Hospital
DUNS Number: 8081809420000
Street 1: 1513 Race Street
Street 2:
City: Philadelphia
State: PA: Pennsylvania
Province:
Country: USA: UNITED STATES
ZIP / Postal Code: 19102

County:

Project/Performance Site Congressional District: PA-002

Project/Performance Site Location 10

☐ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: Thomas Jefferson University
DUNS Number: 0532846590000
Street 1: 909 Walnut Street
Street 2: Suite 300
City: Philadelphia
State: PA: Pennsylvania
Province:
Country: USA: UNITED STATES
ZIP / Postal Code: 19107-5211

County:

Project/Performance Site Congressional District: PA-001

Project/Performance Site Location 11

☐ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: University Health Network, Univ Toronto
DUNS Number: 1856410520000
Street 1: 190 Elizabeth Street
Street 2:
City: Toronto
State:
Province: Ontario
Country: CAN: CANADA
ZIP / Postal Code: M5G 2C4

County:

Project/Performance Site Congressional District: 00-000

Project/Performance Site Location 12

☐ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name:
DUNS Number:
Street 1:
Street 2:
City:
State:
Province:
Country:
ZIP / Postal Code:

County:

Project/Performance Site Congressional District:

Project/Performance Site Location 13

☐ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name:
DUNS Number:
Street 1:
Street 2:
City:
State:
Province:
Country:
ZIP / Postal Code:

County:

Project/Performance Site Congressional District:

Project/Performance Site Location 14

☐ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name:
DUNS Number:
Street 1:
Street 2:
City:
State:
Province:
Country:
ZIP / Postal Code:

County:

Project/Performance Site Congressional District:

Project/Performance Site Location 15

☐ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name:
DUNS Number:
Street 1:
Street 2:

City:
State:
Province:
Country:
ZIP / Postal Code:

County:

Project/Performance Site Congressional District:

Project/Performance Site Location 16

☐ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name:
DUNS Number:
Street 1:
Street 2:
City:
State:
Province:
Country:
ZIP / Postal Code:

County:

Project/Performance Site Congressional District:

Project/Performance Site Location 17

☐ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name:
DUNS Number:
Street 1:
Street 2:
City:
State:
Province:
Country:
ZIP / Postal Code:

County:

Project/Performance Site Congressional District:

Project/Performance Site Location 18

☐ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name:
DUNS Number:
Street 1:
Street 2:
City:
State:
Province:
Country:
ZIP / Postal Code:

County:

Project/Performance Site Congressional District:

Project/Performance Site Location 19

☐ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name:
DUNS Number:
Street 1:
Street 2:
City:
State:
Province:
Country:
ZIP / Postal Code:

County:

Project/Performance Site Congressional District:

Project/Performance Site Location 20

☐ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name:
DUNS Number:
Street 1:
Street 2:
City:
State:
Province:
Country:

County:

ZIP / Postal Code:

Project/Performance Site Congressional District:

Project/Performance Site Location 21

☐ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name:
DUNS Number:
Street 1:
Street 2:
City:
State:
Province:
Country:
ZIP / Postal Code:

County:

Project/Performance Site Congressional District:

Project/Performance Site Location 22

☐ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name:
DUNS Number:
Street 1:
Street 2:
City:
State:
Province:
Country:
ZIP / Postal Code:

County:

Project/Performance Site Congressional District:

Project/Performance Site Location 23

☐ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name:
DUNS Number:
Street 1:
Street 2:
City:
State:
Province:
Country:
ZIP / Postal Code:

County:

Project/Performance Site Congressional District:

Project/Performance Site Location 24

☐ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name:
DUNS Number:
Street 1:
Street 2:
City:
State:
Province:
Country:
ZIP / Postal Code:

County:

Project/Performance Site Congressional District:

Project/Performance Site Location 25

☐ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name:
DUNS Number:
Street 1:
Street 2:
City:
State:
Province:
Country:
ZIP / Postal Code:

County:

Project/Performance Site Congressional District:

Project/Performance Site Location 26

Organization Name:
DUNS Number:
Street 1:
Street 2:
City:
State:
Province:
Country:
ZIP / Postal Code:

☐ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

County:

Project/Performance Site Congressional District:

Project/Performance Site Location 27

Organization Name:
DUNS Number:
Street 1:
Street 2:
City:
State:
Province:
Country:
ZIP / Postal Code:

☐ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

County:

Project/Performance Site Congressional District:

Project/Performance Site Location 28

Organization Name:
DUNS Number:
Street 1:
Street 2:
City:
State:
Province:
Country:
ZIP / Postal Code:

☐ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

County:

Project/Performance Site Congressional District:

Project/Performance Site Location 29

Organization Name:
DUNS Number:
Street 1:
Street 2:
City:
State:
Province:
Country:
ZIP / Postal Code:

☐ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

County:

Project/Performance Site Congressional District:

Additional Location(s):

Budget Justification
The Methodist Hospital Research Institute
The Methodist Hospital – NACTN/NRN Coordinating Center

PERSONNEL

Robert G. Grossman, M.D. - Principal Investigator (10% Effort)

Dr. Robert Grossman, PI - Dr. Grossman will oversee all aspects of the proposed clinical trial. This includes research participant recruitment, screening, enrollment, and compliance with all requirements of the HRPO and local site IRBs. He will have quarterly conference calls with the site physicians to maintain standardization across sites and discuss medically related issues. He will collaborate with the medical monitor to ensure oversight of adverse events and data accuracy and protocol compliance. Along with the other investigators, Dr. Grossman will assist in data interpretation and editing/preparing manuscripts. Dr. Grossman is the Principal Investigator of the NACTN and has collaborated with physicians, scientists and administrators to implement a network of hospitals whose mission is to bring promising therapies out of the laboratory and into clinical trials, in a manner that provides incontrovertible evidence of effectiveness and safety.

Elizabeth G. Toups, MS, RN, CCRP - Project Manager (24% Effort)

Elizabeth G. Toups, MS, RN, CCRP, Project Manager and Point of Contact for the DOD HRPO ORP - She is responsible for the day-to-day activities of NACTN's clinical activities. She provides support to Dr. Grossman, other Principal Investigators and other NACTN and NRN personnel. Her activities include protocol development, submissions and regulatory approvals, organizing and conducting NACTN/NRN meetings, project management and site management for planning, initiating and conducting clinical trials and facilitating communication between NACTN/NRN centers.

Julia S. Benoit – Nested New Investigator (34% Effort)

Julia Benoit, Nested New Investigator. The opportunity to become a nested new investigator on a multi-site spinal cord injury rehabilitation clinical trial is a perfect fit for me. Although I have gained invaluable experience working in a brain trauma injury clinical trial (Effects of Erythropoietin on Vascular Dysfunction and Anemia in Traumatic Brain Injury), I am ready to be challenged further with multiple site clinical trial repeated measures outcome data and the potential for applying my statistical research directly to the outcomes of proposed Phase 11b locomotor randomized clinical trial. In addition, the mentoring in this program provided by the faculty of the Clinical Coordinating Center and the Data Analysis Center on the epidemiology of spinal cord injury and the historical and current understandings and approaches to the design of spinal cord clinical trials will provide me with a substantial foundation to further my commitment and competitiveness for pursuing an academic career in spinal cord research.

PATIENT COSTS

The recruitment, data collection, data management and treatment interventions will all be supported to some extent by the existing NACTN and NRN infrastructure. Roles and responsibilities for the investigators, coordinators and data managers that are coincident with

those in the current grant will be leveraged and thus have resulted in requiring substantially less cost for personnel than would usually be needed if a trial was conducted without these already established infrastructures

Funds are requested for compensation to the ten clinical sites to cover the cost of screening, evaluations, and interventions. Sites will be compensated based on the number of patients enrolled and the data collected each quarter. Invoices will be generated by the Data CrossIQ/ITW system and management team quarterly.

Per Patient Cost Locomotor Training Group (n=32, \$8840 per patient)

Each patient randomized to the Locomotor Training group will undergo screening and all outcome measures (detailed below) and received 80 sessions of Locomotor Training. The funding is requested for up to 40 sessions per patient in the inpatient rehabilitation sites. Once the individual is discharged they will enter the NRN program undergoing the same protocol for the additional number of sessions needed to reach 80 sessions. These will already be covered within the NRN program.

Per Patient Cost Usual Rehabilitation Group (n=32, \$1790 per patient)

Each patient randomized to the Usual Rehabilitation group will undergo screening and all outcome measures (detailed below). Sites will be compensated also for acquiring rehabilitation intervention from patient records.

The cost for the screening was based on the estimated time required by the study coordinator to conduct the procedures required for screening. The cost for the locomotor, spasticity, cardiovascular and pulmonary outcomes was based on the estimated time required to conduct the evaluations. Cost for lab work determined by an average fee for these tests reported by the seven clinical sites. The cost for locomotor training was determined by calculating the average cost from the existing NRN sites that routinely provide this intervention.

Screenings at the rate of \$200 each

Behavioral evaluations at the rate of \$90 each with 6 evaluations per patient

Cardiovascular evaluations at the rate of \$75 per evaluation with 2 evaluations per patient

Pulmonary evaluations at the rate of \$75 per evaluation with 2 evaluations per patient

Rehabilitation Data Acquisition at the rate of \$75 each with 6 evaluations per patient.

Locomotor training sessions at the rate of \$190 per session for up to 40 sessions per patient.

OTHER EXPENSES

Funds are requested for ITW data acquisition, software site maintenance, data integrity, invoice generation and project revision updates (approx \$26,090 per year) to be provided by Systemax, Inc.

ATTACHMENTS FORM

Instructions: On this form, you will attach the various files that make up your grant application. Please consult with the appropriate Agency Guidelines for more information about each needed file. Please remember that any files you attach must be in the document format and named as specified in the Guidelines.

Important: Please attach your files in the proper sequence. See the appropriate Agency Guidelines for details

- 1) ProjectNarrative.pdf
- 2) Support.pdf
- 3) TechAbs.pdf
- 4) PublicAbs.pdf
- 5) SOW.pdf
- 6) HumSubProc.pdf
- 7) Intervention.pdf
- 8) Data_Manage.pdf
- 9) Personnel.pdf
- 10) Surveys.pdf
- 11) Impact.pdf
- 12) Transition.pdf
- 13) Military.pdf
- 14) Letter.pdf
- 15)

PROJECT NARRATIVE

1. Background:

This proposal addresses the SCI community's critical needs related to clinical rehabilitation and secondary complications of chronic spinal cord injury (SCI). The specific areas that this clinical trial will address are: i) understanding the physiological basis (neuroplasticity) for rehabilitation therapies and evaluating whether there are quantitative benefits of activity dependent training ii) development and refinement of rehabilitation strategies and technologies to deliver improved functional capacity for people living with SCI, iii) utilization of existing network infrastructure and established collaborations to enable rapid initiation of research that leverages available systems for structured data collection, analyses, and outcome assessment, and iv) providing comprehensive information regarding specific standardized rehabilitation for those with traumatic SCI..

The hypothesis to be tested in this proposal is that in incomplete SCI individuals who have impaired descending excitatory input to the spinal cord, *Locomotor Training (LT)* can provide stimulation and develop plasticity in these pattern generating networks enabling generation of improved walking in response to descending voluntary supraspinal motor impulses and result in greater functional recovery than usual rehabilitation.

a. Rehabilitation in SCI

The ability to walk has consistently been a major goal for persons with SCI. The proportion of persons that sustain a SCI that have incomplete injuries now forms the majority of cases in the United States (39). An incomplete injury exists when there is preservation of sensory or motor function below the level of injury including the lowest sacral segments (S4/S5), thus increasing the chances of ambulation as a functional goal. These individuals using the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) are classified on the American Spinal Injury Association Impairment Scale (AIS) as C and D (3,38). Rehabilitation approaches to facilitate recovery of standing and walking after an incomplete SCI have recently been directed toward LT, an activity-dependent rehabilitation therapy that provides repetitive stepping facilitated by manual assistance and body weight support on a treadmill (6,7,19,20,28,40,51). LT allows for loading and unloading of the body weight, improved head, neck and trunk postural alignment, and improved coordination of the lower limbs. The efficacy of LT for walking suggests that movement patterns associated with ambulation can be generated by afferent input interacting with interneurons within the spinal cord known in mammals as central pattern generators. And with residual supraspinal circuitry available to the networks, functional over ground walking has been achieved with this repetitive task specific training in individuals with AIS C and D injuries from months to years after injury. In addition, the rate of recovery was dependent on the time since injury (*see Preliminary Studies, page 3*) (24,54). These individuals had received usual rehabilitation that was available to them prior to receiving LT in an outpatient setting. This study will directly compare LT to usual rehabilitation and enroll patients at the earliest time point in inpatient rehabilitation.

LT in individuals with chronic motor incomplete SCI has resulted in functional improvements in gait. Clinical studies in chronic incomplete SCI individuals showed that LT was more effective at restoring walking when compared retrospectively to conventional physiotherapy (50). Prospective cohort studies on LT have reported favorable effects on gait in persons who have a motor incomplete SCI even years after injury (6,7,19,20,28,40,51,54). In one randomized clinical trial of individuals with motor incomplete SCI (AIS C and D) treated within 60 days of SCI, the effects of LT was exceptional at 6 months follow-up (> 1.0 m/s mean walking speed), but not superior to the control group that had been trained with the same intensity of weight bearing over ground (19). Those in the LT group who initially walked slowest (initial speed < 0.3 m/s) and the fastest initial walkers (> 0.6 m/s) had the greatest level and rate of recovery. The investigators noted that all individuals with SCI in both groups had received 60 minutes of weight-bearing and 60 sessions of intense therapy and avoided anti-spasticity medication, factors which may have contributed to recovery of walking in both groups. Thus, intensity, duration, and load during training were interpreted as being critical components of activity-based therapy.

Although LT is rapidly expanding across the United States as an activity-based rehabilitative intervention, there have been no prospective, randomized controlled clinical trials conducted with LT and compared with usual rehabilitation. The “standard of care” can be different across rehabilitation centers and also be dependent on individual physical therapists’ decisions so can be highly variable. In this study, we propose to compare a standardized therapy LT to usual care that is routinely given at the different rehabilitation centers. This will be the first study, to our knowledge, that documents specific details of the rehabilitation being provided across multiple rehabilitation sites and correlates the therapy intensity and content to rates of recovery.

b. Health Effects of Rehabilitation

Approximately 1,275,000 people in the U.S. live with paralysis SCI (21). Disabling SCI sequelae include impairments of sensory and autonomic functions and can have devastating results on health and quality of life (5,18). Many measures of health such as the functioning of the cardiopulmonary systems have also been shown to improve with LT, even in individuals who do not regain walking ability (8,9,12,15,16,36,53,54). Harkema et al. (25) conducted a prospective assessment of cardiovascular control in response to an orthostatic stress (blood pressure and heart rate) before and after stand training in clinically complete SCI. The authors demonstrated a significant increase in seated systolic blood pressure (24%) after stand training in individuals with cervical SCI as well as an abolition of standing orthostasis. They attributed these results to repetitive neuromuscular activation of the legs from loading and/or conditioning of cardiovascular responses from repetitively assuming an upright posture. Presumably, given that LT involves both standing and walking, cardiovascular responses would be enhanced due to the dynamic training effects. Results from this study will assess whether cardiovascular function recovers to a greater extent with LT as compared to usual rehabilitation.

Respiratory dysfunction is a common issue in chronic SCI. Without intervention, Stolzmann et al. (43) reported that change in body mass index, respiratory muscle strength and age were significantly related to a decline in forced expiratory volume in 1 sec (FEV) and that forced vital capacity (FVC) was not related to level or severity of SCI, although earlier studies dispute this (31,37). Silva et al.(42) found a significant increase in FVC after a six-week arm-crank ergometry intervention. Janssen et al. (33) reported a 37% increase in pulmonary function after leg cycle ergometry with electrical stimulation. The importance of the proposed study, which includes an examination of pulmonary function after LT in SCI, will be a significant contribution to the field, given the dearth of studies on walking, exercise and pulmonary function in SCI. Moreover, several pulmonary limitations, including lower FEV-1 and FVC, have been associated with lower health related quality of life (HRQoL) (32) and FEV-1 has been correlated with lower the risk of hospitalizations in a group of veterans with chronic SCI (47). These findings support our proposed investigation of pulmonary function and its impact on QOL as secondary measures.

c. Continuum of care from acute injury through rehabilitation

We propose to link acute surgical care with inpatient and outpatient rehabilitation to comprehensively study the recovery of individuals with traumatic SCI. We will use the clinical resources and databases of the **North American Clinical Trials Network for Treatment of Spinal Cord Injury (NACTN)** and the **NeuroRecovery Network (NRN)** in a prospective, Phase II multi-site clinical trial.

NACTN is a consortium of university affiliated hospital neurosurgery departments that was established in 2004 with support from the Christopher Reeve Foundation (CRF); NACTN has been supported by the Department of Defense since 2007. The NACTN clinical centers are: The Methodist Hospital, Houston, the Coordinating Center for NACTN, Robert G. Grossman, MD, Principal Investigator; University of Texas Health Science Center, Houston; University of Toronto; University of Virginia; University of Louisville; University of Maryland; Walter Reed National Military Medical Center; University of Miami; and Thomas Jefferson University. NACTN has a database of over 500 SCI individuals.

NRN, is a consortium of 7 rehabilitation centers funded by CRF through a Cooperative Agreement with the Centers for Disease Control that provides standardized, activity-dependent rehabilitation to individuals with SCI. Five NACTN sites are currently linked to 4 NRN sites in terms of patient flow from acute care to rehabilitation (*See table 2, page 7*). The four linked NRN centers are: Frazier Rehabilitation Institute,

Louisville, the Coordinating Center for NRN, Dr. Susan Harkema, Network Director; Magee Rehabilitation in Philadelphia; The Institute for Rehabilitation and Research in Houston and Lyndhurst Rehabilitation in Toronto. The other NRN centers include Shepherd Center, Atlanta; Boston Medical Center; Kessler Institute for Rehabilitation, West Orange; and Ohio State University Medical Center. Lyndhurst Rehabilitation is now joining the NRN as an additional clinical site and will be available to participate in the trial. The purpose of the NRN is to implement standardized activity-based interventions designed from scientific and clinical evidence for individuals with SCI and obtain comprehensive outcome measures on function, health and quality of life. The NRN consists of collaborating scientists, clinicians and administrators from seven rehabilitation centers in the United States. Currently, the NRN is prospectively studying the effects of LT in persons with chronic incomplete SCI (26,27). Improvements in general health and cardiovascular, pulmonary and quality of life measures have also been observed. Currently, the NRN has a database of over 430 individuals who have received LT as a standardized rehabilitation intervention.

The study design for this proposal utilizes (1) the patient-flow linkage between five of the NACTN clinical centers and four of the NRN centers; (2) the NACTN and NRN databases that contain radiological, physiological, pharmacologic and neurological data for matching patient groups who will then receive rehabilitation. NACTN sites are acute centers which enroll individuals with acute SCI and subsequently transfer the patients to rehabilitation. The linkages between NACTN and NRN sites allows for the investigators to explore the outcomes of combined therapies such as biologic treatments administered early after injury followed by an intense activity based rehabilitation protocol such as LT. These linkages provide the opportunity to enroll individuals early after injury and engage in LT while still in the acute and sub-acute phases of recovery. Furthermore, the NACTN and NRN linkages provide the opportunity to enroll all three groups of patients within the same network. Both the usual care and treatment group subjects can be recruited from this combined network. This will allow collection of detailed and quantitative data on patients through the continuum of care allowing comprehensive evaluation of their recovery in response to standardized LT and usual rehabilitation.

The hypothesis to be tested in this proposal is that in SCI individuals with AIS impairment scores of C or D, who have impaired descending excitatory input to the central pattern generating networks of the spinal cord, LT can provide stimulation and develop plasticity in these pattern generating networks enabling generation of improved walking in response to descending voluntary supraspinal motor impulses to a greater extent than usual rehabilitation. The secondary aims focus on complications associated with SCI and the inability to bear weight and examine the effects of LT on: 1) Cardiovascular Function; 2) Pulmonary Function; 3) ISNCSCI Motor Score impairment; 4) SC Independence Measure (SCIM); and 6) Quality of Life.

d. Preliminary Studies

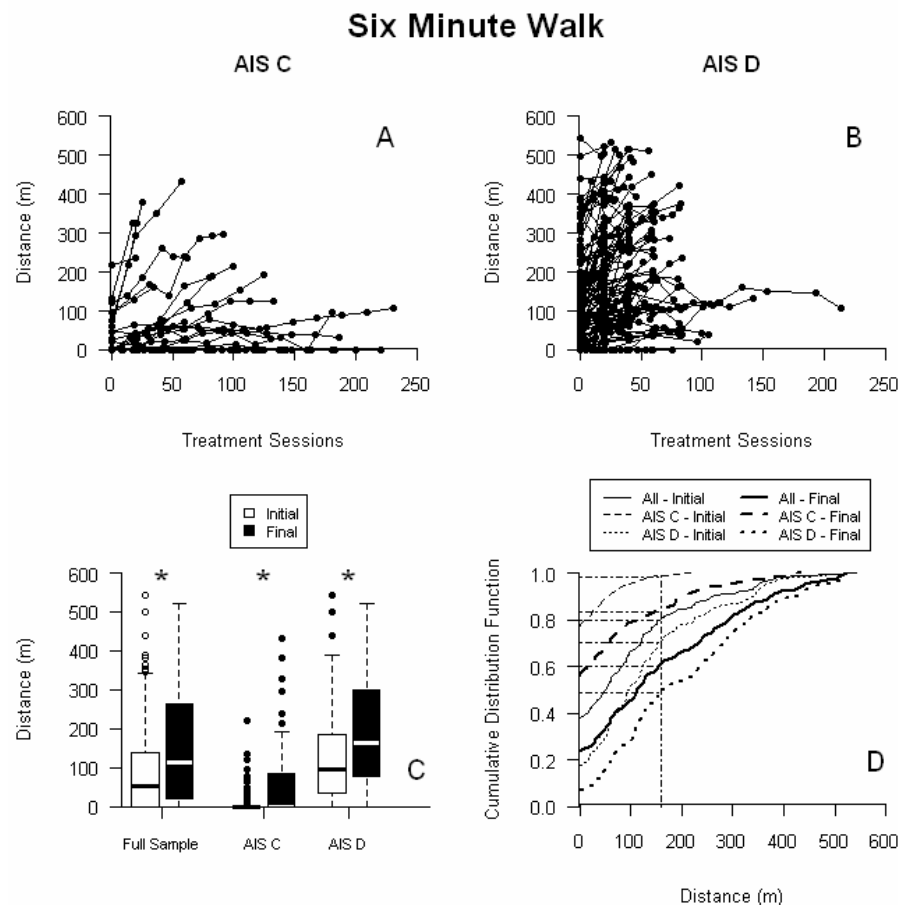
Recovery of walking with Locomotor Training (LT) in individuals with chronic incomplete SCI

Shown below are clinical characteristics and demographic data (Table 1) from 196 individuals with clinically incomplete SCI (AIS C and D) from the NRN that were provided standardized LT across the seven NRN clinical sites including those collaborating in the proposed Phase II multi-site clinical trial. The study was a prospective, non-controlled, multi-site study of a population with medical referral by a NRN site physician. These individuals had a non-progressive, spinal cord lesion above T11, some lower limb movement or visible voluntary contraction and the capacity for generating a lower limb reciprocal alternating flexion/extension stepping pattern in the step training environment using body weight support on a treadmill (BWST) with manual facilitation (*for details see Attachment 7*). The physician initially directed the eventual elimination of the use of any anti-spasticity medications and monitored other medical issues that may have interacted with training effectiveness. The use of Botox or other medications for chemodenervation for spasticity were avoided.

Table 1. Demographic and Clinical Characteristics, Full Sample (N=196)

Gender	AIS Level		Injury Level		Time Since Injury (years)	
Male	148 (76%)	C	66 (34%)	Cervical	138 (70%)	Less than 1 year
Female	48 (24%)	D	130 (66%)	Thoracic	58 (27%)	1-3 years
Age	41 ± 15				Greater than 3 years	52

Significant functional recovery occurred months to years after injury in these individuals with clinically incomplete SCI over a period of at least 60 sessions (approximately 4 -5 months) of LT (Figures 1 and 2). The Six-Minute Walk Test (Figure 2) distances and 10-Meter Walk Test speeds (Figure 3) of all NRN patients significantly improved by an average of 63 m and 0.20 m/s, respectively (signed-rank test, $P<.001$). Significant increases also occurred in the AIS grades C and D groups (signed-rank test, $P<.001$) and were significantly different from each other (rank-sum test, $p<.001$). Twenty-eight (41%) of the 69 patients who were unable to complete the Six-Minute Walk Test and 10-Meter Walk Test became ambulatory by completing 1 of the walk tests at their last evaluation, with 15 of 50 patients with AIS grade C (30%) and 13 of 19 with AIS grade D (68%).

**Figure 1.** Plots of the Six-Minute Walk Test for NRN patients.

Line plots of individual patient progress in patients with (A) AIS grade C (n=66) and (B) AIS grade D (n=130). (C) Box plot of initial and final evaluations for the full sample and by AIS grade. *Significant improvement from initial to final evaluation (Wilcoxon rank-sum test, $P<.001$). (D) Cumulative distribution functions (smoothed by a cubic spline) of initial and final evaluations for the full sample and patients with AIS grades C and D. Dash-dotted vertical line at distance of 158.4m indicates a threshold equivalent to a safe speed for community ambulation (0.44m/s), and dash-dotted horizontal lines provide the empirical cumulative distribution functions at 158.4m.

Ten Meter Walk

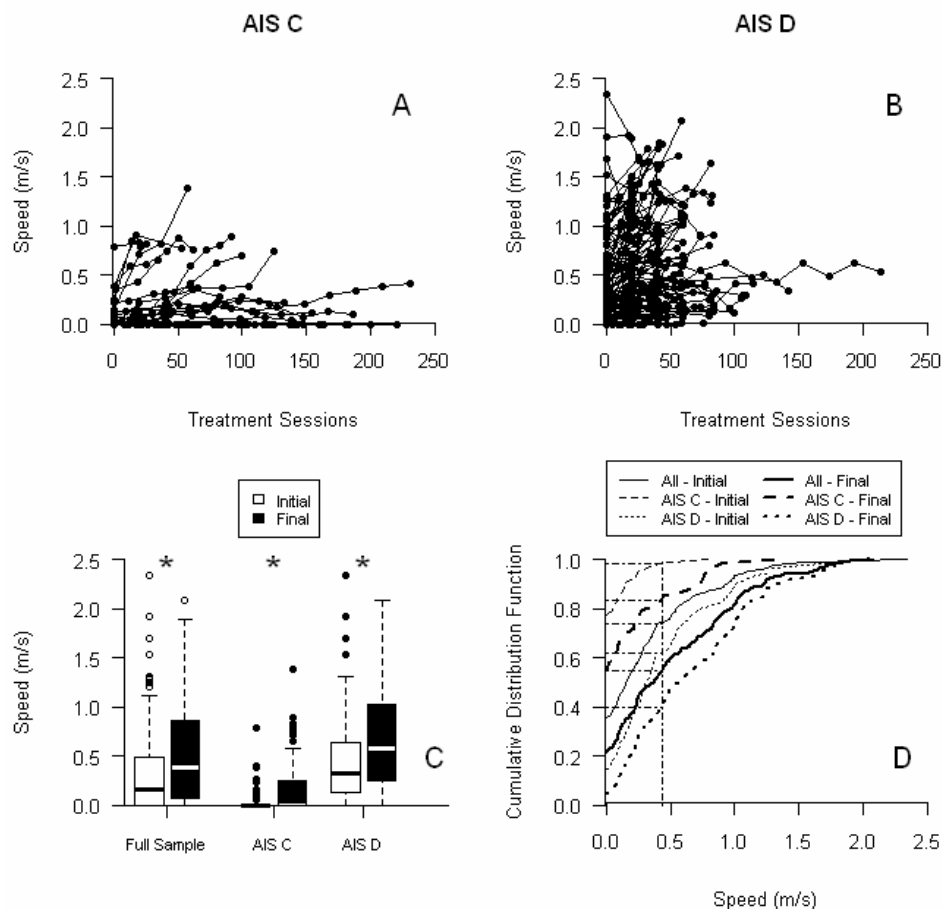


Figure 2. Plots of the 10-Meter Walk Test for NRN patients.

Line plots of individual patient progress in patients with (A) AIS grade C (n=66) and (B) AIS grade D (n=130). (C) Box plot of initial and final evaluations for the full sample and by AIS grade. *Significant improvement from initial to final evaluation (Wilcoxon rank-sum test, $P < .001$). (D) Cumulative distribution functions (smoothed by a cubic spline) of initial and final evaluations for the full sample and patients with AIS grades C and D. Dash-dotted vertical line at speed of 0.44m/s indicates a threshold equivalent to a safe speed for community ambulation, and dash-dotted horizontal lines provide the empirical cumulative distribution functions at 0.44m/s.

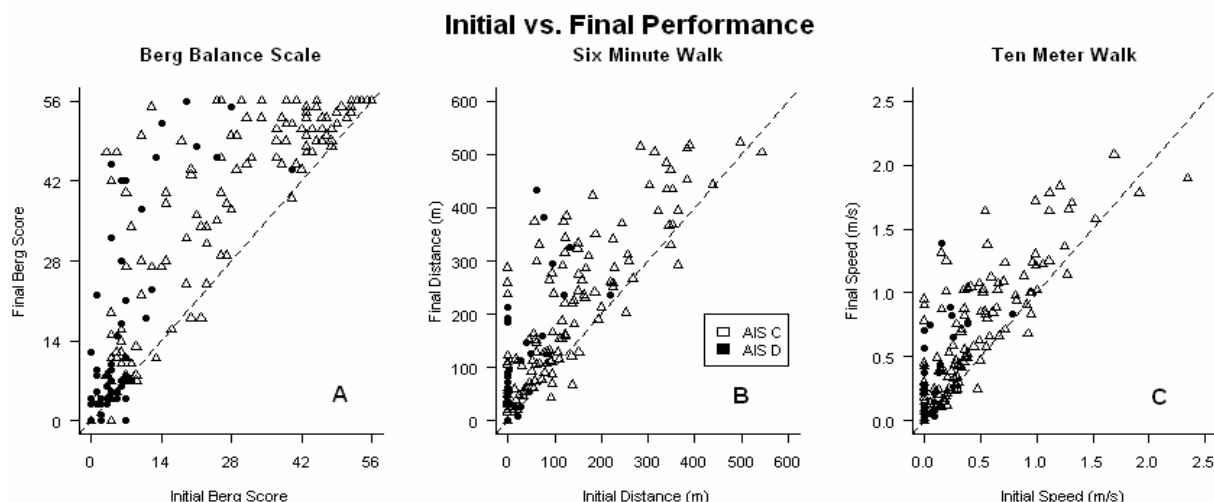


Figure 3. Initial versus final performance.

Scatterplot of final evaluation (y-axis) against initial evaluation (x-axis) for the (A) Berg Balance Scale, (B) Six-Minute Walk Test, and (C) 10-Meter Walk Test for patients with AIS grades C (n=66) and D (n=130) enrolled in the NRN. Significant improvement from initial to final evaluation occurred for each measure ($P < .001$), reflected in the plot as points lying in the left upper half of the plane.

There was high variability in the initial walking outcomes and with the magnitude of improvements in the chronic SCI population of those individuals classified as AIS C and D. We have recently modeled the progression of three functional outcome measures from patients with incomplete spinal cord injury (SCI) receiving standardized Locomotor Training in 337 patients with incomplete SCI (AIS C and D) who were enrolled in the NRN between February 2008 and March 2011. Patients varied significantly across groups defined by recovery status and American Spinal Injury Association (ASIA) Impairment Scale (AIS) level at enrollment with respect to baseline performance and rates of change over time. There was significant improvement on each outcome measure and significant attenuation of improvement over time that was significantly impacted by the time since SCI. Variability in patterns of recovery over time suggest that time since SCI and patient functional status at enrollment are important predictors of performance and recovery as measured by the targeted outcome measures.

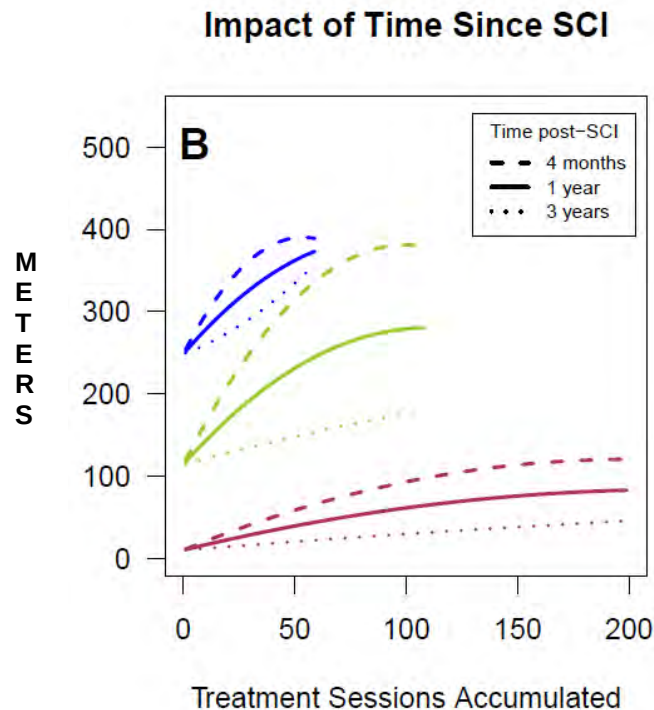


Figure 4. Impact of time since SCI on recovery.

Population-level average recovery curves of the 6 Minute Walk in which time since SCI significantly impacted recovery rates. Curves are plotted up to the lesser of the maximum number of treatment sessions. Blue, green and red colors indicate classification based on the newly developed NeuroRecovery Scale developed by the NRN investigators. In brief, the lowest phase, red, represents those who cannot stand, the green represents those who can stand but not walk, and the blue represents those who enrolled with the ability to walk with deficits.

These results show that post-injury recovery can continue to occur over a period of months, or even several years, after injury with LT. The magnitude of recovery varied among the patients. Subsequent modeling of 396 patients identified that the longer the time since injury the lower the rate of recovery suggesting that earlier intervention of LT may have an even higher rate of recovery than observed in this AIS C and D population.

2. Objectives/Hypotheses/Specific Aims

a. Objectives

We propose to conduct a prospective, randomized, controlled, multi-site Phase II clinical trial to test whether LT significantly increases the ability to walk longer distances as compared to usual rehabilitation after clinically incomplete SCI. We also will test, as secondary measures, whether cardiovascular and pulmonary function improves to a greater extent with LT, if voluntary motor activity is greater and whether ultimately their ability to function independently and their quality of life is improved as compared to those who receive usual rehabilitation.

The Study Design utilizes (1) the patient-flow linkage between five NACTN clinical centers and 4 of the NRN centers; (2) the NACTN and NRN databases that contain radiological, physiological, pharmacologic and neurological data for matching patient groups.

Table 2. Linked NACTN-NRN Centers	
NACTN	NRN
1. The Methodist Hospital (Houston) 2. U of Texas Health Science Center (Houston)	The Institute for Rehabilitation (Houston)
3. University of Louisville (Louisville)	Frazier Rehabilitation (Louisville)
4. Thomas Jefferson University (Philadelphia)	Magee Rehabilitation (Philadelphia)
5. University of Toronto	Lyndhurst Rehabilitation

Outcome measure comparisons will be made between 3 patient groups:

- From linked NACTN-NRN centers
1. LT Therapy (n=32)
2. Usual Rehabilitation (n=16)
- From non-linked NACTN centers
3. Usual Rehabilitation (n=16)

Primary Outcome:

1. 6 Minute Walk Test

Secondary Outcomes:

1. Cardiovascular Function
2. Pulmonary Function
3. ISNCSCI Motor Score
3. SC Independence Measure (SCIM)
4. Quality of Life

b. Aims and hypotheses

The primary aim is to evaluate the efficacy, safety, and acceptability of Locomotor Training compared to Usual Rehabilitation in recovery of ambulation in a pilot stratified randomized comparative efficacy trial. It is expected that the results of this research will produce sufficient evidence to evaluate the merits of conducting a subsequent pivotal randomized national clinical trial on the effectiveness of Locomotor Training.

The primary hypothesis to be tested in this proposal is that in SCI individuals with AIS impairment scores of C or D, who have impaired descending excitatory input to the central pattern generating networks of the spinal cord, LT can provide stimulation and develop plasticity in these pattern generating networks enabling generation of improved standing and stepping in response to descending voluntary supraspinal motor impulses in comparison to Usual Rehabilitation.

The primary outcome measures are based on the Six-Minute Walk Test, a standardized measure of walking recovery. Distance walked in meters and walking speed in meters/second will be assessed at baseline and at intervals of 20 sessions of Locomotor Training and assessed at comparable time points for patients randomized to Usual Rehabilitation.

The secondary aims focus on intercurrent events and neurological correlates associated with SCI and the inability to bear weight; to examine the comparative effects of LT on 1) Cardiovascular Function, 2) Pulmonary Function, Spinal Cord Independence Measure (SCIM); SCI Motor Score; 3) AIS impairment grade; and 4) Quality of Life. Cardiovascular, and quality of life measures will be performed at baseline and at the end of LT training or after 4 months following baseline for Usual Rehabilitation, and 3 months after LT training or 6 months following baseline. The cardiovascular and pulmonary assessments will be conducted within 2 days of the locomotor assessment. The quality of life measurements will be conducted at the convenience of the research participant within one week of the locomotor assessment.

The 6 minute walk, cardiovascular and pulmonary assessments, and quality of life questionnaires will be performed at baseline in all research participants enrolled in the study (n=64). The assessments in the LT group will occur at intervals of 20 sessions. For the groups not receiving LT, assessments will occur at a comparable timeline (1 month intervals) to the LT training groups as specified in detail below.

The *primary outcome measure*, the locomotor assessment, the 6 minute walk, will be obtained at baseline, during the intervention (every 20 LT sessions or monthly), at the end of the intervention (LT training or after 3 months following baseline), and 3 months after the intervention (3 months after LT training has ended or 6 months following baseline; Figure 2).

The *secondary outcome measures* include the (SCIM), cardiovascular function (orthostatic stress test), and pulmonary function (spirometry), and SCI-QOL questionnaires. Cardiovascular, pulmonary and quality of life measures will be performed at baseline, at the end of LT training or after 3 months following baseline, and 3 months after LT training or 6 months following baseline. The cardiovascular and pulmonary assessments will be conducted within 2 days of the locomotor assessment. The quality of life measurements will be conducted at the convenience of the research participant within one week of the locomotor assessment.

Secondary Outcome Measures:

1) SCIM 2) Orthostatic Stress Test; 3) INSCI 4) Spirometry; and 5) Spinal Cord Injury specific Health Related Quality of Life measure (SCI-QOL), SF-36 and Satisfaction with Life Scale.

3. Study Design (Overall design, details of specific outcome measures in sections below):

The study design selected is a Phase IIb comparative effectiveness pilot study design with a total 64 patients randomized to either Locomotor Training or Usual Rehabilitation Care. The design is stratified by AIS grade (C versus D) as a technique to improve the comparability of the treatment groups and as an analytical design method to increase the precision of the comparison of the primary Six-Minute Walk Test outcome measures between treatment groups.

The study design also provides for an additional external control group which will be derived from a sample of 32 patients enrolled in the registry of the North American Clinical Trials Network for Spinal Cord Injury. This external control group will provide additional information about recovery of walking at six-months and 12-months following SCI from the non-linked NACTN centers. The sample will be balanced to match the main features of the randomized Usual Rehabilitation Care group.

a. Enrollment

The study site PI's from the eight NACTN sites will recruit enroll the patients into the study. Participants may discontinue from the trial at any time at their own request, or they may be withdrawn at the discretion of the site investigators for safety, behavioral, or other reasons. If a participant does not return for a scheduled visit, every effort will be made to contact the participant. The site investigator will inquire about the reason for withdrawal, request that the participant return for a final visit, and follow-up with the participant regarding any unresolved adverse events.

b. Randomization

The study design is a parallel group randomized design with equal allocation to LT or Usual Rehabilitation. The randomization will be blocked and stratified by AIS C and AIS D since preliminary data and recent literature suggests AIS grade is an important prognostic factor for recovery of walking. Within each clinical center patients will be randomized within AIS strata to either Locomotor Training or Usual Rehabilitation using a computer-generated blocked and stratified randomization plan where the size of the blocks are random.. The allocation will be based on randomly permuted blocks to prevent discovery of the random allocation algorithm by clinical investigators. The stratified randomization plan will be designed to allocate 16 patients within each of the two AIS grades to each of the two treatments.

A secure and encrypted website will be developed for randomization. This website will provide for verifying eligibility requirements before a patient is actually randomized and will also assign an identification number to each patient that encodes clinical site and additional patient markers to insure unique identification and proper stratification and randomization. The randomization algorithm will be developed by the Biostatistics Faculty at the University of Texas School of Public Health Data Management Center. Prior to the start of randomization, the central randomization algorithm and website will be tested by each clinical center.

c. Primary Outcome Measure

Six Minute Walk Test

The individual's ability to walk independently will be assessed using standardized and validated clinical measures (i.e. 6 minute walk test (30,45,46)). Assistive devices will be allowed during the testing with the same device being used during all testing sessions. The assessment will be conducted between 10 am in the morning and 2 pm in the afternoon for all participants across sites to minimize the variability of spasticity known to occur throughout the day. The research participant will be advised to take their medication on the day of testing. A list of instructions will be provided to the research participant that will require them to avoid intense exercise, alcohol, restrict caffeine intake, and get adequate rest. Research participants are asked to complete their bowel programs at their usual times and to catheterize as needed prior to testing. Whenever possible the individual research participant will repeat this measure as close to the time obtained for baseline measures.

Equipment:

- uninterrupted walking course with measured distances
- digital stopwatch
- blood pressure cuff
- stethoscope
- heart rate/oxygen saturation meter
- video camera
- tape
- 2 small cones

Instructions for the examiner:

Establish a measured course indoors to accommodate a continuous walking pattern. If possible, this course should be 100 ft in length with a cone demarcating each end of the distance. If a 100 ft path can not be located, the longest straight path available should be used. If a straight path is unavailable, select a course with as few turns as possible and the longest straight paths between turns as possible. Always use the same path for testing of all research participants. Discuss the test with the participant using the standard language. For instance, explain that he/she is going to walk for 6 minutes, “As far as you can.”

Instruct the participant using the starting instructions detailed in protocol procedure. The participant may stop to rest standing stationary or leaning against a wall. Use a stopwatch and start timing when the participant takes his/her first step. Measure and record the total distance walked in meters during the 6 minutes (rounded to the nearest tenth). Perform the protocol with the Initial Device, which is the first device used by the participant. If he or she uses a different assistive device now, ask him/her to use the assistive device they used in the first test. No bracing, facilitation or assistance is allowed during the 6 minute walk test. The examiner should walk behind the participant so as not to influence his/her pace. Providing assistance/guarding should be avoided but may be necessary if the participant becomes unsafe. Remove assistance once safety has been restored and continue with the test. If walking cannot continue without assistance, then stop the test.

d. Secondary Outcome Measures

Orthostatic Stress Test

Equipment:

- stopwatch
- automatic sphygmomanometer
- automatic vital signs monitor
- heart rate/oxygen saturation meter
- wheelchair or chair with arms
- cardiac chair or 3 section tilt table

Place the blood pressure cuff around one arm and the oximeter on the opposite arm’s index finger. Keep these placements consistent throughout the duration of the measurements. Record the time for each measurement using a stopwatch. Record the time measurement that is displayed on the automatic vital signs monitor

Supine: Instruct the participant to rest quietly in the supine position for at least 5 to 10 minutes. Explain that you will not talk to him/her, and ask them to remain quiet until all measurements are taken. Take 3 blood pressure and heart rate measurements at 1-minute intervals. Record time, systolic, diastolic, and heart rate.

Supine to Sit: Passively sit the participant up to 90 degrees (hip), with legs down (knee flexed at 90 degrees). Explain to the participant to remain relaxed and not assist in sitting up. Record the time when supine to sit is completed. Begin blood pressure recordings immediately. Record time, systolic, diastolic, and heart rate.

Sitting: Participant should be supported to maintain their sitting position passively. Take 10 measurements at 1-minute intervals. Record time, systolic pressure, diastolic pressure, and heart rate and oxygen saturation.

Blood pressure, heart rate, and oxygen saturation should be assessed before therapy while participant is sitting in a wheelchair or a chair with arms

Spirometry

Standard spirometry (35) will be performed in a seated position with nose clip on by using BreezeSuite System (MedGraphics, St. Paul, MN). We will measure the rate at which the lung changes volume during forced breathing maneuvers beginning with a full inhalation, followed by a forced expiration that rapidly empties the lungs. Expiration will be continued until a plateau in exhaled volume is reached. Forced vital capacity and forced expiratory volume in 1 second will be measured and expressed as the percent of the predicted value for each research participant based on a database of individuals that are neurologically intact with no known

pulmonary complaints that was derived based on gender, age, and height (22). Three acceptable spirograms will be obtained and the result of the best attempt will be used (1).

Neurological Assessment: ISNCSCI Sensory, Motor, and AIS Impairment Scale Evaluations

The AIS scale assessment is to be performed at the screening visit (3, 38). If the individual enrolls in the study, the AIS will be repeated at the end of the intervention. This tool assesses sensory function (light touch and pinprick) in each dermatome and motor function (6-point Medical Research Council Scale where 0 = total paralysis and 5 = normal strength) in ten key muscles. It determines the neurological level of injury (NLI), defined as the lowest spinal level (most caudal segment) with normal neurological function, and assigns a classification of severity according to the AIS. Briefly, AIS grade A is assigned to subjects with no sensory or motor function in the lowest sacral segments (S4-S5). These individuals are considered to have *sensory and motor complete injuries*. AIS grade B indicates that there is some sensory, but not motor function, in the lowest sacral segments. AIS grade C indicates some motor function, defined by presence of voluntary anal contraction or sparing of motor function more than 3 levels below the motor level in which more than half of the key muscles below the neurological level have a muscle grade less than 3 (i.e. grade 0-2). AIS grade D denotes substantial motor function beneath the NLI in which at least half of the key muscles below the neurological level have a muscle grade greater than or equal to 3. Both AIS grade C and grade D are considered *motor incomplete injuries*, and these are the subjects eligible for this study.

Spinal Cord Independence Measure (SCIM)

The SCIM is used routinely to assess the ability of individuals after SCI to function independently in daily activities of living. This measure has shown reliability and validity for this population and shown to be effective for use in clinical trials. For details on scoring and measures see *Attachment 6*.

Quality of Life Assessments

Health-related quality of life (HRQOL or simply “QOL”) , a subjectively evaluated multidimensional construct, “refers to the extent to which one’s usual or expected physical, emotional, and social well-being are affected by a medical condition or its treatment”(11). HRQOL is an increasingly important patient reported outcome in SCI clinical trials, as traditional outcomes measures fail to account for the overall functioning of an individual or the direct and indirect impact of new treatments on all aspects of a person with SCI. Researchers have come to recognize that global quality of life (QOL) outcomes measures, including physical health, level of social support, participation in the community, and level of everyday functioning, predict satisfaction over the long term.

The SCI-QOL/SCI-CAT is a comprehensive, SCI-specific QOL measurement system covering four major domains, namely Physical-Functional Health (including Mobility, Upper Extremity, and Activities of Daily Living subdomains), Physical-Medical Health (including Respiratory, Skin/Pressure Ulcers, Bowel, Bladder and Pain subdomains), Emotional Health (including Positive Psychological Function, Anxiety, Depression, Stigma, Trauma, Loss, Self-Esteem, and Resilience), and Social Participation (including Social Role Performance, Social Role Satisfaction, and Independence/Autonomy). It is linked to some large measurement initiatives advanced by the NIH. Since 2002, the NIH has sponsored large initiatives to develop measurement tools for use across all of their patient populations. This includes the Patient Reported Outcomes Measurement Information System (PROMIS) (www.nihpromis.org), and the Neuro-QOL measure for individuals with neurological disorders (www.neuroqol.org.) The resulting tools have been developed using state of the art measurement theory and methodology including item banking (13,14,14), Item Response Theory (IRT)(29), and Computerized Adaptive Testing (CAT)(10). Due to the nature and extent of federal funding for these projects, it is likely that the PROMIS and Neuro-QOL measures will be measures of choice across NIH-funded clinical trials. The SCI-QOL/SCI-CAT project has extended the PROMIS/Neuro-QOL measurement system into spinal cord injury specifically by validating the PROMIS/Neuro-QOL items in an SCI sample and developing new, targeted items to adequately capture the most important HRQOL issues for individuals with SCI.

The SCI-QOL/SCI-CAT was developed using a participatory action research methodology (52), which enlisted individuals with SCI and SCI clinicians as key stakeholders in measure development. A series of 32 focus groups (n=24 groups of individuals with SCI and n=8 groups with SCI clinicians) were held and all focus group feedback was analyzed to ensure conceptual grounding of this measurement system with regard to key QOL issues in SCI. This community feedback was used to extend the Neuro-QOL/PROMIS measurement system into SCI. Item response theory will be used to develop short forms and a computerized adaptive test (CAT) version of the SCI-QOL/SCI-CAT.

The SF-36(49), developed by RAND to assess outcomes of medical care, is the most widely used health status measure in the world(2). The SF-36 contains 36 items across eight subscales (Physical Functioning, Role Limitations: Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role Limitations: Emotional, and Mental Health) and two higher-order component scores, Physical and Mental and has successfully demonstrated reliability(23,48) and validity(34). Its holistic conceptualization of health is generally appropriate, but it is widely criticized by disability researchers for its tendency to “conflate functional ability with health status”(2). The SF-36(49), which is not specific for SCI disease burden but has been widely applied and validated, will be utilized as a legacy measure.

The Satisfaction with Life Scale (SWLS)(17) is a 5-item measure of the single concept of global life satisfaction. The SWLS has been shown to be both reliable and valid in general health populations(17) and also exhibits sensitivity to change (41). While reliability specifically within an SCI sample has yet to be examined, the SWLS is currently used in SCI Model Systems dataset, and normative data for individuals with SCI is available. The SWLS will serve as a legacy measure of overall QOL. LT will be prescribed 5 days/week (1.5 hours/session) for a total of 86 sessions that included step training, overground assessment, and community integration.

4. Statistical Plan and Data Analysis:

Sample size was based both on statistical grounds and clinical judgments with the objective of gaining useful preliminary comparative information about the feasibility, safety, and efficacy of Locomotor Training compared Usual Rehabilitation Care.

A sample size of 16 patients per treatment group for AIS C patients and 16 patients per group for AIS D patients will be able to detect a 50% or greater increase in walking distance with power of at least 80% at the 10% level of significance for a two-sided test of hypothesis. This sample size estimate is based 1 baseline measurement and 3 follow-up measurements, assuming a within person standard deviation of 40 meters and a correlation of 0.80 between baseline and follow-up measurements and a correlation of 0.80 between follow-up measurements. This sample size estimate is based on an analysis of covariance model where the baseline measurement for each patient is considered as a covariate in a general linear model for treatment comparison of repeated follow-up measurements.

The sample size proposed in this project is consistent with the sample sizes of 23 patients per group proposed in a recently published protocol for a randomized multicenter controlled trial evaluating the effectiveness of automated locomotor training in patients with acute incomplete spinal cord injury using walking speed as the primary outcome.

In addition to the analysis of covariance models for walking distance and walking speed, these two outcomes will also be compared in the stratified groups using the difference at 6 months after injury and baseline at the start of Locomotor training or usual care. Walking distance and walking speed will be considered as bivariate normal and Hotelling's T-squared test will be used to compare the two treatment groups.

The repeated measures of both the primary and secondary outcome measures will also be analyzed using random-effect models for longitudinal analysis of the outcome measures. In particular, level-1 and level-2 random effect submodels for individual change over time will be estimated for the primary and secondary outcome measurements. These models will be preceded by empirical profile plots of individuals comparing profiles in the two treatment groups. This is approximately equivalent to comparing the slopes of individual

patients within and between the two treatment groups. The estimation will be done using generalized estimation equations (GEE) and its variants suitable for unequal time points and imputation of non-informative and informative missing data. GEE models allow for repeated or dependent and the ability to specify the correlation structure of the repeated measures.

One distinct advantage of having access to NACTN registry data for the linked NACTN-NRN centers is the ability to add to randomized cases individual data on the key secondary measures including, motor score, and AIS grades measured at the time of admission of SCI treatment, and at time of discharge from acute care for inclusion in enhanced longitudinal models of primary and secondary outcomes. The registry also has SCIM at the time of hospital discharge from acute care giving another time point for measurement of mobility, self-care and respiration and sphincter management. Lastly for all randomized patients, the registry can provide detailed data on the course of SCI treatment, radiology, and complications ascertained during acute care. The data protocol available in the NACTN registry is given in Attachment 10.

Attachment 2: Supporting Documentation:

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2. Acronyms and Symbol Definitions:

6MW	Six Minute Walk Test
10MW	Ten Meter Walk Test
AE	Adverse Events
AIS	ASIA Impairment Scale
ALT	Alanine Aminotransferase Test
ANOVA	Analysis of Variance
ASIA	American Spinal Injury Association
AST	Aspartate Aminotransferase
BID	Twice Daily
BP	Blood Pressure
BUN	Blood Urea Nitrogen
BWL	Body Weight Load
BWS	Body Weight Support
BWST	Body Weight Support on a Treadmill
CARF	Commission on Accreditation of Rehabilitation Facilities
CAT	Computerized Adaptive Testing
CDC	Centers for Disease Control
CDRF	Christopher & Dana Reeve Foundation
CNS	Central Nervous System
CRF	Case Report Form
DOD	Department of Defense
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
EMG	Electromyography
FDA	Food and Drug Administration
FEV1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
GABA	Gamma Aminobutyric Acid
HEENT	Examination of Head, Eyes, Ears, Nose and Throat
HR	Heart Rate
HRPO	Human Research Protections Office
HRQoL	Health Related Quality of Life
IQR	Interquartile Range
IRB	Institutional Review Board
IRT	Item Response Theory
ISNCSCI	International Standards for Neurological Classification of Spinal Cord Injury
ITW	Web-based Data Collection System
LDH	Lactate Dehydrogenase
LT	Locomotor Training
MS	Multiple Sclerosis
NACTN	North American Clinical Trial Network
NIDRR	National Institute on Disability and Rehabilitation Research
NIH	National Institutes of Health
NLI	Neurological Level of Injury
NRN	NeuroRecovery Network
ORP	Office of Research Protections
OT	Occupational Therapist
PACT	Preservation and Amputee Care and Treatment
PI	Principal Investigator
PROMIS	Patient Reported Outcome Measurement Information System

PT	Physical Therapist
QID	Four Times per Day
QOL	Quality of Life Measures
RBC	Red Blood Cell Count
RR&D	Rehabilitation Research and Development
SAE	Serious Adverse Event
SCI	Spinal Cord Injury
SCIM	Spinal Cord Independence Measure
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SPO2	Saturation of Peripheral Oxygen
SWLS	Satisfaction With Life Scale
TMH	The Methodist Hospital
TIRR	The Institute for Rehabilitation and Research
TJU	Thomas Jefferson University
UM	University of Miami
UMD	University of Maryland
UofL	University of Louisville
USAMRMC	US Army Medical Research and Material Command
UTSPH	University of Texas Public School of Health
UVA	University of Virginia
VA	Veterans Affairs
VAMC	VA Medical Center
WBC	White Blood Cell Count

3. Facilities, Existing Equipment, and Other Resources:

a. NACTN Coordinating Center - The Methodist Hospital

Facilities

The Methodist Hospital System has 1,510 beds and 72,598 admissions in 2010. The main hospital is located centrally in Houston in the Texas Medical Center. The hospital system includes four satellite hospitals placed in the four quadrants of the city surrounding the center. .

The Methodist Hospital Neurological Institute (TMH-NI) was established in 2004 by the Chair of Neurosurgery, Dr. Robert G. Grossman. The TMH NI integrates the activities of neurology, neurosurgery, neuro-radiology, neuro-rehabilitation, neuro-ophthalmology, neuro-intensive care, neuro-anesthesia, neuropathology and psychiatry.

The TMH-NI has extensive contiguous facilities at TMH that facilitate patient care and research. The 4th floor in the main hospital contains 40 inpatient neurosurgical beds, 20 fully monitored neurointensive care unit beds, the clinical neurophysiology unit with 5 video/EEG monitoring rooms. Seven operating rooms dedicated to Neurosurgery are on the 3rd floor. The operating rooms are equipped with image-guided navigation for cranial and spinal surgery, microelectrode recording and for angiography. Neuroradiology is on the 2nd floor, as are the main laboratories for pathology, chemistry and neuropathology. The Emergency Room is on the first floor.

This facility arrangement allows for rapid care of patients. Outpatient facilities are contiguous in 50,000 square feet on the 8th and 9th floors of Scurlock Tower, connected to the main hospital. Neurorehabilitation, with 30 beds and a gymnasium, is on the 9th and 10th floors of the West Pavillion attached to the outpatient towers.

Over the past six years, the PI of the present proposal and the program coordinator, Elizabeth G. Toups, have coordinated the North American Clinical Trials Network for Treatment of Spinal Cord Injury (NACTN), an international (US-Canadian) consortium of Neurosurgery departments of University affiliated hospitals. NACTN's goal is to bring promising new therapies from the laboratory to clinical trials. NACTN has built a registry of over 500 acute spinal cord injury patients with detailed information from the time of injury to one year post-injury of the physiological, neurological, radiological findings following spinal cord injury, medical and surgical treatments employed and neurological outcome data.

b. NACTN - University of Texas Health Science Center

Facilities

The University of Texas Health Science Center at Houston (UTHealth), the most comprehensive academic health center in The UT System and the U.S. Gulf Coast region, is home to schools of biomedical informatics, biomedical sciences, dentistry, medicine, nursing and public health. UTHealth educates more healthcare professionals than any health-related institution in the State of Texas and features the nation's seventh-largest medical school. It also includes a psychiatric hospital and a growing network of clinics throughout the region. The university's primary teaching hospitals include Memorial Hermann-Texas Medical Center, Children's Memorial Hermann Hospital and Lyndon B. Johnson General Hospital. Founded in 1972 by the U.T. System Board of Regents, UTHealth's 10,000-plus faculty, staff, students and residents are committed to delivering innovative solutions that create the best hope for a healthier future.

c. NACTN - University of Texas School of Public Health Data Management Center

Facilities

The University of Texas School of Public Health provides a direct service to communities through the research efforts of its campuses, divisions and research centers and the Institute for Health Policy. It is the school's objective to translate its discoveries into policies and programs that have a beneficial impact on the health of the public across Texas and globally.

The school's research centers have been developed by faculty to enhance areas of interdisciplinary research. The centers play an important role in supporting the diverse areas of public health and give students excellent opportunities to interact in real world work environments.

Biostatisticians play a key role in the design, conduct, and analysis of research studies and develop new methods to address emerging problems.

Faculty members in the Division of Biostatistics have led and contributed to the development of statistical methods for many areas including clinical trial design and analysis, Bayesian statistics, statistical genomics and genetics, statistical learning methodology and applications, stochastic processes, longitudinal and correlated data analysis, and bioinformatics. These methods are applied to a wide range of problems including hypertension, stem cells, cancer, cervical cancer detection using optical spectroscopy, US-Mexico border health issues, environmental health, prevention of HIV, molecular evolution and phylogenetics, vision research, and Parkinson's disease. In addition, Biostatistics faculty have led and contributed to important public health projects that have made a difference in people's lives.

Equipment

UTSPH operates its own computer facility dedicated to research and education. Networks of servers support UNIX-based systems and Windows-based systems for simulation. A wide variety of state-of-the-art statistical software is available to students and WiFi is also available on campus. Computer Services staff are available to aid students in using the equipment, the various analytical and data management software packages, and the large library of health information research databases.

d. NRN - The Institute for Rehabilitation and Research (TIRR)

Facilities

TIRR's Spinal Cord Injury Center was initiated in 1961. Today, TIRR provides the full array of services, both diagnostic and therapeutic and acts as the hub for care of patients with SCI. TIRR currently has 96 inpatient beds, approximately 35 percent of which are usually devoted to patients with SCI. Locomotor training facility at TIRR is 700 square feet and is located near rehabilitation services where the research participants will be seen by the site physician for screening and medical oversight.

Equipment

The NRN Centers have standardized equipment required to provide the locomotor training intervention: (1) one closed loop computer-controlled Body Weight Support system with a treadmill that allows speeds from 0.5 – 10 mph, the option to resume at the most recent stepping speed, and change grades. The treadmill also includes a seating system with ergonomically appropriate support design for staff safety and effectiveness of providing manual assistance during locomotor training. (2) Medical harnesses in a range of sizes. (3) Hi-Lo mat for harness application and stretching. (4) Automatic blood pressure monitoring equipment, including a cardiac chair or mat that can quickly change position to a 90 degree hip/90 degree knee position for measuring orthostatic hypotension. (5) Basic spirometry equipment. (6) Digital video camera, tripods, and external hard drives for video storage. (7) Computer with secured internet access for data entry in ITW.

e. NACTN - University of Louisville

Facilities

University of Louisville Hospital has been a presence in the Louisville area for nearly 200 years. The current facility was built in 1979, has 404 beds and has undergone several major renovations and expansions. Affiliated with the University of Louisville School of Medicine, U of L Health Care is staffed with more than 500 physicians. University of Louisville Hospital is the region's preeminent medical teaching and research hospital, and plays a key role in ensuring the quality of health care in the community. U of L Hospital has also developed a robot system for providing specialty health care to rural health partners. It is the only Level 1 Trauma Center in this region and our residents spend nearly half of their residency training assigned to U of L.

University Hospital is the area's only Level I Trauma Center. The Trauma Team is a multidisciplinary team and offers everything from ultrasound procedures for obstetrics and trauma emergencies to the area's only decontamination facility for chemical and biological decontamination of individuals exposed to hazardous materials. The Trauma Center is located in 56,000 sq. ft. and capable of treating 86 patients simultaneously, has 43 patient bays, 14 trauma/surgical ICU beds, 5 burn beds, 49 critical care beds. It has a 24 hour dedicated operating room. In 2010, University Hospital treated 3,000 trauma and burn patients.

Outpatient care for individuals with SCI is provided through the Center for Advanced Neuroscience clinic. Opened in 2008, the Center is located on the 11th floor of FRNC in five rooms (2,629 sq ft). Through a unique collaboration of Frazier Rehab and the University of Louisville (UofL), this convenient, centralized outpatient facility provides continued comprehensive medical and rehabilitative management for patients with SCI throughout their life span by UofL board-certified specialists in physical medicine and rehabilitation, as well as a number of other medical specialists. In addition to its role in the medical management of outpatients, the Center is also the point of integration of SCI clinical and research activities.

f. NRN - University of Louisville and Frazier Rehab Institute:

Facilities

Frazier Rehab and Neuroscience Center is a 15-story rehabilitation facility that covers more than 320,000 square feet and houses 135 inpatient beds. In conjunction with the University of Louisville School of Medicine, Frazier Rehab Institute conducts a residency program in physical medicine and rehabilitation. Along with medical care and rehab nursing, this rehab hospital offers physical, occupational and speech therapies, therapeutic recreation, psychology and neuropsychological testing services to each patient in the acute care, inpatient and outpatient rehab settings at this location.

The tenth floor, with 28 beds, is dedicated to inpatient care for individuals with SCI. It features an inpatient therapy gym, used exclusively for the rehabilitation of SCI patients. In addition, there is a 6,500 square feet outpatient gym that contains two Innoventor Body Weight Support Systems used for Locomotor Training of SCI patients.

Locomotor Training will occur in the 2,900 square foot Spinal Cord Medicine Gym which includes the two Innoventor Body Weight Support Systems. It also allows for maintaining clinical records and gathering and sharing data that includes networking software and server capacity for data entry and reporting. The Spinal Cord Medicine Clinic is located on the eleventh floor and will be utilized for research participant screening and physician visits.

Equipment

The NRN Centers have standardized equipment required to provide the locomotor training intervention: (1) two closed loop computer-controlled Body Weight Support system with a treadmill that allows speeds from 0.5 – 10 mph, the option to resume at the most recent stepping speed, and change grades. The treadmill also includes a seating system with ergonomically appropriate support design for staff safety and effectiveness of providing manual assistance during locomotor training. (2) Medical harnesses in a range of sizes. (3) Hi-Lo mat for harness application and stretching. (4) Automatic blood pressure monitoring equipment, including a cardiac chair or mat that can quickly change position to a 90 degree hip/90 degree knee position for measuring orthostatic hypotension. (5) Basic spirometry equipment. (6) Digital video camera, tripods, and external hard drives for video storage. (7) Computer with secured internet access for data entry in ITW.

Other Resources

Dr. Susan Harkema and research staff offices are located at Frazier Rehab and Neuroscience Center, on the fifteenth floor (3600 sq. ft) and include a 430 sq.ft office that is utilized by the CrossIQ/ITW data management team. Faculty offices are adjacent to the data analysis room, with one office dedicated for collaborating faculty. There are two additional offices utilized by post-docs, graduate students, and research technicians.

g. NACTN - Thomas Jefferson University

Facilities

Jefferson, in affiliation with Magee Rehabilitation Hospital, is designated as one of the nation's 14 Model Spinal Cord Injury Centers by the National Institute on Disability and Rehabilitation Research (NIDRR) in the U.S. Department of Education's Office of Special Education and Rehabilitative Services (OSERS), and the only one in the Delaware Valley.

Jefferson is one of only a few hospitals in the U.S. that is both a Level 1 Trauma Center and a federally designated regional spinal cord injury center. The center, which has treated more than 3,000 persons with spinal cord injury, provides for the multidisciplinary coordination of emergency and acute medical/surgical care, rehabilitation beginning at the onset of acute care, vocational-evaluation and training, and lifetime follow-up care for persons with spinal cord injury. With over 50 percent of persons with spinal cord injury admitted within three days of injury, the Regional Spinal Cord Injury Center has demonstrated a mortality rate of 5 percent and has significantly reduced the severe secondary complications of traumatic spinal cord injury.

h. NRN - Magee Rehabilitation Hospital

Facilities

Magee Rehabilitation offers one of the nation's leading rehabilitation programs for people with spinal cord injuries (SCI). With more than 4,000 SCI patients in its system, Magee has the clinical experience and the unique peer resources that no other Greater Philadelphia rehabilitation program can offer.

Magee's SCI services include an expert clinical inpatient program; state-of-the-art assistive and therapeutic technology; unique outpatient therapy programs; and community reintegration services. Lifetime follow-up care is coordinated through Magee to address the unique health and community reintegration concerns of people with SCI.

The Locomotor Training Clinic at Magee Rehabilitation Hospital occupies 754 square feet and includes both gym space for providing the intervention with all required equipment. Adjacent offices are available for patient screening and physician visits.

Equipment

The NRN Centers have standardized equipment required to provide the locomotor training intervention: (1) one closed loop computer-controlled Body Weight Support system with a treadmill that allows speeds from 0.5 – 10 mph, the option to resume at the most recent stepping speed, and change grades. The treadmill also includes a seating system with ergonomically appropriate support design for staff safety and effectiveness of providing manual assistance during locomotor training. (2) Medical harnesses in a range of sizes. (3) Hi-Lo mat for harness application and stretching. (4) Automatic blood pressure monitoring equipment, including a cardiac chair or mat that can quickly change position to a 90 degree hip/90 degree knee position for measuring orthostatic hypotension. (5) Basic spirometry equipment. (6) Digital video camera, tripods, and external hard drives for video storage. (7) Computer with secured internet access for data entry in ITW.

i. NACTN - University of Toronto

Facilities

The Department of Surgery has approximately 225 full-time faculty, 30 part-time faculty, 60 adjunct faculty and 30 research scientists located both on campus and at our six fully affiliated teaching hospitals and two partially affiliated teaching hospitals. Our large faculty contributes extensively to our three core missions: excellent clinical care, outstanding research productivity and the delivery of state of the art educational programs. Our Department receives approximately over \$46 million annually of external peer-reviewed funding. We have a Surgeon Scientist Program aimed at providing master's or doctoral level training for our surgical trainees. There are 35 trainees registered in this research stream. We train approximately 200 residents and 175 fellows per year.

The University of Toronto has a large program in educational scholarship and a vibrant Surgical Skills Centre. With this strong platform for future success, the University of Toronto Department of Surgery aspires to continue to be a leading Department in academic surgery nationally and internationally.

j. NRN – University of Toronto/Lyndhurst Centre

Facilities

The Toronto Rehabilitation Institute, Lyndhurst Centre is an 80 bed unit devoted entirely to Spinal Rehabilitation. Also a University of Toronto affiliated Centre. This facility houses 15 Senior Scientists, 13 Scientists, and 60 Research Associates. Of the eight key areas of research the Mobility, Neural Engineering & Therapy and Optimization of Rehab Services are the key areas which align with the work done in the NRN and NACTN. Toronto Rehab Institute also houses the iDAPT facility which is a virtual environment created for research.

Equipment

This facility houses standard therapy equipment, including physical and occupational therapy equipment for patients with SCI: standard treadmills, leg and arm functional electrical stimulation motorized ergometers, a Recumbent Cross Trainer, an accessible cardiovascular fitness machine, a Dual Cable Cross Over multiexercise unit, parallel bars, a SCI Fit bike and upright bike, a glider standing frame, Reformer Pilates equipment, a stationary bike and upper extremity ergometer, a Bowflex machine that has been adapted for wheelchair users, and an Upper Tone (a pulley system specifically designed for individuals with SCI who use a wheelchair; it has adapted handles for those unable to grip equipment that allow for incremental increases in resistance). The ARmeo System, Rejoyce System, and Compex FES systems for both upper and lower extremities are available. A lift system which is used to transfer patients from their wheelchairs to gym equipment; gait harnesses can also be used with this lift system for standing and gait training in the gym.

TRI's SCI services include an expert clinical inpatient program; state-of-the-art assistive and therapeutic technology; unique outpatient therapy programs; and community reintegration services. The rehabilitation space is comprised of 3000 square feet equipped with two body weight support treadmills and space for additional treadmills. Adjacent space is available for patient screening and physician visits. The REL lab space is also available and equipped with many technologies to assist in clinical research.

k. NACTN - University of Maryland

Facilities

The University of Maryland Medical Center (UMMC) is a teaching hospital with 705 beds based in Baltimore, Maryland, that provides the full range of health care to people throughout Maryland and the Mid-Atlantic region. It gets more than 35,000 inpatient admissions and 165,000 outpatient visits each year. UMMC has approximately 6,500 employees as well as 1,000 attending physicians, and provides training for about half of Maryland's physicians and other health care professionals. All members of the medical staff are on the faculty of the University of Maryland School of Medicine.

The University of Maryland Medical Center is one of the nation's oldest teaching hospitals. It was created in 1823 as the Baltimore Infirmary. It is a referral center for trauma, cancer care, neurocare, cardiac care and heart surgery, women's and children's health and organ transplants.

The R. Adams Cowley Shock Trauma Center, known as Shock Trauma, is the world's first center dedicated to saving lives of people with severe, life-threatening injuries sustained in motor vehicle collisions, violent crimes and other traumatic incidents. Shock Trauma has more than 100 inpatient beds dedicated to emergency surgery, resuscitation, intensive care, and acute surgical care. The trauma staff treat more than 7,500 critically injured patients each year who arrive by helicopter or ambulance.

Every year nearly 8,000 people are brought here with critical injuries that can range from car crashes, motorcycle crashes, falls, and violence related injuries. 97% of those patients survive because of the intricate, complex care that is provided here at the Shock Trauma Center.

l. NACTN - University of Virginia

Facilities

The University of Virginia Health System is a nationally renowned healthcare provider based in Charlottesville, Virginia and associated with the University of Virginia. The health system includes a medical center, school of medicine and health sciences library. The health system provides inpatient and outpatient care, patient education and medical research and education in Charlottesville and at satellite care locations throughout Virginia. With a history dating back more than 180 years to the founding of the nation's 10th medical school, the UVA Health System's patient care, research and medical education are routinely ranked among the best in the country by U.S. News & World Report and other independent sources.

The University of Virginia Medical Center provides primary, specialty and emergency care throughout Central Virginia through a network of clinics as well as a main hospital that has more than 500 beds. The hospital serves as a Level 1 trauma center for the region and is accessible by ambulance as well as Pegasus, UVA Health System's air and ground transport service for critically ill and injured patients. As an academic medical center, patients at UVA are treated by physicians who also serve as faculty members at the University of Virginia School of Medicine, providing access to state-of-the-art treatments researched by the faculty physicians. In the 2010 fiscal year, the UVA Medical Center treated 27,087 inpatients and had a total of 735,631 outpatient visits.

m. NACTN - University of Miami

Facilities

Relevant Facilities at the University of Miami include the Ryder Trauma Center, Jackson Memorial Hospital, The University of Miami Hospital, and The Miami Project to Cure Paralysis. These facilities are all on the same campus in easy proximity. The Ryder Trauma center is the primary level 1 trauma center for Dade County and also serves surrounding counties. This busy center currently provides training to US Army medical field teams. Patients with acute SCI arrive in the centre soon after injury and are triaged for the scope of their injuries. Single system spinal cord injuries are then referred to the Neuro ICU at Jackson Memorial for surgical consultation and acute SCI care. The neurosurgical department is extensively staffed by several spine trained neurosurgeons and there are active clinical trials. Some of these surgeons are also active scientific investigators at the Miami Project to Cure Paralysis. In addition to local trauma victims, UM also receives a substantial number of referred SCI patients from the Caribbean and Latin America. Many of these patients go on to rehabilitation at Jackson Hospital. The Department of Physical Medical and Rehabilitation is chaired by Dr. Diana Cardenas, a national leader in SCI care. The institution has recently received SCI model system status and provides comprehensive standard of care SCI rehabilitation. Outpatient services are provided at Jackson and the University of Miami hospital where extensive clinic facilities are available. The Miami Project to Cure Paralysis has several active experimental rehabilitation programs that address physiology and metabolism after SCI, activity dependent plasticity, quality of life, and community integration and accessibility. The Miami Project patient outreach program is directed by Dr. Kim Anderson.

4. Publications and/or Patent Abstracts:

a. Published

Harkema SJ, Behrman AL, Barbeau H. *Locomotor Training: Principles and Practice*, Oxford Press, May 2011.

Datta S, Lorenz DJ, Morrison S, Ardolino E, Harkema SJ. (2009) A Multivariate Examination of Temporal Changes in Berg Balance Scale Items for Patients with ASIA Impairment Scale C and D Spinal Cord Injuries. *Arch Phys Med Rehabil* July;90(7):1208-1217. (Attached)

Harkema SJ, Schmidt-Read M, Behrman AL, Bratta A, Sisto SA, Edgerton VR. *Archives of Physical Medicine and Rehabilitation*. [Epub ahead of print] (Attached)

Harkema SJ, Schmidt-Read M, Lorenz D, Edgerton VR, Behrman AL. Balance and ambulation improvements in individuals with chronic incomplete spinal cord injury using Locomotor Training-based rehabilitation. *Archives of Physical Medicine and Rehabilitation*. [Epub ahead of print] (Attached)

Lorenz DJ, Datta S, Harkema SJ. Marginal association measures for clustered data. *Stat Med* [Epub ahead of print]

b. In Press

Behrman AL, Ardolino E, VanHiel L, Kern M, Atkinson D, Lorenz D, Harkema S. Assessment of functional improvement without compensation reduces variability of outcome measures after human spinal cord injury. *Archives of Physical Medicine and Rehabilitation*.

Morrison S, Forrest GF, VanHiel LR, Dave M, DeLorenzo D. NeuroRecovery Network Provides Standardization of Locomotor Training for Persons with Incomplete Spinal Cord Injury. *Archives of Physical Medicine and Rehabilitation*.

Forrest GF, Lorenz DJ, Hutchinson KA, VanHiel L, Basso DM, Datta S, Sisto SA, Harkema SJ. Ambulation and balance outcomes measure different aspects of recovery in individuals with chronic incomplete spinal cord injury. *Archives of Physical Medicine and Rehabilitation*.

Morrison S, Pomeranz JL, Yu N, Read MS, Wescott C, Sisto SA, Behrman A. Life Care Planning Outcomes for Two Individuals with Motor Incomplete Spinal Cord Injury Pre and Post Locomotor Training. *Archives of Physical Medicine and Rehabilitation*.

c. In Review

Datta S, Lorenz DJ, Harkema SJ. A dynamic longitudinal evaluation of the utility of the Berg Balance Scale in patients with motor incomplete spinal cord injury. *Archives of Physical Medicine and Rehabilitation*.

Lorenz, DJ, Datta S, Harkema SJ. Longitudinal patterns of functional recovery in patients with incomplete spinal cord injury receiving activity-based rehabilitation. *Archives of Physical Medicine and Rehabilitation*.

Grossman R, Frankowski R, Burau K, Toups E, Johnson M, Fehlings M, Shaffrey C, Harkema S, Hodes J, Aarabi B, Rosner M, Guest J, and Harrop J. Acute Complications after Spinal Cord Injury – A Multicenter Prospective Study of the Spectrum. Incidence and Severity: The North American Clinical Trials Network (NACTN) for Treatment of Spinal Cord Injury;. *J Neurotrauma*.

d. Patents

A Bejczy, K Day, R Edgerton, S Harkema, J Weiss. Method, Apparatus and System for Automation of Body Weight Support Training (BWST) of Biped Locomotion Over a Treadmill Using a Programmable Stepper Device (PSD) Operating Like an Exoskeleton Drive System From a Fixed Base, Patent # 6,666,831 B1 (United States), December, 2003.

5. Letters of Organizational Support:



Edward A. Jones
Chief Operating Officer

6670 Bertner Street
Houston, Texas 77030
www.tmhri.org

November 28, 2011

TO: Robert G. Grossman, M.D.
Chairman, Department of Neurosurgery
Co-Director, The Neurological Institute
The Methodist Hospital, Houston, Texas

Regarding: Funding Opportunity Number: W81XWH-11-SCIRP-CTA-R
Letter of Organizational Support for the protocol:

**A Phase II Trial of Body Weight Support Locomotor Training in Gait Rehabilitation
After Spinal Cord Injury: A Collaboration of NACTN and NRN**

This letter is to confirm the support of The Methodist Hospital Research Institute (TMHRI) for the above named Spinal Cord Injury Research Program (SCIRP) Clinical Trial application. If awarded, TMHRI will provide Dr. Grossman with all of the necessary resources to support as both the local PI as well as the Coordinating Center for this important initiative. As you are aware, Dr. Grossman and his team have been instrumental in the pivotal North American Clinical Trials Network (NACTN), which is currently funded by the Christopher and Dana Reeve Foundation and the Department of Defense. The linkage between NACTN and the Neuro-Recovery Network (NRN) will allow investigators to more effectively explore the outcomes of combined therapies in spinal cord injury patients.

The Methodist Hospital Research Institute, Houston, TX, is the research enterprise for The Methodist Hospital System and is affiliated with the Weill Cornell Medical College in New York City. Located in a new 440,000-square-foot research building that is connected to and integrated with The Methodist Hospital within the Texas Medical Center, Houston, TX, the Research Institute is equipped with advanced technologies and facilities including: cyclotron, pre-clinical and clinical imaging (MRI, PET, CT, SPECT, in vivo bioluminescence/fluorescence imaging, Preclinical High Intensity Ultrasound, 2 photon Intra-Vital Microscope), flow cytometry/cell sorting, confocal microscope, live cell imaging, Scanning and Transmission Electron Microscopes, small and large animal vivarium, GMP facility for nanoparticles, contrast agents, vaccines and therapeutic molecules. Our faculty members also have access to institutional core services in research histopathology, biostatistics/bioinformatics, serum and tissue biorepository, mass spectrometry and proteomics, and high throughput DNA sequencing and gene expression profiling. The Research Institute offers vertically integrated, state-of-the-art laboratory and technological resources for translational and clinical research, allowing translational researchers and physician scientists to bring ideas to clinical applications in a single facility.

I am encouraged by the therapeutic/interventional possibilities being explored by the NACTN and NRN collaboration and fully support your efforts with this application.

Sincerely,

Edward A. Jones
Chief Operating Officer
The Methodist Hospital Research Institute

LETTER OF INTENT TO ENTER INTO A CONSORTIUM AGREEMENT

Prime Applicant: Methodist Hospital Research Institute
Primary Principal Investigator: Robert Grossman, M.D.

Consortium Institution: University of Louisville Research Foundation, Inc.
Consortium Principal Investigator: Susan Harkema, Ph.D.

Application Title: "A Phase II Trial of Body Weight Support
Locomotor Training in Gait Rehabilitation after
Spinal Cord Injury: A Collaboration of NACTN
and NRN"

Proposed Project Period: October 1, 2012 – June 30, 2015

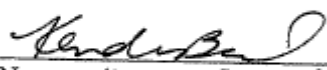
It is the intent of the Prime Applicant and the Consortium Institution to enter into the necessary inter-institutional agreement if an award is made. Any resulting agreement will conform to the DOD guidelines and requirements for consortium agreements.

We agree to accept the budget for our site as submitted with this application.

By signing below and agreeing to participate in this research project, each institution certifies to the best of its knowledge and belief that neither they nor their principals are presently debarred, suspended, proposed for debarment, declared ineligible or voluntarily excluded from covered transactions by any federal department or agency and are not delinquent on any federal debt.

Prime Applicant:

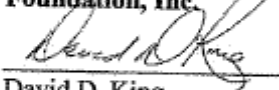
Methodist Hospital Research Institute


Name: Kendra Bernal
Title: Manager

11/30/11
Date

Consortium Institution:

University of Louisville Research
Foundation, Inc.


David D. King
Director, Office of Industry Contracts

11/28/2011
Date

November 21, 2011

TO: Robert G. Grossman, M.D.

Chairman, Department of Neurosurgery

Co-Director, The Neurological Institute

The Methodist Hospital, Houston, Texas

Funding Opportunity Number: W81XWH-11-SCIRP-CTA-R

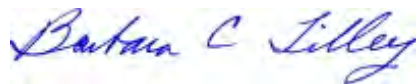
From: Barbara C. Tilley, Ph.D.

Lorne C. Bain Distinguished Professor and Director

Division of Biostatistics

University of Texas Health Science Center at Houston

School of Public Health



Subj: Letter of Organizational Support

A Phase II Trial of Body Weight Support Locomotor Training in Gait Rehabilitation

After Spinal Cord Injury: A Collaboration of NACTN and NRN

This letter is to confirm organizational and resource support for the above named SCIRP grant application from the University of Texas School of Public Health at Houston, Division of Biostatistics. The Division of Biostatistics will provide organizational support by subcontract with the PI of the grant, Dr. Robert G. Grossman, Methodist Hospital Neurological Institute.

The Division of Biostatistics includes 29 faculty members with expertise in a wide array of theoretical and applied Biostatistics. The Division also includes a Coordinating Center for Clinical Trials that has active funded research programs in Phase I, Phase II, and Phase III clinical trials. The Division through the School's IT program maintains an extensive state-of-the-art computer network and has advanced computing resources for the conduct, quality assurance, and analysis of data generated by multi-site clinical trials. The faculty and nested new investigator named in this grant will be housed in private offices on the 9th and 10th floor of the School of Public Health Reuel A. Stallones Building. Offices are fully equipped with customary office furnishings, secure storage, telephone, desktop computers, and full computer links to the network.

Main phone 713.500.9505 Fax 713.500.9525

1200 Herman Pressler, RAS E833

Houston, TX 77030



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Boston University School of Medicine

STEVE WILLIAMS, MD

Chief, Rehabilitation Medicine
Director, New England Regional Spinal Cord In
Boston Medical Center

Associate Professor and Chairman
Department of Rehabilitation Medicine
Boston University School of Medicine

Dr. Robert G. Grossman
The Methodist Hospital
6560 Fannin Suite 944
Houston, TX 77030

Dear Dr. Grossman,

It will be my pleasure to serve as Medical Monitor for your DOD CDMRP SCIRP Clinical Trial – Rehabilitation grant, “A Phase II Trial of Body Weight Support Locomotor Training in Gait Rehabilitation after Spinal Cord Injury: A Collaboration of NACTN and NRN”, if funded.

By utilizing the clinical resources and databases of the North American Clinical Trials Network for Treatment of Spinal Cord Injury (NACTN) and the NeuroRecovery Network (NRN), this Phase II trial would be the first randomized clinical trial to directly compare a standardized activity-dependent rehabilitation intervention (Locomotor Training) to an SCI control group (no intervention) in a chronic SCI population with detailed information on their clinical outcomes since the time of injury.

In my role as Medical Monitor, I agree to oversee the safety of all phases of the study to ensure that the study is performed according to common guidelines for clinical trials. I will review all unanticipated problems involving risk to study subjects and “serious adverse events” and will provide an unbiased written report of any events within 10 calendar days. I will comment on the outcomes of the adverse event and relationship of the event to the protocol. I will also indicate whether I concur with the details of the report provided by the PI. I promise to promptly forward all SAE events to the HRPO. Finally, I will act as a liaison between the PIs, the site-PIs and physicians and their respective IRBs.

I have served as a PI and co-investigator on several investigator-initiated and industry-sponsored, multi-center clinical trials in persons with SCI so I am familiar with the basic elements for designing, carrying out, and reporting clinical trials in accordance with “good clinical practice”. Finally, I assure you that my participation as Medical Monitor on this study does not represent a conflict of interest.

I look forward to this exciting collaboration.

Sincerely,

November 28, 2011

Dr. Robert G. Grossman
The Methodist Hospital
6560 Fannin Suite 944
Houston, TX 77030

Dear Dr. Grossman,

It is my pleasure to take part in your collaborative DOD CDMRP SCIRP Clinical Trial – Rehabilitation grant, “A Phase II Trial of Body Weight Support Locomotor Training in Gait Rehabilitation after Spinal Cord Injury: A Collaboration of NACTN and NRN”.

This study addresses a critical need of the SCI community, determining the best therapy for recovery of walking. By utilizing the clinical resources and databases of the North American Clinical Trials Network for Treatment of Spinal Cord Injury (NACTN) and the NeuroRecovery Network (NRN), this Phase II trial would be the first randomized clinical trial to directly compare a standardized activity-dependent rehabilitation intervention (Locomotor Training) to an SCI control group (no intervention) in a chronic SCI population with detailed information on their clinical outcomes since the time of injury. An innovative aspect of the proposal is that the patients will be followed prospectively from the time of injury through rehabilitation making it possible to accurately match the control and the treatment groups. In addition, there will be available a quantitative benchmark for recovery of walking with intense rehabilitation in chronic SCI individuals that can be used for comparison as other therapies become available for evaluation.

I look forward to this exciting collaboration.

Sincerely,



Maxwell Boakye, MD
Associate Professor of Neurosurgery
Medical Director, Neurological Surgery
Frazier Rehab Institute, University of Louisville



November 25, 2011

Dr. Robert G. Grossman
The Methodist Hospital
6560 Fannin Suite 944
Houston, TX 77030

Dear Dr. Grossman,

It is my pleasure to take part in your collaborative DOD CDMRP SCIRP Clinical Trial – Rehabilitation grant, "A Phase II Trial of Body Weight Support Locomotor Training in Gait Rehabilitation after Spinal Cord Injury: A Collaboration of NACTN and NRN".

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I look forward to this exciting collaboration.

Sincerely,

A handwritten signature in black ink, appearing to read "Kimberly N. Atkinson, PT, NCS".

Kimberly N Atkinson, PT, NCS
Director, Spinal Cord Medicine Program
Clinical Site Director, NeuroRecovery Network

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(502) 582-7400 phone
(502) 582-7477 fax
www.frazierrehab.org

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Chair, Department of Neurological Surgery
Professor of Neurological Surgery and Radiology

David W. Andrews, MD, FACS
Professor

Deborah L. August, MD, MPH
Instructor of Medicine and Neurological Surgery

M. Beverly Downes-Phillips, MS, DABR
Clinical Instructor

James J. Evans, MD, FACS
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Jon Glass, MD
Associate Professor of Neurology and Neurosurgery

L. Fernando Gonzalez, MD
Assistant Professor

James S. Harrop, MD, FACS
Associate Professor of Neurological Surgery
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Larry A. Hartsbryne, PhD
Instructor

Pascal M. Jabbour, MD
Assistant Professor

Jack Falbo, MD, PhD, FACS
Professor

Srinivas K. Prasad, MD
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Associate Professor of Neurological Surgery
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Ashwini D. Sharan, MD, FACS
Associate Professor of Neurological Surgery
and Neurology

Stavroula I. Tjoumakaris, MD
Instructor

Elisabeth Van Bockstaele, PhD
Professor of Neurological Surgery and
Psychology, Anatomy and Cell Biology

Dr. Robert G. Grossman
Chairman, Department of Neurosurgery
Director, The Neurological Institute
The Methodist Hospital
6560 Fannin, Suite 944
Houston, TX 77030

Dear Dr. Grossman,

I thank you for the opportunity to participate in your collaborative DOD CDMRP SCIRP Clinical Trial - Rehabilitation grant, "A Phase II Trial of Body Weight Support Locomotor Training in Gait Rehabilitation after Spinal Cord Injury: A Collaboration of NACTN and NRN".

There have been great advancements in the care and treatment of SCI patients over the last several decades. However an area which would greatly benefit patients in terms of functional independence is defining the therapy which maximizes walking recovery. The North American Clinical Trials Network for Treatment of Spinal Cord Injury (NACTN) and the NeuroRecovery Network (NRN) are in a unique situation to perform and address these issues. Due to their collaboration and close working relation they have the resources and personnel to complete a clinical Phase II trial on walking recovery.

A randomized clinical trial directly comparing a standardized activity-dependent rehabilitation intervention (Locomotor Training) to an SCI control group (no intervention) in a sub-acute/chronic SCI population through detailed quantitative outcome measures is necessary. This specific proposal is innovative in that patients will be followed prospectively from the time of injury through rehabilitation

making it possible to accurately match the control and the treatment groups.

I look forward to participating in this exciting collaboration and improving outcomes for our SCI patient population.

Sincerely,

James S Harrop, MD
Associate Professor of Neurological Surgery
And Orthopedic Surgery

November 28, 2011

Dr. Robert G. Grossman
The Methodist Hospital
6560 Fannin Suite 944
Houston, TX 77030

Dear Dr. Grossman,

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This study addresses a critical need of the SCI community, determining the best therapy for recovery of walking. By utilizing the clinical resources and databases of the North American Clinical Trials Network for Treatment of Spinal Cord Injury (NACTN) and the NeuroRecovery Network (NRN), this Phase II trial would directly compare a standardized activity-dependent rehabilitation intervention (Locomotor Training) to an SCI control group (no intervention) in a chronic SCI population with detailed information on their clinical outcomes since the time of injury. An innovative aspect of the proposal is that the patients will be followed prospectively from the time of injury through rehabilitation making it possible to accurately match the control and the treatment groups. In addition, there will be available a quantitative benchmark for recovery of walking with intense rehabilitation in chronic SCI individuals that can be used for comparison as other therapies become available for evaluation.

As one of the combined NACTN and NRN sites, we are in a unique position to support this effort.

We look forward to this exciting collaboration.

Sincerely,

Mary Schmidt Read, PT, DPT, MS
Spinal Cord Injury Program Director &
Research Coordinator
Magee Rehabilitation
Regional Spinal Cord Injury Center of the Delaware Valley
NeuroRecovery Network



University Health Network

Toronto General Hospital Toronto Western Hospital Princess Margaret Hospital



**Spinal Program
Krembil Neuroscience Centre**

November 28, 2011

Dr. Robert G. Grossman
The Methodist Hospital
6560 Fannin Suite 944
Houston, TX 77030

Dear Dr. Grossman:

It is my pleasure to take part in your collaborative DOD CDMRP SCIRP Clinical Trial – Rehabilitation grant, *"A Phase II Trial of Body Weight Support Locomotor Training in Gait Rehabilitation after Spinal Cord Injury: A Collaboration of NACTN and NRN"*.

This study addresses a critical need of the SCI community, determining the best therapy for recovery of walking. By utilizing the clinical resources and databases of the North American Clinical Trials Network for Treatment of Spinal Cord Injury (NACTN) and the NeuroRecovery Network (NRN), this Phase II trial would be the first randomized clinical trial to directly compare a standardized activity-dependent rehabilitation intervention (Locomotor Training) to an SCI control group (no intervention) in a chronic SCI population with detailed information on their clinical outcomes since the time of injury. An innovative aspect of the proposal is that the patients will be followed prospectively from the time of injury through rehabilitation making it possible to accurately match the control and the treatment groups. In addition, there will be available a quantitative benchmark for recovery of walking with intense rehabilitation in chronic SCI individuals that can be used for comparison as other therapies become available for evaluation.

I look forward to this exciting collaboration.

Sincerely,

Michael G. Fehlings, MD, PhD, FRCSC, FACS
Professor of Neurosurgery
Krembil Chair in Neural Repair and Regeneration
McLaughlin Scholar in Molecular Medicine
University of Toronto
Medical Director, Krembil Neuroscience Program
Head, Spinal Program
Toronto Western Hospital, University Health Network

MGF/al

From the office of: Michael G. Fehlings
Toronto Western Hospital, 399 Bathurst Street, 4W449, Toronto, ON M5T 2S8.
tel. 416-603-5627 fax 416-603-5298; michael.fehlings@uhn.on.ca

Department of Neurological Surgery

November 26, 2011

Spinal Services

University of Virginia
Charlottesville

Medical School, 300 Patton
Hall, Room 100

Charlottesville, VA

Emergency Room, 300 Patton
Hall, 4th Floor, Room 100

Charlottesville, VA

Dr. Robert G. Grossman
Chairman, Department of Neurosurgery
Director, The Neurological Institute
The Methodist Hospital
6560 Fannin, Suite 944
Houston, TX 77030

Dear Dr. Grossman,

It is my pleasure to take part in your collaborative DOD CDMRP SCIRP Clinical Trial – Rehabilitation grant, “A Phase II Trial of Body Weight Support Locomotor Training in Gait Rehabilitation after Spinal Cord Injury: A Collaboration of NACTN and NRN”.

This study addresses an unmet need for spinal cord injured patients that could potentially widely impact the standard of care. At this time there is no widely accepted best practice for determining the best therapeutic strategy for optimizing locomotor training. By combining both the clinical resources and databases of the North American Clinical Trials Network for Treatment of Spinal Cord Injury (NACTN) and the NeuroRecovery Network (NRN), this Phase II trial would be the first randomized clinical trial to directly compare a standardized activity-dependent rehabilitation intervention (Locomotor Training) to an SCI control group (no intervention) in a sub-acute/chronic SCI population with detailed information on their clinical outcomes since the time of injury. A unique aspect of this proposed trial is to prospectively follow patients from the time of injury through rehabilitation making it possible to accurately match the control and the treatment groups. This will represent an opportunity to develop a quantitative benchmark for recovery of walking with intense rehabilitation in chronic SCI individuals that can be used for comparison as other therapies become available for evaluation.

I look forward to this exciting collaboration.

Sincerely,



Christopher I. Shaffrey, MD, FACS
Harrison Distinguished Teaching Professor
Department of Neurological and Orthopaedic Surgery
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MILLER

SCHOOL OF MEDICINE

Dr. Robert G. Grossman
Chairman, Department of Neurosurgery
Director, The Neurological Institute
The Methodist Hospital
6560 Fannin, Suite 944
Houston, TX 77030

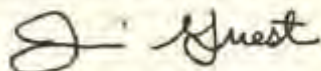
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I look forward to this exciting collaboration.

Sincerely,



James D. Guest MD, PhD, FRCS (C), FACS
Associate Professor of Neurological Surgery
Neurosurgery and the Miami Project to Cure Paralysis
University of Miami, 1095 NW 14th Terrace
305-243-7144
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Department of Neurological Surgery • Leonard M. Miller School of Medicine
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6. Intellectual and Material Property Plan:

Not applicable. There is nothing proprietary involved in this study.

7. Data and Research Resources Sharing Plan:

The results of this trial will be disseminated to the field of Spinal Cord Injury (SCI) Medicine in a number of ways; including presentation at SCI related clinical and research forums as well as in print journals. The impact would be felt immediately as this will allow clinicians evidence for providing LT as an activity-based intervention program involving persons with SCI. The investigators will the data at scientific meetings; clinical grand rounds and prioritize invitations that are sponsored by consumer advocacy groups.

There is potential for an immediate impact in the clinical aspects of care for all persons with upper motor neuron related SCI, both military and non-military; specifically in regards to the treatment for the recovery of the ability to walk. The recovery rates of individuals receiving usual rehabilitation would also be available with discrete documentation of those specific rehabilitation programs in combination with detailed clinical information from the first few weeks after injury. To our knowledge, this will be the first dataset of clinical information throughout the continuum of care of early neurological intervention thru inpatient and outpatient rehabilitation. Further, the effects of LT training as well as in other domains, including medical (i.e. respiratory, cardiovascular) and quality of life will be better understood providing evidence to guide clinical practice.

Immediately, the results of this study would impact the current NeuroRecovery Network (NRN) that is a collaborative project by the four rehabilitation sites involved in this study. If LT provided earlier after injury significantly improved walking capability, inclusion criteria would change for persons eligible for this program at the other remaining four NRN sites . We believe this would also change eligibility for other clinical trials as well as other clinically based activity-based rehabilitation programs.

This project has followed the recommendations for utilizing the spinal cord injury Common Data Element (CDE) standards developed through the collaboration of the International Spinal Cord Society, the American Spinal Injury Association, and the National Institute of Neurological Disorders and Stroke CED team whenever available. All International SCI Core Data set variables will be collected at the NACTN sites. The cardiovascular outcomes selected for this project (orthostatic hypotension, systolic and diastolic blood pressures and heart rate) selected for this project are included in the International SCI Cardiovascular Function Basic Data Set. The pulmonary outcomes including all spirometry measures are included in the International SCI Pulmonary Function Basic Data Set. There are not yet available International SCI Quality of Life Basic Data sets, however we are using long-standing legacy measures and incorporating measures that have ongoing development by NIH (Promise, NeuroQoL and SCIQoL projects). We will follow the consistent variable names for these data elements to facilitate data sharing with other related databases.

8. Mentor Letter of Support for Optional Nested New Investigator:



School of Public Health
Division of Biostatistics

November 21, 2011

To: Robert G. Grossman, M.D.

Professor and Chairman, Department of Neurosurgery
The Methodist Hospital Neurological Institute

From: Wenyaw Chan, PhD

A handwritten signature in black ink, appearing to read "Wenyaw Chan", written over a horizontal line.

Professor of Biostatistics, Division of Biostatistics
University of Texas School of Public Health

Subj: Julia Sanders Benoit

Nested New Investigator Phase II Trial of BWSLT – NACTN/NRN

This letter is in support of the appointment of Ms. Julia Benoit as a Nested New Investigator in the proposed "Phase II Trial of Body Weight Support Locomotor Training in Gait Rehabilitation after Spinal Cord Injury". Julia is an advanced doctoral graduate student in biostatistics and I am Julia's academic and research advisor. Julia's professional goals are in the planning, conduct, and analysis of clinical trials. The Nested New Investigator award is an ideal match for Julia's academic and professional goals. I recommend Julia with enthusiasm for this award and will be her statistical mentor for this award. During the award Julia will gain significant experience in conduct and analysis of a Phase IIb comparative efficacy clinical trials and will also develop special expertise in the design of randomized spinal cord injury rehabilitation clinical trials.

Julia's dissertation research focuses on Hidden Markov Process models. She is working on developing statistical models for longitudinal ternary outcomes that are subject to misclassification. Her statistical research includes derivations of appropriate likelihood functions, examination of the estimability and identifiability, computation simulation and applications to repeated measures of outcomes in neurological disease clinical interventions. Her research is directly applicable to the primary and secondary statistical objectives of the SCIRP grant application.

Julia's statistical preparation includes substantial coursework in the Theory of Biostatistics, Linear Models, Multivariate Analysis, Longitudinal Models for Repeated Measures, Statistical Methods for Missing Data and Imputation, Bayesian Statistics, and Stochastic Processes. Her computational skills in statistical software include STATA, SAS, and R. She is quite capable of writing independent computer programs for simulating and validating complex statistical models. In addition, she has completed a minor in epidemiology and has completed courses in research ethics.

Julia will commit one-third time and effort to the grant. In addition to learning theoretical, practical, and analytic dimensions of Phase II clinical trials, Julia will complete mentored research training with grant faculty of the Clinical Coordinating Center and Data Analysis Center to advance her understanding of the epidemiology of spinal cord injury and the unique problems posed in SCI clinical trials research.

713.500.9505 phone 713.500.9526 fax
1200 Herman Presler, E835
Houston, Texas 77030

A Multivariate Examination of Temporal Changes in Berg Balance Scale Items for Patients With ASIA Impairment Scale C and D Spinal Cord Injuries

Somnath Datta, PhD, Douglas J. Lorenz, MA, Sarah Morrison, PT, Elizabeth Ardolino, MPT, Susan J. Harkema, PhD

ABSTRACT. Datta S, Lorenz DJ, Morrison S, Ardolino E, Harkema SJ. A multivariate examination of temporal changes in Berg Balance Scale items for patients with ASIA Impairment Scale C and D spinal cord injuries. *Arch Phys Med Rehabil* 2009;90:1208-17.

Objective: To provide a multivariate examination of the Berg Balance Scale (BBS) in patients with spinal cord injury (SCI) as a first step in developing a balance tool for the SCI population.

Design: Observational cohort.

Setting: The NeuroRecovery Network (NRN), a specialized network of treatment centers providing standardized, activity-based therapy for patients with SCI.

Participants: Patients (N=97) with American Spinal Injury Association Impairment Scale C or D SCI who were enrolled in the NRN between March 1, 2005, and June 12, 2007.

Interventions: All enrolled patients received 3 to 5 locomotor training sessions a week, according to NRN protocol, and were periodically evaluated for progress on functional outcome measurements.

Main Outcome Measures: Scores on the items of the BBS, six-minute walk test distances, ten-meter walk test speeds, and scores on the SCI Functional Ambulation Index. Temporal rates of change of the BBS items were examined with a principal components and correlation analysis.

Results: The first principal component accounted for nearly half of the overall variability in the BBS, correlated well with rates of change in functional mobility measures, and had good stability in its composition as verified by a resampling analysis. Further analysis showed that the composition of the first principal component varied with the patient's level of recovery.

Conclusions: The BBS captures a significant amount of information about balance recovery in persons with SCI and may be a good foundation for a balance tool. However, the utility of BBS items may be dependent on a patient's level of

recovery. A dynamic balance instrument for the SCI population may be needed.

Key Words: Principal components analysis; Rehabilitation; Spinal cord injuries.

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THERE ARE APPROXIMATELY 12,000 new SCI cases each year.¹ In this population, the percentage of persons with a neurologically (sensory and/or motor) incomplete injury has steadily increased from 45.9% in the 1970s to 55.3% in 2005. For persons who are diagnosed with a motor-incomplete injury, 28% of the injuries were classified (as defined by the International Standards for Neurological Classification of SCI) as "motor functional" (AIS D) and 11.6% as "motor non-functional" (AIS C) at the time of inpatient discharge.² It was estimated in 1999 that between one quarter and one third of persons with an SCI regain some ability to walk by the time of discharge from an inpatient rehabilitation program.³

An important component of recovery from SCI is the recovery of balance function. However, there currently is no valid and reliable instrument for measuring balance in the SCI population. The BBS is a 14-item instrument originally designed to assess the risk for falls in community-dwelling elders.⁴ The test is fairly simple to implement, taking approximately 20 minutes to administer and requiring only a chair, step or stool, ruler, and stopwatch. The items of the BBS have been formulated to evaluate an individual's ability to maintain position, adjust posture to voluntary motion, and react to external impetus (appendix 1). The scale is designed so that sequentially, each item tested increases difficulty by decreasing the base of support from sitting, to standing, to a single-leg stance. Each item is scored on a 5-point (0–4) ordinal scale.

Evaluation of the psychometric properties of the BBS has largely been restricted to the community-dwelling elderly population,⁴⁻⁶ those experiencing acute stroke,⁷ and those with Parkinson disease.⁸ Although the BBS has been used in SCI populations^{9,10} and the items on the scale possess reasonable face validity with respect to evaluating balance in the SCI population, a formal examination of the BBS in the SCI population has yet to be conducted.

Principal components analysis is a statistical technique that is useful for visualizing and interpreting multivariate data¹¹

From the Departments of Bionformatics and Biostatistics, School of Public Health and Information Science (Datta, Lorenz) and Neurological Surgery (Harkema), University of Louisville, Louisville, KY; Frazier Rehab Institute, Louisville, KY (Harkema); Shepherd Center Inc, Atlanta, GA (Morrison); Magee Rehabilitation, Philadelphia, PA (Ardolino).

Presented in poster form to the American Spinal Injury Association, May 30–June 2, 2007, Tampa, FL.

Supported through a cooperative agreement by the Christopher and Dana Reeve Foundation and the Centers for Disease Control and Prevention (Grant/Cooperative Agreement no. U10.CC0220379).

No commercial party having a direct financial interest in the results of the research supporting this article has or will confer a benefit on the authors or any organization with which the authors are associated.

Correspondence to Susan J. Harkema, PhD, 220 Abraham Flexner Way, Ste 1506, Louisville, KY 40202, e-mail: susan.harkema@jhsnh.org. Reprints are not available from the author.

0003-9993/09/9007-00563\$36.00/0
doi:10.1016/j.apmr.2008.09.577

List of Abbreviations

AIS	American Spinal Injury Association Impairment Scale
BBS	Berg Balance Scale
NRN	NeuroRecovery Network
SCI	spinal cord injury
SCI-FAI	Spinal Cord Injury Functional Ambulation Index

and, in particular, examining the items of a measurement scale. Each item on the BBS contributes variability to the full scale. However, it is not clear that a simple sum of the 14 BBS items provides the best summary of the scale with respect to explaining the total variation in the data. Some items may contribute less variability to the full scale than others (as applied to a specific population), and consequently would be of lesser utility. For example, if patients with SCI all performed very well on the first BBS item, then its utility in measuring balance recovery would be low. Formally, the principal components of a multivariate data set are orthogonal (ie, independent) directions in the multivariate data space that explain the most variability among the subjects. Thus, the first principal component is a linear combination of the BBS scores that is most variable among the patients, the second principal component is the next most variable combination among all directions that are orthogonal to (ie, independent of) the first, and so forth. The orthogonality of successive principal components guarantees that each principle component captures a unique component of variation in the multivariate data set. In particular, the first principal component defines the optimal way to combine the component item scores. Typically, the first few principal components explain a substantial proportion of the total variance present in the data, and offer an effective summary of the data by reducing the multivariate dimension. One also gets a sense of the relative utility of each item through consideration of the loading coefficients that define the principal components. Specifically, items with large loading coefficients explain more of the full scale variability and are of greater utility in summarizing the data.

Aside from being a useful data reduction and visualization technique, a principal components analysis has other benefits. Often the directions computed by a principal components analysis have clinical relevance and interpretability (see, for example, Olney, et al¹² for clinical interpretation of principal components from gait data in a population of patients with stroke). Further, a correlation analysis between the principal component scores and the scores on individual items from the scale can identify items that most substantially differentiate patient recovery. In this article, we provide the results of a principal components analysis of the BBS in patients with motor incomplete (AIS C or D) SCI as an important, albeit preliminary, step in evaluating the utility of the scale for use in the SCI population.

METHODS

Subjects

Data from 97 participants in NRN with incomplete AIS C or D spinal cord injuries were analyzed (table 1). The patient population was derived from 7 rehabilitation sites that provided a standardized activity-based intervention for the recovery of posture, standing, and walking and improvements in health and quality of life. Quantitative assessment tools were administered to document changes over time in a specific patient population (table 2). The Institutional Review Board for each of the NRN centers approved the submission of demographic and outcome data to the centralized NRN database, from which the data for this analysis were gathered. Each patient signed an informed consent form prior to the collection of data. The data analyzed here were collected at 5 NRN centers from March 4, 2005, to June 12, 2007.

Table 1: Demographic and Clinical Characteristics

Clinical Characteristics	Full Sample (N=97)	Phase at Enrollment			P
		Phase I (n=44)	Phase II (n=25)	Phase III (n=28)	
Sex					.04*
Male	71 (73)	31 (70)	15 (60)	25 (89)	
Female	26 (27)	13 (30)	10 (40)	3 (11)	
Age (y)	38±17	37±18	40±18	38±15	.72 [†]
Mechanism of injury					NT
Motor vehicle accident	34 (35)	17 (39)	10 (40)	7 (25)	
Fall	29 (30)	9 (20)	10 (40)	10 (36)	
Sporting accident	16 (16)	8 (18)	1 (4)	7 (25)	
Other nontrauma	8 (8)	6 (14)	1 (4)	1 (4)	
Medical/surgical	6 (6)	3 (7)	2 (8)	1 (4)	
Violence	4 (4)	1 (2)	1 (4)	2 (7)	
Assistive walking device [‡]					NT
Nonambulatory	20 (21)	20 (45)	0 (0)	0 (0)	
Walker	42 (43)	18 (41)	21 (84)	3 (11)	
Cane/crutches	22 (23)	6 (14)	4 (16)	12 (43)	
None	13 (13)	0 (0)	0 (0)	13 (46)	
Time since SCI (mo)	11.9 [0.5, 248]	15 [1, 248]	11 [2, 82]	14 [0.5, 242]	.63 [§]
NRN participation data					
NRN enrollment time (d)	119±99	129±80	144±145	76±53	.03 [†]
Cumulative treatment sessions received	48±39	62±42	49±41	27±17	<.001 [†]
Cumulative number of evaluations	3 [2, 13]	4 [2, 13]	3 [2, 13]	3 [2, 6]	.007 [§]
Treatment sessions per evaluation	14.6±7.8	14.6±5.9	16.0±11.6	13.0±5.5	.32 [†]

NOTE. Values are mean ± SD, median [min, max], or counts (percentages).

Abbreviation: NT, not tested for differences among phases.

*Fisher exact test.

[†]Analysis of variance.

[‡]Assistive walking device refers to walking device used at tests of six-minute walk and ten-meter walk, during which physical assistance may have been provided.

[§]Kruskal-Wallis test.

Table 2: Eligibility Criteria for the NRN

1. Not actively participating in an inpatient rehabilitation program.
2. Stable with no deteriorating medical condition. No pacemaker present.
3. Nonprogressive spinal cord lesion at level T10 or above; T11 and T12 may be considered in the absence of lower motor neuron signs.
4. Not ventilator-dependent.
5. Able to extend head voluntarily.
6. No painful musculoskeletal dysfunction or unhealed fractures.
7. Able to follow/understand verbal commands.
8. AIS C or D with upper motor neuron lesion.
9. Demonstrates capacity for generating a lower extremity reciprocal alternating flexion/extension stepping pattern.
10. Normal or hypertonicity present in the absence of antispasticity medication.
11. No use of BTX-A within the previous 3 months.
12. Compliance to eliminate or minimize lower extremity orthotics.
13. No current illegal drug use.

Procedures

Locomotor training is an activity-based therapeutic intervention for standing and walking that facilitates input to the neuromuscular system below the level of lesion to induce neuroplasticity and promote recovery of function.^{9,13-18} Based on the findings of an initial evaluation, the treating therapist establishes goals for treatment and implements a standardized plan of care. A typical locomotor training session has 3 components. The step training component is comprised of task-specific retraining of the nervous system for standing and walking that occurs in a controlled environment using a body weight support treadmill system with verbal and manual facilitation by trainers. The second component is overground assessment that evaluates the transfer of the current capacity of the neuromuscular system to mobility, posture, and walking skills over level ground and to establish priorities for further retraining. The third component is community integration that provides instruction for the individual to perform their daily activities in the home and community environments and achieve safe, efficient mobility. The NRN treatment protocol required 3 to 5 locomotor training sessions a week, depending on therapeutic necessity. Patient evaluations, conducted by the treating physical therapist, were scheduled for every 20 treatment sessions or 30 days. At each evaluation, functional outcome measures were assessed, including the BBS, six-minute walk test,¹⁹ ten-meter walk test,¹⁹ and SCI-FAI,²⁰ which were the measures of primary interest. A description of the methods for evaluation for each of these measurements is contained in [appendix 2](#). The NRN implements procedures to optimize uniform administration of treatment across all NRN centers. There are uniform procedures for locomotor training including patient selection (see [table 2](#)), evaluation, medical management, plan of treatment, and documentation. Physical therapists from each center were trained by the NRN during a 5-day conference. The reliability of the assessments of the outcome measures by the physical therapists was monitored by the NRN via video review. Data from all centers were compiled into a centralized database.

Data Analysis

The purpose of this analysis was to examine the joint distribution of the 14 items of the BBS, and subsequently deter-

mine its capability as a measure of balance recovery for the SCI population. This was accomplished through a principal components analysis of the longitudinally collected BBS variables.

Each patient had a sequence of evaluations of the 14 BBS items over time. Because the purpose of the analysis was related to the recovery of balance rather than balance (at a given point of time), preprocessing of the data prior to the principal components analysis was necessary. This was accomplished by calculating the average rate of change between successive observed evaluations for each BBS item for each patient. This is an overall measure of recovery as captured by the temporal profile of a given BBS item. Because any smooth curve can be approximated by a piecewise linear curve, this measure provided the best summary of recovery—the rate calculated between consecutive evaluations defined the piecewise linear recovery curve, and averaging over all evaluations provided the summary measure. For example, for each patient, the difference between successive evaluations was calculated for BBS item 1 (sitting to standing); these differences were divided by the number of treatment sessions received between the successive evaluations and averaged, leading to an overall measure of change in BBS item 1 per treatment session for that patient. Principal components were constructed to examine the most informative directions of average changes in successive evaluations. This type of marginal analysis has several technical advantages. Each individual contributes 1 multivariate observation in the analysis irrespective of how many potentially dependent temporal evaluations the patient had. Furthermore, in the marginal model, these multivariate observations are independent and identically distributed across the patients, and hence, the usual inferential calculations are valid. This does not require the modeling of the data mechanism for the number of temporal observations, nor the modeling of the dependence structure between the temporal observations for a given individual.^{21,22}

In the remainder of the article, we omit the phrase “rate of change” in describing these variables, for simplicity. For example, “BBS item 1 for patient 5” will refer to the average per treatment session change in BBS item 1 scores for patient 5 during the enrollment period.

The principal components were examined empirically, by consideration of the loading coefficients and variance accounting. The principal component scores were correlated with scores on the individual BBS items through a nonparametric (rank-based) correlation analysis to identify BBS items that most substantially differentiated patient recovery. The stability of the first 3 principal components was analyzed by repeatedly computing the first 3 principal components over pseudo-samples generated using a resampling scheme described in detail in the Results. The interpretation of the first 3 principal components was augmented by a nonparametric correlation analysis between the principal component scores and the average rates of change on 5 different measures of walking function—six-minute walk distances, ten-meter walk speeds, and the 3 subscales of the SCI-FAI instrument: Gait Parameters, Assistive Devices, and Walking Mobility.

Finally, we also conducted principal components analyses within (temporally varying) subgroups of our data set to determine whether the utility of the BBS items varied as a function of the patients’ level of recovery. To this end, 3 phases of recovery for patients with SCI were defined: I, II, and III. Patients in phase I were unable to stand or walk, were highly dependent on caregivers for mobility and activities of daily life, and experienced a multitude of symptoms from secondary complications. Phase II included patients who were able to stand for limited periods with assistive devices and physical

assistance; however, they primarily used wheelchairs for mobility at home and in the community. Phase III patients were able to ambulate but needed assistive devices and were limited in speed or endurance or had significant gait deviations. At each evaluation, each patient was classified as being in 1 of the 3 phases, so that a patient's phase could change as the patient recovered. Then, the same calculation of the average rates of change on the BBS items and functional measures of walking were conducted within each of the 3 phase-specific data sets obtained by the current phase at the first of the 2 successive evaluations. A principal components analysis was then conducted on each of the 3 data sets. All statistical analyses detailed were conducted using the open-source R software.²³

RESULTS

Demographic and Clinical Characteristics

A brief examination of the demographic and clinical characteristics of our data set preceded the analysis (see [table 1](#)). We noted representation from both sexes and a wide array of ages, mechanisms of injury, times since injury, and assistive walking devices at enrollment in NRN. The distribution of these characteristics in our sample roughly corresponded to that in the SCI population, which was important to note because these characteristics were observed rather than fixed (ie, it was not possible to randomize patients with respect to these characteristics).

On average, patients were enrolled in NRN for approximately 4 months and received just fewer than 50 treatment sessions over the course of enrollment. The median number of evaluations contributed by the patients to this analysis was 3. In terms of the processing of the data described, the average rate of change calculated for each patient involved averaging a median of 2 rates of change. Between consecutive evaluations, patients received an average of 14.6 treatment sessions, although there was a fair amount of variability in the number of treatment sessions per evaluation ($SD=7.8$).

General Description of Changes in BBS Items

As a first step of our multivariate examination of the BBS item scores, we investigated the relationships between each pair of BBS items graphically and through a nonparametric correlation analysis. Because there are 91 possible pairings of the 14 BBS items—which is a rather large number—we provide a general discussion of the relationships among the BBS items and focus on selected key aspects of the data. With the exception of correlations involving BBS item 3 (sitting with back unsupported), all correlation coefficients (Spearman rank correlation²⁴) were positive, which presumably suggested that a higher rate of change in each of these BBS variables indicated faster recovery for a patient. The size of the correlation coefficients ranged from very small ($\rho=.03$ for items 1, sitting to standing, and 14, standing on 1 leg) to very large ($\rho=.85$ for items 9, pick up object from the floor from a standing position, and 10, turning to look behind over left and right shoulders while standing). This indicated varying strengths of association among the items.

The pairs of BBS items plotted in [figure 1](#) were chosen to illustrate both strong and weak correlations and describe important phenomena in the BBS data. In the first column, BBS item 3 (sitting with back unsupported) was plotted against other BBS items. The observed weak correlations ($\rho \leq .01$ for all 3) were largely a product of the lack of variability in item 3—note that most of the data points fell on the vertical line at 0.0, indicating that most patients exhibited little change in item 3.

BBS item 3 was also weakly associated with the other items not shown in [figure 1](#). This characteristic of item 3 will be revisited. It is interesting to note that item 3 was the only item in BBS that assessed static sitting balance.

The second column plotted pairs of BBS items to illustrate weak associations. In particular, each plot of the second column paired an early BBS item, such as item 1 (sitting to standing), with a late BBS item, such as item 14 (standing on 1 leg). The weak relationships between early and late items were sensible, because the BBS was designed so that items escalate in difficulty as one progresses through the scale. Hence, we gathered that recovery of function for simpler balance tasks (early BBS items) was not closely related to the recovery of function for more advanced balance tasks (late BBS items).

The final column plotted pairs of BBS items to illustrate strong correlations. Contrasting the plots in the second column, the selected pairs of BBS items in the third column were in close proximity—for example, items 9 (picking up object from floor while standing) and 10 (turning to look over each shoulder while standing). Again, these strong relationships were sensible given the escalating difficulty of the component items—items in close proximity were of comparable difficulty, and recovery of function on closely related items would be expected to be closely associated. This pattern among the correlations, in which the strength of the correlation varied as a function of the proximity of the items, was generally apparent in the pairwise combinations of BBS items not shown here.

Principal Component 1

The first principal component accounted for 48% of the total variability in the BBS, which clearly dominated the remaining principal components (see Principal Components 2 and 3 below). The loading coefficients for each BBS item detailed the composition of the first principal component ([table 3](#)), but very small coefficients were omitted from [table 3](#) because a very small coefficient signaled a minimal contribution of an item to the given principal component. All items except BBS item 3 loaded onto the first principal component. Among the remaining items, item 14 was a minimal contributor (coefficient=.16), and item 10 contributed maximally (coefficient=.37). The loading coefficients were all positive and of comparable size (with the exception of items 3 and 14), indicating a fair amount of homogeneity among the BBS items with respect to the first principal component.

The correlations between first principal component scores and scores on individual BBS items were calculated to determine items that best differentiated recovery (see [table 3](#)). All BBS items were significantly correlated with the first principal component scores (ρ ranged from .38 to .64) except for BBS item 3. The lack of correlation between first principal component scores and BBS item 3 was presumably a result of the fact that most patients exhibited little change in this item over time (see, for example, the first column of [fig 1](#)).

Principal Components 2 and 3

The second principal component accounted for 12% of the total variability, a precipitous drop from the variability explained by the first principal component. The second principal component exhibited a lower degree of homogeneity than the first—the items loading on the second principal component did not all have the same sign, and the variability in the size of the coefficients was higher (see [table 3](#)).

In general, BBS items that loaded onto the second principal component correlated well with the second principal compo-

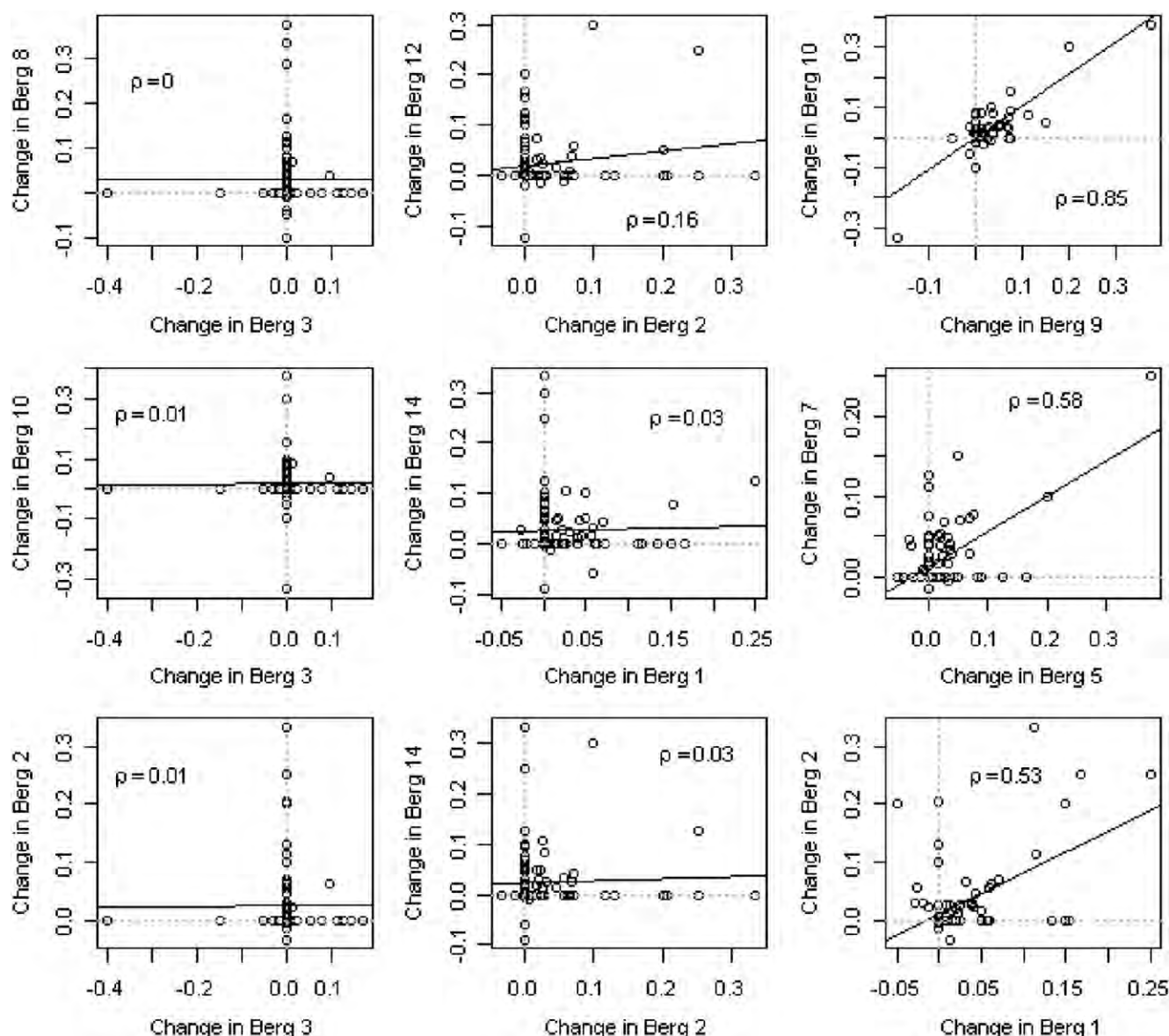


Fig 1. Scatterplots of average changes in selected pairs of BBS (Berg) items along with their rank correlations ρ and the least-squares lines of best fit.

nent scores (see table 3), with the exception of items 1, 9, and 10. The 2 items that did not load onto the second principal component (3 and 5: transfers) did not correlate with the corresponding scores.

The third principal component also accounted for 12% of the total variability. The composition of the third principal component was clearly different from that of the second principal component—4 of the 8 items loaded negatively, and items 9 through 13 (standing unsupported with 1 foot in front) loaded positively (see table 3). Neither the second nor third principal component seemed to capture a significant amount of variability in the BBS nor define an underlying data construct.

Concordance Plots: Stability of Principal Components

The principal components we observed were not based on population quantities but rather were estimated from a sample. Consequently, it was important to examine how sensitive our results were with respect to sampling before recommendation for clinical use. To that end, we created concordance plots¹² (fig 2) for each of the first 3 principal components. We selected 10 patients arbitrarily from our sample. We then created an artificial sample by adding to these 10 patients a randomly selected collection of 40 patients sampled from the remaining 87 patients. This process was independently replicated 5 times, resulting in 5 reduced data sets, each with 50 patients and each

Table 3: Composition of the First 3 Principal Components

BBS Variables	Loading Coefficients			Rank Correlations		
	First PC	Second PC	Third PC	First PC Score	Second PC Score	Third PC Score
1. Sitting to standing	.22	-.16	-.22	.50*	-.19	-.42*
2. Standing unsupported	.25	-.33	-.46	.58*	-.50*	-.49*
3. Sitting with back unsupported but feet supported	NS	NS	NS	-.02	-.12	-.08
4. Standing to sitting	.31	-.11	NS	.48*	-.30*	-.23*
5. Chair transfers	.30	NS	NS	.47*	-.11	-.25
6. Standing unsupported with eyes closed	.27	-.12	-.14	.64*	-.22*	-.28*
7. Standing unsupported with feet together	.22	-.10	NS	.59*	-.22*	-.14
8. Reaching forward with outstretched arm while standing	.24	.35	-.60	.55*	.29*	-.43*
9. Pick up object from floor from standing position	.33	-.18	.16	.63*	-.09	.05
10. Turning to look over left and right shoulders while standing	.37	-.27	.42	.50*	-.15	.22*
11. Turning 360°	.25	.22	.22	.43*	.33*	.36*
12. Placing foot on step or stool while standing unsupported	.28	.27	.28	.51*	.39*	.24*
13. Standing unsupported with 1 foot in front	.34	.15	.17	.58*	.23*	.08
14. Standing on 1 leg	.16	.68	NS	.38*	.64*	.04

NOTE. The left column contains the loading coefficients for the first 3 principal components. The right column contains Spearman rank correlation coefficients for the observed BBS item scores and principal component scores.

Abbreviations: NS, BBS item had a small loading coefficient and was not a significant contributor to the principal component; PC, principal component.

* $P < .05$.

containing the same original 10 patients. We then looked at the relative ranks of the initially selected 10 patients using each of the first 3 principal components, calculated from each of the 5 reduced data sets. The concordance plot provided a visual comparison of these rankings for each of these reduced data sets, together with the rankings of the scores derived from the principal components for the full data set. Ideally, the line segments joining the rank coordinates would be horizontal straight lines indicating perfect agreement and stability.

As can be seen from figure 2, the degree of agreement among the rankings for the first principal component was high, indicating that the first principal component was stable as an instrument measuring the rate of improvement of the BBS activities (basic motor skills). The level of stability was much worse for the second and third principal components, as shown by the jagged concordance lines. Such instability is an indicator that a principal component is compounded by chance variation rather than being a systematic construct of the data.

Association With Temporal Changes in Clinical Measures

In an attempt to provide an interpretation for the first principal component, we performed a correlation analysis with the 5 clinical measures of walking: six-minute walk distances, ten-meter walk speeds, and the 3 subscales of the SCI-FAI. The Kendall τ^{25} was used in addition to the Spearman rank correlation as a measure of association. By definition, these measures technically exemplify different characterizations of association. While the Spearman measure is an ordinary correlation between the 2 vectors of ranks, the Kendall measure is based on the number of pairs that are concordant in terms of the 2 variables. Nevertheless, both measures are appropriate for discrete data and for measuring nonlinear associations, and both perform generally similarly with respect to measuring association (both will tend to have high values when associations are strong and low values when associations are weak). We present both correlations to provide a more complete picture of the relevant associations, but will generally refer to the Spearman correlation coefficients when citing specific relationships.

The first principal component correlated significantly with all measures of functional mobility except the SCI-FAI Assis-

sive Device subscale (table 4). Hence, improvement on the BBS corresponded well with improvement on 4 of the functional measures—that is, those improving rapidly on the BBS also improved rapidly on the 4 walking measures, and those improving slowly or even getting worse on the BBS improved slowly or got worse on the walking measures.

The longitudinal plots in figure 3 provided visual evidence of the relationships between the first principal component and the 4 functional measures of recovery, suggesting that the first principal component did a reasonable job of differentiating patients on the degree of their recovery as measured by these 4 measures of walking function. Three patients with high scores and 3 with low scores on the first principal component were selected, and their measurements on the six-minute walk test, ten-meter walk test, SCI-FAI Gait Parameters subscale score, and SCI-FAI Walking Mobility subscale score plotted longitudinally. The 3 patients with high first principal component scores, represented by dashed lines, exhibited dramatic improvement in each of these parameters—sharp increases in six-minute walk distance, ten-meter walk speed, and SCI-FAI Gait Parameters and Walking Mobility subscale scores. Conversely, the 3 patients with low first principal component scores (solid lines) exhibited little, varied, or no improvement on these 4 measurements.

Principal Components by Phase of Recovery

Before proceeding with the analysis by phase of recovery, we compared the demographic characteristics of the patients in each of the phase groups. Because phase was time-varying, we conducted these comparisons relative to the patient's phase at enrollment. Patient ages and times since injury did not significantly differ across the phases, whereas sex did (see table 1). Patients earlier in recovery tended to remain enrolled in the NRN for longer periods and hence to receive more treatment sessions and undergo more evaluations, but the number of treatment sessions per evaluation (an indicator of treatment intensity) did not significantly vary across the phases at enrollment.

The principal components analysis of the BBS in the phase subgroups indicated that the utility of BBS items in measuring balance recovery was dependent on the patient's phase of

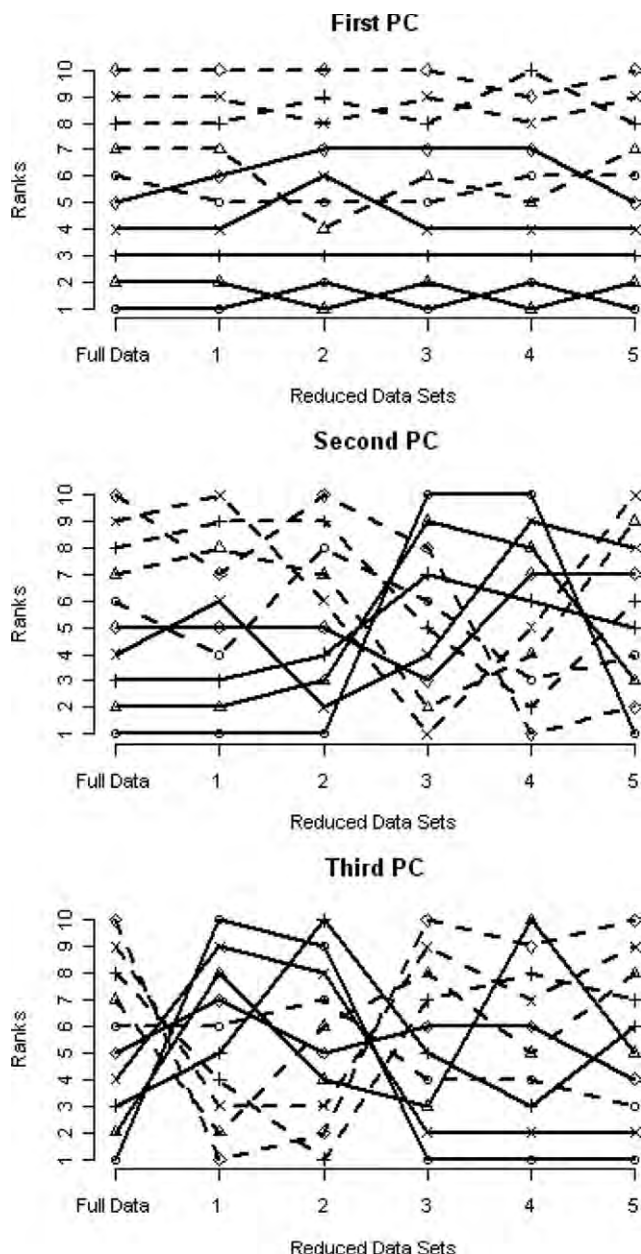


Fig 2. Plots illustrating the sampling variability in the calculation of the first 3 PCs. Ten patients were randomly selected and ranked by each of the first 3 principal components in the full data as well as in 5 reduced data sets artificially constructed by randomly selecting an additional 40 of the remaining 87 patients. Perfectly horizontal lines indicate perfect stability of a principal component against resampling. Abbreviation: PC, principal components.

recovery (table 5). The composition of the first principal component was clearly different in each of the 3 phase groups. In phase I patients, BBS items 1, 3, and 5 loaded onto the first principal component, which accounted for 53% of the total variability in the scale. BBS item 3 clearly dominated the first principal component, in stark contrast with its absence from the first principal component in the full data set. A further inspection of the data provided additional details on this phenomenon. As mentioned, 376 of the

429 unique assessments of BBS item 3 were given the highest score of 4. Of the 53 assessments not scored a 4, 48 occurred in phase I patients. Any variability in BBS item 3 almost exclusively occurred among phase I patients. Further, the remaining BBS items did not vary greatly in phase I patients (most could not complete them and scored 0), hence their absence from the first principal component in phase I patients.

Among phase II patients, the first principal component accounted for only 29% of the total variability. The items that loaded onto the first principal component were scattered across the scale, and BBS item 3 did not load on the first principal component. The loading coefficients were of differing signs, and the magnitudes varied quite a bit. While the principal component in phase II patients clearly differed from that in the full sample, the scattering and variability of the coefficients and the limited variance accounting made interpretation of this component difficult. The first principal component for phase III patients most closely mirrored that of the full sample, and accounted for 44% of the variance in the full scale for phase III patients. All BBS items except 3 and 8 (reaching forward while standing) loaded onto the first principal component in phase III patients, and the loading coefficients were uniformly positive. There was more variability in the magnitude of the coefficients than in the full sample, because coefficients ranged from .11 to .46. Items later in the scale tended to have higher loading coefficients than items earlier in the scale.

DISCUSSION

The first principal component of the full data set had several desirable properties—homogeneous loading coefficients, high variance accounting, stability with respect to sampling variability, and association with other clinical measures of recovery. Because the loading coefficients (except the third) were of the same sign and of similar magnitude, we conclude that recovery was fairly consistent across all BBS items. This inference is supported by the signs of the pairwise correlations between BBS items, namely that all were positive except those involving the third item. We can then interpret the first principal component as an overall measure of balance recovery in the general SCI population. We can be reasonably confident of the composition of the first principal component given its stability with respect to sampling variability as shown in the concordance plots.

The analysis by phase of recovery seemed to demonstrate that the utility of the individual BBS items in measuring balance recovery varied with the patient's phase of recovery. Earlier BBS items played an important role in phase I (early stages of recovery) patients, and BBS item 3 (sitting with back unsupported), seemingly noninformative in the full sample analysis, was the dominating contributor to the first principal component. This confirmed intuition: early BBS items are designed to assess sitting and standing balance, and are least difficult to perform but a challenge to patients early in recovery.

The picture was not as clear for phase II patients. The first principal component explained a low percentage of the cumulative variance and the loading coefficients lacked homogeneity and any simple interpretation. In a way, this was a reasonable phenomenon. By definition, phase II encompasses a diverse set of patients, from those unable or barely able to stand to those just beginning to walk. Hence, BBS items relevant for patients entering phase II, who have just regained the ability to stand, may not be relevant for those soon to leave phase II, who are on the verge of walking.

Things were far clearer in phase III patients. Most of the BBS items seemed to measure balance recovery adequately, but there was a clear division with respect to relative utility. Specifically, the later items were weighted more heavily than

Table 4: Kendall τ and Spearman Rank Correlation ρ Between the First Principal Component of Change in BBS Items and Changes in Clinical Measures of Walking

	Six-Minute Walk Distance (m)		SCI-FAI Gait Subscale		SCI-FAI Assistive Device Subscale		SCI-FAI Walking Mobility Subscale		Ten-Meter Walk Speed (m/s)	
	τ	ρ	τ	ρ	τ	ρ	τ	ρ	τ	ρ
First principal component score	.34 (*)	.48 (*)	.22 (*)	.31 (*)	-.07 (.42)	-.10 (.40)	.33 (*)	.44 (*)	.34 (*)	.46 (*)

* $P < .01$.

earlier items, signaling a greater relative importance. Again, this made intuitive sense. Late BBS items test more advanced balance function involving motion (eg, turning 360°, stepping on a stool), changing the base of support (standing with feet staggered), and limiting the base of support (standing on 1 leg). These are precisely the items that challenge patients more advanced in recovery, and hence phase III patients exhibited considerable variability in performance on these items.

Study Limitations

The patients considered in this analysis were all part of the NRN, which involves a standardized and fairly rigorous schedule of training. Because of this, it may be the case that participants in NRN are not representative of the general motor incomplete SCI population—that is, persons that chose to participate in NRN may be characteristically different from those who chose not to participate. Hence, the results presented here

may not extend to the general SCI population. In particular, the imbalance in sex across the phase groupings at enrollment may be of some concern in that the conclusions from a marginal analysis may not hold if the population demographic characteristics are substantially different from those observed in the study population.

The analysis of the average rates of change in the BBS items tacitly assumes that the method for calculating said averages provides a reasonable approximation to the true rate of change and is a reasonable estimate of the construct of balance recovery. However, if the rates of change between successive evaluations are highly variable—that is, if the rates differ substantially as a function of the number of treatment sessions accumulated—the average rate of change as calculated here may be a poor estimate of balance recovery.

The calculation of the principal components by phase suffers from small sample sizes in each of the phase groupings, par-

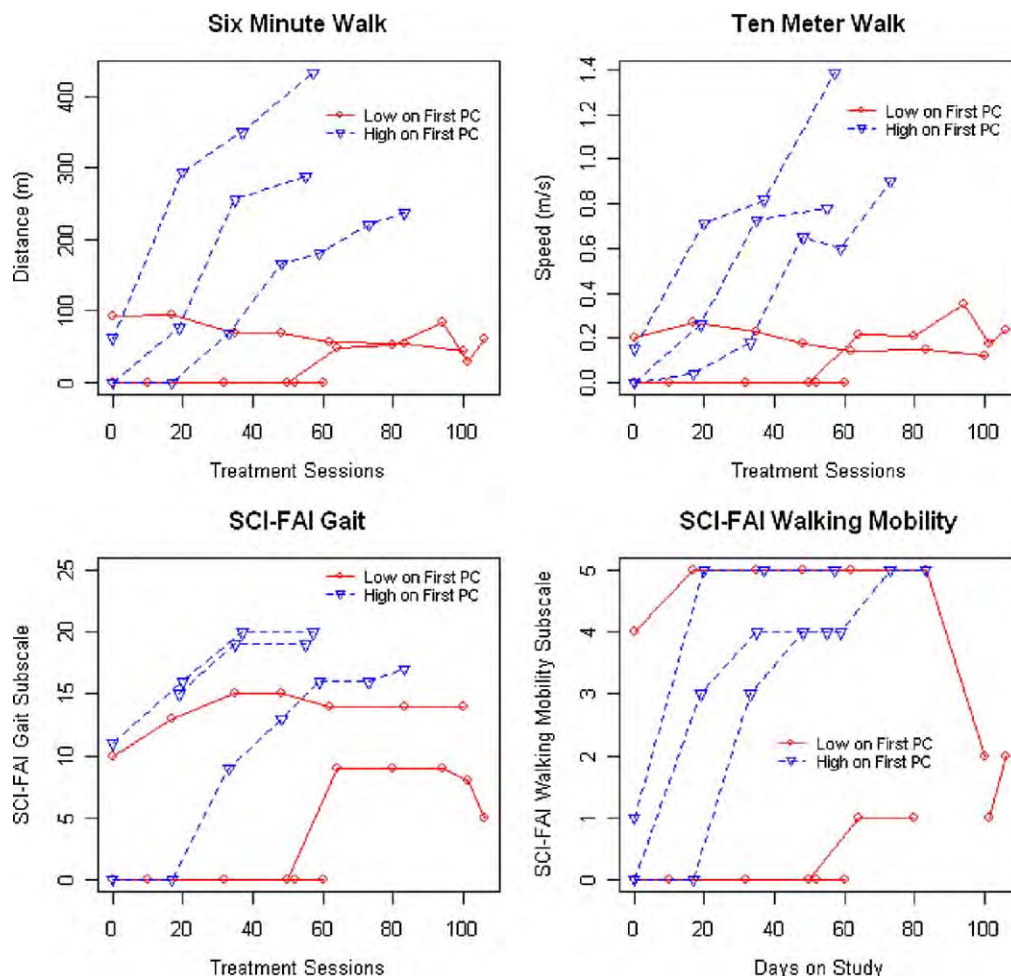


Fig 3. Longitudinal (temporal) clinical profiles for 3 patients who scored low (solid lines) and for 3 patients who scored high (dashed lines) on the first PC of the BBS items. The plots are the distances for the six-minute walk test, the speed of the ten-meter walk test, scores on the Gait Parameters component of the SCI-FAI, and scores on the Walking Mobility component of the SCI-FAI. Abbreviation: PC, principal component.

Table 5: Composition of the First Principal Component in Each Phase of Recovery Grouping

BBS Variables	First Principal Component Loadings		
	Phase I (n=26), 53% Variance Accounted	Phase II (n=36), 29% Variance Accounted	Phase III (n=40), 44% Variance Accounted
1. Sitting to standing	-.12	.16	.11
2. Standing unsupported	NS	.18	.15
3. Sitting with back unsupported but feet supported	.99	NS	NS
4. Standing to sitting	NS	.19	.17
5. Chair transfers	.11	NS	.27
6. Standing unsupported with eyes closed	NS	.17	.27
7. Standing unsupported with feet together	NS	NS	.15
8. Reaching forward with outstretched arm while standing	NS	-.42	NS
9. Pick up object from floor from standing position	NS	.43	.27
10. Turning to look over left and right shoulders while standing	NS	.52	.34
11. Turning 360°	NS	NS	.32
12. Placing foot on step or stool while standing unsupported	NS	NS	.42
13. Standing unsupported with 1 foot in front	NS	.16	.46
14. Standing on 1 leg	NS	-.47	.32

Abbreviation: NS, BBS item had a small loading coefficient and was not a significant contributor to the principal component.

ticularly in the phase I group. Hence, the results of the phase-specific analysis should be viewed as preliminary and in need of additional validation. The differences we observed across the phases in NRN enrollment statistics were expected—patients earlier in recovery at enrollment needed more treatment and were subsequently enrolled for longer periods. However, these differences were handled by the marginal rate of improvement calculations before the principal components analyses were applied.

CONCLUSIONS

The analysis presented here is a first step in developing a balance tool for the SCI population starting with the BBS. We have identified a single interpretable principal component in the BBS that accounted for 48% of the total variability for the full population. This principal component was related to overall recovery of balance and consisted of all the items on the BBS except the third. A simple sum of the BBS items (less the third) provided a reasonable approximation to the first principal component, and could be regarded as a summary measure of balance in the general SCI population. However, the usefulness of the individual BBS items seemed to vary as a function of the patient’s phase of recovery. Specifically, earlier, simpler BBS items were more appropriate for patients in early stages of recovery, and later, more difficult BBS items were more appropriate for patients in latter stages of recovery. These results suggested that use of the simple sum of BBS items (less the third) as a measure of balance recovery may not be appropriate for the entire SCI population. A dynamic balance scale for the SCI population, in which the items comprising the scale change as the patient’s level of recovery changes, may be needed. This concept needs additional research, and future work toward developing a balance tool for the SCI population will include repeating this analysis on larger data sets, and further exploring the idea of phase dependence. A good balance instrument for SCI populations may also require inclusion of additional measures of sitting balance ability. Such measures may come from other balance measurement instruments, such as the Tinetti Performance Oriented Mobility Assessment balance scale²⁶ and the Modified Functional Reach,²⁷ or may need to be created and developed.

Acknowledgments: We thank the NeuroRecovery Network team, including Assistant Director Andrea L. Behrman, PhD, PT, and the Center Directors, Mark Sheridan, MSSW, Douglas Stevens, MD (Frazier Rehab Institute), Mary Schmidt Read, PT, DPT, MS (Magee Rehabilitation Hospital), Daniel E. Graves, PhD (Memorial Hermann/The Institute for Rehabilitation and Research), Steve Williams, MD (Boston Medical Center), Gail F. Forrest, PhD, Sue Ann Sisto, PT, MA, PhD (Kessler Institute for Rehabilitation/Kessler Medical Rehabilitation Research and Education Corp), and D. Michele Basso, EdD, PT (The Ohio State University Medical Center). For a list of all NRN team members, please visit <http://louisville.edu/medschool/neurosurgery/harkema/NRN>. We also thank Dr. Graves for his helpful commentary on this article.

APPENDIX 1: DEFINITIONS OF BERG BALANCE SCALE VARIABLES

1. Sitting to standing: Patient attempts to stand from a seated position in an armless chair, using hands as little as possible.
2. Standing unsupported: Patient attempts to stand for up to 2 minutes with no support.
3. Sitting with back unsupported but feet supported on floor or stool: Patient attempts to sit in a chair for 2 minutes with no support.
4. Standing to sitting: Patient attempts to sit in an armless chair from standing position, using hands as little as possible.
5. Transfers: Patient attempts to move from an armless chair to a chair with arms, placed at a 90° angle from the armless chair, with minimal use of hands. Patient then attempts to move back to the armless chair, again with minimal use of hands.
6. Standing unsupported with eyes closed: Patient attempts to stand for up to 10 seconds with eyes closed and no support.
7. Standing unsupported with feet together: Patient attempts to stand with feet together and no support for up to 1 minute.
8. Reaching forward with outstretched arm while standing: Patient reaches forward as far as possible from a standing position by bending at the waist and returns to standing position with no support.

APPENDIX 1: DEFINITIONS OF BERG**BALANCE SCALE VARIABLES (Cont'd)**

9. Pick up object from the floor from a standing position: Patient attempts to pick up an object on the floor 15 to 30 centimeters (6–12 in) in front of his or her feet from a standing position with no support.
10. Turning to look behind over left and right shoulders while standing: Patient attempts to look at an object behind the patient over left and right shoulders, keeping feet planted on the ground and with no support.
11. Turn 360°: Patient attempts to turn in a full circle as safely and quickly as possible with no support.
12. Placing alternate foot on step or stool while standing unsupported: Patient attempts to place each foot alternately on a step or stool of 16 to 20 centimeters (6.5–8 in) until each foot has touched the step or stool 4 times with no support.
13. Standing unsupported 1 foot in front: Patient attempts to place 1 foot directly in front of the other and hold the position for 30 seconds with no support.
14. Standing on 1 leg: Patient attempts to stand on 1 leg for longer than 10 seconds with no support.

APPENDIX 2: DEFINITIONS OF CLINICAL MEASURES AS MEASURED IN THE NEURORECOVERY NETWORK

Six-minute walk: A sitting rest period of at least 10 minutes precedes the six-minute walk, during which vital signs are measured. The patient is instructed to walk as far as possible on a level surface over a period of 6 minutes. Patients are permitted to stop and rest during the walk by standing stationary or leaning against a wall, but not by sitting; the timing of the walk continues during such rest periods. Patient is alerted of the time every minute for the first 5 minutes and every 15 seconds during the last minute, and given standardized encouragement at each time update. The test concludes after 6 minutes or when the patient sits to rest.

Ten-meter walk: A sitting rest period precedes the ten-meter walk, during which vital signs are measured. The patient is instructed to walk a distance of 14m as quickly as possible. The walk is timed in the interval from 2m to 12m in the 14-m walk.

SCI-FAI: Parameters of the SCI-FAI are measured during the first 2 minutes of each six-minute walk. The 3 SCI-FAI subscales are Gait, Assistive Device, and Walking Mobility. The Gait subscale measures the quality of a patient's gait by evaluating the patient's weight shift, step width, step rhythm, step height, foot contact, and step length while walking. The Assistive Devices subscale quantifies the type of assistive device a patient uses according to the amount of assistance the device provides. The Walking Mobility subscale measures the capability for and frequency with which a patient walks in everyday life.

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SPECIAL COMMUNICATION

Establishing the NeuroRecovery Network: Multisite Rehabilitation Centers That Provide Activity-Based Therapies and Assessments for Neurologic Disorders

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ABSTRACT. Harkema SJ, Schmidt-Read M, Behrman AL, Bratta A, Sisto SA, Edgerton VR. Establishing the NeuroRecovery Network: multisite rehabilitation centers that provide activity-based therapies and assessments for neurologic disorders. *Arch Phys Med Rehabil* 2011;xx:xxx.

The mission of the NeuroRecovery Network (NRN) is to provide support for the implementation of specialized centers at rehabilitation sites in the United States. Currently, there are 7 NRN centers that provide standardized activity-based interventions designed from scientific and clinical evidence for recovery of mobility, posture, standing, and walking and improvements in health and quality of life in individuals with spinal cord injury. Extensive outcome measures evaluating function, health, and quality of life are used to determine the efficacy of the program. NRN members consist of scientists, clinicians, and administrators who collaborate to achieve the goals and objectives of the network within an organizational structure by designing and implementing a clinical model that provides consistent interventions and evaluations and a general education and training program.

Key Words: Activity-based therapy; Evidence-based therapy; Locomotor training; Recovery; Rehabilitation; Spinal cord injuries.

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THE MISSION OF THE Christopher and Dana Reeve Foundation (CDRF) NeuroRecovery Network (NRN) is to support the development of specialized centers that provide activity-based rehabilitation in the clinical environment. The network's primary objective is to evaluate the effect of rehabilitative interventions formulated from scien-

tific and clinical evidence on function, health, and quality of life for people with SCI and other selected neurologic disorders. To achieve these goals, the NRN provides supervisory and financial resources to establish rehabilitative environments that reliably deliver appropriate and standardized interventions for regaining locomotor function by skilled therapists and technicians. A comprehensive battery of quantitative assessment tools are administered to document changes over time and determine the efficacy of the program. The resources provided to each NRN center by the cooperative agreement between the Centers for Disease Control and Prevention and the CDRF are intended specifically for the development of treatment and care programs for individuals with neurologic disorders. The NRN services are funded by a combination of resources, including institutional support, health insurance, and supplemental external research funds, each covering different functions. Furthermore, we anticipate that our centers will continue to seek supplemental funds to develop ancillary translational research projects. We have enrolled and acquired functional, health, and quality-of-life data for 296 participants with SCI (table 1), the neurologic disorder targeted to date based on the extensive amount of research examining the effects of locomotor training on SCI.¹⁻¹⁵

Locomotor training is an activity-based therapeutic intervention for standing and walking that emphasizes activation of the neuromuscular system below the level of the lesion to induce neuroplasticity and promote recovery of function.¹⁴ The NRN initially focused on implementing locomotor training in individuals with clinically incomplete SCI after their discharge from inpatient rehabilitation. Previously, physical rehabilitation focused predominantly on the neuromuscular system above the level of the lesion as a means of achieving compensation-based strategies to enhance mobility.¹⁶⁻¹⁸ Based on our growing understanding of the residual functional capacity of the neural networks within the spinal cord, clinical strategies based on aggressive activation and reincorporation of the impaired neuromuscular system below the level of the lesion now can be implemented.^{2-7,19-26} For example, the sensorimotor circuitry within the spinal cord has significantly greater control over complex movements, such as stepping and standing, than previously recognized.

Mammalian studies have shown that in the case of incomplete SCI lesions, locomotion is controlled at multiple levels of the nervous system and the injury results in a devastating imbalance among these levels of control.²⁷ Traditionally, the role of supraspinal contributions has been viewed as singularly critical, with little control attributed to spinal mechanisms. The

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Supported by the Centers for Disease Control and Prevention and the Christopher and Dana Reeve Foundation (grant/cooperative agreement no. U10/CCU220379).

No commercial party having a direct financial interest in the results of the research supporting this article has or will confer a benefit on the authors or on any organization with which the authors are associated.

The contents of this article are solely the responsibility of the authors and do not necessarily represent the official views of the CDRF or Centers for Disease Control and Prevention, Department of Veterans Affairs, and the U.S. Government.

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0003-9993/11/xxxS-00592\$36.00/0
doi:10.1016/j.apmr.2011.01.023

List of Abbreviations

CDRF	Christopher and Dana Reeve Foundation
NRN	NeuroRecovery Network

Table 1: Description of Participants Enrolled in the NRN Program

No. of patients enrolled	296
Sex (%)	Men, 74; women, 26
Age (y)	39 (2, 79)
Time since injury (y)	0.9 (0.1, 25.8)
No. of therapy per patient	40 (2, 319)

NOTE. Values expressed as median (minimum, maximum) unless noted otherwise.

underlying theory of using locomotor training in individuals with clinically incomplete SCI is that the remaining descending pathways have a facilitatory role in the reorganization of spinal circuitry. This occurs during retraining when appropriate sensory information related to locomotion is provided to the spinal circuitry driving activity-dependent plasticity at spinal and supraspinal levels. In cases ranging from extensive to complete loss of supraspinal input to the spinal cord, effective weight-bearing stepping can be generated, but does not translate to overground walking. However, when some descending input is available and the sensorimotor networks within the spinal cord receive afferent input through task-specific locomotor training, gains occur that exceed those seen during spontaneous recovery or with conventional therapy.^{1,14,28} This suggests that combined with optimal retraining of spinal circuitry, only very limited residual descending input may be needed for significant functional improvements.

Improvements in multiple physiologic systems also were reported with locomotor training after SCI.²⁹⁻³⁵ Individuals with SCI that repetitively performed weight-bearing showed improvements in blood pressure stability,²⁹ muscle mass,³⁶ and bone density.³⁰ Anecdotal clinical observations also showed changes in bowel and bladder activity. Changes in these parameters are being documented using quantitative evaluations under well-controlled conditions within the NRN.

A UNIQUE DELIVERY MODEL FOR TRANSLATION OF EVIDENCE INTO PRACTICE

The NRN is a unique delivery model for evidence-based practice of physical rehabilitation services to individuals with SCI and other neurologic disorders. The network draws on a partnership among stakeholders invested in scientific inquiry, rehabilitation service delivery, health care policy, and medical informatics to expedite translation of basic and applied scientific findings to clinical practice. Scientists, hospital administrators and managers, physical therapists, and physicians provide the leadership. As scientific discovery continues, activity-based therapies will be refined, standardized, evaluated, and integrated into clinical practice. This partnership is bidirectional because the clinical experience may direct researchers on critical paths of inquiry, whereas researchers reciprocally can inform clinical practice.

One of the most challenging obstacles to translation is the lack of standardization during implementation and evaluation of clinical interventions.^{11,26} The NRN is designed to ensure that the programs, based on the recommendations and expectations of the network leaders, are implemented uniformly across its centers. Patient selection, evaluation, medical management, plan of treatment, and documentation all have standardized protocols. The resultant data are compiled from all centers into a centralized database. Systemax Corporation^a has developed a custom-built web-based clinical documentation system that tracks clinical information, such as medical history, treatment plan, intervention documentation, and assessments of

health, function, and quality of life, as well as demographic and financial information, including cost of treatment and reimbursement. Information from the central database is available to NRN centers or committees with approval of the directors and is compliant with the Commission on Accreditation of Rehabilitation Facilities, the Joint Commission on Accreditation of Health Care Organizations, and respective local institutional review boards and state regulatory guidelines. In addition to a comprehensive database of clinical information and standardized outcomes supporting program evaluation and clinical decision making, the NRN further bridges the chasm between scientific evidence and clinical practice by addressing other practical aspects of translation,^{37,38} including staff training and scheduling. Members are educated through annual national training, monthly conference calls, and regional courses on locomotor training.

NETWORK DESIGN AND ORGANIZATIONAL STRUCTURE

The primary NRN objective is to develop and maintain an infrastructure that implements the network goals into rehabilitation environments and provides consistent care across centers. The design of the NRN is based on the philosophy that the clinicians, scientists, and administrators will be continuously reexamining and identifying new strategies to achieve the mission, goals, and objectives of the network. A consensus on the implementation of all policy and strategic issues identified by team leaders at each center are reached in conjunction with the NRN Advisory Board and the oversight provided by the CDRF and Centers for Disease Control and Prevention. Network annual staff meetings and an ongoing conference call mechanism allow for continual review and upgrading of procedures.

Site Selection of Centers

The CDRF requests applications to join the NRN by using postings on their web site and email distribution from profit and nonprofit organizations, both public and private, such as universities, hospitals, and rehabilitation centers in the United States. The application outlines the NRN requirements, including the center's roles and responsibilities, equipment and facilities, personnel, and institutional commitment. Applicants report institutional and center resources, reimbursement practices, clinical environment, a clinical plan to execute the objectives of the network, and a plan for integration of the rehabilitative therapies into the surrounding community and the clinical research environment. External reviewers not associated with the network with expertise in clinical care, administration of clinical care, and research in the area of SCI review and assign priority scores for the applications. The NRN Advisory Board convenes and selects new centers based on these priority scores and evaluation of the applicant's ability to achieve the goals and objectives of the NRN.

Network Structure and Administration

The network director is responsible for the overall network operation as designated by the CDRF and Advisory Board (fig 1). The co-network directors support the functions of the director. Center directors are responsible for the overall operation of their sites (centers), oversee all financial expenditures and institutional review board procedures, and provide annual progress and financial reports to the network director. The center physician determines the diagnosis, medical eligibility, and other health-related issues of participating individuals during the treatment intervention. The center administrator man-

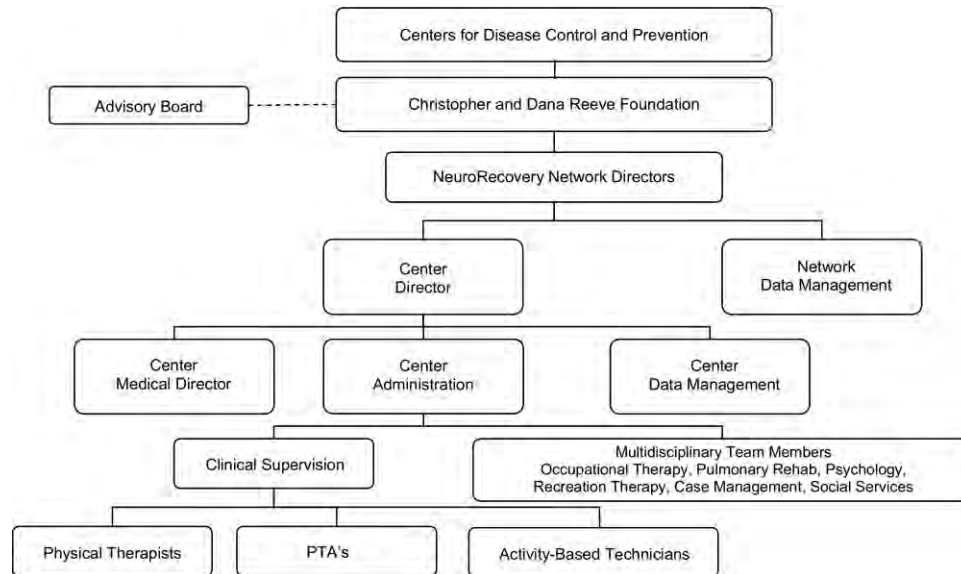


Fig 1. Illustration of the organization of the NRN. Abbreviation: PTA, physical therapist assistant.

ages the authorization and admission processes, interfaces with third-party payers, and manages the facility's staffing, scheduling, and financial processes related to clinical operations. The center clinical supervisor, a licensed physical therapist, oversees the daily functions of the center with primary responsibility to ensure clinically effective delivery of activity-based interventions and valid and reliable collection of outcome measurements. This person interacts with the center administrator regarding authorization and admission processes, third-party payer requirements, facility staffing, and scheduling. The clinical team consists of physical therapists, physical therapist assistants, rehabilitation technicians, students, and volunteers who are trained in activity-based therapy with emphasis on locomotor training. Personnel also are dedicated to managing all aspects of data entry. NRN personnel communicate on a monthly basis by means of a multisite conference call system targeted toward facilitating network functions and also meet annually for a multiday conference.

The network directors maintain the governance policies and procedures as designated by the CDRF and NRN Advisory Board, as well as the clinical policies and procedures developed by consensus of the center directors. The NRN director communicates all new policies and revisions to the center directors and other collaborators. Center directors are responsible for communication with their respective team members and execution of all NRN policies and procedures. New policies and revisions are executed through a committee structure. Consultants are retained by the director of the NRN to provide guidance and advice in their area of expertise.

Standing and ad hoc committees develop and revise policies and procedures as needed and implement the goals and objectives of the network. Standing committees are appointed by the network director and address long-term issues critical to the goals and objectives of the network. The designated standing committees include Health, Data Integrity and Dissemination Oversight, Finance, Education and Training, Quality of Life, and Translation of Interventions to Clinical Practice. The ad hoc committees, which can be initiated by a center director and at least 1 other director, are organized for the purpose of analyzing, interpreting, and publishing data and initiating

changes to existing or recommending new policies and procedures. External reviewers not associated with the network, with expertise in clinical care, administration of clinical care, and research in the area of SCI, also may participate in this process.

STANDARDIZED CLINICAL MODEL

Patient Selection Guidelines

Current criteria for patient enrollment in the NRN locomotor training program include the presence of a nonprogressive spinal cord lesion above T11, no current participation in an inpatient rehabilitation program, and medical referral by an NRN physician. Patients must have some lower-limb movement or visible voluntary contraction and the capacity to generate a lower-limb reciprocal alternating flexion/extension stepping pattern in the step training environment using body-weight support on a treadmill with manual facilitation. According to established NRN protocol, the NRN physician also directs the eventual elimination of antispasticity medications to avoid inhibiting neuromuscular activity and monitors other medical issues that may interact with training effectiveness. Also established in the medical protocol, the use of onabotulinumtoxinA or other medications for chemodenervation for spasticity likewise is avoided for the 3 months before NRN admission. Standardization of medical care associated with the locomotor training program is regulated by the health committee, composed of physicians from all centers.

Activity-Based Intervention: Locomotor Training

After physician referral, the screening process continues with the physical therapy evaluation. This evaluation focuses on the potential for recovery and occurs in the overground and body-weight support and treadmill environments. On a standard therapy mat, the patient is asked to execute a series of tasks: sitting and reaching with an upright posture, a reverse sit-up (controlled sitting to supine), sit-up, trunk extension in sitting (from a forward flexed position), sit to stand, stand, and components of walking (eg, lateral weight shift, weight shift in the diagonal position, stepping). The patient's movements are



Fig 2. Participants in each of the 3 therapeutic environments.

assessed relative to a description of the preinjury movement pattern specific to the task. Physical assistance is allowed to help the patient into any position needed, but the assistance then is removed at certain body segments (eg, trunk, hips, knees) to determine areas of independent control. Thus, recovery of function is relative to movements that can be executed by the patient without compensation and all tasks are performed without assistive devices or bracing.

When assessment in this overground environment has been concluded, the patient is positioned wearing a trunk and pelvic harness in a body-weight support system over a treadmill. In this environment and with manual assistance of trainers, the therapist tests the capacity and independence of the patient's neuromuscular system to stand and generate steps in a safe and permissive environment. The capacity of the neuromuscular system, termed retraining, is assessed by identifying treadmill speed (stepping only) and body-weight support with manual facilitation to generate the stepping pattern or standing as close to preinjury as possible as judged by the physical therapist and training team. The independence of the neuromuscular system is referred to as adaptability and is assessed by identifying the treadmill speed (stepping only) and body-weight support at which independence from manual facilitation is achieved.

Body-weight support and treadmill afford an assessment of physical capacity not available in the overground environment for standing and stepping. Treadmill speed and body-weight support offer systematic control and can be adjusted (decreased or increased) while the patient regains trunk alignment and limb position consistent with premorbid control for the specific task.

Based on the findings of the evaluation, the therapist will establish goals for treatment and implement a standardized plan of care. Therapists and trainers implement well-established locomotor training principles, including (1) maximizing weight bearing on the lower extremities and minimizing it on the upper extremities, (2) optimizing sensory input consistent with each activity, (3) optimizing the proper kinematics for each task, and (4) maximizing independence and recovery of movements while minimizing compensation.^{11,39} A typical episode of care includes progressive retraining in functional skills, including balance, transfers, activities of daily living, and ambulation. Compliance to eliminate or minimize lower-limb orthotics also is expected to optimize sensory input to the spinal cord and promote optimal recovery. Initially, intensive therapy occurs in all 3 environments (fig 2), is preferred 5 times a week for

90-minute comprehensive sessions, and goals progress with recovery and functional change.

A typical locomotor training session has 3 components and occurs 5 times a week in the early phases of recovery with a minimum of 3 times a week in the later stages of recovery.⁴⁰ The step-training component is composed of task-specific retraining of the nervous system for standing and walking that occurs in a controlled environment using body-weight support on a treadmill with verbal and manual facilitation by trainers. Training is composed of (1) stand retraining, (2) stand adaptability, (3) step retraining, and (4) step adaptability and takes place for a minimum of 55 to 60 minutes. Retraining (stand or step) requires therapist/trainer manual facilitation to optimize the neuromuscular response to the sensorimotor experience. During retraining, the body-weight load is maximized while maintaining the appropriate task-specific kinematics with trainer facilitation for standing and stepping. During step retraining, treadmill speed is set for 2.0mph or greater to promote a stepping pattern as consistent with a preinjury pattern as possible. Step retraining occurs for a minimum of 20 minutes of the total 60-minute session. Adaptability (stand or step) reflects the patient's ability to perform the task independent of trainer facilitation, although body-weight support and treadmill speed are adjusted to grade progression of independence in a preinjury manner. The proportion of retraining and adaptability components of the total session time varies according to the extent of a patient's neuromuscular recovery. Thus, a greater proportion of retraining is necessary for a patient with severely impaired trunk posture and motor control in the trunk and extremities requiring a high percentage of body-weight support (up to 60%) and moderate to maximum amount of facilitation to achieve standing and stepping. As a patient progresses and shows neuromuscular recovery, retraining remains a fundamental component of training. However, time spent in stand and step adaptability increases, affording the practice and development of independent control. Each step training session ends with a bout of step retraining.

The second component is overground assessment that evaluates the transfer of the present capacity of the patient's neuromuscular system to mobility, posture, and walking skills over level ground and establishes priorities for further retraining. This assessment immediately follows the step training component. The patient walks off the treadmill with assistance if feasible or is placed in a wheelchair to move from the treadmill environment. Depending on the patient's current goals targeting recovery, the patient is asked to either stand or step in the overground environment and/or perform the sitting or trunk control tasks identified as a goal during the evaluation. The aim is to assess the immediate effect of locomotor training on the patient's abilities over ground, allow the patient and therapist to assess the patient's recovery, and identify critical elements limiting recovery at this stage. The identified elements become the aim of community integration and the next day's step-training session. Physical assistance is minimized during this assessment, and the evaluation is conducted without the use of assistive devices or bracing.

The third component is community integration that provides instruction for the individual to perform daily activities in the home and community environments and achieve safe efficient mobility. In this component, the individual is able to continually practice and integrate skills and abilities into the everyday routine. Although a locomotor training session takes place during a 1.5-hour session, the potential to advance the recovery of the nervous system continues outside of body-weight support on a treadmill and clinic environments to the patient's activities in the home and community. The patient, in consul-

tation with and guidance from the therapist, applies the locomotor training principles in everyday activities and specific exercises to promote continued recovery. In addition, the use of assistive devices to achieve ambulation is introduced. The least restrictive assistive device is selected for use in the home and community, and instructions are provided for how to use the device consistent with the locomotor training principles. Depending on patient goals, multiple devices may be used. For example, depending on the extent of recovery and the specific recovery goal (eg, endurance in community ambulation vs improved adaptability in the home), a rolling walker and bilateral crutches may be selected and used alternately. Selection of a device is made repeatedly, and choices will change to meet new goals for progression.

Patient Progression

Patients progress through defined phases of recovery related to mobility, standing, and stepping, especially in regard to the level of physical independence for trunk, pelvis, and leg control within the step-training environment and the patient's abilities over ground without compensation. Initially, most of the time spent in a session would be in the step-training environment with physical assistance of up to 3 trained clinicians/aides. Over time, physical assistance may be decreased and more time may be spent on independence during the 90-minute session. Expectations for progression do not take strategies for compensation into account and are used to guide the clinician and participants to achieve higher levels of independent performance, which are critical to optimal recovery. Patients are challenged to advance by progressively changing the parameters of the intervention as appropriate, including treadmill speed, amount of body-weight support versus load, or manual facilitation of legs and hips. A standardized algorithm has been developed to guide physical therapists in which parameter to progress and when and in what order to optimize the work and neuromuscular recovery. Use of lower-extremity orthotics is avoided during locomotor training sessions and is considered only for safety use in the outdoor environment or at home. Patients are encouraged to use orthotic devices as little as possible at home and maximize practice without this alternative stabilization.

Patients are maintained in the program as long as they continue to progress, as shown in the ongoing evaluations performed on admission, discharge, and at approximately every 20 sessions of locomotor training. This reevaluation is a comprehensive battery of outcome measures examining neurologic motor function, balance, autonomic function, functional skills, and gait parameters. A standardized discharge algorithm has been developed to be used across all NRN sites, quantifying changes in neuromuscular activity and functional skills that support the therapist's decision to request more sessions or terminate the episode of care. Durability of outcomes is monitored by scheduling 6- and 12-month follow-up evaluations, including the same outcome measures previously performed. Some patients return to active treatment after a time if their clinical picture appears to have changed or new goals are established.

Staffing

Manually facilitated step training requires the hands-on attention and coordination of a team of personnel, potentially covering each leg and the hips and 1 for computer operation of body-weight support on a treadmill system. All new NRN facilities begin with a maximum of 2 therapists: 2 activity-based technicians staffing model. As staff expertise improves,

they move to a 1 therapist: 3 (or fewer) skilled technicians staffing model. As the patient's treatment progresses, a decrease in direct manual facilitation is expected, potentially decreasing the number of staff required for each session. This parallels other common therapeutic approaches to gait training, in which more than 1 staff member may assist with ambulation and assistive device use, although multiple staff members are not required throughout an entire session. Time spent on preparation and closure of the sessions, as well as overground assessment and community integration components, also may require less staff.

Center clinical staff are trained with skill competencies specific to locomotor training to facilitate efficient and effective service delivery and accurate assessment by using the standardized outcome measurements. A locomotor training manual is used to promote standardization of therapeutic interventions across centers. A comprehensive outcome measures manual was developed to provide standardization to the measurement techniques chosen by the network. All NRN staff members are provided with specific training for the theory and clinical skills of therapeutic application and clinical progression decision making. Intensive training for the skills needed to provide locomotor training is important for proper therapeutic facilitation, as well as from a staff risk management perspective. Improper body mechanics and manipulation of difficult patient types can result in injury to staff or ineffective treatment.

Clinical supervisors' conference calls occur monthly with a representative from each NRN center to foster standardization and clinical problem solving regarding pertinent patient care issues. Video feedback also is provided by clinical supervisors to promote the skill development of trainers and clinical problem solving for challenging patients. Center directors' conference calls also occur monthly to ensure consistency in overall management and promote the clinical, administrative, and dissemination goals of the NRN.

Equipment

The equipment used in the locomotor training program of the NRN includes a closed-loop computer-controlled body-weight support system^b that allows center of mass movement while controlling forces, controls treadmill speeds from 0.5 to 10mph, and has seating and foot-support systems that include ergonomically appropriate support design for staff safety. Additionally, the NRN uses harnesses^c of various sizes, front and side mirrors that provide visual feedback, a variety of assistive devices, automatic blood pressure monitoring equipment, a computerized pressure-sensitive walkway that records footfall pattern^d and provides spatial-temporal parameters of gait, a portable step counter, and supplies that include a stop watch, yardstick, curbs, reclining chair, and automatic blood pressure, heart rate, and oxygen saturation monitor.

ASSESSMENTS

A critical component of the NRN is a Health Insurance Portability and Accountability Act–compliant and institutional review board–approved comprehensive database^a that includes information from all centers for health, function, and quality-of-life outcomes, as well as financial parameters, such as cost and reimbursement. All outcome measures are collected as part of the NRN initiative at program admission and discharge with patient informed consent approval, and interim assessments occur approximately every 20 sessions. Follow-up assessments are targeted to be performed 6 and 12 months post–therapy discharge. A critical feature of the NRN infrastructure is stan-

dardization of assessments used for all outcome measures. This is accomplished through regional training opportunities, a mandatory annual national summit, and regular video review during conference calls that are weekly for new centers and monthly for existing centers. Clinical supervisors have monthly conference calls in which protocols for assessments are clarified and disseminated to their respective clinical teams. All NRN members follow a detailed operations manual to further ensure standardization of assessments. The annual NRN National Conference includes face-to-face practice of outcome measures by physical therapists from each center for continued assurance that standard procedures for outcome measure assessments are followed.

Functional outcomes measured routinely include a variety of neurologic dysfunction, balance, and gait measures that target all aspects of the *International Classification of Function, Disability and Health* model, including outcomes related to impairments in body function or structure, activity outcomes related to the capacity to execute tasks, and participation outcomes related to performance of tasks in the individual's current environment.⁴¹

Assessment of body structure and function focuses on neurologic dysfunction, completed at admission and discharge from the therapeutic episode of care by using the International Standards for Neurological Classification of SCI⁴² examination, American Spinal Injury Association Impairment Scale,^{43,44} and health measures, such as blood pressure, heart rate, respiration rate, and oxygen saturation at rest and orthostatic hypotension in response to a sit-up test.^{45,46} These measures are used routinely throughout the episode of care to monitor changes in intrathoracic pressure from harness application, exercise tolerance, and incidence of autonomic dysreflexia and to measure changes in cardiovascular activity before and after locomotor training.^{29,47} In addition, lipid metabolism is monitored initially and with follow-up if abnormalities are found. Other impairment outcomes measured include the Modified Ashworth Scale,⁴⁸ clonus, reflexes, pain, and grip strength tests.

Functional activity outcome measures routinely performed include balance measures, including the Modified Functional Reach (seated reach),⁴⁹ Tinetti^{50,51} and Berg Balance Scale⁵² tests, and functional walking measures, including the 10-Meter Walk Test⁵³ using a computerized pressure-sensitive mat^{54,55} and the 6-Minute Walk Test,⁵³ along with the SCI Functional Ambulation Inventory.⁵⁶ Each is assessed approximately every 20 treatment sessions.

The Modified Functional Reach is performed according to Lynch,⁵⁷ Adegoke, and colleagues.⁴⁹ The subject is seated with the feet supported and the trunk rested on the back of the chair (reclined 10° from vertical). The subject raises his/her preferred shoulder to 90° and parallel to, but not touching, a wall-mounted yardstick. The location of the ulnar styloid of the raised arm is noted before and after maximal reach. If a patient is unable to raise the arms to 90°, the acromion is used as the point of reference. Two practice trials are followed by 3 scored trials, the mean of which constitutes the Modified Functional Reach score.

Tinetti Balance and Gait scores are assessed according to Tinetti⁵⁰ with slight scoring modifications. NRN subjects are instructed to avoid using the hands when rising to standing (item 2) and returning to a seated position (item 9). Also, balance during sitting is scored zero if the subject needs to hold the seat to stay upright for item 1. For Tinetti Gait, the assistive device is allowed for only items 4 (immediate standing balance) and 5 (standing balance) because these are the only items for which an assistive device is mentioned in the possible scores.

The Berg Balance Scale originally was developed to assess fall risk in community-dwelling elders. However, a number of studies have reported data for the SCI population.^{39,58-63} NRN standardizations for testing include slight modifications, such as not allowing the participant to use lower-extremity bracing during the test. Item 5 requires transfers from chair to chair, and within the NRN, a therapy mat is not used for this test because it gives an unrealistic stable surface. For item 9, NRN uses a slipper to allow the participant to slide his/her hand easily inside it to pick up the item, which ensures that the test is scoring balance regardless of grip strength.

To perform the 6-Minute Walk Test, a 100-ft [30.48m] walkway is designated at each facility for testing the distance traveled back and forth along the walkway during 6 minutes. Using standardized language, subjects are instructed to walk as far as possible (measured in meters) in this time frame. If the participant requires rest, he/she could do so while standing with the timer still running, but if the participant needs to sit or needs assistance, the test is complete.⁵³ For the 10-Meter Walk Test, the time to walk the middle 10 meters of a 14-m walkway is recorded in seconds and rounded to the nearest 0.1 second.⁵³ At re-evaluation, these 2 tests are performed using the baseline/initial ambulation device (eg, walker, cane) first and then repeated using the current ambulation device. However, no lower-extremity bracing is allowed during execution of these ambulatory tests.

The GaitRite^d computerized pressure-sensitive walkway is used in conjunction with the 10-Meter Walk Test to record footfall patterns and provide spatial-temporal parameters of gait. This information is recorded on a laptop computer and parameters are included in the central database. Because the GaitRite mat is 14 meters long, it affords the opportunity to manage the 2 outcome measures simultaneously.

The SCI Functional Ambulation Inventory⁵⁶ is scored during the first 2 minutes of the 6-Minute Walk Test. The Gait subscale assesses qualitative measures of gait (eg, step width, height, clearance on swing); the Assistive Devices subscale quantifies the upper- and lower-extremity assistive devices used (although braces were never used during these assessments); and the Mobility subscale assesses patient report of the extent of ambulatory activity in the home and community relative to use of a wheelchair. All ambulation outcome measures together offer sequential information related to changes in speed, endurance, assistive device use, therapist assistance, and qualitative information about gait parameters and patient perception of ambulation ability.

Finally, participation outcomes include quality-of-life measures, such as the Quality of Life Index for SCI (version III),⁶⁴ the Center for Epidemiological Studies Depression Scale,⁶⁵ Katz Index of Independence in Activities of Daily Living,⁶⁶ and the Craig Handicap Activity Reporting Technique-Short Form.⁶⁷ The Quality of Life Index for SCI III asks patients about health, relationships, work, religion, and personal lifestyle. The Center for Epidemiological Studies Depression Scale assesses patients' feelings about aspects of their life during the past week. The Katz addresses the patient's perception of functional activities, such as bathing, dressing, toileting, transfers, continence, and feeding.⁶⁸ The Craig Handicap Activity Reporting Technique-Short Form evaluates physical and cognitive independence, mobility, occupation, social integration, and economic self-sufficiency relative to family size versus medical expenses.⁶⁹

FINANCING SERVICE DELIVERY

Another objective of the NRN is to define the financial cost of intensive activity-based therapies for a patient with a given type and severity of sensorimotor dysfunction. Because staff costs are the primary contributor to overall expenses, various staffing algorithms have been tested and refined, along with efficient scheduling and maximum use of equipment. Routine physical therapy charging procedures are used, with standardized Current Procedural Terminology coding based on physical therapy procedures. The subsequent financial analysis of clinical care includes demographic information related to primary and secondary payers and participant volume information, including procedure units and other routine expenses. Revenue tracking includes actual insurance payment, self-pay, or copay revenue. Net revenue is calculated and compared with actual institutionally based costs to produce accurate information for net income and actual charges and costs. The goal is to continually develop and implement strategies that address the unique reimbursement challenges for providing intensive activity-based therapy programs. To that end, the NRN's goal is to effect reimbursement policy for the delivery of activity-based therapies. Additionally, results of outcome measures collected regularly are examined to draw conclusions about cost-effectiveness and the financial impact, calculated through life care planning. Dissemination of these results to various payers is paramount to acceptance of locomotor training in the payer community.

EDUCATION AND TRAINING

One of the basic philosophies of the network is to provide consistent activity-based therapeutic interventions across all facilities based on the best scientific and clinical evidence available. To ensure this goal, consistent education of all NRN staff in locomotor training theory, manual facilitation techniques, progression, and outcome measurement is necessary both within and among NRN centers. To expand the availability of this intervention to as many patients as can potentially benefit from it, the network is committed to sharing this information throughout the community in both clinic- and community-based programs.

New Center Development

As the network has grown, each new center commits to an intensive training regimen that includes on-site skills training, ongoing educational development, regular video review of therapy provision, and weekly conference calls to collaborate with clinical staff from other network sites to further promote skill development and clinical decision making for the comprehensive care of NRN patients. New sites are led through the development process with guidance from network directors, consultant staff, and experienced clinical staff.

Training Opportunities

The NRN fosters a variety of educational and training opportunities for both network and non-network staff. A yearly national conference brings together staff from all NRN sites to review and advance skills in therapeutic delivery and clinical problem solving and progression, as well as reinforce the importance of standardization of the interventions and outcome measures. The committee structure of the NRN provides another ongoing avenue for continued growth and education across the network for such issues as financial management, data management, medical considerations, scheduling, staff training, equipment, and other practical issues. Specific projects defined within the NRN also facilitate continued collabora-

ration of members, including outcome measure development, standardized training tools, and age-specific applications.

Another objective of the NRN is to develop a core of regional clinical centers with highly trained personnel skilled in activity-based rehabilitation therapy. Annually, they provide training and information about the logistics of implementation, such as administration and reimbursement to community clinics in their region to promote dissemination of activity-based rehabilitation strategies rapidly and effectively across the United States. Regional training seminars are held at network centers throughout the year, with enrollment from the therapeutic and wellness communities. Multiple network sites represent geographic diversity in dissemination of education, although the content is standardized within the regional training curriculum. Therapy teams are encouraged to participate in either a 1-day lecture or a combination 4-day lecture series and intensive skills training educational seminar. This information will provide the groundwork for development within their own facility by providing practical implementation of the clinical model, including administration, resource use, and financial aspects of billing and reimbursement.

Finally, the NRN is committed to communicating the scientific evidence of activity-based interventions to the rehabilitation community. Members of the NRN present relevant information at local, regional, national, and international levels in such venues as professional association and multidisciplinary organization meetings, research seminars, and professional and academic school curricula. The NRN also offers clinical internship opportunities for physical therapy professional students at various centers.

NRN AS AN SCI NETWORK

The NRN is similar to other SCI networks, but also has distinct differences. The US SCI Model Systems of Care (see www2.ed.gov/programs/sci for more information), funded by the National Institute on Disability and Rehabilitation Research, has included prominent inpatient rehabilitation centers (currently 14) that gather important demographic and clinical data for the life span of a patient after acute traumatic SCI. Additional goals include conducting site-specific and collaborative research among the sites to advance the treatment and quality of life of those living with SCI. The European Multi-center Study About Spinal Cord Injury (see www.emsci.org for more information) has 18 paraplegic centers for which the goal is to establish a multicenter basis for future therapeutic interventions in human SCI. They conduct a standard set of neurologic, neurophysiologic, and functional assessments that is gathered at a coordinated center and central database. The NRN differs from these centers because it specifically focuses on translation of new rehabilitation therapies with rigorous evaluation of the standardized intervention in a specific patient population. Thus, the information that the European Multi-center Study About Spinal Cord Injury gathers for each individual is more extensive, and is collected during the interval of the intervention and within a 1-year follow-up. The collaboration of these networks can accelerate the achievement of synergistic goals and increase the efficiency of delivery of new therapeutic interventions.

The most recent results of the NRN's current intervention are reported in articles within this supplement and indicate the effectiveness of locomotor training as standardized by these centers. These data cannot support whether locomotor training is superior to other rehabilitation interventions and cannot address specific hypotheses of the underlying theory of locomotor training in humans. However, it can provide information regarding a specific population, time frame, and intervention

for improvements in function, health, and quality of life and is an example of using these theories to develop new rehabilitation strategies.

CONCLUSIONS

The CDRF NRN is a collaboration of specialized centers dedicated not only to providing activity-based rehabilitation in the clinical environment, but also to evaluating the effect of locomotor training and other evidence-based rehabilitative interventions in clinical environments. The network achieves these goals within established rehabilitative environments with clinicians with specialized training to deliver interventions and document patient progress using standardized protocols. The resultant partnership among basic scientists, clinical scientists, clinicians, and administrators provides a rich resource for continual refinement and analysis of new and promising therapies. The NRN and the development of its various protocols present an opportunity for accelerated translation of basic research to the clinic because the network is a readily available arena for multisite execution of the most current options for intervention after SCI.

Acknowledgments: We thank Joe Canose, BA, MLS, Susan Howley, BA, and Michael Mangienello, MPA, from the CDRF for dedication and support. The extraordinary vision, compassion, and dedication of Christopher and Dana Reeve made the NRN possible. We acknowledge the other current or past NRN Center Directors: Steve Ahr, MSSW, and Linda Shelburne, PT (Frazier Rehab Institute); Steve Williams, MD (Boston Medical Center); Daniel Graves, PhD (Memorial Hermann/The Institute of Rehabilitation and Research); Sarah Morrison, PT, and Keith Tansey, MD, PhD (Shepherd Center); Gail Forrest, PhD (Kessler Medical Rehabilitation Research and Education Corporation); and D. Michele Basso, PT, EdD (The Ohio State University Medical Center), plus all other current and previous network members (<http://louisville.edu/med-school/neurosurgery/harkema/nrn>); the critical review and editorial support of Jessica Hillyer, PhD; and the leadership, foresight, and support of the NRN Advisory Board, Reggie Edgerton, PhD, Moses Chao, PhD, Michael Fehlings, MD, PhD, Andrei Krassioukov, MD, PhD, and Shelly Sorani, MA.

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Suppliers

- a. Systemax Corp, 9509 Hwy 42, Ste 100, PO Box 907, Prospect, KY 40059.
- b. Therastride, Innoventor 3600 Rider Trail South, St Louis, MO 63045.
- c. Robertson Harness, PO Box 90086, Henderson, NV 89009-0086.
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ORIGINAL ARTICLE

Balance and Ambulation Improvements in Individuals With Chronic Incomplete Spinal Cord Injury Using Locomotor Training–Based Rehabilitation

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ABSTRACT. Harkema SJ, Schmidt-Read M, Lorenz D, Edgerton VR, Behrman AL. Balance and ambulation improvements in individuals with chronic incomplete SCI using locomotor training–based rehabilitation. *Arch Phys Med Rehabil* 2011;xx:xxx.

Objective: To evaluate the effects of intensive locomotor training on balance and ambulatory function at enrollment and discharge during outpatient rehabilitation after incomplete SCI.

Design: Prospective observational cohort.

Setting: Seven outpatient rehabilitation centers from the Christopher and Dana Reeve Foundation NeuroRecovery Network (NRN).

Participants: Patients (N=196) with American Spinal Injury Association Impairment Scale (AIS) grade C or D SCI who received at least 20 locomotor training treatment sessions in the NRN.

Interventions: Intensive locomotor training, including step training using body-weight support and manual facilitation on a treadmill followed by overground assessment and community integration.

Main Outcome Measures: Berg Balance Scale; Six-Minute Walk Test; 10-Meter Walk Test.

Results: Outcome measures at enrollment showed high variability between patients with AIS grades C and D. Significant improvement from enrollment to final evaluation was observed in balance and walking measures for patients with AIS grades C and D. The magnitude of improvement significantly differed between AIS groups for all measures. Time since SCI was not associated significantly with outcome measures at enrollment, but was related inversely to levels of improvement.

Conclusions: Significant variability in baseline values of functional outcome measures is evident after SCI in individuals

with AIS grades C and D and significant functional recovery can continue to occur even years after injury when provided with locomotor training. These results indicate that rehabilitation, which provides intensive activity-based therapy, can result in functional improvements in individuals with chronic incomplete SCI.

Key Words: Gait disorders; neurologic; Locomotion; Rehabilitation; Spinal cord injuries; Walking.

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LOCOMOTOR TRAINING is a rehabilitation strategy designed to enhance the recovery of postural control, balance, standing, walking, health, and quality of life after neurologic injury or disease based on scientific and clinical evidence.¹⁻⁶ As an activity-based therapy, locomotor training is a therapeutic intervention that results in neuromuscular activation below the level of the lesion to promote recovery of motor function with the goal of retraining the nervous system to recover a specific task.⁷⁻¹¹ Activation of the neuromuscular system occurs during repetitive and progressive practice of the desired task; “activity-dependent plasticity” promotes functional reorganization of the neuromuscular system.

The loss of balance and ambulation after neurologic injury has been attributed primarily to the dominance of supraspinal over spinal mechanisms.^{6,12} Thus, the role of the spinal cord and importance of afferent input in the recovery of function has not been considered predominantly during rehabilitation. However, there is extensive evidence in vertebrates that through interaction with task-specific afferent input, the spinal neural circuitry can support recovery of standing and stepping.¹³⁻¹⁵ Evidence suggests that the human spinal circuitry has maintained properties similar to those of other vertebrates.^{7,10,16}

However, many therapeutic interventions have not taken full advantage of these properties and focus primarily on using the uninjured components of the neuromuscular system to accommodate and compensate for neurologic deficits.¹⁷⁻²¹ For example, during the rehabilitation process, therapists will use assistive devices (eg, braces to support weak limbs, a wheelchair for mobility) or alternative behavioral strategies that tend to minimize the use of the injured components of the neuromuscular system as the means for patients to achieve a functional goal. Such strategies do not capitalize on the significant functional potential remaining below the lesion after SCI. Determinations of the progress of neurologic rehabilitation then may rely on

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Supported by the Centers for Disease Control and Prevention and the Christopher and Dana Reeve Foundation (grant/cooperative agreement no. U10/CCU220379).

No commercial party having a direct financial interest in the results of the research supporting this article has or will confer a benefit on the authors or on any organization with which the authors are associated.

The contents of this article are solely the responsibility of the authors and do not necessarily represent the official views of the Christopher and Dana Reeve Foundation or Centers for Disease Control and Prevention, Department of Veterans Affairs, and the U.S. Government.

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0003-9993/11/xxxS-00593\$36.00/0
doi:10.1016/j.apmr.2011.01.024

List of Abbreviations

AIS	American Spinal Injury Association Impairment Scale
NRN	NeuroRecovery Network

therapists' subjective and objective reports (eg, FIM) and assessment of the success of the compensatory strategies, which may not be consistent with the patients' expectations of recovery.²² Locomotor training focuses on task-specific training of the injured components to return functioning as closely as possible to preinjury levels of neuromuscular control.^{2,23}

Although the objective is to reach the highest level of functioning that can be regained to benefit the patient, the cost of the intervention also must be considered. Presently, the number of physical therapy outpatient visits is dictated by insurance coverage annual limits, which are based on traditional compensatory interventions, or the patient's ability to self-pay with little consideration of the number of visits that may result in therapeutic and meaningful benefit. Justifying insurance reimbursement for therapy sessions that focus on recovery of neuromuscular control for achieving balance and walking is critically important. Thus, it is important to define the efficacy and effectiveness of locomotor training for a given number of training sessions by providing clear evidence of functional improvements gained in specific populations.²⁴⁻²⁶

Despite the prevalence of activity-based interventions in the literature, there is a remarkable lack of standardization for techniques and methods of assessment.²⁵⁻²⁷ Some studies have emphasized the body-weight support and treadmill environment as the sole training environment, whereas others have identified a need to transfer skills from the treadmill environment to over ground and to home and community.^{2,28-31} The number and duration of rehabilitative sessions differ between studies. Additionally, the combination of lack of standardization of outcome measures used to determine efficacy and the often small sample sizes have resulted in critically underpowered studies from a statistical perspective.^{25,26} The largest population of individuals with SCI studied to date is the acute SCI-Locomotor Training trial with an intent-to-treat analysis of 117 participants, 58 receiving locomotor training with 26 individuals classified with upper motor neuron injuries as American Spinal Injury Association Impairment Scale (AIS) grade C and 1 classified as AIS grade D compared with control participants receiving usual care (26 with AIS grade C, 1 with AIS grade D).³² Most other studies have assessed outcomes in cohorts of fewer than 20 patients.^{11,25,30,33} Thus, there is a need to evaluate the effectiveness of locomotor training by using a standardized protocol and outcomes with a large sample of participants with upper motor neuron incomplete SCI.

The NeuroRecovery Network (NRN) has provided a means to enroll, evaluate, and train a sufficiently large number of individuals with incomplete SCI with a focus on recovery to begin to establish the functional consequences of locomotor training under well-controlled conditions (see the introductory article in this supplement). The purpose of this study was to examine balance and walking outcomes in a large number of individuals (N=196) across the 7 NRN centers by using a standardized locomotor training protocol and standardized assessments of balance and gait outcomes with the Berg Balance Scale, Six-Minute Walk Test, and 10-Meter Walk Test. Our aim was to assess whether individuals with clinically incomplete SCI could respond to task-specific training that focuses on providing appropriate afferent input to facilitate the functional reorganization of spinal circuitry to improve functional outcomes. We hypothesized that individuals with motor-incomplete SCI would benefit from 20 or more sessions of locomotor training with significantly improved walking speed and distance and higher scores when assessing balance.

METHODS

Participants

Consecutive patients (N=196) with incomplete SCI were enrolled from February 2005 through June 2009 across 7 outpatient clinical sites in the Christopher and Dana Reeve Foundation NRN. These centers include Boston Medical Center, Boston, MA; Frazier Rehab Institute, Louisville, KY; Kessler Institute for Rehabilitation, West Orange, NJ; Magee Rehabilitation Hospital, Philadelphia, PA; Ohio State University Medical Center, Columbus, OH; Shepherd Center, Atlanta, GA; and The Institute for Rehab and Research, Houston, TX. Patients were selected for participation in the NRN locomotor training program and data evaluation based on (1) the presence of a nonprogressive spinal cord lesion above T11, (2) no current participation in an inpatient rehabilitation program, (3) no use of onabotulinumtoxinA or other medications for chemodeneration for spasticity for the prior 3 months, (4) some lower-limb movement or visible voluntary contraction, (5) the capacity to generate a lower-limb reciprocal alternating flexion/extension stepping pattern in the step-training environment, (6) medical referral by a physician for physical therapy, and (7) had received a minimum of 20 locomotor training therapy sessions. Patients using antispasticity medications were weaned from their use during participation in the NRN program and as directed by the NRN physician according to the standardized NRN protocol.

Outcome Measures

Physicians or physical therapists conducted the International Standards for the Neurological Classification of SCI examination and classification to determine AIS^{34,35} designation when the individual enrolled in the program. Therapists assessed patients using the Berg Balance Scale,³⁶⁻³⁸ Six-Minute Walk Test,³⁹⁻⁴² and 10-Meter Walk Test^{40,41} for baseline evaluation, interim testing approximately every 20 therapy sessions (17 ± 5 sessions), and postintervention evaluation upon discharge with a median of 4 (minimum, 2; maximum, 14) evaluations per patient. The 10-Meter Walk and Six-Minute Walk Tests were conducted according to defined standardized procedures for these measures,^{40,42} with the patient instructed to walk "as fast as you can." The patient was tested by using the same assistive device used on the initial evaluation for every reevaluation even if they had advanced to another assistive device in the home and community. No bracing, facilitation, or physical assistance was allowed during the tests. If the individual was unable to walk or required physical assistance during the tests, scores for the 10-Meter Walk and Six-Minute Walk Tests were recorded as zero.

Intervention

Patients received a median of 47 (minimum, 20; maximum, 251) total treatment sessions of a standardized protocol of locomotor training, with a median of 112 (minimum, 28; maximum, 649) days of enrollment. Locomotor training includes 3 components: (1) 1 hour of step training in the body-weight support on a treadmill environment, followed by 30 minutes of (2) overground assessment and (3) community integration. The step-training component consists of task-specific activities to retrain standing and walking with appropriate posture and kinematics using the body-weight support, treadmill, and manual facilitation of trainers, as well as verbal, visual, and tactile cues. The overground assessment provides the therapist and patient with the opportunity to assess carryover from gains made in the body-weight support on a treadmill environment^a

to the patient's postural and mobility strategy over ground and is a means to identify areas of focus for further retraining. The community integration component consists of instruction and discussion regarding how patients can implement the principles of locomotor training and integrate the therapeutic goals into their daily routines. Locomotor training guiding principles are followed in all 3 components and are to (1) maximize weight bearing in the legs, (2) optimize sensory cues appropriate for the specific motor task, (3) optimize posture and kinematics for each motor task, and (4) maximize recovery and minimize compensation. The equipment used included a closed-loop computer-controlled body-weight support system that controls treadmill speeds from 0.5 to 10mph and seating systems that include ergonomically appropriate support design for staff safety, harnesses of various sizes, front and side mirrors that provide visual feedback, and a variety of assistive devices, including rolling walkers, bilateral or unilateral crutches or canes, or trekking poles while avoiding the use of bracing. Discharge was standardized using an NRN discharge algorithm that considered functionally related changes other than balance and walking outcomes so that a patient could stay enrolled in the program without improving in these outcomes. Discharge also could occur due to the unavailability of resources or other patient-related considerations (see introductory article in this supplement).

Data Analysis

Demographic and clinical characteristics were summarized by using mean $\pm$ SD values for continuous data, median and minima and maxima or interquartile extrema values for skewed

continuous and ordinal data, and counts and percentages for categorical data. Our statistical analyses evaluated improvements from NRN enrollment to last evaluation for the Berg Balance Scale, Six-Minute Walk Test, and 10-Meter Walk Test. We used nonparametric methods in evaluating our hypotheses to provide sufficient generality against violations of assumptions for parametric tests, such as the normality assumption. Enrollment to final evaluation changes for all patients and within the AIS grades C and D groups were tested nonparametrically by using Wilcoxon signed-rank test. Enrollment measurements and enrollment to final evaluation changes were compared between AIS groups by using the Wilcoxon rank-sum test regardless of the total number of therapy sessions. Associations between time since SCI and performance at enrollment and improvement from enrollment to the last evaluation were tested nonparametrically by using the Spearman rank-correlation coefficient. Analyses were conducted using the open-source R software program,^{43,b} and all hypothesis tests were conducted at the .05 level.

RESULTS

Demographic and Clinical Characteristics

Patients enrolled (N=196) in the NRN primarily were men with AIS grade D and cervical lesions (table 1). Most patients' injuries occurred traumatically, whether from motor vehicle collisions, falls, sports-related injuries, or violence. A notable characteristic of the NRN sample was the wide distribution of time since SCI, ranging from months to more than 2 decades. Patients' enrollment times and number of sessions ranged over

Table 1: Demographic and Clinical Characteristics at Enrollment of NRN Sample

Demographic and Clinical Characteristics	Full Sample (N=196)	AIS Grade C (n=66)	AIS Grade D (n=130)
Sex			
Men	148 (76)	53 (80)	95 (73)
Women	48 (24)	13 (20)	35 (27)
Age (y)	41 $\pm$ 15	36 $\pm$ 14	44 $\pm$ 16
Injury level			
Cervical	138 (70)	38 (58)	100 (77)
Thoracic	58 (30)	28 (42)	30 (23)
Mechanism of injury			
Motor vehicle collision	68 (35)	24 (36)	44 (34)
Fall	45 (23)	18 (27)	27 (21)
Sporting accident	32 (16)	9 (14)	23 (18)
Nontrauma	19 (10)	4 (6)	15 (12)
Medical/surgical	18 (9)	7 (11)	11 (8)
Violence	11 (6)	4 (6)	7 (5)
Assistive walking device*			
Nonambulatory	71 (36)	49 (74)	22 (17)
Walker	71 (36)	15 (23)	56 (43)
Cane(s)/crutch(es)	41 (21)	2 (3)	39 (30)
None	13 (7)	0 (0)	13 (10)
Time since SCI (y)			
<1	101 (52)	36 (55)	65 (50)
1–3	43 (22)	18 (27)	25 (19)
$\geq$ 3	52 (27)	12 (18)	40 (31)
Treatment and enrollment characteristics			
Time of NRN enrollment (d)	112 (28, 649)	166 (35, 649)*	95 (28, 562)*
Cumulative treatment sessions received	47 (20, 251)	60 (20, 251)*	40 (20, 213)*
Cumulative no. of evaluations	4 (2, 14)	5 (2, 14)*	4 (2, 12)*
Treatment intensity (treatment/evaluation)	17 $\pm$ 5	17 $\pm$ 5	16 $\pm$ 5

NOTE. Values expressed as count (%) for categorical variables and mean $\pm$ SD or median (minimum, maximum) for continuous variables.

*Patients with AIS grades C and D significantly differed (Wilcoxon rank-sum test, $P<.001$).

a wide distribution from weeks to months. Patients with AIS grade C were enrolled longer, received more cumulative treatment sessions, and were evaluated on more occasions than those with AIS grade D (Wilcoxon rank-sum test, $P < .001$ for each), indicative of those with more severe impairment receiving more substantial treatment. The median time since injury and intensity of treatment per evaluation were not different between patients with AIS grades C and D.

Functional Ability at Enrollment

At enrollment into the NRN, values from the 3 functional outcome measures were highly variable across patients (figs 1–3) (table 2). One hundred sixty-eight (86%) NRN patients (66 of 66 AIS grade C, 102 of 130 AIS grade D) scored lower than 45, the reported threshold for risk for falls for the Berg Balance Scale⁴⁴ (see fig 1D). Patients with AIS grade C SCI had significantly lower scores at enrollment than those with AIS grade D classification (Wilcoxon rank-sum test, $P < .001$).

Initial Six-Minute Walk Test distances and 10-Meter Walk Test speeds spanned a very wide range (see figs 1A–C, 2A–C) (see table 2). Most patients with AIS grade C were unable to complete the Six-Minute Walk Test or 10-Meter Walk Test evaluations (see fig 2C) without therapist assistance at enrollment (see table 2). In contrast, most patients with AIS grade D

were able to complete the Six-Minute Walk Test and 10-Meter Walk Test at enrollment (see fig 2D) (see table 2). Patients with AIS grade D SCI walked significantly farther than those with AIS grade C SCI (rank-sum test, $P < .001$).

Functional Improvement

There was statistically significant functional improvement over time for NRN patients measured by using the Berg Balance Scale, Six-Minute Walk Test, and 10-Meter Walk Test (figs 1–4) (see table 2). Fifty-seven percent of NRN patients improved on all 3 outcome measures, 87% improved on at least 1 outcome measure, 83% improved or remained stable on all 3 of these outcome measures, and 99% improved or were stable on at least 1 outcome measure.

Scores on the Berg Balance Scale significantly improved by an average of 9.6 points (see table 2) (Wilcoxon signed-rank test, $P < .001$). Increases were significant for patients with AIS grades C and D, and the amount of improvement was significantly different between these groups (see fig 1C) (rank-sum test, $P = .008$). Of the 168 patients classified as at risk for falls at enrollment, 27% improved their scores to a value reflecting minimal risk for falls (11% AIS grade C, 37% AIS grade D) (see fig 1D).

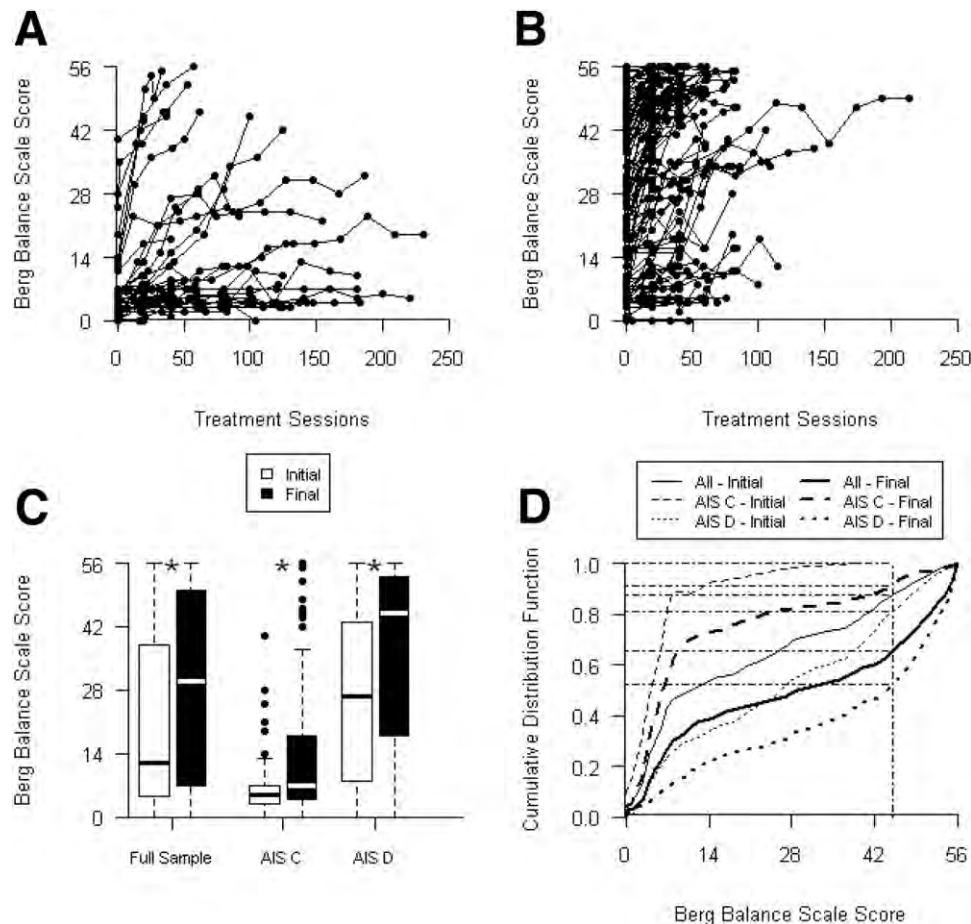


Fig 1. Plots of the Berg Balance Scale for NRN patients: Line plot of individual patient progress in patients with (A) AIS grade C (n=66) and (B) AIS grade D (n=130). (C) Box plot of initial and final evaluations for the full sample and by AIS grade. *Significant improvement from initial to final evaluation (Wilcoxon rank-sum test, $P < .001$). (D) Cumulative distribution functions (smoothed by a cubic spline) of initial and final evaluations for the full sample and patients with AIS grades C and D. Dash-dotted vertical line at Berg score of 45 indicates the threshold for fall risk, and dash-dotted horizontal lines provide the empirical cumulative distribution functions at 45.

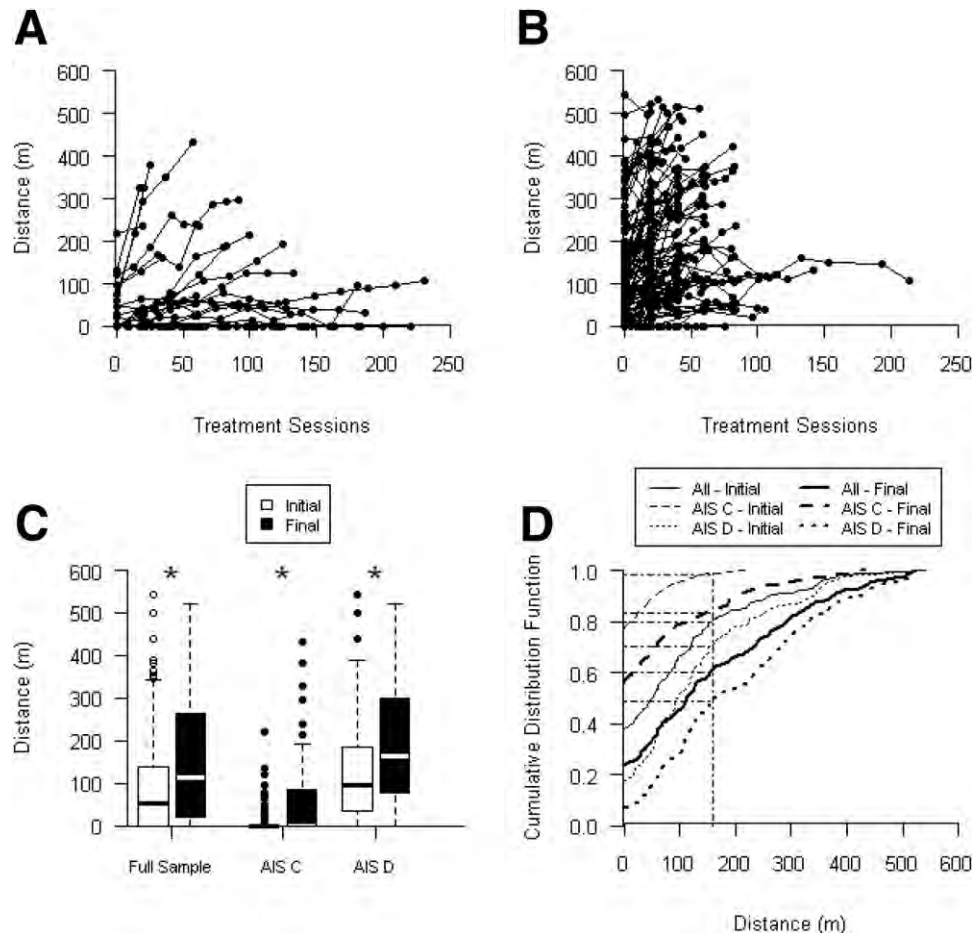


Fig 2. Plots of the Six-Minute Walk Test for NRN patients. Line plots of individual patient progress in patients with (A) AIS grade C (n=66) and (B) AIS grade D (n=130). (C) Box plot of initial and final evaluations for the full sample and by AIS grade. *Significant improvement from initial to final evaluation (Wilcoxon rank-sum test, $P < .001$). (D) Cumulative distribution functions (smoothed by a cubic spline) of initial and final evaluations for the full sample and patients with AIS grades C and D. Dash-dotted vertical line at distance of 158.4m indicates a threshold equivalent to a safe speed for community ambulation (0.44m/s), and dash-dotted horizontal lines provide the empirical cumulative distribution functions at 158.4m.

The Six-Minute Walk Test distances and 10-Meter Walk Test speeds of all NRN patients significantly improved by an average of 63m and 0.20m/s, respectively (signed-rank test, $P < .001$). Significant increases also occurred in the AIS grade C and AIS grade D groups (signed-rank test, $P < .001$) and were significantly different from each other (rank-sum test, $P < .001$). Twenty-eight (41%) of the 69 patients who were unable to complete the Six-Minute Walk Test and 10-Meter Walk Test became ambulatory by completing 1 of the walk tests at their last evaluation, with 15 of 50 patients with AIS grade C (30%) and 13 of 19 with AIS grade D (68%).

Time Since SCI, Functional Ability, and Functional Improvement

Time since SCI was distributed widely among NRN patients, ranging from 32 days to more than 25 years (see table 1). Performances at enrollment on the 3 outcome measures were not associated with time since SCI for Berg Balance Scale scores, Six-Minute Walk Test distances, or 10-Meter Walk Test speeds ($\rho = -.06$, $P = .43$; $\rho = .001$, $P = .98$; $\rho = .01$, $P = .90$ for each measure, respectively). Conversely, patients further removed from their injury improved to a lesser degree than those enrolled sooner after injury because im-

provements from enrollment to last evaluation significantly correlated negatively with time for Berg Balance Scale scores, Six-Minute Walk Test distances, and 10-Meter Walk Test speeds (SCI: $\rho = -.35$, $P < .001$; $\rho = -.46$, $P < .001$; $\rho = -.43$, $P < .001$ for each measure, respectively). Improvements in the 3 outcome measures were significantly different (Kruskal-Wallis test, $P < .001$, all measures) for the 3 groups defined by time since SCI: (1) less than 1 year from injury, (2) 1 to 3 years from injury, and (3) 3 or more years since injury (table 3). Improvements from enrollment to the last evaluation were significant within each group (signed-rank test, $P < .001$), indicating that although patients further removed from SCI did not improve as much, they still improved significantly.

Nonresponders

Twenty-four (12%) NRN patients failed to respond to locomotor training treatment, for which nonresponse was defined as showing no change or a decrease in each of the 3 functional outcome measures. Twenty-two of these 24 patients were nonambulatory at enrollment and could not perform the Six-Minute Walk and 10-Meter Walk Tests without therapist assistance at their last evaluation. Each of these 22 patients

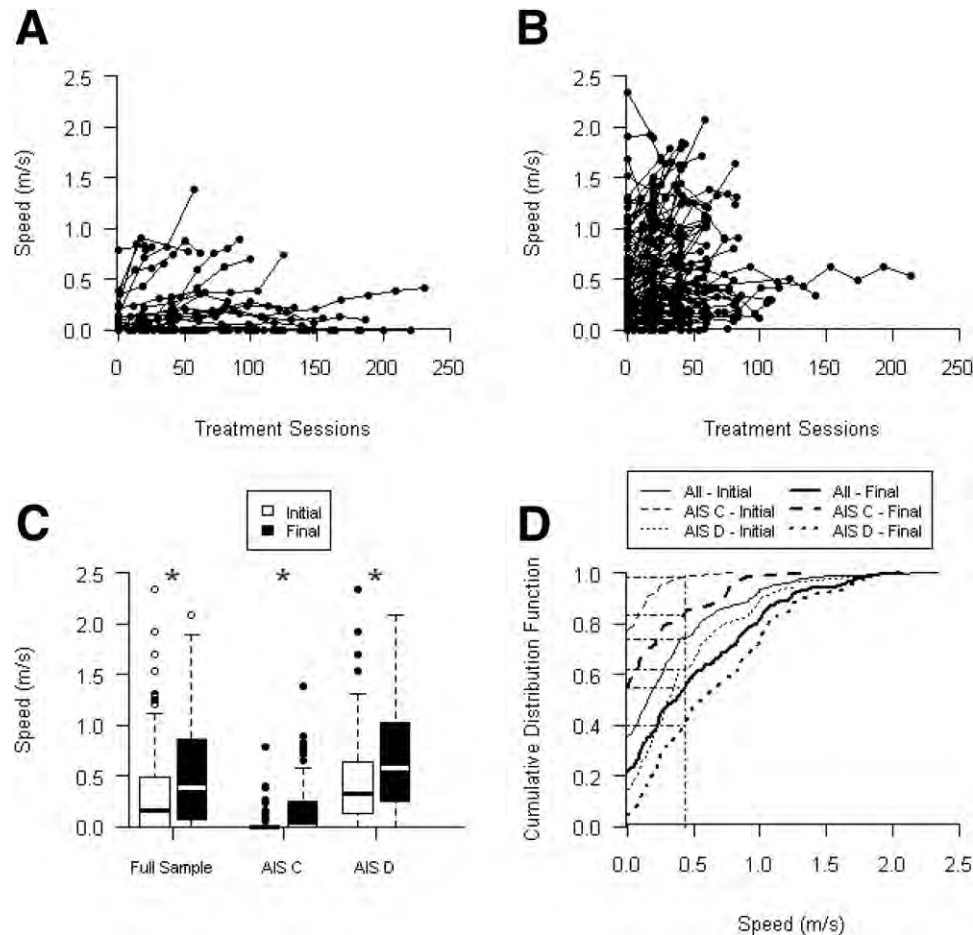


Fig 3. Plots of the 10-Meter Walk Test for NRN patients. Line plots of individual patient progress in patients with (A) AIS grade C (n=66) and (B) AIS grade D (n=130). (C) Box plot of initial and final evaluations for the full sample and by AIS grade. *Significant improvement from initial to final evaluation (Wilcoxon rank-sum test, $P<.001$). (D) Cumulative distribution functions (smoothed by a cubic spline) of initial and final evaluations for the full sample and patients with AIS grades C and D. Dash-dotted vertical line at speed of 0.44m/s indicates a threshold equivalent to a safe speed for community ambulation, and dash-dotted horizontal lines provide the empirical cumulative distribution functions at 0.44m/s.

showed low Berg Balance Scale scores (≤ 7) and either did not improve or experienced decreases in Berg Balance Scale scores. Nineteen of these 22 nonambulatory patients had AIS grade C SCI, but there were no other definitively identifying characteristics of these nonresponders. Average age was 38 years, 10 had injuries in the cervical region, 12 had injuries in

the thoracic region, and time since SCI was well distributed among them. These 22 patients received an average of 55 ± 41 locomotor training sessions, with a median of 41 (minimum, 20; maximum, 180) sessions.

Two ambulatory nonresponders had AIS grade D injuries in the thoracic region. One patient was 1.8 years removed

Table 2: Summary Statistics for Initial and Final Evaluations of the Berg Balance Scale, Six-Minute Walk Test, and 10-Meter Walk Test in NRN Patients

Outcome	Evaluation	Full Sample	AIS Grade C	AIS Grade D
Berg Balance Scale score	Initial	20 $\pm$ 17.7; 12 (4.8, 38)	6.4 $\pm$ 6.9; 5 (3, 7)*	26.8 $\pm$ 17.5; 26.5 (8.2, 43)
	Final	29.1 $\pm$ 20.6; 30 (7, 50) [†]	14.3 $\pm$ 16; 7 (4, 17.8) ^{††}	36.6 $\pm$ 18.5; 45 (18.2, 52.8) [†]
Six-Minute Walk Test (m)	Initial	91 $\pm$ 116; 53 (0, 137)	15 $\pm$ 39; 0 (0, 0)*	130 $\pm$ 123; 96 (36, 185)
	Final	154 $\pm$ 148; 114 (20, 261) [†]	60 $\pm$ 102; 0 (0, 81) ^{††}	202 $\pm$ 145; 163 (81, 300) [†]
10-Meter Walk Test (m/s)	Initial	0.31 $\pm$ 0.41; 0.15 (0, 0.48)	0.05 $\pm$ 0.13; 0 (0, 0)*	0.44 $\pm$ 0.44; 0.32 (0.12, 0.63)
	Final	0.51 $\pm$ 0.5; 0.38 (0.07, 0.85) [†]	0.18 $\pm$ 0.3; 0 (0, 0.24) ^{††}	0.68 $\pm$ 0.51; 0.57 (0.25, 1.02) [†]

NOTE. Values expressed as mean $\pm$ SD or median (25th, 75th percentiles).

*Initial evaluation significantly different between patients with AIS grades C and D (Wilcoxon rank-sum test, $P<.001$).

[†]Final evaluation represents statistically significant improvement from initial results (Wilcoxon signed-rank test, $P<.001$).

^{††}Improvement from initial to final evaluation significantly different between patients with AIS grades C and D (rank-sum test, $P<.01$).

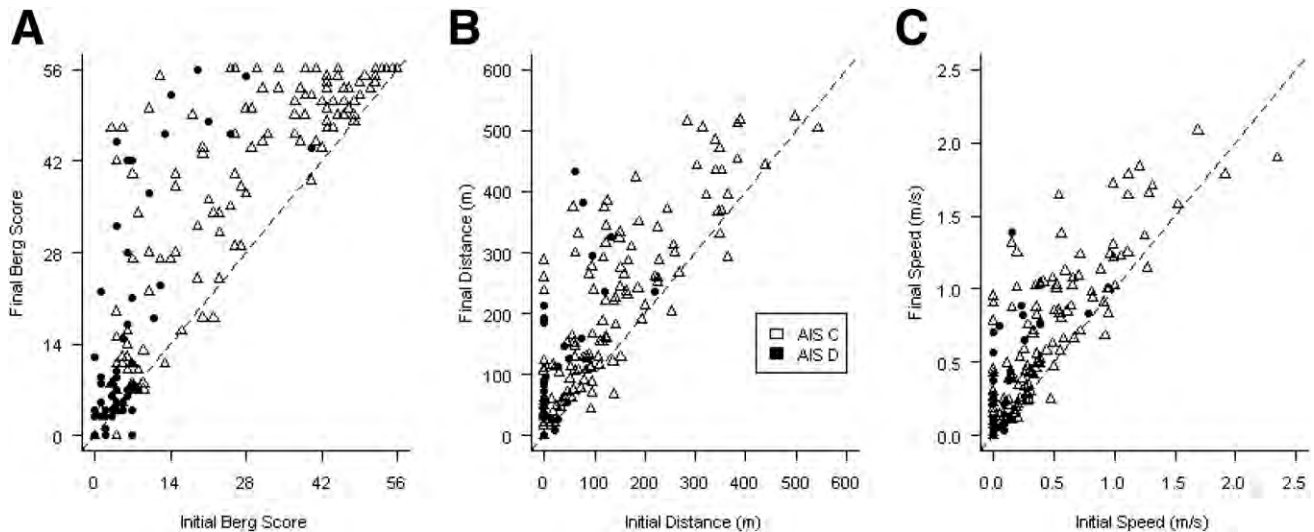


Fig 4. Initial versus final performance. Scatterplot of final evaluation (y-axis) against initial evaluation (x-axis) for the (A) Berg Balance Scale, (B) Six-Minute Walk Test, and (C) 10-Meter Walk Test for patients with AIS grades C (n=66) and D (n=130) enrolled in the NRN. Significant improvement from initial to final evaluation occurred for each measure ($P<.001$), reflected in the plot as points lying in the left upper half of the plane.

from injury, 35 years old, and experienced decreases from 9 to 8 in Berg Balance Scale score, from 92 to 43.4m in the Six-Minute Walk Test, and an increase from 50 to 82 seconds in 10-Meter Walk Test times while receiving 100 treatment sessions during the course of 209 days. The other patient was 0.9 years removed from injury, 43 years old, and experienced decreases from 9 to 7 in Berg Balance Scale score, from 95 to 70.4m in Six-Minute Walk Test times, and an increase from 37 to 43 seconds in 10-Meter Walk Test times while receiving 20 treatment sessions during the course of 43 days.

DISCUSSION

Results of this cohort study of 196 patients showed that significant functional recovery can occur months to years after incomplete SCI with rehabilitation that involves intensive activity-based therapy. Significant improvements in walking distance, speed, and balance were observed when locomotor training was delivered as a standardized therapy to individuals with clinically incomplete SCI across 7 rehabilitation centers. Functional improvements occurred in 88% of NRN patients with AIS grade C and grade D classifications during episodes of care ranging from 20 to 251 sessions of treatment months to years after injury. These results support the concept that there is an intrinsic capacity of the human spinal cord circuitry that responds to task-specific sensory cues and can result in recovery in walking, as shown in other mammals.

Variable Functional Ability in Incomplete SCI

Patients with AIS grades C and D had varied baseline measurements spanning the full range of values at enrollment and discharge from therapy. In all measures, median values for patients with AIS grade D were significantly higher than for patients with AIS grade C, but there were prominent overlaps in these measures between the 2 groups. Low values also were observed in our AIS grade D sample. This indicates that voluntary motor scores from manual muscle testing as conducted in the International Standards for the Neurological Classification of SCI examination (or AIS) may not sufficiently predict potential functional recovery in individuals with chronic SCI.⁴⁵ These results are consistent with statistical testing that showed that although manual muscle testing provides strong interrater reliability and validity, especially compared with the sensory portion of the examination, it is limited in predicting functional capacity for walking,^{27,45,46} especially in the chronic SCI population. Future studies specifically examining the lower motor scores and improvements in function would provide more insight into the relationship between voluntary control of a muscle and the potential for improvements in walking in patients with chronic SCI.

The high variability in the initial functional outcome measures in this population when classified by AIS grade alone is a limitation for clinical trials testing a therapeutic intervention. This inherent variability in the population limits the power of

Table 3: Enrollment to Last Evaluation Changes in Berg Balance Scale, Six-Minute WalkTest, and 10-Meter Walk Test Results by Time Since SCI Group

Outcome	<1y Post-SCI (n=101)	1-3y Post-SCI (n=43)	≥3y Post-SCI (n=52)
Berg Balance Scale score	12±12, $P<.001$	7±10, $P<.001$	4±6, $P<.001$
Six-Minute Walk Test (m)	91±89, $P<.001$	44±71, $P<.001$	24±43, $P<.001$
10-Meter Walk Test (m/s)	0.29±0.31, $P<.001$	0.11±0.23, $P=.002$	0.09±0.14, $P<.001$

NOTE. Values expressed as mean ± SD. P values from Wilcoxon signed-rank test of significance of the enrollment to last evaluation difference.

directly comparing data between 2 groups receiving an intervention and increases the number of subjects needed for sufficient statistical power. This is an important consideration in SCI given the relatively low numbers available at any given rehabilitation center. This appeared to be the case in an acute SCI clinical trial in which the trial was stopped because the 2 groups had high variability and similar and unexpected outcomes with intense activity-based therapy that rendered it not possible to reach the numbers needed to test statistical significance of the 2 interventions.³² In the present study, we were able to show a statistically significant improvement in the sample before and after treatment by using each individual's initial assessment as the control value. Therefore, using quantitative and sensitive baseline functional scores for classification of groups rather than AIS grade or level of injury may significantly improve experimental designs of randomized clinical trials designed to evaluate therapeutic interventions.

Balance Improvements Measured by Using the Berg Balance Scale

Patients with AIS grades C and D significantly improved in overall Berg Balance Scale scores, which indicates better functional ability during sitting or standing. In our study, the average change was consistent with change that has been reported as clinically meaningful in other populations^{47,48} and resulted in individuals increasing their scores to higher than the threshold reported for increased risk for falls in the elderly. These improvements in overall Berg Balance Scale scores likely responded to the intense retraining of standing and stepping, as well as integration of the practice of sitting and transitional movements in their daily lives. It also may be important to interpret changes in the context of thresholds that may allow very significant changes in care giving and quality of life. Many individuals who did not recover walking after locomotor training with only a 4-point change in overall Berg Balance Scale score were able to regain the ability to sit independently, and this had a tremendous impact on their daily lives. This change in balance could transpose into decreasing the burden of care for transfers to and from all surfaces, greater independent use of wheelchair mobility and pressure relief, less use of upper extremities for function, and less need for assistance and durable medical equipment to lessen the overall financial burden.

Walking Improvements Measured by Speed and Distance

Patients with AIS grades C and D significantly improved in walking distance and speeds at levels that have been considered clinically meaningful, depending on the classification of injury impairment.^{39,48,49} Patients with AIS grade D had a greater magnitude of increase than those with AIS grade C. However, those with AIS grade C and already ambulatory improved their walking distances to a greater extent than the AIS grade D group, indicating potential for recovery.

Our study presents the largest increase in gait speed and distance reported in a population of this magnitude (N=196) for persons with chronic motor-incomplete SCI receiving manually facilitated locomotor training,^{25,28} walking using body-weight support in combination with functional electrical stimulation,^{28,50} or robotic-assisted locomotor training.⁵¹ One randomized study of 51 individuals with incomplete SCI who could step received 1 of 4 interventions: stepping on a treadmill in combination with manual assistance, functional electrical stimulation (peroneal nerve) or robotic training, or training over ground with electrical stimulation (peroneal nerve), body-weight support, and assistive devices.³¹ There were no signif-

icant differences among these groups in gait parameters. However, our study used both retraining by using body-weight support on a treadmill and translation to the overground and community environments. Studies of locomotor training are difficult to compare because of lack of standardization of the intervention and outcome measures, variability in functional capacity, and the number of individuals studied.^{30,51}

Clinical Relevance

Determining clinical relevance, even for established outcome measures, is a critical and widely debated topic.^{46,52} Established thresholds for clinically meaningful changes in Berg Balance Scale, Six-Minute Walk Test, and 10-Meter Walk Test results are limited in identifying therapeutic benefit for individuals with more debilitating injuries.⁴⁸ Measures that assess the capacity to increase speed during short periods (such as the ability to reach the 1.2m/s required to make it safely across a normal crosswalk) are reasonable benchmarks for relevance in daily life.³⁹ However, the ability to walk 50ft [15.24m] independently to the bathroom can make meaningful and valued changes in a person's daily life and determine whether a caregiver is necessary. Small gains in distance or speed and/or functional improvement, which lead to the use of a less restrictive assistive device, could be of great personal relevance to these individuals. Clinical significance then is a concept that must be defined specifically for populations, interventions, and expectations, especially when considering groups of patients with SCI with large variability in initial outcome measures.

Individuals in the AIS grade D group received therapy twice as often as those in the AIS grade C group, which may have been due to clinical expectations of potential for recovery and thus higher likelihood to be deemed eligible for physical therapy. Although the benefit of locomotor training for persons with chronic SCI has been viewed in a recent literature review as equivocal,²⁹ in this study, only 12% of individuals with chronic SCI failed to improve on the functional outcome measures reported. These results are evidence that intensive activity-based rehabilitation interventions can result in significant functional recovery, even in individuals with AIS grade C classifications and even months to years after injury. Thus, activity-based therapy interventions should be considered for patients with chronic SCI (AIS grades C and D). Clinical practice in rehabilitation has been altered significantly during the past several decades, with episodes of care significantly shortened for both inpatient acute and subacute rehabilitation programs. These results contend that when focused on neuromuscular recovery, clinical practice for persons with SCI calls for more intense therapy sessions for longer periods than currently available. If implemented, these interventions can have a positive impact with long-term outpatient therapy.

Study Limitations

This study does not provide information about whether locomotor training is a more effective therapeutic intervention than no therapy or other rehabilitation interventions and does not reach the level of evidence of a randomized clinical trial. Rather, it only shows that from either months to years after injury, individuals have the capacity to improve balance and walking outcomes when provided with an intensive activity-based therapy. Van Hedel et al⁴¹ reported that for individuals with incomplete SCI who were ambulating at 1 month postinjury, Six-Minute Walk Test and 10-Meter Walk Test results did not change with routine rehabilitation. In contrast, our data showed significant increases in both measurements for individ-

uals during this time frame (and up to several years after injury) with locomotor training. However, this should be interpreted cautiously because there were only 22 subjects in their study and they were selected based on a higher level of functioning than in our study (similar to 20% with similar initial walking speeds and distances) (see [figs 2D, 3D](#)).

Although the improvements reported in this sample were based on a standardized intervention, analyses were conducted at only the initial and discharge evaluations. This study therefore does not examine the progression of recovery over time or assess the impact of time since injury, age, number of sessions received, or initial functional capacity on the improvements in walking and balance measures over time. It is probable that many or all of these factors influenced the magnitude of the outcomes within individuals and would provide valuable information to the rehabilitation community and thus should be addressed in the future. Finally, our sample was dominated by patients with AIS grade D injuries, who outnumbered patients with AIS grade C nearly 2 to 1. Although we were able to show significant improvement not only in all patients, but also within the AIS grades C and D groups, conclusions about patients with AIS grade C from this analysis were slightly weakened by this sample size disparity, and conclusions about the full sample were largely reflective of improvements shown by patients with AIS grade D. In the future, we will place additional focus on the recruitment and enrollment of patients with AIS grade C to balance our sample and examine other populations of SCI, including those with AIS grades A and B and those in earlier times since injury.

CONCLUSIONS

These results suggest that intensive activity-based rehabilitation interventions can result in significant functional recovery throughout an individual's lifetime. The present results provide a benchmark for the level of recovery that can be expected in an incomplete SCI population and may be used as a relative comparison or predictor when other interventions are assessed in cohort populations. Conducting randomized multicenter clinical trials in a chronic SCI population poses significant challenges because of the insensitivity of outcome measures, variability of function in the population, ability to standardize the implementation of rehabilitation interventions, and appropriate assignment of a control group. In this study, we standardized the locomotor training intervention and conducted sequential quantitative evaluations to better understand the capacity for recovery with rehabilitation in a relatively chronic SCI population, and these data may be used for estimating the number of subjects needed when other interventions are compared in a clinical trial. Future studies from the NRN are focused on developing a more sensitive classification system that stratifies patients by level of recovery rather than ability to reach functional goals using compensation or the AIS and would result in a more homogenous group in respect to function.

Acknowledgments: The authors thank Joe Canose, BA, MLS, Susan Howley, BA, and Michael Mangienello, MPA, from the Christopher and Dana Reeve Foundation for dedication and support. The extraordinary vision, compassion, and dedication of Christopher and Dana Reeve made the NRN possible. The authors acknowledge the other current or past NRN Center Directors: Steve Ahr, MSSW, and Linda Shelburne, PT, MSW (Frazier Rehab Institute); Steve Williams, MD (Boston Medical Center); Daniel Graves, PhD (Memorial Hermann/The Institute of Rehabilitation and Research); Sarah Morrison, PT, and Keith Tansey, MD, PhD (Shepherd Center); Gail Forrest, PhD (Kessler Medical Rehabilitation Research and Education Corp); and D. Michele Basso, PT, EdD (The Ohio State University Medical Center),

plus all other current and previous network members (<http://louisville.edu/medschool/neurosurgery/harkema/nrn>); the critical review and editorial support of Jessica Hillyer, PhD; and the leadership, foresight, and support of the NRN Advisory Board, Reggie Edgerton, PhD, Moses Chao, PhD, Michael Fehlings, MD, PhD, Andrei Krassioukov, MD, PhD, and Shelly Sorani, MA.

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Supplier

- a. Innoventor, 3600 Rider Trail South, St Louis, MO 63045.
- b. The R Foundation for Statistical Computing. Open source software. Available at: <http://www.r-project.org>.

Attachment 3: Technical Abstract:

1. Background:

This proposal addresses community's critical needs related to clinical rehabilitation and secondary complications of chronic spinal cord injury (SCI). The specific areas that this clinical trial will address are: i) understanding the physiological basis (neuroplasticity) for rehabilitation therapies and evaluating whether there are quantitative benefits of activity dependent training ii) development and refinement of rehabilitation strategies and technologies to deliver improved functional capacity for people living with SCI, iii) utilization of existing network infrastructure and established collaborations to enable rapid initiation of research that leverages available systems for structured data collection, analyses, and outcome assessment, and iv) providing comprehensive information regarding specific standardized rehabilitation for those with traumatic SCI.

The ability to walk has consistently been a major goal for persons with SCI. The proportion of persons that sustain a SCI that have incomplete injuries now forms the majority of cases in the United States (39). An incomplete injury exists when there is preservation of sensory or motor function below the level of injury including the lowest sacral segments (S4/S5), thus increasing the chances of ambulation as a functional goal. These individuals using the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) are classified on the American Spinal Injury Association Impairment Scale (AIS) as C and D. Rehabilitation approaches to facilitate recovery of standing and walking after an incomplete SCI have recently been directed toward LT, an activity-dependent rehabilitation therapy that provides repetitive stepping facilitated by manual assistance and body weight support on a treadmill. LT allows for loading and unloading of the body weight, improved head, neck and trunk postural alignment, and improved coordination of the lower limbs. The efficacy of LT for walking suggests that movement patterns associated with ambulation can be generated by afferent input interacting with interneurons within the spinal cord known in mammals as central pattern generators. And with residual supraspinal circuitry available to the networks, functional over ground walking has been achieved with this repetitive task specific training in individuals with AIS C and D injuries from months to years after injury. In addition, the rate of recovery was dependent on the time since injury. These individuals had received usual rehabilitation that was available to them prior to receiving LT in an outpatient setting. This study will directly compare LT to usual rehabilitation and enroll patients at the earliest time point in inpatient rehabilitation.

2. Objective/Hypothesis:

The hypothesis to be tested in this proposal is that in incomplete SCI individuals who have impaired descending excitatory input to the spinal cord, *Locomotor Training (LT)* can provide stimulation and develop plasticity in these pattern generating networks enabling generation of improved walking in response to descending voluntary supraspinal motor impulses and result in greater functional recovery than usual rehabilitation.

3. Specific Aims:

The primary aim to be tested in this proposal is that in spinal cord injured (SCI) individuals with AIS impairment scores of C or D, who have impaired descending excitatory input to the LPG, LT can provide stimulation and develop plasticity in the LPG enabling it to generate improved standing and stepping in response to descending voluntary supraspinal motor impulses.

The *primary outcome measure*, the locomotor assessment, the 6 minute walk, will be obtained at baseline, during the intervention (every 20 LT sessions or monthly), at the end of the intervention (LT training or after 3 months following baseline), and 3 months after the intervention (3 months after LT training has ended or 6 months following baseline; Figure 2).

The *secondary outcome measures* include the (SCIM), cardiovascular function (orthostatic stress test), and pulmonary function (spirometry), and SCI-QOL questionnaires. Cardiovascular, pulmonary and quality of life measures will be performed at baseline, at the end of LT training or after 3 months following baseline, and 3 months after LT training or 6 months following baseline. The cardiovascular and pulmonary assessments will

be conducted within 2 days of the locomotor assessment. The quality of life measurements will be conducted at the convenience of the research participant within one week of the locomotor assessment.

4. Research Strategy:

We propose to conduct a prospective, randomized, controlled, multi-site Phase II clinical trial to test whether LT significantly increases the ability to walk longer distances as compared to usual rehabilitation after clinically incomplete SCI. We also will test, as secondary measures, whether cardiovascular and pulmonary function improves to a greater extent with LT, if voluntary motor activity is greater and whether ultimately their ability to function independently and their quality of life is improved as compared to those who receive usual rehabilitation.

The Study Design utilizes (1) the patient-flow linkage between five NACTN clinical centers and 4 of the NRN centers; (2) the NACTN and NRN databases that contain radiological, physiological, pharmacologic and neurological data for matching patient groups.

Table 2. Linked NACTN-NRN Centers	
NACTN	NRN
1. The Methodist Hospital (Houston) 2. U of Texas Health Science Center (Houston)	The Institute for Rehabilitation (Houston)
3. University of Louisville (Louisville)	Frazier Rehabilitation (Louisville)
4. Thomas Jefferson University (Philadelphia)	Magee Rehabilitation (Philadelphia)
5. University of Toronto	Lyndhurst Rehabilitation

Outcome measure comparisons will be made between 3 patient groups:

From linked NACTN-NRN centers	1. LT Therapy (n=32)
	2. Usual Rehabilitation (n=16)
From non-linked NACTN centers	3. Usual Rehabilitation (n=16)

5. Clinical Impact:

The study addresses a critical need of the SCI community, determining the best therapy for recovery of walking. A positive outcome will strongly influence the methods used in clinical practice and will support the hypothesis that the excitability and activity of the central pattern generating networks in the lumbosacral spinal cord can be modulated by patterned sensory input. An innovative aspect of the proposal is that the patients will be followed prospectively from the time of injury through rehabilitation making it possible to accurately match the usual care and the treatment groups.

6. Military Relevance:

Military personnel served by the Walter Reed Army Medical Center will be eligible for enrollment in this study and the NRN is committed to support the development of an NRN Center when funded.

This study is applicable to the health care of military personnel both directly and indirectly. Several VA SCI Services are actively involved with the study centers, and they will be actively recruiting veterans to participate in this Phase II clinical trial. Indirectly, as this study intends to improve our understanding and treatment of SCI, veterans and current members of the military who have a SCI will benefit from these advances.

Attachment 4: Public Abstract:

The goal of this proposal is to understand the effect of Locomotor Training (LT) on the recovery of walking in people after spinal cord injury (SCI). We will conduct a clinical trial with 64 people with SCI and compare whether LT results in people walking farther than usual rehabilitation.

The ability to walk has consistently been a major goal for persons with SCI. Rehabilitation approaches to facilitate recovery of standing and walking after a SCI have recently been directed toward LT, an activity-dependent rehabilitation therapy that provides repetitive stepping facilitated by manual assistance and body weight support on a treadmill. Benefits of activity-based therapies include functional improvements in gait, endurance, and walking speed.

This study has the potential to impact the entire field of SCI treatment and rehabilitation. Most importantly, more participants could be included in activity-dependent rehabilitation studies and programs, a type of treatment that shows promise for improving walking.

We will also monitor the effectiveness of LT on functional outcomes that are not normally analyzed, such as cardiovascular and pulmonary function, which will give researchers and therapists, alike, an idea of how to improve these critical behaviors. This study will have immediate clinical effects as it will be conducted in patient treatment centers across the country that have experience in working together in this type of program.

The participants in this study will face minimum risks and have the potential for significant benefit. Risks include exercise-induced effects such as increased respiration and heart rate. SCI research in general will also be furthered by this study as it will provide investigators with a better understanding of the relationship between locomotion, health and quality of life.

Attachment 5: Statement of Work (SOW):

Timeframe for Study: October 1, 2012- September 30, 2015

Primary Aim - The primary aim of this proposal is to evaluate the efficacy, safety, and acceptability of Locomotor Training compared to Usual Rehabilitation in recovery of ambulation in a pilot stratified randomized comparative efficacy trial.

Objective 1: To test the hypothesis that in spinal cord injured (SCI) individuals with AIS impairment scores of C or D, who have impaired descending excitatory input to the central pattern generating networks of the spinal cord, LT can provide stimulation and develop plasticity in these pattern generating networks enabling generation of improved standing and stepping in response to descending voluntary supraspinal motor impulses in comparison to Usual Rehabilitation.

Task 1. Complete regulatory requirements (6 months) - Year1 Q1-2

- 1.a. We plan to begin IRB approval processes before our start date of Oct 2012, but will complete regulatory requirements during the first 6 months of the funding period.

Task 2. Develop stratified randomization plan (6 months) Year 1 Q1-2

- 2.a. Create secure and encrypted website
- 2.b. Create randomization algorithm
- 2.c. Test website and algorithm at each clinical center before starting randomization

Task 3. Form Usual Rehabilitation subject groups (2.5 years) – Year 1 Q3-4, Year 2 Q1-4, Year 3 Q1-4

- 3.a. Begin enrollment of 16 randomized AIS C patients at the NACTN sites for Usual Rehabilitation
- 3.b. Begin enrollment of 16 randomized AIS D patients at the NACTN sites for Usual Rehabilitation
- 3.c. Complete Spinal Cord Independence Measure (SCIM) on each AIS C and D patient as they are enrolled.
- 3.d. Determine SCI Motor Score on each AIS C and D patient as they are enrolled
- 3.e. Determine AIS impairment grade on each AIS C and D patient as they are enrolled.
- 3.f. Utilizing the Six-Minute Walk Test, assess the distance walked in meters and walking speed in meters/second at baseline and at intervals of six-months and 12-months post SCI for each AIS C and AIS D patient in this Usual Rehabilitation subject group

Task 4. Form Locomotor Training subject groups (2.5 years) – Year 1 Q3-4, Year 2 Q1-4, Year 3 Q1-4

- 4.a. Begin enrollment of 16 randomized AIS C patients at the NRN sites for Locomotor Training treatments
- 4.b. Begin enrollment of 16 randomized AIS D patients at the NRN sites for Locomotor Training treatment
- 4.c. Complete Spinal Cord Independence Measure (SCIM) on each AIS C and D patient as they are enrolled.
- 4.d. Determine SCI Motor Score on each AIS C and D patient as they are enrolled.
- 4.e. Determine AIS impairment grade on each AIS C and D patient as they are enrolled.
- 4.f. Utilizing the Six-Minute Walk Test, assess the distance walked in meters and walking speed in meters/second at baseline and at intervals of 20 sessions of Locomotor Training for each AIS C and AIS D patient in this LT subject group

Secondary Aims - The secondary aims focus on intercurrent events and neurological correlates associated with SCI and the inability to bear weight

Objective 2: To examine the comparative effects of LT on 1) Spinal Cord Independence Measure (SCIM); 2) SCI Motor Score; 3) AIS impairment grade; 4) Cardiovascular Function; 5) Pulmonary Function; and 6) Quality of Life.

Task 5. In the Usual Rehabilitation subject group, perform cardiovascular, pulmonary and quality of life measures (refer to chart)

5.a. To be performed at baseline, 3 months following baseline, and 6 months following baseline.

Task 6. In the Locomotor Training subject group, perform cardiovascular, pulmonary and quality of life measures (refer to chart)

6.a. Cardiovascular, pulmonary and quality of life measures will be performed at baseline, at the end of LT training, and 3 months after LT training.

6.b. The cardiovascular and pulmonary assessments will be conducted within 2 days of the locomotor assessment.

6.c. The quality of life measurements will be conducted at the convenience of the research participant within one week of the locomotor assessment.

STUDY LOCATIONS

NACTN Locations

The Methodist Hospital (Coordinating Center)
6670 Bertner Avenue
Houston, TX 77030
Robert Grossman, MD (Principal Investigator)

University of Texas Health Science Center
Hermann Hospital
6400 Fannin, Suite 2800
Houston, TX 77030
Michele Johnson, MD (Site PI)

University of Texas School of Public Health
Data Management Center
1200 Herman Pressler W1004
Houston, TX 77030
Keith Burah, PhD (Statistician/Site PI)

University of Louisville
220 Abraham Flexner Way
Louisville, KY 40202
Susan Harkema, PhD (Co-I)
Maxwell Boakye, MD (Site PI)

Thomas Jefferson University
909 Walnut Street, Suite 300
Philadelphia, PA 19107
James Harrop, MD (Site PI)

University of Toronto
Toronto Western Hospital
399 Bathurst Street, W-449
Toronto, Ontario M5T-2S8
Michael Fehlings, MD, PhD (Site PI)

University of Maryland
22 South Greene Street, S12D
Baltimore, MD 21201
Bizhan Aarabi, MD (Site PI)

University of Virginia
P. O. Box 800212
Charlottesville, VA 22908
Christopher Shaffrey, MD (Site PI)

University of Miami
1095 NW 14th Terrace
Miami, FL 33136
James Guest, MD, PhD (Site PI)

NRN Locations

The Institute for Rehabilitation and Research
(TIRR)
1333 Moursund A-222
Houston, TX 77030
Rhonda Abbott (Site PI)

Frazier Rehab Institute
220 Abraham Flexner Way
Louisville, KY 40202
Kim Atkinson (Site PI)

Magee Rehabilitation Hospital
1513 Race Street
Philadelphia, PA 19102
Mary Schmidt Read (Site PI)

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Attachment 6: Human Subject Recruitment and Safety Procedures:

1. Study Population:

The target population for this study is individuals with acute, non-progressive incomplete SCI above T12. Based on statistics from this specific population (n=32 enrolled within 3 years at the seven clinical sites collaborating in the study), the population available is approximately 73% male, 46% female (average age 42±15); 84% white, 14% black, 7% Hispanic, 3% Asian and 4% other. This demographic representation is consistent with other national databases. Specific information related to the study population is described for each clinical site below.

Recruitment of participants will be performed through the NACTN sites. The incidence of SCI at a given institution may vary over time. For this reason, we have provided compensation per procedure for each participant enrolled rather than confine an absolute number of enrolled patients per site. We will make every effort for a uniform distribution of enrollees across sites, however if a site has an unexpected limitation for enrollment we will have access to six other facilities to assure we reach the (n=64) enrollment for the study.

a. The Methodist Hospital

The Methodist Hospital is responsible for the administration of NACTN, including but not limited to maintaining communication and teleconferencing between the centers, coordination of the research, oversight of compliance with regulatory requirements, interactions with the Department of Defense Office of Human Protection, all centers local IRB, oversight of Informed Consent Forms and daily interactions with all of the centers including the Data Management Center and the Christopher Reeve Foundation.

b. The University of Texas Health Science Center

The University of Texas Health Science Center at Houston (UTHealth), the most comprehensive academic health system in The University of Texas System and the U.S. Gulf Coast region, is home to schools of biomedical informatics, biomedical sciences, dentistry, medicine, nursing and public health. It also includes a psychiatric hospital, multiple institutes and centers, a growing network of clinics and outreach programs in education and care throughout the region. The university's primary teaching hospitals include Memorial Hermann-Texas Medical Center, Children's Memorial Hermann Hospital and Lyndon B. Johnson General Hospital. Founded in 1972, its faculty, staff and students are committed to delivering innovative solutions that create the best hope for a healthier future.

Total NACTN enrollees: 110 in the past 7 years.

c. University of Louisville

University Hospital is the area's only Level I Trauma Center, and no other facility in the region has the staff, resources and technology to manage the complex medical care a seriously injured patient can require at a moment's notice. All the surgeons on our team are University of Louisville professors, who not only provide leading-edge surgical expertise and care, but also constantly strive to discover the latest and most effective treatments. In 2010, University Hospital treated 3,000 trauma and burn patients and nearly 50% of patients reside in counties outside Jefferson County.

Total NACTN enrollees: 107 in the past 6 years.

d. Thomas Jefferson University

In 2011, *U.S. News & World Report* rated Thomas Jefferson University Hospital among the nation's top medical centers in 11 specialties: Orthopedics; Rehabilitation; Cancer; Diabetes & Endocrinology; Ear, Nose and Throat; Gastroenterology; Geriatrics; Gynecology; Neurology & Neurosurgery; Pulmonology; and Urology. Established in 1825, the Hospital has 957 licensed acute care beds, with major programs in a wide range of clinical specialties. Services are provided at five locations — the main hospital facility and Jefferson Hospital for Neuroscience, both in Center City Philadelphia; Methodist Hospital in South Philadelphia; Jefferson at the Navy Yard, just past the sports complex; and Jefferson-Voorhees in South Jersey. Thomas Jefferson University

Hospitals, an academic medical center within the Jefferson Health System, serves patients in Philadelphia and the surrounding communities in the Delaware Valley.

Total NACTN enrollees: 18 in the past 4 years.

e. University of Toronto

The Department of Surgery has approximately 225 full-time faculty, 30 part-time faculty, 60 adjunct faculty and 30 research scientists located both on campus and at our six fully affiliated teaching hospitals and two partially affiliated teaching hospitals. Our large faculty contributes extensively to our three core missions: excellent clinical care, outstanding research productivity and the delivery of state of the art educational programs. Our Department receives approximately over \$46 million annually of external peer-reviewed funding. We have a Surgeon Scientist Program aimed at providing master's or doctoral level training for our surgical trainees. There are 35 trainees registered in this research stream. We train approximately 200 residents and 175 fellows per year.

Total NACTN enrollees: 87 in the past 7 years.

f. University of Maryland

The University of Maryland Medical System (UMMS) was created in 1984 when the state-owned University Hospital became a private, nonprofit organization. It has evolved into a multi-hospital system with academic, community and specialty service missions reaching every part of the state and beyond. UMMS is a national and regional referral center for trauma, cancer care, neurocare, cardiac care, women's and children's health and physical rehabilitation. It also has one of the world's largest kidney transplant programs, as well as scores of other programs that improve the physical and mental health of thousands of people daily. The Medical System generates nearly \$3.5 billion in economic activity in Maryland. It has 15,000 employees, approximately 2,300 licensed beds, 115,000 annual patient admissions and gross patient revenues of \$2 billion.

Total NACTN enrollees: 74 in the past 5 years.

g. University of Virginia

The University of Virginia Medical Center provides primary, specialty and emergency care throughout Central Virginia through a network of clinics as well as a main hospital that has more than 500 beds. The hospital serves as a Level 1 trauma center for the region and is accessible by ambulance as well as Pegasus, UVA Health System's air and ground transport service for critically ill and injured patients. As an academic medical center, patients at UVA are treated by physicians who also serve as faculty members at the University of Virginia School of Medicine, providing access to state-of-the-art treatments researched by the faculty physicians. In the 2010 fiscal year, the UVA Medical Center treated 27,087 inpatients and had a total of 735,631 outpatient visits.

Total NACTN enrollees: 57 in the past 7 years.

h. University of Miami

The Miami Project to Cure Paralysis is the world's most comprehensive spinal cord injury research center and is dedicated to finding more effective treatments for, and ultimately a cure for paralysis. A Center of Excellence at the University of Miami Miller School of Medicine, The Miami Project is housed at the Lois Pope LIFE Center.

The Miami Project has assembled a broad spectrum of researchers, clinicians, and therapists whose expertise relate directly to the problem of SCI and whose full-time focus is SCI research. By uniting this broad range of knowledge and talents, The Miami Project team of scientists is accelerating the search for effective treatments for SCI.

Total NACTN enrollees: 42 in the past 3 years.

2. Inclusion/Exclusion Criteria:

We propose to recruit for screening approximately 75 subjects to reach the required enrollment (n=32) with SCI from the 8 clinical rehabilitation sites using the criteria listed below

a. Inclusion Criteria

- (1) have a non-progressive, neurological impairment secondary to a spinal cord injury;
- (2) the neurological level of the injury is above T11 and is motor incomplete (AIS grade C or grade D);
- (3) are between 18 and 70 years of age, inclusive; and
- (5) are able and willing to comply with the protocol, including availability for all scheduled clinic and training visits.

b. Exclusion Criteria

- (1) painful musculoskeletal dysfunction, unhealed fracture, contracture, pressure sore or urinary tract infection that might interfere with locomotor training;
- (2) clinically significant depression or ongoing drug abuse;
- (3) botulinum toxin injection to the lower extremity muscles;
- (4) pregnant or nursing women;
- (5) abnormal renal function;
- (6) history of seizures;
- (7) history of adverse reaction or allergy to baclofen;
- (8) participation in a research study that would interfere with the results of the proposed study; and
- (11) significant medical complication and/or psychiatric condition that would interfere with the conduct of the study or interpretation of the study results.

c. Inclusion of Women and Minorities in Study

Based on the low incidence rate of SCI in women, the selection of these participants is constrained, however, every effort will be made to recruit women. The ethnic makeup of the NACTN and NRN databases are representative of the minority population in the United States and Canada.

3. Description of the Recruitment Process:

Recruitment of participants will be performed through NACTN clinical sites. Each NACTN clinical site already has the infrastructure in place for patient recruitment and the potential research participants will be from the same population as those eligible for the NACTN registry. The clinical staff members will provide the potential research participant with the overview of the study (the purpose of the research, highlight any potential benefits to the participants (or report that there may be no benefit), list potential risks, outline the basic inclusion criteria, and give a simple list of the procedures) and instruct them to contact the study coordinator listed if they are interested in learning more about the study.

During their initial interviews, potential participants will be informed that any additional evaluations or examinations required for the study including physician visits, required testing, and inpatient LT sessions will be provided at no cost to them; however this should not be considered a medical treatment. There will be no additional compensation provided for their participation in the study.

4. Description of the Informed Consent Process:

a. Screening Informed Consent Process

The screening informed consent form will explain to potential research participants that they will be asked to participate in a screening process to determine their potential participation in the study. All potential research

participants will discuss the complete screening protocol as well as the entire study and their respective risks and benefits with the site PI and/or Site Clinical Coordinator at the site's designated consenting office. All potential research participants will be encouraged to read the informed consent for screening given by the Coordinator and discuss the study with his or her physician, family and friends, before signing the IRB approved informed consent. The screening informed consent will be written so that it could be understood by an eighth-grade language student and will contain information on all tests to be performed as well as contact information should the research participant or his or her associates have any questions. The research participant can take as long as necessary to reach their decision to be screened for the study. All research participants will have the capacity to give their own consent and no minors will be included in the study.

If an individual volunteers to participate in this screening process, and signs the consent form, he/she will be asked to visit the site physician who will perform a general physical examination and neurological examination. Also, the site physician or a physical therapist will perform the ISNSCI AIS examination. The potential research participant may be asked to participate in unanticipated tests depending on the results of the physical examination, and those will be discussed with the site physician.

b. Study Informed Consent Process

If the results of the screening indicate that the individual meets the inclusion/exclusion criteria for the study, he or she will be asked to discuss the complete clinical trial protocol and its risks and benefits with the physician (in the physician's office) and site PI and/or Coordinator. The consent form for the study will again be provided to the research participant at this time.

The research participant can take as long as necessary to reach their decision to enroll in the study. During this period, all potential research participants will again be asked to take the consent form home with them and will be encouraged to discuss the study with his or her physician, family and friends, before signing the IRB approved informed consent.

The informed consent will be written so that it could be understood by an eighth-grade language student and will contain information on all tests to be performed as well as contact information for the site PI, site physician and study coordinator should the research participant or his or her associates have any questions. If the research participant does not speak English as their primary language, all documentation will be translated into their first language and a copy will be provided to the HRPO for review.

The original signed informed consents (both screening and study) and two copies will be kept in the site PI's locked office in a secured cabinet.

5. Screening Procedures:

a. Initial Screening

Research participants will be recruited by the site coordinator. The study coordinator or site PI will explain the research study to the potential research participants including the required commitment, the randomization process, the risks and potential benefits. The research participant will be evaluated by the site physician who will complete a medical history, physical and neurologic examination, and AIS classification.

b. Physical Examination

A physical examination by the site physician will be performed during the screening procedure. This includes the following: 1

- General appearance
- Weight assessment
- Vital signs (heart rate, blood pressure and temperature)
- HEENT (examination of head, eyes, ears, nose, and throat)
- Pulmonary (auscultation of lung fields)

- Cardiovascular
- Abdominal
- Skin

Additional physical assessments may be performed during the study, as necessary, to evaluate the individual, with careful consideration to risks specific to participation in the study.

c. Neurological Examination

The neurological examination will be completed by a physician including mental state, reflexes and muscle tone. Additional neurological assessments may be performed during the study, as necessary, to evaluate the individual, with careful consideration to risks specific to participation in the study.

d. Neurological Assessment: AIS Sensory, Motor, and Impairment Scale Evaluations

The AIS scale assessment is to be performed at the screening visit (3, 38). If the individual enrolls in the study, the AIS will be repeated at the end of the intervention. This tool assesses sensory function (light touch and pinprick) in each dermatome and motor function (6-point Medical Research Council Scale where 0 = total paralysis and 5 = normal strength) in ten key muscles. It determines the neurological level of injury (NLI), defined as the lowest spinal level (most caudal segment) with normal neurological function, and assigns a classification of severity according to the AIS. Briefly, AIS grade A is assigned to subjects with no sensory or motor function in the lowest sacral segments (S4-S5). These individuals are considered to have *sensory and motor complete injuries*. AIS grade B indicates that there is some sensory, but not motor function, in the lowest sacral segments. AIS grade C indicates some motor function, defined by presence of voluntary anal contraction or sparing of motor function more than 3 levels below the motor level in which more than half of the key muscles below the neurological level have a muscle grade less than 3 (i.e. grade 0-2). AIS grade D denotes substantial motor function beneath the NLI in which at least half of the key muscles below the neurological level have a muscle grade greater than or equal to 3. Both AIS grade C and grade D are considered *motor incomplete injuries*, and these are the subjects eligible for this study.

e. Eligibility Determination

The physicians will also discuss the risks and potential benefits of the study with the individual. The physician will recommend to the site PI whether the individual is medically eligible for the study after completion of their assessment. If the research participant is medically eligible then site PI will confirm that the participant meets all inclusion and exclusion criteria. Then the site PI or study coordinator will in detail explain the research study to the potential research participants including the required commitment, the randomization process, the risks and potential benefits. If the research participant is interested the study coordinator or site PI will give s/he the consent form to take home for review with family, friends and physicians. After 72 hours the research participant may sign the consent form and be enrolled into the study.

6. Risks/Benefits Assessment:

a. Foreseeable risks

Locomotor Training Sessions - All research participants must be in good health and will undergo a thorough physical exam in order to ensure they meet inclusion/exclusion criteria before being enrolled in the study. The study may involve the following physical risks and/or discomforts during step training and experiments: 1) increased respiration or shortness of breath; 2) increased heart rate; 3) muscle and joint soreness; 4) lowering or elevation of blood pressure; 5) dizziness; 6) skin irritation from recording electrodes, or hand placements of trainers; 7) skin abrasion from hand placements of trainers; 8) chest pain; 9) muscle strain or joint sprain from weight-bearing during stepping, or the force exerted by the trainers; and 10) fracture from weight-bearing during stepping, or the force exerted by the trainers.

Most research participants will have increased respiration and heart rate due to an increase in activity. Exercise bouts are relatively short in duration; thus increases in respiration and heart rate or blood pressure will be generally short-lasting and we do not expect these increases to be greater than what is normally experienced

during regular exercise. Many participants will likely sustain skin irritation from hand placements of the trainer during training. These conditions are considered to be minimal risks and are reversible. There is some chance that research participants may sustain muscle and joint soreness, lowering or elevation of blood pressure, or dizziness. If these events occur during the training session, then the session will cease immediately. The study site physician will be alerted if the condition persists. These conditions are reversible and are considered to be minimal risks.

It is highly unlikely that a research participant would feel chest pain or experience high blood pressure that did not resolve within several minutes, as these events have not occurred in our past experience. Muscle strain, joint sprain, or fractures from stepping or standing are moderate but rare risks. In the event of these conditions, the research participant would immediately stop training and would be evaluated by the site physician.

Standard medical procedures will be provided if necessary.

b. Risk management and emergency response

To protect confidentiality, each research participant will be assigned a coded identification number with no association to their identity. This number will distinguish all evaluations and analyses. Only the site PI will have access to the coding of the identification number to the research participants for their own site that will be secured in a locked cabinet and within a locked office.

No individual will be allowed to participate in the study without being examined by the site physician and all eligible research participants will be encouraged to discuss the study with their primary physician, in order to minimize physical risks. To further minimize risks, the following precautions will be taken:

Locomotor Training sessions - During training, every research participant will be slowly acclimated to the body-weight support (BWS) system to make him/her feel comfortable in an upright position. This procedure typically helps the research participants avoid experiencing a lowered blood pressure or dizziness. However, if these conditions should occur, the research participant will immediately be unhooked from the system, removed from an upright position, placed in a supine position with his/her legs elevated, and the blood pressure monitored. Each research participant will be closely monitored (blood pressure, oxygen saturation, and heart rate) throughout each training session. Stepping will immediately cease if these values become abnormal or if the research participant feels tired, winded, or has chest pain. If these conditions persist, the site physician will be immediately contacted to assess the research participant and will notify the person's primary care provider when necessary.

Before and after every training session, a physical therapist will examine the research participant's skin for irritations and abrasions. If skin irritations or abrasions are caused by the recording electrodes or hand placements of trainers, electrode and hand placement will be modified appropriately. Further, the physical therapist and research team will constantly monitor the research participant's skin and muscle for signs of muscle strain, joint sprain and skin irritation as signs of skin redness, swelling of joints, or spasticity can be indicators of injury in individuals with impaired sensation.

The site physical therapist will continually assess the appropriate body weight support and manual facilitation provided by the trainers to avoid joint sprain and fracture. Research participants will also be stretched by the physical therapist or trained staff member before and after the training session to prevent injury.

If any signs of risks or discomfort are noted, the experiment or training session will be immediately discontinued. If any complications arise, step training will stop and the site physician will immediately be informed. The physician, or a designated associate, will be available on campus during all training sessions and data collections. In addition, the research participant's primary care provider will be notified as necessary.

c. Potential benefits

Exercise is considered beneficial for people with SCI who are confined to a wheelchair, as immobilization can contribute to secondary pathologies such as osteoporosis, leg muscle contractures, decreased cardiovascular health, pressure sores and muscle atrophy. Because individuals respond differently, it cannot be predetermined whether this research will be beneficial to a specific research participant. Potential benefits may include: an

increase in cardiovascular fitness; bone density; a decrease in spasticity; or an improved ability to stand or step. This information will be used to develop rehabilitation strategies that will be used to enhance walking ability in individuals impaired by spinal cord injury or other neurological conditions.

d. Intent to benefit

Principal Investigators (PIs) will not use, employ, or subcontract for the use of any human participants, including the use of human anatomical substances and/or human data, until applicable regulatory documents are reviewed, and approved by the U.S. Army Medical Research and Materiel Command (USAMRMC) to ensure that Department of Defense (DOD) regulations are met.

This study will be performed according to common guidelines for clinical trials (4, 44). All participants will provide written informed consent before being included in accordance with procedures approved by each collaborative site's respective Institutional Review Board. The informed consent of the subject will be obtained in advance of any study procedures. Individuals not legally competent to consent (e.g., incapacitated individuals, incompetents, minors) will not be enrolled in this study.

e. Withdrawal from the Protocol

Research participants may discontinue or withdraw from the study for any of the following reasons, which will be recorded on the appropriate CRF:

- At the participant's request
- Participant experiences an adverse event requiring study discontinuation
- At the discretion of the Investigator or the Sponsor, if deemed appropriate, for any reason

Efforts will be made to complete all Study Visit procedures required at the last study visit at the time of withdrawal, including an ECG and blood draw if on study medication (baclofen). All subjects are free to withdraw from participation at any time, without prejudice. The site physician will be required to determine the cause of early termination and to document the reason on the appropriate CRF as fully as possible, with any more detailed remarks deemed relevant appended as necessary.

f. Modifications to the Protocol

In the event that a major protocol modification or any modification that could increase risk to volunteers is required, the study PI will submit the modification to the HRPO for approval prior to implementation. Major modifications include a change in PI, the addition of a study site, changes in study design, and the addition or widening of a study population.

After the study PI receives approval from the HRPO, the study PI will send the approved modification to the PI at each study site, who will request review and approval for the modification from their site IRB, noting that the modification has been approved by HRPO.

Each site's PI will send the IRB submission and approval notification to the study PI. When the study PI has received IRB approvals from every study site, the study PI will notify all sites to begin implementation of the modification.

All other amendments will be submitted with the continuing review report to the HRPO for acceptance.

g. Protocol Deviations

Any deviation to the protocol that may have an effect on the safety or rights of the volunteer or the integrity of the study will be reported to the HRPO by the study PI as soon as the deviation is identified. In addition, the site PI will notify the site's IRB using the appropriate forms or computerized process.

h. Reporting of Serious Adverse Events and Unanticipated Problems

Adverse Event - An adverse event considered any untoward medical event (clinical or laboratory) experienced by a participant during the course of the clinical trial, whether or not it is related to the investigational product.

The site PI and the physician will monitor each participant closely for the development of adverse events and record all such events on the *Adverse Events (AE)* page of the case report form (CRF). For any laboratory abnormality, the site PI or physician will make a judgment as to clinical significance. All clinically significant laboratory abnormalities will be recorded on the *Adverse Events (AE)* page of CRF. If the laboratory value is outside the normal range, the physician must comment on the findings on laboratory report.

All adverse events should be followed up in accordance with Good Clinical Practice.

Severity - Adverse events will be graded for severity and noted in the description of the event. A severity category of mild, moderate or severe, as defined below, will be determined and entered on the AE form.

- Mild - causing no limitation of usual activities.
- Moderate - causing some limitation of usual activities.
- Severe - causing inability to carry out usual activities.

The site-investigator will be asked to document his/her opinion of the relationship of the event to the study drug/intervention as follows:

- None - the event can be readily explained by the participant's underlying medical condition or concomitant therapy and no relationship exists between the study drug and the event. In this event, the Investigator must indicate an alternative etiology.
- Unlikely - the temporal relationship between the event and the administration of the study drug is uncertain and it is likely that the event can be explained by the participant's medical condition or other therapies.
- Possible - there is some logical temporal relationship between the event and the administration of the study drug and the event is unlikely to be explained by the participant's medical condition or other therapies.
- Probable - the temporal relationship is compelling between the administration of the study drug and the event cannot be explained by the participant's medical condition or other therapies.

Serious Adverse Events - A Serious Adverse Event (SAE) includes any experience that

- is fatal or immediately life-threatening;
- results in or prolongs inpatient hospitalization;
- results in persistent or significant disability/incapacity;
- results in a congenital anomaly/birth defect;
- is unusual or, in the opinion of the Investigator, presents a significant hazard to the participant;

Any serious adverse event, including death due to any cause that occurs during this study must be reported **immediately** (by the end of the next business day) to the medical monitor (Dr. Dyson-Hudson).

In addition to the initial telephone report, all SAEs must be recorded on the *Adverse Events* page of the CRF and a *Serious Adverse Event* form must be completed and sent via facsimile immediately to the Clinical Monitor. All SAEs will require telephone notification and written SAE report within 24 hours. All SAEs must be reported to the local IRB within 3 days.

Each week of follow up, the research participants will undergo a questionnaire by the study coordinator to assure adverse events are not occurring. If any significant side effects are reported, the coordinator will contact the study physician at the respective site to discuss whether the dosage should be adjusted. If there are no side effects reported, the study coordinator will give the subject the next numbered card and bottle of medications. Every 4 weeks, the participants will have physical examination by the site study physician, to complete a brief evaluation as completed during the screening visit.

Adverse experiences will be elicited by nonspecific questions such as: "Have you experienced any changes in your health status since your last visit?" Subjects will be encouraged to report each adverse event at its onset.

Any adverse experience spontaneously reported by or elicited from the research participant or observed by the study personnel from the start of study drug administration will be followed and recorded on the appropriate Adverse Event Case Report Form, whether or not the event is considered by the site-PI to be related to study drug or LT intervention.

Adverse experience(s) will be recorded on the Adverse Event Case Report Form, including the date and time of onset, severity, the relationship to study medication and/or intervention, the date of resolution (or the fact that the event is still continuing), the action taken, and the outcome of the adverse experience. The responsible physician will make a causality assessment for every adverse experience.

For any laboratory abnormality the physician responsible will make a judgment as to its clinical significance. If the laboratory value is outside the safety limits and is felt to represent a clinically significant change from the baseline value, an assessment will be made as to its drug/intervention relatedness and recorded on the *Adverse Events* page of the Case Report Form.

The responsible site PI and/or physician must determine whether the seriousness of the event warrants removal of any participant from the study. He/she should, in any case, institute appropriate diagnostic and therapeutic measures and keep the participant under observation for as long as is medically indicated.

Attachment 7: Intervention

1. Description of the Intervention

a. Locomotor Training Intervention (LT)

The primary purpose of LT is to provide sensory cues to re-train neural patterns that will result in effective locomotion. This is accomplished by integrating strategies called “locomotor training principles” throughout the three therapeutic components of locomotor training: step training on treadmill, overground walking training, and community integration training (Figure 1. Attachment 7).



Figure 1. Attachment 7. Locomotor Training Components: Step training on treadmill, overground assessment, and community integration.

Step Training on treadmill (60 minutes)

The goal of step training is to re-train individuals to step by taking advantage of the intrinsic mechanisms of the nervous system that generate neuromuscular activity. Step training uses a body weight support and treadmill system (BWST) in combination with manual facilitation to implement the LT principles. The primary neural re-training occurs in this component as the nervous system re-learns motor patterns associated with walking (retraining phase). Step training using BWST and manual assistance is also used to address limitations to independent walking including gait deviations and promote independence and balance (adaptability phase).

During the step training session, step training participants will be placed on the treadmill in an upright position and suspended in a harness by an overhead pulley at the maximum load at which knee buckling and trunk collapse can be avoided. A trainer positioned behind the participant will aid in pelvis and trunk stabilization, as well as appropriate weight shifting and hip rotation during the step cycle. The trainer will ensure that the trunk and pelvis are not flexed or hyper-extended during stepping. Trainers positioned at each limb will provide manual facilitation using a customized technique developed that facilitates knee extension during stance and knee flexion and toe clearance during swing. Trainers promote knee extension by applying gentle pressure at the tibial tuberosity and stimulation of the patellar tendon. They will promote knee flexion and toe clearance by applying a gentle force at the semitendinosus tendon. Manual facilitation at the trunk-pelvis and at the legs will be used only when needed. During the session, the treadmill speed will be adjusted to promote the best stepping pattern at the given body weight load (BWL). Speeds will be maintained within a normal walking speed range (0.89-1.34 m/s). BWS will be continuously reduced over the course of the training sessions as the subjects increase their ability to bear weight on the lower limbs. Manual facilitation will be reduced with independence of stepping.

Overground walking training (15 minutes)

The goal of overground walking training is to translate the stepping capacity gained by re-training the nervous system during step training to the overground environment. The participant is instructed on ways to implement the locomotor training principles in the overground environment both comfortably and safely. In addition, limitations to independent walking are identified and specifically targeted in the next step training session where the BWST environment allows easier intervention by the trainer.

Community integration training (15 minutes)

The goal of community integration training is to translate the stepping capacity gained by re-training the nervous system during step training into safe overground ambulation. The same locomotor training principles used during step training and overground walking training are used to promote ambulation outside of the clinical environment. If required, the therapist selects the least restrictive assistive device that provides safe and independent ambulation. The participant is instructed on strategies to use the device in a manner that is consistent with the locomotor training principles. The participant is also instructed on strategies to safely implement the locomotor training principles in the home environment without the assistive device.

2. Study procedures:

a. Primary Outcome Measure

Six Minute Walk Test

The individual's ability to walk independently will be assessed using standardized and validated clinical measures (i.e. 6 minute walk test (30, 45, 46). Assistive devices will be allowed during the testing with the same device being used during all testing sessions. The assessment will be conducted between 10 am in the morning and 2 pm in the afternoon for all participants across sites to minimize the variability of spasticity known to occur throughout the day. The research participant will be advised to take their medication on the day of testing. A list of instructions will be provided to the research participant that will require them to avoid intense exercise, alcohol, restrict caffeine intake, and get adequate rest. Research participants are asked to complete their bowel programs at their usual times and to catheterize as needed prior to testing. Whenever possible the individual research participant will repeat this measure as close to the time obtained for baseline measures.

Equipment:

- uninterrupted walking course with measured distances
- digital stopwatch
- blood pressure cuff
- stethoscope
- heart rate/oxygen saturation meter
- video camera
- tape
- 2 small cones

b. Secondary Outcome Measures

Cardiovascular - Orthostatic Stress Test

Equipment:

- stopwatch
- automatic sphygmomanometer
- automatic vital signs monitor
- heart rate/oxygen saturation meter
- wheelchair or chair with arms
- cardiac chair or 3 section tilt table

Place the blood pressure cuff around one arm and the oximeter on the opposite arm's index finger. Keep these placements consistent throughout the duration of the measurements. Record the time for each measurement using a stopwatch. Record the time measurement that is displayed on the automatic vital signs monitor

Supine: Instruct the participant to rest quietly in the supine position for at least 5 to 10 minutes. Explain that you will not talk to him/her, and ask them to remain quiet until all measurements are taken. Take 3 blood pressure and heart rate measurements at 1-minute intervals. Record time, systolic, diastolic, and heart rate.

Supine to Sit: Passively sit the participant up to 90 degrees (hip), with legs down (knee flexed at 90 degrees). Explain to the participant to remain relaxed and not assist in sitting up. Record the time when supine to sit is completed. Begin blood pressure recordings immediately. Record time, systolic, diastolic, and heart rate.

Sitting: Participant should be supported to maintain their sitting position passively. Take 10 measurements at 1-minute intervals. Record time, systolic pressure, diastolic pressure, and heart rate and oxygen saturation.

Blood pressure, heart rate, and oxygen saturation should be assessed before therapy while participant is sitting in a wheelchair or a chair with arms

Spirometry

Standard spirometry (35) will be performed in a seated position with nose clip on by using BreezeSuite System (MedGraphics, St. Paul, MN). We will measure the rate at which the lung changes volume during forced breathing maneuvers beginning with a full inhalation, followed by a forced expiration that rapidly empties the lungs. Expiration will be continued until a plateau in exhaled volume is reached. Forced vital capacity and forced expiratory volume in 1 second will be measured and expressed as the percent of the predicted value for each research participant based on a database of individuals that are neurologically intact with no known pulmonary complaints that was derived based on gender, age, and height (22). Three acceptable spirograms will be obtained and the result of the best attempt will be used.

Neurological Assessment: AIS Sensory, Motor, and Impairment Scale Evaluations

The AIS scale assessment is to be performed at the screening visit (3, 38). If the individual enrolls in the study, the AIS will be repeated at the end of the intervention. This tool assesses sensory function (light touch and pinprick) in each dermatome and motor function (6-point Medical Research Council Scale where 0 = total paralysis and 5 = normal strength) in ten key muscles. It determines the neurological level of injury (NLI), defined as the lowest spinal level (most caudal segment) with normal neurological function, and assigns a classification of severity according to the AIS. Briefly, AIS grade A is assigned to subjects with no sensory or motor function in the lowest sacral segments (S4-S5). These individuals are considered to have *sensory and motor complete injuries*. AIS grade B indicates that there is some sensory, but not motor function, in the lowest sacral segments. AIS grade C indicates some motor function, defined by presence of voluntary anal contraction or sparing of motor function more than 3 levels below the motor level in which more than half of the key muscles below the neurological level have a muscle grade less than 3 (i.e. grade 0-2). AIS grade D denotes substantial motor function beneath the NLI in which at least half of the key muscles below the neurological level have a muscle grade greater than or equal to 3. Both AIS grade C and grade D are considered *motor incomplete injuries*, and these are the subjects eligible for this study.

Spinal Cord Independence Measure (SCIM)

The SCIM is used routinely to assess the ability of individuals after SCI to function independently in daily activities of living. This measure has shown reliability and validity for this population and shown to be effective for use in clinical trials. For details on scoring and measures see *Attachment 6*.

Quality of Life Assessments

Health-related quality of life (HRQOL or simply “QOL”), a subjectively evaluated multidimensional construct, “refers to the extent to which one’s usual or expected physical, emotional, and social well-being are affected by a medical condition or its treatment”(11). HRQOL is an increasingly important patient reported outcome in SCI clinical trials, as traditional outcomes measures fail to account for the overall functioning of an individual or the direct and indirect impact of new treatments on all aspects of a person with SCI. Researchers have come to recognize that global quality of life (QOL) outcomes measures, including physical health, level of social support, participation in the community, and level of everyday functioning, predict satisfaction over the long term.

The SCI-QOL/SCI-CAT is a comprehensive, SCI-specific QOL measurement system covering four major domains, namely Physical-Functional Health (including Mobility, Upper Extremity, and Activities of Daily Living subdomains), Physical-Medical Health (including Respiratory, Skin/Pressure Ulcers, Bowel, Bladder and Pain subdomains), Emotional Health (including Positive Psychological Function, Anxiety, Depression, Stigma, Trauma, Loss, Self-Esteem, and Resilience), and Social Participation (including Social Role Performance, Social Role Satisfaction, and Independence/Autonomy). It is linked to some large measurement initiatives advanced by the NIH. Since 2002, the NIH has sponsored large initiatives to develop measurement tools for use across all of their patient populations. This includes the Patient Reported Outcomes Measurement Information System (PROMIS) (www.nihpromis.org), and the Neuro-QOL measure for individuals with neurological disorders (www.neuroqol.org.) The resulting tools have been developed using state of the art measurement theory and methodology including item banking (13, 14), Item Response Theory (IRT) (29), and Computerized Adaptive Testing (CAT) (10). Due to the nature and extent of federal funding for these projects, it is likely that the PROMIS and Neuro-QOL measures will be measures of choice across NIH-funded clinical trials. The SCI-QOL/SCI-CAT project has extended the PROMIS/Neuro-QOL measurement system into spinal cord injury specifically by validating the PROMIS/Neuro-QOL items in an SCI sample and developing new, targeted items to adequately capture the most important HRQOL issues for individuals with SCI.

The SCI-QOL/SCI-CAT was developed using a participatory action research methodology (52), which enlisted individuals with SCI and SCI clinicians as key stakeholders in measure development. A series of 32 focus groups (n=24 groups of individuals with SCI and n=8 groups with SCI clinicians) were held and all focus group feedback was analyzed to ensure conceptual grounding of this measurement system with regard to key QOL issues in SCI. This community feedback was used to extend the Neuro-QOL/PROMIS measurement system

into SCI. Item response theory will be used to develop short forms and a computerized adaptive test (CAT) version of the SCI-QOL/SCI-CAT.

The SF-36 (49), developed by RAND to assess outcomes of medical care, is the most widely used health status measure in the world (2). The SF-36 contains 36 items across eight subscales (Physical Functioning, Role Limitations: Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role Limitations: Emotional, and Mental Health) and two higher-order component scores, Physical and Mental and has successfully demonstrated reliability (23, 48) and validity (34). Its holistic conceptualization of health is generally appropriate, but it is widely criticized by disability researchers for its tendency to “conflate functional ability with health status” (2). The SF-36 (42), which is not specific for SCI disease burden but has been widely applied and validated, will be utilized as a legacy measure.

The Satisfaction with Life Scale (SWLS) (17) is a 5-item measure of the single concept of global life satisfaction. The SWLS has been shown to be both reliable and valid in general health populations {Diener, 1985 DIENER1985 /id} and also exhibits sensitivity to change (41). While reliability specifically within an SCI sample has yet to be examined, the SWLS is currently used in SCI Model Systems dataset, and normative data for individuals with SCI is available. The SWLS will serve as a legacy measure of overall QOL. LT will be prescribed 5 days/week (1.5 hours/session) for a total of 86 sessions that included step training, overground assessment, and community integration.

Attachment 8: Data Management

1. Data Management:

a. Methods used for data collection

All data will be entered by the examiner into ITW, a web-based data collection system. ITW is an interdisciplinary documentation system that is fully HIPPA compliant. ITW guides the clinician and researcher through Evaluations, Plans of Treatment and Sessions/Interventions. Through the use of form templates, designers can direct the user to document critical areas of information. This is important not only for quality clinical documentation, but also for capturing key data points for research. The clinician can enter information once and satisfy multiple requests; even for different research projects.

The architecture of the system allows the researcher to extract discrete information for analysis. Also, because all information in the system is stored discretely the researcher can blend additional information captured historically as new correlations are discovered.

The topology of the system is client/server allowing access with a standard internet browser over a secure connection. This means that clients will probably have any required software and access can be achieved over standard public network connections. The datacenter used is FITS 140-2 compliant (arguably level 4). Only the sites computers are able to connect and all transmissions to the site are AES 128 encrypted.

The NRN has used this system since 2004 and already customized the templates for the outcome measures in this clinical trial. We will leverage the resources already invested in developing this specialized web-based program for the proposed clinical trial. Thus, for relatively low cost we can utilize an already established secure web-based data collection system.

b. Identifiers

All data extracted for analyses will be de-identified electronically. A 32 bit GUID is randomly created for each patient. The data center maintains a link between this GUID and an SHA512 cryptographic hash of the patients SSN. Even though the cryptographic hash is not reversible it never leaves the datacenter. All evaluations and analyses are then associated with this GUID code. Only the site PI will have access to the codes for the research participants enrolled at their own site [I'm not sure I understand what this is supposed to mean but the word "codes" at least needs to be changed because I use it differently in the preceding sentences]. This access will be protected by a highly secure password. Only members of the research data management team will have access to the de-identified data for analyses.

c. Confidentiality

Every effort will be made to protect the health information regarding participants. Only the site principal investigator and study personnel will have access to the information for a specific research participant. The data management team will only have information that has been de-identified and coded.

At the specific clinical site, health information about research participants may be looked at or given out to others, including the people and organizations who conduct, analyze, and understand this study, The research participant or his or her personal representative, others as allowed or required by law, government entities that have the responsibility to oversee this research, the offices and departments responsible for oversight of research at the research institution, health care providers and others where the research participant receives care during his or her participation in this study, health care providers and others, as appropriate, for compliance oversight, and if applicable, people responsible for sending and receiving payments related to participation in the study. In addition, the sponsor of the study (the DOD and USAMRMC) and the people that the sponsor may contract with for the study and investigators and research staff at other places that are participating in the study may share, receive and/or look at the information of research participants.

While we are required to protect health information, once any information leaves our institutions, we cannot promise that others will keep it private (confidential). The information we look at or give to others as part of the

research will be analyzed and further studied to answer the research questions and to make sure that the research was done correctly.

Research participants have the right to cancel the permission they have given at any time. This means they can tell us to stop using and sharing their information. If a research participant cancels his or her permission, we will stop collecting information about him or her. However, the research participant may not withdraw information that we had before we were told to stop because we may already have used it or shared it, and because we may need it to complete the research.

The USAMRMC are eligible to review study records.

d. Disposition of data

Data for each phase of the study will be periodically extracted from the web-based data collection system into a compressed, multi-table Microsoft Access database. This compressed Access file, and all other related files discussed below, extraction database will be stored on a network folder at the Frazier Rehab Institute. The server is backed up daily with a differential strategy (only those files modified or created since previous back up are backed up). Full backups are performed weekly on selected high traffic drives. Full backups are performed monthly on all drives. Full backups are performed over the weekends to minimize disruption of other server activities. Daily backup are performed after midnight. Full backups and differential backups are kept for a period of 6 months. Server analysts review backup logs on a daily basis to assess any problems with drives or files, they will inform research personnel immediately is any consistent problems are observed.

The compressed Access file will be decompressed into a Microsoft Access database, termed the extraction database. The database will consist of one participant information table, containing demographic and baseline clinical characteristics, which will act as the “parent” table for all established relationships. The remaining data tables will contain the data collected for each evaluation of each participant in the study, and will serve as the “children” in established database relationships. Study data will be distributed across these data tables in logical groupings, (e.g.) walking assessments, spasticity measurements, etc. The parent data table will contain a non-descriptive, unique identifier for each participant enrolled in the study. This identifier will be present in the data tables as well to serve as the foreign key.

A duplicate copy of the processed database will be created and stored on the Frazier Rehab Institute network and will be utilized for database processing, to be termed the processed database. From the processed database, a processing routine will be applied to prepare the database for use. This processing routine will accomplish the following tasks: (1) create the primary key in the primary participant information table, (i.e.) the parent table, (2) establish one-to-many relationships between the parent table and all remaining data/child tables, and (3) establish one-to-one relationships between the records of each data/child table.

A duplicate copy of the processed database will be created and utilized for data integrity checking, to be termed the correction database. For each study variable collected, range/plausibility checks will be identified, (e.g.) systolic blood pressures must be between no less than 50 and no more than 300. These data checks will be coded into multiple queries in the correction database. Upon execution, the queries will create site-specific reports listing data entries in which an erroneous entry is suspected. These reports will be distributed to each study site for rectification. Each site will be responsible for indicating whether the listed data entries are indeed data entry errors or confirming their accuracy. In the former case, a corrected data point will be supplied. The sites will return the list of suspect of data entries with corrections/confirmations. All data corrections will be made in the correction database. Upon completion of the data integrity process, the correction database will be locked for editing. After the locking of the correction database, queries will be written to provide data files for statistical analysis. These queries will be designed and executed within Microsoft Access, exported as text files, and distributed to study personnel for analysis.

As a consequence of the above listed procedures, four copies of the database will be maintained at the Frazier Rehab Institute: (1) the compressed database – the compressed Microsoft Access file extracted from the web-based data collection system, (2) the extraction database – the compressed Microsoft Access file extracted from the web-based data collection system, (3) the processed database – the duplicate copy of the extraction database

from which database processing is conducted, and (4) the correction database – the duplicate copy of the processed database from which the data integrity procedure will be run and data corrections made. Although extractions from the web-based data collection system will be periodic, the above-detailed procedures will only be implemented for the final extraction, (i.e.) the extraction conducted after all study data have been entered into the web-based data collection system.

e. Sharing study results

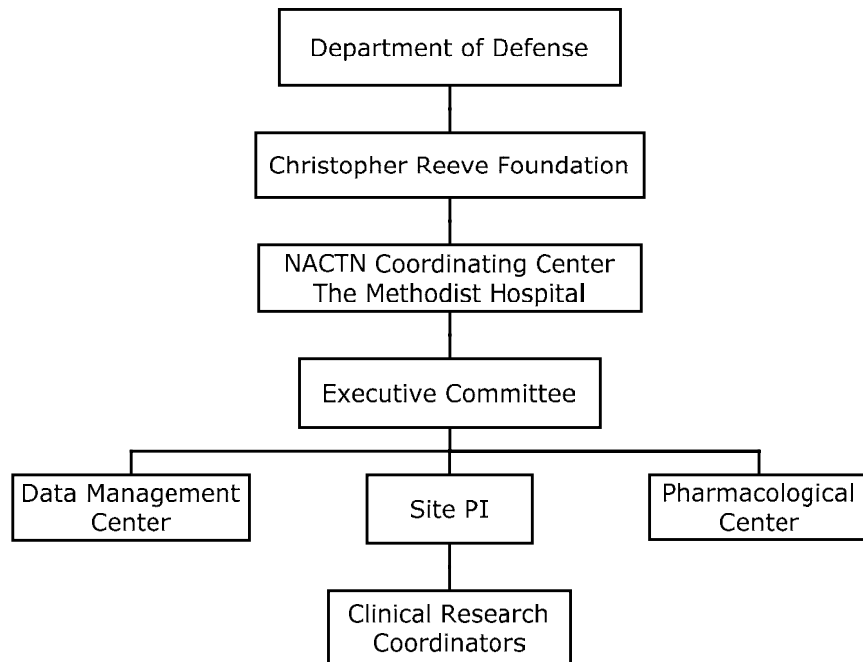
There is no intent for the individuals' results to be used to guide clinical care. However, research participants will be informed if the protocol results if the site physician identifies any possible benefit medically or otherwise. Only if the research participant provides permission we will release this information to their health care provider. The research participant will be provided with the results of all their own tests and evaluations

2. Laboratory Evaluations:

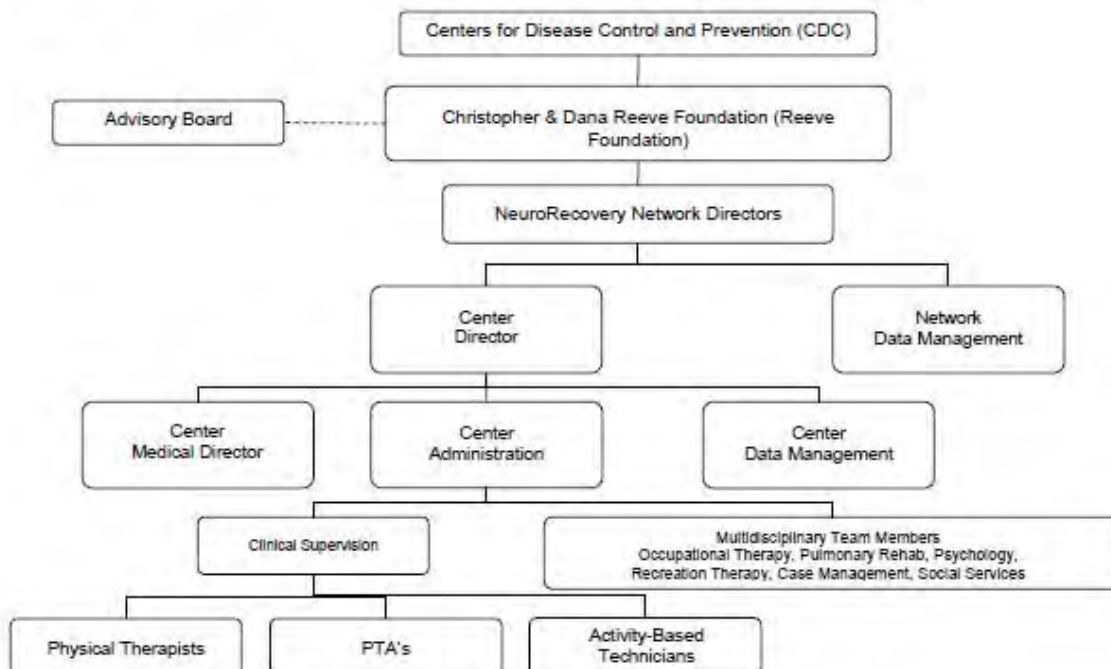
None

Attachment 9: Study Personnel and Organization

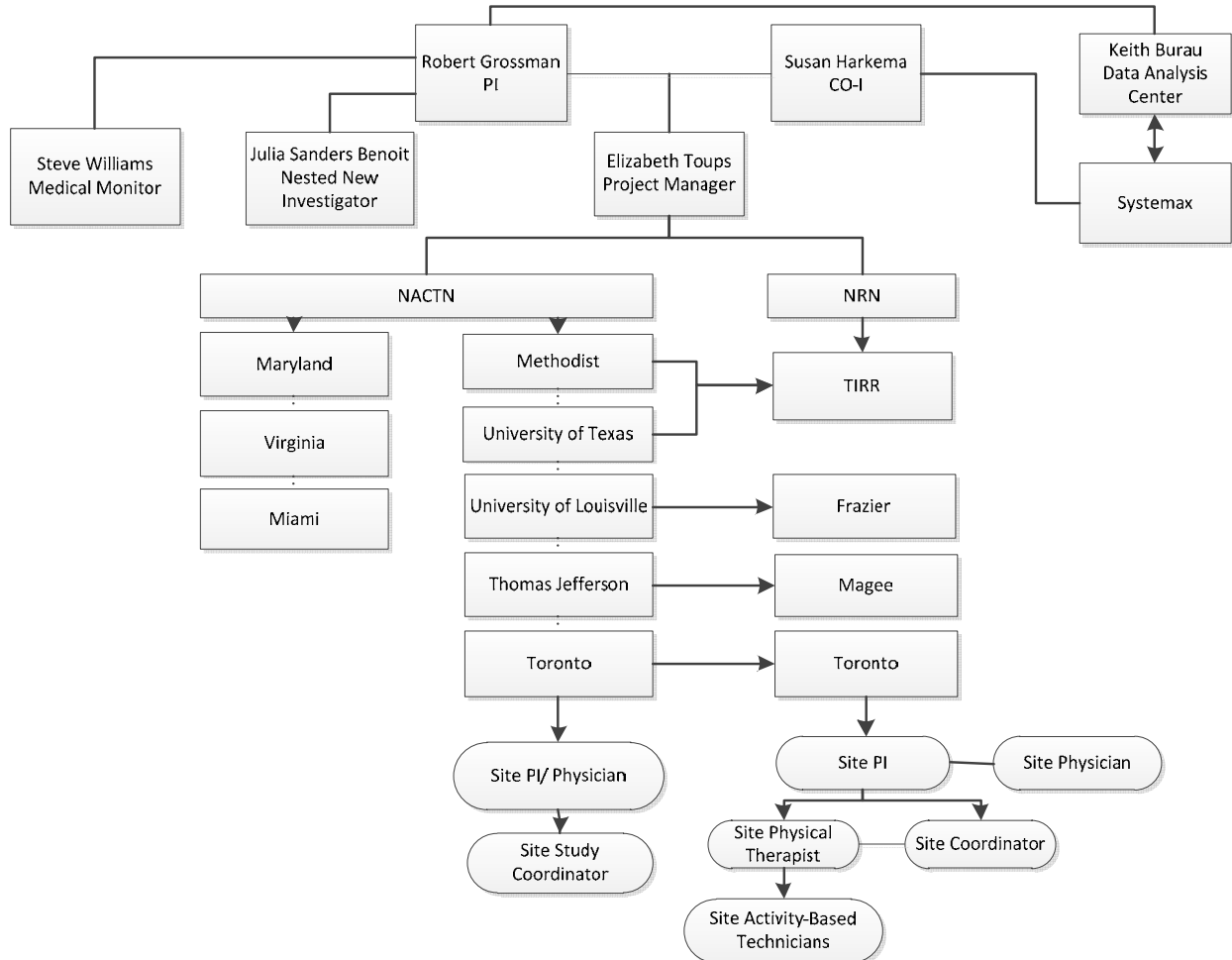
North American Clinical Trials Network Table of Organization



NeuroRecovery Network Table of Organization



Study Personnel and Organization



1. Principal Investigator/Study Staff:

a. Principal Investigator

Dr. Grossman will oversee all aspects of the proposed clinical trial. This includes research participant recruitment, screening, enrollment, and compliance with all requirements of the HRPO and local site IRBs. He will have quarterly conference calls with the site physicians to maintain standardization across sites and discuss medically related issues. He will collaborate with the medical monitor to ensure oversight of adverse events and data accuracy and protocol compliance. Along with the other investigators, Dr. Grossman will assist in data interpretation and editing/preparing manuscripts. Dr. Grossman is the Principal Investigator of the NACTN and has collaborated with physicians, scientists and administrators to implement a network of hospitals whose mission is to bring promising therapies out of the laboratory and into clinical trials, in a manner that provides incontrovertible evidence of effectiveness and safety.

b. Nested New Investigator

Julia Benoit, Nested New Investigator. As the Nested New Investigator for this study, Julia will have the opportunity to become familiar with the planning, conduct and analysis of a Phase IIb comparative efficacy clinical trial and will also develop special expertise in the design of randomized spinal cord injury rehabilitation

clinical trials. Her current research work is directly applicable to the primary and secondary statistical objectives of this SCIRP grant application.

c. Study Staff

Dr. Susan J. Harkema, Co-I – Dr. Harkema will collaborate with Dr. Grossman in overseeing research participant recruitment, screening, enrollment, and compliance with all requirements of the HRPO and local site IRBs. She will oversee all aspects of training interventions, data acquisition and management. She will oversee standardization of outcome measures to ensure appropriate implementation of study procedures. Along with the other investigators, Dr. Harkema will assist in data interpretation and editing/preparing manuscripts. Dr. Harkema is the Director of the NRN and has collaborated with physicians, scientists and administrators to implement a network of rehabilitation centers that provide specialized, standardized activity-based therapies and obtain standardized outcome measures on function, health and quality of life since 2004.

Keith Burau, Statistician/Site PI - Dr. Burau is an associate professor of Biostatistics is the Statistician/Site PI of this contract and will have the responsibility for the oversight of all data analysis activities conducted under this contract. Dr. Burau will develop a secure and encrypted system for downloading data and related documents from an electronic data capture system developed by the Clinical Coordinating Center located at the University of Louisville, Department of Neurosurgery. Dr Burau will commit 5% time and effort to the project in its first two years and 10% time and effort in year 03 which is devoted to data analyses and manuscript preparation.

Elizabeth Toups, Project Manager - Ms. Toups, Project Manager and Point of Contact for the DOD HRPO ORP will be responsible for the day-to-day activities of NACTN's clinical activities. She provides support to Dr. Grossman, other Principal Investigators and other NACTN and NRN personnel. Her activities include protocol development, submissions and regulatory approvals, organizing and conducting NACTN/NRN meetings, project management and site management for planning, initiating and conducting clinical trials and facilitating

Dr. Steve Williams, Medical Monitor – Dr. Williams will serve as Medical Monitor for this study. He will oversee the safety of all phases of the study to ensure that the study is performed according to common guidelines for clinical trials. Dr. Williams will review all unanticipated problems involving risk to study participants or others, and “serious adverse events” (SAEs), including all study subject deaths, and provide an unbiased written report of the event within 10 calendar days. Dr. Williams will comment on the outcomes of the adverse event and relationship of the event to the protocol. He will also indicate whether he concurs with the details of the report provided by the principal investigator. Dr. Williams will promptly forward all SAE events determined by either the investigator or him to be possibly or definitely related to participation, including reports of events resulting in death to the HRPO.

d. NACTN Site Personnel

Site PI/Physicians: The site PIs will be responsible for overseeing all grant activities at the site, as well as the grant budget. They will direct the efforts of the Site Study Coordinator. All Site PIs are NACTN Center Directors and/or Physicians, and will leverage the existing NACTN infrastructure for communication that will include monthly conference calls with Drs. Grossman and Harkema to maintain standardization and discuss study related issues.

Site Study Coordinators: The Site Study Coordinators will be responsible for recruiting and consenting volunteers, maintaining study records, entering data into the computer database, and guiding the protocol through the IRB approval process at the site. All Site Study Coordinators are either currently involved with NACTN or have been involved in the past. They will have monthly conference calls to maintain standardization across sites and discuss protocol related issues led by Dr. Harkema and Elizabeth Toups.

e. NRN Site Personnel

Site PIs: The site PIs will be responsible for overseeing all grant activities at the site, as well as the grant budget. They will direct the efforts of the Site Coordinator and Physical Therapist, and collaborate with the Site Physician. All Site PIs are either NRN Center Directors and/or Physicians, and will leverage the existing NRN infrastructure for communication that will include monthly conference calls with Drs. Grossman and Harkema to maintain standardization and discuss study related issues.

Site Physical Therapists: The Site Physical Therapists will be responsible for administering the locomotor training intervention, including supervising the Activity-Based Technicians. All Site Physical Therapists are also NRN Clinical Supervisors and have received at least 3 years of locomotor training that includes standardization of the intervention among sites. The Site Physical Therapists will have monthly conference calls to maintain the standardization across sites led by Dr. Harkema and Elizabeth Toups.

Site Coordinators: The Site Coordinators will be responsible for recruiting and consenting volunteers, maintaining study records, entering data into the computer database, and guiding the protocol through the IRB approval process at the site. All Site Coordinators are either currently involved with the NRN or have been involved in the past, so they are already familiar with the locomotor training intervention and using the computer database system. They will have monthly conference calls to maintain standardization across sites and discuss protocol related issues led by Dr. Harkema and Elizabeth Toups.

Site Activity-Based Technicians: The Site Activity-Based Technicians will provide the locomotor training intervention under the supervision of the Site Physical Therapists. All Site Activity-Based Technicians are experienced with providing the locomotor training intervention and have attended at least one off-site 4-day regional training in session.

2. Study Management Plan

The investigators, key personnel and study personnel have been collaborating for 3-5 years (depending on when the site joined NACTN or NRN) as collaborators within NACTN and/or NRN. Since 2005, Dr. Grossman has been the principal investigator of NACTN. Since 2004, Dr. Susan Harkema has led the development and implementation of an infrastructure to provide standardized activity-based rehabilitation across seven rehabilitation sites and implement standardized outcome measures in individuals with incomplete SCI. In this proposal, Drs. Grossman and Harkema will leverage the already existing infrastructures of NACTN and NRN to conduct this Phase II clinical trial.

The clinical trial study personnel will receive a detailed policy and procedure manual and a conference call schedule will be implemented for communication and facilitation of standardization of protocols, intervention and outcome measures. The site PI's will have monthly conference calls with Drs. Grossman and Harkema to maintain standardization of protocols and discuss study related issues. Dr. Harkema and Elizabeth Toups will have weekly conference calls with the site PI's and coordinators in the initial start up of the study to verify that all procedures are in place to begin enrollment of research participants. Dr. Grossman will have quarterly conference calls with the site physicians to maintain standardization and discuss medically related issues. Conference calls will be convened more often if needed. Drs. Grossman and Harkema will have a scheduled conference call every month to discuss the progress of the study. Webinar and video presentation will be available as needed for all conference call groups. This system has been in place within the NACTN and NRN, with the majority of current study investigators and personnel since 2004.

Attachment 10: Surveys, Questionnaires, and Other Data Collection Instruments

Spinal Cord Independence Measure (SCIM)

The SCIM is used routinely to assess the ability of individuals after SCI to function independently in daily activities of living. This measure has shown reliability and validity for this population and shown to be effective for use in clinical trials.

The SCIM Assessment Form is attached to this document

Quality of Life Measurement

The NRN-QOL is a web-based Quality of Life (QOL) measurement. Data collection is via the Assessment CenterSM platform. The NRN QOL Assessment is designed to assess functional abilities, physical-medical health, and social participation. The Assessment CenterSM website version of the test includes the previous legacy measures such as the Quality of Life SCI v.III, *CES-D*, and *KATZ*. The website version, however, does not include the CHART, which must still be filled out in ITW.

QOL is an increasingly important patient reported outcome in SCI clinical trials, as traditional outcomes measures fail to account for the overall functioning of an individual or the direct and indirect impact of new treatments on all aspects of a person with SCI. Researchers have come to recognize that global quality of life (QOL) outcomes measures, including physical health, level of social support, participation in the community, and level of everyday functioning, predict satisfaction over the long term.

An NRN Site Coordinator will register each patient on the Assessment CenterSM website. The following information is required to complete the registration: Patient's age (no one under 18 years of age), gender, year of injury and EpNum. Once patient is registered a unique username and password will be provided for each episode number. No other identifying information will be entered in the Promis Assessment Center website.

The Quality of Life Survey is attached to this document.

The SF-36(49)

The SF-36(49), developed by RAND to assess outcomes of medical care, is the most widely used health status measure in the world. Its holistic conceptualization of health is generally appropriate, but it is widely criticized by disability researchers for its tendency to "conflate functional ability with health status"(2). The SF-36(49), which is not specific for SCI disease burden but has been widely applied and validated, will be utilized as a legacy measure.

The SF-36 is attached to this document.

The Satisfaction with Life Scale

The Satisfaction with Life Scale (SWLS)(17) is a 5-item measure of the single concept of global life satisfaction. The SWLS has been shown to be both reliable and valid in general health populations(17) and also exhibits sensitivity to change (41). While reliability specifically within an SCI sample has yet to be examined, the SWLS is currently used in SCI Model Systems dataset, and normative data for individuals with SCI is available. The SWLS will serve as a legacy measure of overall QOL. LT will be prescribed 5 days/week (1.5 hours/session) for a total of 86 sessions that included step training, overground assessment, and community integration.

The SWLS survey is attached to this document.

All NACTN patients should be evaluated by the SCIM™ at discharge from the Acute Care Facility as well as the Rehabilitation Facility. In addition, this evaluation should be conducted at 3-month, 6-month, and 12-month intervals following the date of injury. Scores for each item are defined in the NACTN Manual of Operations.

1. Date of SCIM™ Evaluation:

 ____ / ____ / 20 ____
 Month Day Year

2a. Indicate which follow-up visit this SCIM™ was completed during:

- ☐ Acute Care Discharge
☐ Rehabilitation Discharge
☐ 3-month
☐ 6-month
☐ 12-month

2b. Is this SCIM™ based on examination or interview?

- ☐ Examination
☐ Interview

☐ ASSESSMENT NOT OBTAINED (STOP)

SPINAL CORD INDEPENDENCE MEASURE (SCIM™)

Self-Care

3. Feeding	0 1 2 3
4A. Bathing Upper Body	0 1 2 3
4B. Bathing Lower Body	0 1 2 3
5A. Dressing Upper Body	0 1 2 3
5B. Dressing Lower Body	0 1 2 3
6. Grooming	0 1 2 3 4

Respiration and Sphincter Management

7. Respiration	0 2 4 6 8 10
8. Sphincter Management/Bladder	0 4 8 12 15
9. Sphincter Management/Bowel	0 5 10
10. Use of Toilet	0 1 2 3 4 5

19. Subtotal (0-59)

Mobility (room and toilet)

11. Mobility in Bed and Action to Prevent Pressure Sores	0 1 2 3 4 5 6
12. Transfers: bed-wheelchair	0 1 2
13. Transfers: wheelchair-toilet-tub	0 1 2

Mobility (indoors and outdoors)

14. Mobility Indoors	0 1 2 3 4 5 6 7 8
15. Mobility for Moderate Dist.	0 1 2 3 4 5 6 7 8
16. Mobility Outdoors	0 1 2 3 4 5 6 7 8
17. Stair Management	0 1 2 3
18. Transfers: wheelchair-car	0 1 2 3

20. Subtotal (0-40)

21. Total SCIM™ Score (0-100)

22. Who completed the examination or interview?

- ☐ Therapist
☐ Study Coordinator
☐ Physician
☐ Other _____

Quality of Life Assessment Tool

Order	Context/Stem/ Question	Responses	Parent Study
1	Does this statement apply to you? I walk at least some of the time.	0=No 1=Yes	SCI-CAT
2	Does this statement apply to you? I use a cane, walker, or other walking device at least some of the time.	0=No 1=Yes	SCI-CAT
3	Does this statement apply to you? I use a manual wheelchair at least some of the time.	0=No 1=Yes	SCI-CAT
4	Does this statement apply to you? I use a power wheelchair at least some of the time.	0=No 1=Yes	SCI-CAT
5	How much DIFFICULTY do you currently have standing up from an armless straight chair (e.g., dining room chair)?	5=No Difficulty 4=A Little Difficulty 3=Some Difficulty 2=A Lot of Difficulty 1=Can't Do	SCI-CAT
6	How much DIFFICULTY do you currently have sitting down on and standing up from a chair with arms?	5=No Difficulty 4=A Little Difficulty 3=Some Difficulty 2=A Lot of Difficulty 1=Can't Do	SCI-CAT
7	How much DIFFICULTY do you currently have moving from sitting at the side of the bed to lying down on your back?	5=No Difficulty 4=A Little Difficulty 3=Some Difficulty 2=A Lot of Difficulty 1=Can't Do	SCI-CAT
8	How much DIFFICULTY do you currently have standing up from a low, soft couch?	5=No Difficulty 4=A Little Difficulty 3=Some Difficulty 2=A Lot of Difficulty 1=Can't Do	SCI-CAT
9	How much DIFFICULTY do you currently have going up and down a flight of stairs inside, using a handrail?	5=No Difficulty 4=A Little Difficulty 3=Some Difficulty 2=A Lot of Difficulty 1=Can't Do	SCI-CAT
10	How much DIFFICULTY do you currently have walking on uneven surfaces (e.g., grass, dirt road or sidewalk)?	5=No Difficulty 4=A Little Difficulty 3=Some Difficulty 2=A Lot of Difficulty 1=Can't Do	SCI-CAT
11	How much DIFFICULTY do you currently have walking around one floor of your home?	5=No Difficulty 4=A Little Difficulty 3=Some Difficulty 2=A Lot of Difficulty 1=Can't Do	SCI-CAT

12	How much DIFFICULTY do you currently have taking a 20-minute brisk walk, without stopping to rest?	5=No Difficulty 4=A Little Difficulty 3=Some Difficulty 2=A Lot of Difficulty 1=Can't Do	SCI-CAT
13	How much DIFFICULTY do you currently have walking on a slippery surface, outdoors?	5=No Difficulty 4=A Little Difficulty 3=Some Difficulty 2=A Lot of Difficulty 1=Can't Do	SCI-CAT
14	How much DIFFICULTY do you currently have climbing stairs step over step without a handrail? (alternating feet)?	5=No Difficulty 4=A Little Difficulty 3=Some Difficulty 2=A Lot of Difficulty 1=Can't Do	SCI-CAT
15	How much DIFFICULTY do you currently have walking in a dark room without falling?	5=No Difficulty 4=A Little Difficulty 3=Some Difficulty 2=A Lot of Difficulty 1=Can't Do	SCI-CAT
16	Are you able to push open a heavy door?	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT
17	Are you able to get in and out of a car?	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT
18	Are you able to go for a walk of at least 15 minutes?	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT
19	Are you able to step up and down curbs?	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT
20	Are you able to get up off the floor from lying on your back without help?	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT
21	Are you able to get out of bed into a chair?	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT
22	Are you able to run errands and shop?	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	DELETED FROM SCI-CAT

23	Are you able to get on and off the toilet?	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT
24	How much DIFFICULTY do you currently have sitting down on and standing up from a chair with arms with your walking aid?	5=No Difficulty 4=A Little Difficulty 3=Some Difficulty 2=A Lot of Difficulty 1=Can't Do	SCI-CAT
25	How much DIFFICULTY do you currently have walking on uneven surfaces (e.g., grass, dirt road or sidewalk) with your walking aid?	5=No Difficulty 4=A Little Difficulty 3=Some Difficulty 2=A Lot of Difficulty 1=Can't Do	SCI-CAT
26	How much DIFFICULTY do you currently have sitting down or standing up from a low, soft couch with your walking aid?	5=No Difficulty 4=A Little Difficulty 3=Some Difficulty 2=A Lot of Difficulty 1=Can't Do	SCI-CAT
27	How much DIFFICULTY do you currently have going up and down three flights of stairs inside, using a handrail with your walking aid?	5=No Difficulty 4=A Little Difficulty 3=Some Difficulty 2=A Lot of Difficulty 1=Can't Do	SCI-CAT
28	How much DIFFICULTY do you currently have going up and down a flight of stairs inside, using a handrail with your walking aid?	5=No Difficulty 4=A Little Difficulty 3=Some Difficulty 2=A Lot of Difficulty 1=Can't Do	SCI-CAT
29	How much DIFFICULTY do you currently have getting into and out of a truck, bus, shuttle van, or sport utility vehicle with your walking aid?	5=No Difficulty 4=A Little Difficulty 3=Some Difficulty 2=A Lot of Difficulty 1=Can't Do	DELETED FROM SCI-CAT
30	How much DIFFICULTY do you currently have descending 3-5 stairs without a handrail with your walking aid?	5=No Difficulty 4=A Little Difficulty 3=Some Difficulty 2=A Lot of Difficulty 1=Can't Do	SCI-CAT
31	Are you able to go for a walk of at least 15 minutes with your walking aid?	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT
32	Are you able to get in and out of a car with your walking aid?	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	DELETED FROM SCI-CAT
33	How much DIFFICULTY do you currently have sitting down on an armless straight chair, using a wheelchair?	5=No Difficulty 4=A Little Difficulty 3=Some Difficulty 2=A Lot of Difficulty 1=Can't Do	SCI-CAT

34	How much DIFFICULTY do you currently have propelling / driving a wheelchair for at least 15 minutes?	5=No Difficulty 4=A Little Difficulty 3=Some Difficulty 2=A Lot of Difficulty 1=Can't Do	SCI-CAT
35	How much DIFFICULTY do you currently have getting into and out of a truck, bus, shuttle van, or sport utility vehicle from a wheelchair?	5=No Difficulty4=A Little Difficulty3=Some Difficulty2=A Lot of Difficulty1=Can't Do	SCI-CAT
36	Are you able to get in and out of a car from a wheelchair?	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT
37	For this section, please respond with how much difficulty you have WITHOUT the use of any kind of device or assistance. If you are not able to do the activity without a device or assistance, please respond "Unable to Do" or "Can't Do".	n/a	n/a
38	Are you able to move your upper body while lying down in bed?	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT
39	When I am in bed, I can roll from my back to my side...	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT
40	When you are in bed, are you able to turn your lower body?	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT
41	Are you able to move from lying down to sitting up (legs straight in front) in a regular bed?	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT
42	How much difficulty do you currently have moving from lying on your back to sitting on the side of the bed?	5=No Difficulty 4=A Little Difficulty 3=Some Difficulty 2=A Lot of Difficulty 1=Can't Do	DELETED FROM SCI-CAT
43	Are you able to sit in a chair with a firm seat and a back when you can use your arms for support?	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT

44	Are you able to sit in a chair with a firm seat and a back, when you can't use your arms for support?	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT
45	Are you able to sit on a bench without a back, when you are able to use your arms for support?	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT
46	Are you able to sit on a bench without a back, when you can't use your arms for support?	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT
47	Are you able to sit in a car going around a corner, without losing your balance?	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT
48	Are you able to reach for a book on a table when sitting in a chair with a firm seat and a back?	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT
49	When sitting, are you able to reach over your head to take a book off a shelf while using one arm for support?	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	DELETED FROM SCI-CAT
50	When sitting, are you able to reach down to pick up a shoe from the floor while using one arm for support?	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT
51	Are you able to stand without any support for 1 minute, for example, long enough to brush your teeth?	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT
52	Are you able to stand without any support for 5 minutes, for example, long enough to wash dishes?	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT
53	How much difficulty do you currently have sitting down on a low, soft couch?	5=No Difficulty 4=A Little Difficulty 3=Some Difficulty 2=A Lot of Difficulty 1=Can't Do	SCI-CAT
54	When transferring into bed, are you able to get your legs onto the bed?	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT

55	Are you able to get out of a chair into bed?	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT
56	I can move on to a shower chair...	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT
57	I can move off of a shower chair...	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT
58	Are you able to get on and off the toilet without an elevated toilet seat?	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT
59	Are you able to get down on the floor (e.g., to play with a child or pet)?	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT
60	I can move into a tub...	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT
61	I can move out of a tub...	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT
62	Are you able to crawl on the floor?	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT
63	I can take a step with each foot...	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT
64	Are you able to walk for 5 minutes inside?	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT
65	Are you able to walk for 5 minutes outside?	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT

66	How much difficulty do you currently have going up and down three flights of stairs inside, using a handrail?	5=No Difficulty 4=A Little Difficulty 3=Some Difficulty 2=A Lot of Difficulty 1=Can't Do	SCI-CAT
67	I can walk up a ramp or steep hill...	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT
68	I can walk down a ramp or steep hill...	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT
69	How much difficulty do you currently have stopping when walking at a brisk pace?	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT
70	How much difficulty do you currently have walking 45 minutes on an even surface?	5=No Difficulty 4=A Little Difficulty 3=Some Difficulty 2=A Lot of Difficulty 1=Can't Do	SCI-CAT
71	Are you able to go up and down 3 steps, using a handrail?	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT
72	I can hold a door open while moving into a room...	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT
73	Are you able to jump up and down?	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT
74	I can walk on a dirt path or hiking trail...	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT
75	Are you able to run for 5 minutes?	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT
76	How much difficulty do you currently have crossing the road at a 4-lane traffic light with curbs?	5=No Difficulty 4=A Little Difficulty 3=Some Difficulty 2=A Lot of Difficulty 1=Can't Do	SCI-CAT

77	How much difficulty do you currently have walking in a busy place (e.g. crowded store) without losing your balance?	5=No Difficulty 4=A Little Difficulty 3=Some Difficulty 2=A Lot of Difficulty 1=Can't Do	SCI-CAT
78	When in my bed, I can roll from my back onto my belly...	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT
79	For the next section, please respond with how much difficulty you have doing the activity with a WALKING DEVICE. Please think about whatever walking device (cane, walker, etc.) you use most often. If you don't use a walking device, please do your best to imagine how much difficulty you WOULD have if you TRIED to do the activity with a walking device.	n/a	n/a
80	How much difficulty do you currently have sitting down on and standing up from a chair with arms with your walking aid?	5=No Difficulty 4=A Little Difficulty 3=Some Difficulty 2=A Lot of Difficulty 1=Can't Do	SCI-CAT
81	Are you able to walk from room-to-room in your house with your walking aid?	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT
82	Are you able to walk from your car into a building with your walking aid?	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT
83	For the next section, please respond with how much difficulty you have doing the activity with a MANUAL WHEELCHAIR. If you don't use a manual wheelchair, please do your best to imagine how much difficulty you WOULD have if you TRIED to do the activity with a manual wheelchair.	n/a	SCI-CAT
84	How much difficulty do you currently have standing up from an armless straight chair, using a wheelchair?	5=No Difficulty 4=A Little Difficulty 3=Some Difficulty 2=A Lot of Difficulty 1=Can't Do	DELETED FROM SCI-CAT

85	Are you able to transfer from your chair to a shower bench in a standard bathtub?	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT
86	Are you able to transfer from a shower bench in a standard tub to your chair?	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT
87	Are you able to get on and off the toilet from your wheelchair?	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT
88	Are you able to put your wheelchair in the car?	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT
89	On a flat surface, I can stop my manual wheelchair before I hit something...	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT
90	In my manual wheelchair, I can turn corners indoors without hitting walls...	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT
91	In my manual wheelchair, I can lean forward to reach for something in front of me...	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT
92	I can push my manual wheelchair in a busy hallway with a lot of people...	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT
93	I can push my manual wheelchair all day...	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT
94	Are you able to propel your wheelchair on a rough gravel driveway?	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT
95	I can push my manual wheelchair on a rug...	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT

96	Are you able to push your chair over rough or uneven surfaces?	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT
97	In your manual wheelchair, are you able to go up and down a slight incline?	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT
98	In my manual wheelchair, I can cross the street at a traffic light...	5=Without any difficulty4=With a little difficulty3=With some difficulty2=With much difficulty1=Unable to do	SCI-CAT
99	I can push my manual wheelchair down a ramp...	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT
100	I can push my manual wheelchair up a ramp...	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT
101	I can push my manual wheelchair down a curb...	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT
102	I can push my manual wheelchair up a curb...	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT
103	How much difficulty do you currently have using a spoon to eat a meal?	5=No Difficulty 4=A Little Difficulty 3=Some Difficulty 2=A Lot of Difficulty 1=Can't Do	SCI-CAT
104	How much difficulty do you currently have putting on a pullover shirt?	5=No Difficulty 4=A Little Difficulty 3=Some Difficulty 2=A Lot of Difficulty 1=Can't Do	SCI-CAT
105	How much difficulty do you currently have taking off a pullover shirt?	5=No Difficulty 4=A Little Difficulty 3=Some Difficulty 2=A Lot of Difficulty 1=Can't Do	SCI-CAT
106	How much difficulty do you currently have removing wrappings from small objects?	5=No Difficulty 4=A Little Difficulty 3=Some Difficulty 2=A Lot of Difficulty 1=Can't Do	SCI-CAT

107	How much difficulty do you currently have opening medications or vitamin containers (e.g., childproof containers, small bottles)?	5=No Difficulty 4=A Little Difficulty 3=Some Difficulty 2=A Lot of Difficulty 1=Can't Do	SCI-CAT
108	Are you able to open previously opened jars?	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	DELETED FROM SCI-CAT
109	Are you able to brush your teeth?	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT
110	Are you able to hold a plate full of food?	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT
111	Are you able to open and close a zipper?	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT
112	Are you able to turn a key in a lock?	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT
113	Are you able to write with a pen or pencil?	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT
114	Are you able to pull on trousers?	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT
115	Are you able to button your shirt?	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	DELETED FROM SCI-CAT
116	Are you able to wash and dry your body?	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT
117	Are you able to pick up coins from a table top?	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT

118	Are you able to shampoo your hair?	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT
119	Are you able to trim your fingernails?	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	DELETED FROM SCI-CAT
120	Are you able to cut your toe nails?	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT
121	Are you able to bend down and pick up clothing from the floor?	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	DELETED FROM SCI-CAT
122	Are you able to make a phone call using a touch tone key-pad?	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT
123	Are you able to hold a small child in your arms?	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT
124	How much difficulty do you currently have picking up a gallon carton of milk with one hand and setting it on the table?	5=No Difficulty 4=A Little Difficulty 3=Some Difficulty 2=A Lot of Difficulty 1=Can't Do	SCI-CAT
125	I can pour from a large bottle of milk.	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	DELETED FROM SCI-CAT
126	Are you able to use one hand to lift a gallon container with a jug handle and pour liquid into a glass?	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	DELETED FROM SCI-CAT
127	Are you able to reach to take a box of cereal from the top shelf at the grocery store?	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT
128	Are you able to push a shopping cart?	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT

129	Are you able to drive from a regular car seat?	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	SCI-CAT
130	Are you able to drive for long distances?	5=Without any difficulty4=With a little difficulty3=With some difficulty2=With much difficulty1=Unable to do	DELETED FROM SCI-CAT
131	Are you able to use public transportation?	5=Without any difficulty 4=With a little difficulty 3=With some difficulty 2=With much difficulty 1=Unable to do	DELETED FROM SCI-CAT
132	How much difficulty do you currently have getting into and out of a truck, bus, shuttle van, or sport utility vehicle?	5=No Difficulty 4=A Little Difficulty 3=Some Difficulty 2=A Lot of Difficulty 1=Can't Do	DELETED FROM SCI-CAT
133	In the past 7 days How much did pain interfere with your day to day activities?	1=Not at all 2=A little bit 3=Somewhat 4=Quite a bit 5=Very much	SCI-QOL
134	In the past 7 days How much did pain interfere with your ability to concentrate?	1=Not at all 2=A little bit 3=Somewhat 4=Quite a bit 5=Very much	DELETED FROM SCI-QOL
135	In the past 7 days How much did pain interfere with your enjoyment of recreational activities?	1=Not at all 2=A little bit 3=Somewhat 4=Quite a bit 5=Very much	DELETED FROM SCI-QOL
136	In the past 7 days How much did pain interfere with doing your tasks away from home (e.g., getting groceries, running errands)?	1=Not at all 2=A little bit 3=Somewhat 4=Quite a bit 5=Very much	DELETED FROM SCI-QOL
137	In the past 7 days How much did pain interfere with your enjoyment of life?	1=Not at all 2=A little bit 3=Somewhat 4=Quite a bit 5=Very much	SCI-QOL
138	In the past 7 days How often did pain keep you from socializing with others?	1=Never 2=Rarely 3=Sometimes 4=Often 5=Always	DELETED FROM SCI-QOL

139	In the past 7 days When I was in pain I became irritable	1=Had no pain 2=Never 3=Rarely 4=Sometimes 5=Often 6=Always	DELETED FROM SCI-QOL
140	In the past 7 days When I was in pain I grimaced	1=Had no pain 2=Never 3=Rarely 4=Sometimes 5=Often 6=Always	DELETED FROM SCI-QOL
141	In the past 7 days When I was in pain I moved extremely slowly	1=Had no pain 2=Never 3=Rarely 4=Sometimes 5=Often 6=Always	DELETED FROM SCI-QOL
142	In the past 7 days When I was in pain I moved stiffly	1=Had no pain 2=Never 3=Rarely 4=Sometimes 5=Often 6=Always	DELETED FROM SCI-QOL
143	In the past 7 days When I was in pain I called out for someone to help me	1=Had no pain 2=Never 3=Rarely 4=Sometimes 5=Often 6=Always	DELETED FROM SCI-QOL
144	In the past 7 days When I was in pain I isolated myself from others	1=Had no pain 2=Never 3=Rarely 4=Sometimes 5=Often 6=Always	DELETED FROM SCI-QOL
145	In the past 7 days When I was in pain I thrashed	1=Had no pain 2=Never 3=Rarely 4=Sometimes 5=Often 6=Always	DELETED FROM SCI-QOL
146	In the past 7 days I had a burning/tingling sensation at or below the level of my injury.	1=Never 2=Rarely 3=Sometimes 4=Often 5=Always	DELETED FROM SCI-QOL
147	In the past 7 days I had pain.	1=Never 2=Rarely 3=Sometimes 4=Often 5=Always	DELETED FROM SCI-QOL

148	In the past 7 days... My life was negatively affected by pain.	1=Never 2=Rarely 3=Sometimes 4=Often 5=Always	DELETED FROM SCI- QOL
149	In the past 7 days I had bone pain.	1=Never 2=Rarely 3=Sometimes 4=Often 5=Always	DELETED FROM SCI- QOL
150	In the past 7 days How often was your pain so severe you could think of nothing else?	1=Never 2=Rarely 3=Sometimes 4=Often 5=Always	SCI-QOL
151	In the past 7 days I had neurogenic pain.	1=Never 2=Rarely 3=Sometimes 4=Often 5=Always	DELETED FROM SCI- QOL
152	In the past 7 days How often did pain make simple tasks hard to complete?	1=Never 2=Rarely 3=Sometimes 4=Often 5=Always	SCI-QOL
153	In the past 7 days Shoulder pain interfered with my ability to do things.	1=Not at all 2=A little bit 3=Somewhat 4=Quite a bit 5=Very much	SCI-QOL
154	In the past 7 days Muscle pain interfered with my daily activities.	1=Not at all 2=A little bit 3=Somewhat 4=Quite a bit 5=Very much	SCI-QOL
155	In the past 7 days Neck pain interfered with my ability to do things.	1=Not at all 2=A little bit 3=Somewhat 4=Quite a bit 5=Very much	DELETED FROM SCI- QOL
156	In the past 7 days Back pain interfered with my ability to do things.	1=Not at all 2=A little bit 3=Somewhat 4=Quite a bit 5=Very much	SCI-QOL
157	In the past 7 days I experienced excruciating pain.	1=Never 2=Rarely 3=Sometimes 4=Often 5=Always	SCI-QOL
158	In the past 7 days I had muscle pain.	1=Never 2=Rarely 3=Sometimes 4=Often 5=Always	DELETED FROM SCI- QOL

159	Lately Bladder management interfered with my sleep.	1=Not at all 2=A little bit 3=Somewhat 4=Quite a bit 5=Very much	SCI-QOL
160	Lately I worried that I would have a bladder accident.	1=Not at all 2=A little bit 3=Somewhat 4=Quite a bit 5=Very much	SCI-QOL
161	Lately I was confident in my ability to follow a bladder emptying program.	1=Not at all2=A little bit3=Somewhat4=Quite a bit5=Very much	DELETED FROM SCI-QOL
162	Lately I was able to maintain my bladder program.	1=Not at all 2=A little bit 3=Somewhat 4=Quite a bit 5=Very much	DELETED FROM SCI-QOL
163	Lately A UTI (urinary tract infection) limited my daily activities.	1=Not at all 2=A little bit 3=Somewhat 4=Quite a bit 5=Very much	SCI-QOL
164	Lately I had an increase in spasms because of a UTI (urinary tract infection).	1=Not at all 2=A little bit 3=Somewhat 4=Quite a bit 5=Very much	SCI-QOL
165	Lately Bladder accidents limited my independence.	1=Not at all 2=A little bit 3=Somewhat 4=Quite a bit 5=Very much	SCI-QOL
166	Lately I was bothered by urine leakage.	1=Not at all 2=A little bit 3=Somewhat 4=Quite a bit 5=Very much	SCI-QOL
167	Lately I restricted my fluid intake in order to manage my bladder.	1=Never 2=Rarely 3=Sometimes 4=Often 5=Always	DELETED FROM SCI-QOL
168	Lately I took steps to prevent a urinary tract infection (UTI).	1=Never 2=Rarely 3=Sometimes 4=Often 5=Always	DELETED FROM SCI-QOL
169	Lately I had trouble with urine backing up into my kidneys.	1=Never 2=Rarely 3=Sometimes 4=Often 5=Always	DELETED FROM SCI-QOL

170	Lately I had a urinary tract infection (UTI).	1=Never 2=Rarely 3=Sometimes 4=Often 5=Always	DELETED FROM SCI-QOL
171	Lately I had trouble with kidney stones.	1=Never 2=Rarely 3=Sometimes 4=Often 5=Always	DELETED FROM SCI-QOL
172	Lately I had to depend on others for help with my bladder program.	1=Never 2=Rarely 3=Sometimes 4=Often 5=Always	DELETED FROM SCI-QOL
173	Lately Bladder accidents have disrupted my daily activities.	1=Never 2=Rarely 3=Sometimes 4=Often 5=Always	SCI-QOL
174	Lately I had a urinary tract infection (UTI) that would not go away.	1=Never 2=Rarely 3=Sometimes 4=Often 5=Always	SCI-QOL
175	Lately I had bladder accidents.	1=Never 2=Rarely 3=Sometimes 4=Often 5=Always	SCI-QOL
176	Lately Bowel accidents limited my independence.	1=Not at all 2=A little bit 3=Somewhat 4=Quite a bit 5=Very much	SCI-QOL
177	Lately I felt confident in my ability to manage my bowel program.	1=Not at all 2=A little bit 3=Somewhat 4=Quite a bit 5=Very much	DELETED FROM SCI-QOL
178	Lately I was embarrassed by my flatulence.	1=Not at all 2=A little bit 3=Somewhat 4=Quite a bit 5=Very much	DELETED FROM SCI-QOL
179	Lately I was bothered by abdominal pain.	1=Not at all 2=A little bit 3=Somewhat 4=Quite a bit 5=Very much	SCI-QOL
180	Lately I was upset because of problems with my bowel functioning.	1=Not at all 2=A little bit 3=Somewhat 4=Quite a bit 5=Very much	SCI-QOL

181	Lately Bowel care interfered with my sleep.	1=Never 2=Rarely 3=Sometimes 4=Often 5=Always	SCI-QOL
182	Lately Bowel accidents have disrupted my daily activities.	1=Never 2=Rarely 3=Sometimes 4=Often 5=Always	SCI-QOL
183	Lately I had bowel accidents	1=Never 2=Rarely 3=Sometimes 4=Often 5=Always	SCI-QOL
184	Lately I was able to have a regular bowel movement.	1=Never 2=Rarely 3=Sometimes 4=Often 5=Always	DELETED FROM SCI- QOL
185	Lately I was successful in maintaining my bowel program.	1=Never 2=Rarely 3=Sometimes 4=Often 5=Always	DELETED FROM SCI- QOL
186	Lately I had to stop what I was doing because of a bowel accident.	1=Never 2=Rarely 3=Sometimes 4=Often 5=Always	SCI-QOL
187	Lately I was able to manage my bowels.	1=Never 2=Rarely 3=Sometimes 4=Often 5=Always	DELETED FROM SCI- QOL
188	Lately I avoided going out in public because of my bowel program.	1=Never 2=Rarely 3=Sometimes 4=Often 5=Always	SCI-QOL
189	Lately I worried that a bowel accident would disrupt my ability to work.	1=Never 2=Rarely 3=Sometimes 4=Often 5=Always	SCI-QOL
190	Lately I worried that my social activities will be interrupted by a bowel accident.	1=Never 2=Rarely 3=Sometimes 4=Often 5=Always	DELETED FROM SCI- QOL
191	Lately I had recurrent respiratory tract infections.	1=Never 2=Rarely 3=Sometimes 4=Often 5=Always	SCI-QOL - TABLED

192	Lately I experienced wheezing during exercise.	1=Never 2=Rarely 3=Sometimes 4=Often 5=Always	SCI-QOL - TABLED
193	Lately I had shortness of breath during normal activities.	1=Never2=Rarely3=Sometimes4=Often5=Always	SCI-QOL - TABLED
194	Lately I had to stop what I was doing to catch my breath.	1=Never 2=Rarely 3=Sometimes 4=Often 5=Always	SCI-QOL - TABLED
195	Lately I was able to expand my chest enough to fill my lungs with air.	1=Never 2=Rarely 3=Sometimes 4=Often 5=Always	SCI-QOL - TABLED
196	Lately I coughed during exercise.	1=Never 2=Rarely 3=Sometimes 4=Often 5=Always	SCI-QOL - TABLED
197	Lately I had pneumonia.	1=Never 2=Rarely 3=Sometimes 4=Often 5=Always	SCI-QOL - TABLED
198	Lately I felt lightheaded because of shortness of breath.	1=Never 2=Rarely 3=Sometimes 4=Often 5=Always	SCI-QOL - TABLED
199	Lately I experienced wheezing during normal breathing.	1=Never 2=Rarely 3=Sometimes 4=Often 5=Always	SCI-QOL - TABLED
200	Lately I was able to cough.	1=Never 2=Rarely 3=Sometimes 4=Often 5=Always	SCI-QOL - TABLED
201	Lately I had difficulty speaking because of shortness of breath.	1=Never 2=Rarely 3=Sometimes 4=Often 5=Always	SCI-QOL - TABLED
202	Lately I was able to cough as forcefully as I needed to.	1=Never 2=Rarely 3=Sometimes 4=Often 5=Always	SCI-QOL - TABLED

203	Lately My respiratory problems interfered with my daily activities.	1=Never 2=Rarely 3=Sometimes 4=Often 5=Always	SCI-QOL - TABLED
204	Lately I had trouble coughing.	1=Never 2=Rarely 3=Sometimes 4=Often 5=Always	SCI-QOL - TABLED
205	Lately My respiratory functioning was impaired.	1=Never 2=Rarely 3=Sometimes 4=Often 5=Always	SCI-QOL - TABLED
206	Lately I had shortness of breath during exercise.	1=Never 2=Rarely 3=Sometimes 4=Often 5=Always	SCI-QOL - TABLED
207	Lately I was hospitalized due to a respiratory problem.	1=Never 2=Rarely 3=Sometimes 4=Often 5=Always	SCI-QOL - TABLED
208	Lately My respiratory problems interfered with my sleep.	1=Not at all 2=A little bit 3=Somewhat 4=Quite a bit 5=Very much	SCI-QOL - TABLED
209	Lately I was limited in my exercise routine because of respiratory problems.	1=Not at all 2=A little bit 3=Somewhat 4=Quite a bit 5=Very much	SCI-QOL - TABLED
210	Lately My respiratory problems interfered with my ability to work.	1=Not at all 2=A little bit 3=Somewhat 4=Quite a bit 5=Very much	SCI-QOL
211	In the past 7 days I can keep up with my family responsibilities	1=Never 2=Rarely 3=Sometimes 4=Often 5=Always	SCI-QOL
212	In the past 7 days I am able to do all of my regular family activities	1=Never 2=Rarely 3=Sometimes 4=Often 5=Always	SCI-QOL
213	In the past 7 days I am able to socialize with my friends	1=Never 2=Rarely 3=Sometimes 4=Often 5=Always	SCI-QOL

214	In the past 7 days I am able to do all of my regular activities with friends	1=Never 2=Rarely 3=Sometimes 4=Often 5=Always	SCI-QOL
215	In the past 7 days I can keep up with my social commitments	1=Never 2=Rarely 3=Sometimes 4=Often 5=Always	SCI-QOL
216	In the past 7 days I am able to participate in leisure activities	1=Never 2=Rarely 3=Sometimes 4=Often 5=Always	SCI-QOL
217	In the past 7 days I am able to perform my daily routines	1=Never 2=Rarely 3=Sometimes 4=Often 5=Always	SCI-QOL
218	In the past 7 days I can keep up with my work responsibilities (include work at home)	1=Never 2=Rarely 3=Sometimes 4=Often 5=Always	SCI-QOL
219	In the past 7 days I am bothered by my limitations in regular family activities	1=Not at all 2=A little bit 3=Somewhat 4=Quite a bit 5=Very much	SCI-QOL
220	In the past 7 days I am disappointed in my ability to socialize with my family	1=Not at all 2=A little bit 3=Somewhat 4=Quite a bit 5=Very much	SCI-QOL
221	In the past 7 days I am bothered by limitations in my regular activities with friends	1=Not at all 2=A little bit 3=Somewhat 4=Quite a bit 5=Very much	SCI-QOL
222	In the past 7 days I am disappointed in my ability to meet the needs of my friends	1=Not at all 2=A little bit 3=Somewhat 4=Quite a bit 5=Very much	SCI-QOL
223	In the past 7 days I am satisfied with my ability to do things for fun outside my home	1=Not at all 2=A little bit 3=Somewhat 4=Quite a bit 5=Very much	SCI-QOL
224	In the past 7 days I am satisfied with the amount of time I spend doing leisure activities	1=Not at all 2=A little bit 3=Somewhat 4=Quite a bit 5=Very much	SCI-QOL

225	In the past 7 days I am satisfied with how much of my work I can do (include work at home)	1=Not at all2=A little bit3=Somewhat4=Quite a bit5=Very much	DELETED FROM SCI-QOL
226	In the past 7 days I am satisfied with my ability to do household chores or tasks	1=Not at all 2=A little bit 3=Somewhat 4=Quite a bit 5=Very much	SCI-QOL
227	I participate in activities that I choose.	1=Almost Never 2=Seldom 3=Sometimes 4=Frequently 5=All the time	SCI-QOL - TABLED
228	I have choices about the activities that I do.	1=Almost Never 2=Seldom 3=Sometimes 4=Frequently 5=All the time	SCI-QOL - TABLED
229	I do things that are important to me.	1=Almost Never 2=Seldom 3=Sometimes 4=Frequently 5=All the time	SCI-QOL - TABLED
230	I am able to go out and have fun.	1=Almost Never 2=Seldom 3=Sometimes 4=Frequently 5=All the time	SCI-QOL - TABLED
231	I participate in a variety of activities.	1=Almost Never 2=Seldom 3=Sometimes 4=Frequently 5=All the time	SCI-QOL - TABLED
232	In the past 7 days I depend on other people to do things for me.	1=Never 2=Rarely 3=Sometimes 4=Often 5=Always	SCI-QOL
233	In the past 7 days I am able to do things without help from other people.	1=Never 2=Rarely 3=Sometimes 4=Often 5=Always	SCI-QOL
234	In the past 7 days My family helps me more than I would like.	1=Never 2=Rarely 3=Sometimes 4=Often 5=Always	DELETED FROM SCI-QOL
235	In the past 7 days I am able to live alone.	1=Never 2=Rarely 3=Sometimes 4=Often 5=Always	DELETED FROM SCI-QOL

236	In the past 7 days I am dependent on other people.	1=Never 2=Rarely 3=Sometimes 4=Often 5=Always	DELETED FROM SCI-QOL
237	In the past 7 days I have to depend on other people to get where I want to go.	1=Never 2=Rarely 3=Sometimes 4=Often 5=Always	SCI-QOL
238	In the past 7 days I can take care of myself.	1=Never 2=Rarely 3=Sometimes 4=Often 5=Always	DELETED FROM SCI-QOL
239	In the past 7 days I am in control of my daily activities.	1=Never 2=Rarely 3=Sometimes 4=Often 5=Always	SCI-QOL
240	How SATISFIED are you with: Your health?	1=Very Dissatisfied 2=Moderately Dissatisfied 3=Slightly Dissatisfied 4=Slightly Satisfied 5=Moderately Satisfied 6=Very Satisfied	QLI - Satisfaction
241	How SATISFIED are you with: Your health care?	1=Very Dissatisfied 2=Moderately Dissatisfied 3=Slightly Dissatisfied 4=Slightly Satisfied 5=Moderately Satisfied 6=Very Satisfied	QLI - Satisfaction
242	How SATISFIED are you with: The amount of pain that you have?	1=Very Dissatisfied 2=Moderately Dissatisfied 3=Slightly Dissatisfied 4=Slightly Satisfied 5=Moderately Satisfied 6=Very Satisfied	QLI - Satisfaction
243	How SATISFIED are you with: The amount of energy you have for everyday activities?	1=Very Dissatisfied 2=Moderately Dissatisfied 3=Slightly Dissatisfied 4=Slightly Satisfied 5=Moderately Satisfied 6=Very Satisfied	QLI - Satisfaction
244	How SATISFIED are you with: Your ability to take care of yourself without help?	1=Very Dissatisfied 2=Moderately Dissatisfied 3=Slightly Dissatisfied 4=Slightly Satisfied 5=Moderately Satisfied 6=Very Satisfied	QLI - Satisfaction

245	How SATISFIED are you with: Your ability to go places outside your home?	1=Very Dissatisfied 2=Moderately Dissatisfied 3=Slightly Dissatisfied 4=Slightly Satisfied 5=Moderately Satisfied 6=Very Satisfied	QLI - Satisfaction
246	How SATISFIED are you with: Your ability to clear your lungs?	1=Very Dissatisfied 2=Moderately Dissatisfied 3=Slightly Dissatisfied 4=Slightly Satisfied 5=Moderately Satisfied 6=Very Satisfied	QLI - Satisfaction
247	How SATISFIED are you with: The amount of control you have over your life?	1=Very Dissatisfied 2=Moderately Dissatisfied 3=Slightly Dissatisfied 4=Slightly Satisfied 5=Moderately Satisfied 6=Very Satisfied	QLI - Satisfaction
248	How SATISFIED are you with: Your chances of living as long as you would like?	1=Very Dissatisfied 2=Moderately Dissatisfied 3=Slightly Dissatisfied 4=Slightly Satisfied 5=Moderately Satisfied 6=Very Satisfied	QLI - Satisfaction
249	How SATISFIED are you with: Your sex life?	1=Very Dissatisfied 2=Moderately Dissatisfied 3=Slightly Dissatisfied 4=Slightly Satisfied 5=Moderately Satisfied 6=Very Satisfied	QLI - Satisfaction
250	How SATISFIED are you with: Your ability to take care of family responsibilities?	1=Very Dissatisfied 2=Moderately Dissatisfied 3=Slightly Dissatisfied 4=Slightly Satisfied 5=Moderately Satisfied 6=Very Satisfied	QLI - Satisfaction
251	How SATISFIED are you with: How useful you are to others?	1=Very Dissatisfied 2=Moderately Dissatisfied 3=Slightly Dissatisfied 4=Slightly Satisfied 5=Moderately Satisfied 6=Very Satisfied	QLI - Satisfaction
252	How SATISFIED are you with: The amount of worries in your life?	1=Very Dissatisfied 2=Moderately Dissatisfied 3=Slightly Dissatisfied 4=Slightly Satisfied 5=Moderately Satisfied 6=Very Satisfied	QLI - Satisfaction
253	How SATISFIED are you with: The things you do for fun?	1=Very Dissatisfied 2=Moderately Dissatisfied 3=Slightly Dissatisfied 4=Slightly Satisfied 5=Moderately Satisfied 6=Very Satisfied	QLI - Satisfaction

254	How SATISFIED are you with: Your chances for a happy future?	1=Very Dissatisfied 2=Moderately Dissatisfied 3=Slightly Dissatisfied 4=Slightly Satisfied 5=Moderately Satisfied 6=Very Satisfied	QLI - Satisfaction
255	How SATISFIED are you with: Your family's health?	1=Very Dissatisfied 2=Moderately Dissatisfied 3=Slightly Dissatisfied 4=Slightly Satisfied 5=Moderately Satisfied 6=Very Satisfied	QLI - Satisfaction
256	How SATISFIED are you with: Your children?	1=Very Dissatisfied 2=Moderately Dissatisfied 3=Slightly Dissatisfied 4=Slightly Satisfied 5=Moderately Satisfied 6=Very Satisfied	QLI - Satisfaction
257	How SATISFIED are you with: Your ability to have children?	1=Very Dissatisfied 2=Moderately Dissatisfied 3=Slightly Dissatisfied 4=Slightly Satisfied 5=Moderately Satisfied 6=Very Satisfied	QLI - Satisfaction
258	How SATISFIED are you with: Your family's happiness?	1=Very Dissatisfied 2=Moderately Dissatisfied 3=Slightly Dissatisfied 4=Slightly Satisfied 5=Moderately Satisfied 6=Very Satisfied	QLI - Satisfaction
259	How SATISFIED are you with: Your spouse, lover, or partner (if you have one)?	1=Very Dissatisfied 2=Moderately Dissatisfied 3=Slightly Dissatisfied 4=Slightly Satisfied 5=Moderately Satisfied 6=Very Satisfied	QLI - Satisfaction
260	How SATISFIED are you with: Not having a spouse, lover or partner (if you do not have one)?	1=Very Dissatisfied 2=Moderately Dissatisfied 3=Slightly Dissatisfied 4=Slightly Satisfied 5=Moderately Satisfied 6=Very Satisfied	QLI - Satisfaction
261	How SATISFIED are you with: The emotional support you get from your family?	1=Very Dissatisfied 2=Moderately Dissatisfied 3=Slightly Dissatisfied 4=Slightly Satisfied 5=Moderately Satisfied 6=Very Satisfied	QLI - Satisfaction
262	How SATISFIED are you with: Your friends?	1=Very Dissatisfied 2=Moderately Dissatisfied 3=Slightly Dissatisfied 4=Slightly Satisfied 5=Moderately Satisfied 6=Very Satisfied	QLI - Satisfaction

263	How SATISFIED are you with: The emotional support you get from people other than your family?	1=Very Dissatisfied 2=Moderately Dissatisfied 3=Slightly Dissatisfied 4=Slightly Satisfied 5=Moderately Satisfied 6=Very Satisfied	QLI - Satisfaction
264	How SATISFIED are you with: Your neighborhood?	1=Very Dissatisfied 2=Moderately Dissatisfied 3=Slightly Dissatisfied 4=Slightly Satisfied 5=Moderately Satisfied 6=Very Satisfied	QLI - Satisfaction
265	How SATISFIED are you with: Your home, apartment, or place where you live?	1=Very Dissatisfied 2=Moderately Dissatisfied 3=Slightly Dissatisfied 4=Slightly Satisfied 5=Moderately Satisfied 6=Very Satisfied	QLI - Satisfaction
266	How SATISFIED are you with: Your job (if employed)?	1=Very Dissatisfied 2=Moderately Dissatisfied 3=Slightly Dissatisfied 4=Slightly Satisfied 5=Moderately Satisfied 6=Very Satisfied	QLI - Satisfaction
267	How SATISFIED are you with: Not having a job (if unemployed, retired, or disabled)?	1=Very Dissatisfied 2=Moderately Dissatisfied 3=Slightly Dissatisfied 4=Slightly Satisfied 5=Moderately Satisfied 6=Very Satisfied	QLI - Satisfaction
268	How SATISFIED are you with: Your education?	1=Very Dissatisfied 2=Moderately Dissatisfied 3=Slightly Dissatisfied 4=Slightly Satisfied 5=Moderately Satisfied 6=Very Satisfied	QLI - Satisfaction
269	How SATISFIED are you with: How well you can take care of your financial needs?	1=Very Dissatisfied 2=Moderately Dissatisfied 3=Slightly Dissatisfied 4=Slightly Satisfied 5=Moderately Satisfied 6=Very Satisfied	QLI - Satisfaction
270	How SATISFIED are you with: Your peace of mind?	1=Very Dissatisfied 2=Moderately Dissatisfied 3=Slightly Dissatisfied 4=Slightly Satisfied 5=Moderately Satisfied 6=Very Satisfied	QLI - Satisfaction
271	How SATISFIED are you with: Your faith in God?	1=Very Dissatisfied 2=Moderately Dissatisfied 3=Slightly Dissatisfied 4=Slightly Satisfied 5=Moderately Satisfied 6=Very Satisfied	QLI - Satisfaction

272	How SATISFIED are you with: Your achievement of personal goals?	1=Very Dissatisfied 2=Moderately Dissatisfied 3=Slightly Dissatisfied 4=Slightly Satisfied 5=Moderately Satisfied 6=Very Satisfied	QLI - Satisfaction
273	How SATISFIED are you with: Your happiness in general?	1=Very Dissatisfied 2=Moderately Dissatisfied 3=Slightly Dissatisfied 4=Slightly Satisfied 5=Moderately Satisfied 6=Very Satisfied	QLI - Satisfaction
274	How SATISFIED are you with: Your life in general?	1=Very Dissatisfied 2=Moderately Dissatisfied 3=Slightly Dissatisfied 4=Slightly Satisfied 5=Moderately Satisfied 6=Very Satisfied	QLI - Satisfaction
275	How SATISFIED are you with: Your personal appearance?	1=Very Dissatisfied 2=Moderately Dissatisfied 3=Slightly Dissatisfied 4=Slightly Satisfied 5=Moderately Satisfied 6=Very Satisfied	QLI - Satisfaction
276	How SATISFIED are you with: Yourself in general?	1=Very Dissatisfied 2=Moderately Dissatisfied 3=Slightly Dissatisfied 4=Slightly Satisfied 5=Moderately Satisfied 6=Very Satisfied	QLI - Satisfaction
277	How IMPORTANT to you is: Your health?	1=Very Unimportant 2=Moderately Unimportant 3=Slightly Unimportant 4=Slightly Important 5=Moderately Important 6=Very Important	QLI - Importance
278	How IMPORTANT to you is: Your health care?	1=Very Unimportant 2=Moderately Unimportant 3=Slightly Unimportant 4=Slightly Important 5=Moderately Important 6=Very Important	QLI - Importance
279	How IMPORTANT to you is: Having no pain?	1=Very Unimportant 2=Moderately Unimportant 3=Slightly Unimportant 4=Slightly Important 5=Moderately Important 6=Very Important	QLI - Importance
280	How IMPORTANT to you is: Having enough energy for everyday activities?	1=Very Unimportant2=Moderately Unimportant3=Slightly Unimportant4=Slightly Important5=Moderately Important6=Very Important	QLI - Importance

281	How IMPORTANT to you is: Taking care of yourself without help?	1=Very Unimportant 2=Moderately Unimportant 3=Slightly Unimportant 4=Slightly Important 5=Moderately Important 6=Very Important	QLI - Importance
282	How IMPORTANT to you is: Being able to go places outside your home?	1=Very Unimportant 2=Moderately Unimportant 3=Slightly Unimportant 4=Slightly Important 5=Moderately Important 6=Very Important	QLI - Importance
283	How IMPORTANT to you is: Your ability to clear your lungs?	1=Very Unimportant 2=Moderately Unimportant 3=Slightly Unimportant 4=Slightly Important 5=Moderately Important 6=Very Important	QLI - Importance
284	How IMPORTANT to you is: Having control over your life?	1=Very Unimportant 2=Moderately Unimportant 3=Slightly Unimportant 4=Slightly Important 5=Moderately Important 6=Very Important	QLI - Importance
285	How IMPORTANT to you is: Living as long as you would like?	1=Very Unimportant 2=Moderately Unimportant 3=Slightly Unimportant 4=Slightly Important 5=Moderately Important 6=Very Important	QLI - Importance
286	How IMPORTANT to you is: Your sex life?	1=Very Unimportant 2=Moderately Unimportant 3=Slightly Unimportant 4=Slightly Important 5=Moderately Important 6=Very Important	QLI - Importance
287	How IMPORTANT to you is: Taking care of family responsibilities?	1=Very Unimportant 2=Moderately Unimportant 3=Slightly Unimportant 4=Slightly Important 5=Moderately Important 6=Very Important	QLI - Importance
288	How IMPORTANT to you is: Being useful to others?	1=Very Unimportant 2=Moderately Unimportant 3=Slightly Unimportant 4=Slightly Important 5=Moderately Important 6=Very Important	QLI - Importance
289	How IMPORTANT to you is: Having no worries?	1=Very Unimportant 2=Moderately Unimportant 3=Slightly Unimportant 4=Slightly Important 5=Moderately Important 6=Very Important	QLI - Importance

290	How IMPORTANT to you is: Doing things for fun?	1=Very Unimportant 2=Moderately Unimportant 3=Slightly Unimportant 4=Slightly Important 5=Moderately Important 6=Very Important	QLI - Importance
291	How IMPORTANT to you is: Having a happy future?	1=Very Unimportant 2=Moderately Unimportant 3=Slightly Unimportant 4=Slightly Important 5=Moderately Important 6=Very Important	QLI - Importance
292	How IMPORTANT to you is: Your family's health?	1=Very Unimportant 2=Moderately Unimportant 3=Slightly Unimportant 4=Slightly Important 5=Moderately Important 6=Very Important	QLI - Importance
293	How IMPORTANT to you is: Your children?	1=Very Unimportant2=Moderately Unimportant3=Slightly Unimportant4=Slightly Important5=Moderately Important6=Very Important	QLI - Importance
294	How IMPORTANT to you is: Being able to have children?	1=Very Unimportant 2=Moderately Unimportant 3=Slightly Unimportant 4=Slightly Important 5=Moderately Important 6=Very Important	QLI - Importance
295	How IMPORTANT to you is: Your family's happiness?	1=Very Unimportant 2=Moderately Unimportant 3=Slightly Unimportant 4=Slightly Important 5=Moderately Important 6=Very Important	QLI - Importance
296	How IMPORTANT to you is: Your spouse, lover, or partner (if you have one)?	1=Very Unimportant 2=Moderately Unimportant 3=Slightly Unimportant 4=Slightly Important 5=Moderately Important 6=Very Important	QLI - Importance
297	How IMPORTANT to you is: Having a spouse, lover, or partner (if you do not have one)?	1=Very Unimportant 2=Moderately Unimportant 3=Slightly Unimportant 4=Slightly Important 5=Moderately Important 6=Very Important	QLI - Importance
298	How IMPORTANT to you is: The emotional support you get from your family?	1=Very Unimportant 2=Moderately Unimportant 3=Slightly Unimportant 4=Slightly Important 5=Moderately Important 6=Very Important	QLI - Importance

299	How IMPORTANT to you is: Your friends?	1=Very Unimportant 2=Moderately Unimportant 3=Slightly Unimportant 4=Slightly Important 5=Moderately Important 6=Very Important	QLI - Importance
300	How IMPORTANT to you is: The emotional support you get from people other than your family?	1=Very Unimportant 2=Moderately Unimportant 3=Slightly Unimportant 4=Slightly Important 5=Moderately Important 6=Very Important	QLI - Importance
301	How IMPORTANT to you is: Your neighborhood?	1=Very Unimportant 2=Moderately Unimportant 3=Slightly Unimportant 4=Slightly Important 5=Moderately Important 6=Very Important	QLI - Importance
302	How IMPORTANT to you is: Your home, apartment, or place where you live?	1=Very Unimportant 2=Moderately Unimportant 3=Slightly Unimportant 4=Slightly Important 5=Moderately Important 6=Very Important	QLI - Importance
303	How IMPORTANT to you is: Your job (if employed)?	1=Very Unimportant 2=Moderately Unimportant 3=Slightly Unimportant 4=Slightly Important 5=Moderately Important 6=Very Important	QLI - Importance
304	How IMPORTANT to you is: Having a job (if unemployed, retired, or disabled)?	1=Very Unimportant 2=Moderately Unimportant 3=Slightly Unimportant 4=Slightly Important 5=Moderately Important 6=Very Important	QLI - Importance
305	How IMPORTANT to you is: Your education?	1=Very Unimportant 2=Moderately Unimportant 3=Slightly Unimportant 4=Slightly Important 5=Moderately Important 6=Very Important	QLI - Importance
306	How IMPORTANT to you is: Being able to take care of your financial needs?	1=Very Unimportant2=Moderately Unimportant3=Slightly Unimportant4=Slightly Important5=Moderately Important6=Very Important	QLI - Importance
307	How IMPORTANT to you is: Peace of mind?	1=Very Unimportant 2=Moderately Unimportant 3=Slightly Unimportant 4=Slightly Important 5=Moderately Important 6=Very Important	QLI - Importance

308	How IMPORTANT to you is: Your faith in God?	1=Very Unimportant 2=Moderately Unimportant 3=Slightly Unimportant 4=Slightly Important 5=Moderately Important 6=Very Important	QLI - Importance
309	How IMPORTANT to you is: Achieving your personal goals?	1=Very Unimportant 2=Moderately Unimportant 3=Slightly Unimportant 4=Slightly Important 5=Moderately Important 6=Very Important	QLI - Importance
310	How IMPORTANT to you is: Your happiness in general?	1=Very Unimportant 2=Moderately Unimportant 3=Slightly Unimportant 4=Slightly Important 5=Moderately Important 6=Very Important	QLI - Importance
311	How IMPORTANT to you is: Being satisfied with life?	1=Very Unimportant 2=Moderately Unimportant 3=Slightly Unimportant 4=Slightly Important 5=Moderately Important 6=Very Important	QLI - Importance
312	How IMPORTANT to you is: Your personal appearance?	1=Very Unimportant 2=Moderately Unimportant 3=Slightly Unimportant 4=Slightly Important 5=Moderately Important 6=Very Important	QLI - Importance
313	How IMPORTANT to you is: Are you to yourself?	1=Very Unimportant 2=Moderately Unimportant 3=Slightly Unimportant 4=Slightly Important 5=Moderately Important 6=Very Important	QLI - Importance
314	In the PAST WEEK: I was bothered by things that don't usually bother me	0=Rarely or None of the time (Less than 1 day) 1=Some of the time (1-2 days) 2=Occasionally (3-4 days) 3=Most of the time (5-7 days)	CESD
315	In the PAST WEEK: I did not feel like eating; my appetite was poor	0=Rarely or None of the time (Less than 1 day) 1=Some of the time (1-2 days) 2=Occasionally (3-4 days) 3=Most of the time (5-7 days)	CESD

316	In the PAST WEEK: I felt that I could not shake off the blues, even with help from my family or friends	0=Rarely or None of the time (Less than 1 day) 1=Some of the time (1-2 days) 2=Occasionally (3-4 days) 3=Most of the time (5-7 days)	CESD
317	In the PAST WEEK: I felt that I was just as good as other people	0=Rarely or None of the time (Less than 1 day) 1=Some of the time (1-2 days) 2=Occasionally (3-4 days) 3=Most of the time (5-7 days)	CESD
318	In the PAST WEEK: I had trouble keeping my mind on what I was doing	0=Rarely or None of the time (Less than 1 day) 1=Some of the time (1-2 days) 2=Occasionally (3-4 days) 3=Most of the time (5-7 days)	CESD
319	In the PAST WEEK: I felt depressed	0=Rarely or None of the time (Less than 1 day) 1=Some of the time (1-2 days) 2=Occasionally (3-4 days) 3=Most of the time (5-7 days)	CESD
320	In the PAST WEEK: I felt that everything I did was an effort	0=Rarely or None of the time (Less than 1 day) 1=Some of the time (1-2 days) 2=Occasionally (3-4 days) 3=Most of the time (5-7 days)	CESD
321	In the PAST WEEK: I felt hopeful about the future	0=Rarely or None of the time (Less than 1 day) 1=Some of the time (1-2 days) 2=Occasionally (3-4 days) 3=Most of the time (5-7 days)	CESD
322	In the PAST WEEK: I thought my life had been a failure	0=Rarely or None of the time (Less than 1 day) 1=Some of the time (1-2 days) 2=Occasionally (3-4 days) 3=Most of the time (5-7 days)	CESD

		0=Rarely or None of the time (Less than 1 day) 1=Some of the time (1-2 days) 2=Occasionally (3-4 days) 3=Most of the time (5-7 days)	
323	In the PAST WEEK: I felt fearful		CESD
		0=Rarely or None of the time (Less than 1 day) 1=Some of the time (1-2 days) 2=Occasionally (3-4 days) 3=Most of the time (5-7 days)	
324	In the PAST WEEK: My sleep was restless		CESD
		0=Rarely or None of the time (Less than 1 day) 1=Some of the time (1-2 days) 2=Occasionally (3-4 days) 3=Most of the time (5-7 days)	
325	In the PAST WEEK: I was happy		CESD
		0=Rarely or None of the time (Less than 1 day) 1=Some of the time (1-2 days) 2=Occasionally (3-4 days) 3=Most of the time (5-7 days)	
326	In the PAST WEEK: I talked less than usual		CESD
		0=Rarely or None of the time (Less than 1 day) 1=Some of the time (1-2 days) 2=Occasionally (3-4 days) 3=Most of the time (5-7 days)	
327	In the PAST WEEK: I felt lonely		CESD
		0=Rarely or None of the time (Less than 1 day) 1=Some of the time (1-2 days) 2=Occasionally (3-4 days) 3=Most of the time (5-7 days)	
328	In the PAST WEEK: People were unfriendly		CESD
		0=Rarely or None of the time (Less than 1 day) 1=Some of the time (1-2 days) 2=Occasionally (3-4 days) 3=Most of the time (5-7 days)	
329	In the PAST WEEK: I enjoyed life		CESD

330	In the PAST WEEK: I had crying spells	0=Rarely or None of the time (Less than 1 day) 1=Some of the time (1-2 days) 2=Occasionally (3-4 days) 3=Most of the time (5-7 days)	CESD
331	In the PAST WEEK: I felt sad	0=Rarely or None of the time (Less than 1 day) 1=Some of the time (1-2 days) 2=Occasionally (3-4 days) 3=Most of the time (5-7 days)	CESD
332	In the PAST WEEK: I felt that people dislike me	0=Rarely or None of the time (Less than 1 day) 1=Some of the time (1-2 days) 2=Occasionally (3-4 days) 3=Most of the time (5-7 days)	CESD
333	In the PAST WEEK: I could not get going"	0=Rarely or None of the time (Less than 1 day) 1=Some of the time (1-2 days) 2=Occasionally (3-4 days) 3=Most of the time (5-7 days)	CESD
334	For each area of functioning listed, please select the description that applies. The word "assistance" means supervision or personal assistance.	n/a	KATZ
335	Please select the description that applies. Bathing (sponge, shower, or tub)	2=Independent: receives no assistance (gets in and out of tub if tub is the usual means of bathing) 1=Assistance: receives assistance in bathing only one part of the body such as the back or a leg 0=Dependent: receives assistance in bathing more than one part of the body (or not bathed)	KATZ

336	Please select the description that applies. Dressing:	2=Independent: gets clothes and gets completely dressed without assistance 1=Assistance: gets clothes and gets completely dressed without assistance except in tying shoes 0=Dependent: receives assistance in getting clothes or in getting dressed or stays partly or completely undressed	KATZ
337	Please select the description that applies. Toileting:	2=Independent: goes to toilet room, cleans self, and arranges clothes without assistance (may use object for support such as cane, walker, or wheelchair and may manage night bedpan or commode, emptying it in the morning) 1=Assistance: receives assistance in going to toilet room or in cleansing self or in arranging clothes after elimination or in use of night bedpan or commode 0=Dependent: doesn't go to room termed toilet" for the elimination process"	KATZ
338	Please select the description that applies. Transfer:	2=Independent: moves in and out of bed and chair without assistance (may use object for support such as cane or walker) 1=Assistance: moves in and out of bed and chair with assistance 0=Dependent: doesn't get out of bed	KATZ
339	Please select the description that applies. Continence:	2=Independent: controls urination and bowel movement completely by self 1=Assistance: has occasional accidents" 0=Dependent: supervision helps keep urine or bowel control; catheter is used or is incontinent"	KATZ

340

Please select the description
that applies. Feeding:

2=Independent: feeds self without assistance
1=Assistance: feeds self except for getting assistance
to cut meat or butter bread
0=Dependent: receives assistance in feeding or is fed
partly or completely by using tubes or intravenous
fluids

KATZ

SF-36® Health Survey Scoring Demonstration

This survey asks for your views about your health. This information will help you keep track of how you feel and how well you are able to do your usual activities.

Answer every question by selecting the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

1. In general, would you say your health is:

Excellent

☐

Very good

☐

Good

☐

Fair

☐

Poor

☐

2. Compared to one year ago, how would you rate your health in general now?

Much better
now than one
year ago

☐

Somewhat better
now than one
year ago

☐

About the
same as one
year ago

☐

Somewhat worse
now than one
year ago

☐

Much worse
now than one
year ago

☐

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

Yes, limited a lot	Yes, limited a little	No, not limited at all

a Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports

☐☐☐

b Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf

☐☐☐

c Lifting or carrying groceries

☐☐☐

d Climbing several flights of stairs

☐☐☐

e Climbing one flight of stairs

☐☐☐

f Bending, kneeling, or stooping

☐☐☐

g	Walking more than a mile	☐	☐	☐
h	Walking several blocks	☐	☐	☐
i	Walking one block	☐	☐	☐
j	Bathing or dressing yourself	☐	☐	☐

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

Yes No

a	Cut down on the amount of time you spent on work or other activities	☐	☐
b	Accomplished less than you would like	☐	☐
c	Were limited in the kind of work or other activities	☐	☐
d	Had difficulty performing the work or other activities (for example, it took extra effort)	☐	☐

5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

Yes No

a	Cut down on the amount of time you spent on work or other activities	☐	☐
b	Accomplished less than you would like	☐	☐
c	Did work or other activities less carefully than usual	☐	☐

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐	☐	☐	☐	☐

7. How much bodily pain have you had during the past 4 weeks?

None	Very mild	Mild	Moderate	Severe	Very severe



8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all



A little bit



Moderately



Quite a bit



Extremely



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

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

All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time

a	Did you feel full of pep?	☐	☐	☐	☐	☐	☐
b	Have you been a very nervous person?	☐	☐	☐	☐	☐	☐
c	Have you felt so down in the dumps that nothing could cheer you up?	☐	☐	☐	☐	☐	☐
d	Have you felt calm and peaceful?	☐	☐	☐	☐	☐	☐
e	Did you have a lot of energy?	☐	☐	☐	☐	☐	☐
f	Have you felt downhearted and blue?	☐	☐	☐	☐	☐	☐
g	Did you feel worn out?	☐	☐	☐	☐	☐	☐
h	Have you been a happy person?	☐	☐	☐	☐	☐	☐
i	Did you feel tired?	☐	☐	☐	☐	☐	☐

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

All of the
time



Most of the
time



Some of the
time



A little of the
time



None of the
time



11.How TRUE or FALSE is each of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false

a	I seem to get sick a little easier than other people	☐	☐	☐	☐	☐
b	I am as healthy as anybody I know	☐	☐	☐	☐	☐
c	I expect my health to get worse	☐	☐	☐	☐	☐
d	My health is excellent	☐	☐	☐	☐	☐

Thank you for completing these questions!

Satisfaction With Life Scale

Diener, E., Emmons, R., Larsen, J., & Griffin, S. (1985). The Satisfaction With Life Scale. *J Personality Assessment*, 49(1), 71-75.

Below are five statements with which you may agree or disagree. Using the 1-7 scale below, indicate your agreement with each item by placing the appropriate number on the line preceding that item. Please be open and honest in your responding. The 7-point scale is as follows:

1 = strongly disagree

2 = disagree

3 = slightly disagree

4 = neither agree nor disagree

5 = slightly agree

6 = agree

7 = strongly agree

___ 1. In most ways my life is close to my ideal.

___ 2. The conditions of my life are excellent.

___ 3. I am satisfied with my life.

___ 4. So far I have gotten the important things I want in life.

___ 5. If I could live my life over, I would change almost nothing.

Attachment 11: Impact Statement

The study addresses a critical need of the SCI community, determining the best therapy for recovery of walking. Results from this study will ***advance the field of SCI research*** by identifying the efficacy of an activity-based therapy, LT, for recovery after SCI when given at the earliest time point available for rehabilitation. A positive outcome will strongly influence the methods used in clinical practice and will support the hypothesis that the excitability and activity of the neural circuits in the lumbosacral spinal cord can be modulated by patterned sensory input.

The knowledge gained from these studies has potential ***to impact standard of care*** for individuals with SCI, by informing clinicians of the recovery rates of specific rehabilitation paradigms that are currently being provided as standard of care. Also, we will have available a comprehensive database that contains radiological, physiological, pharmacologic, neurological and functional data throughout the continuum of care beginning at the onset of injury through acute neurological care and rehabilitation.

Attachment 12: Transition Plan

The results of this trial will be disseminated to the field of Spinal Cord Injury (SCI) Medicine in a number of ways; including presentation at SCI related clinical and research forums as well as in print journals. The impact would be felt immediately as this will allow clinicians evidence for providing LT as an activity-based intervention program involving persons with SCI.

There would also be immediate impact in the clinical aspects of care for all persons with upper motor neuron related SCI, both military and non-military; specifically in regards to the treatment for the recovery of the ability to walk. The recovery rates of individuals receiving usual rehabilitation would also be available with discrete documentation of those specific rehabilitation programs. Further, the effects of LT training as well as in other domains, including medical (i.e. respiratory, cardiovascular) and quality of life will be better understood providing evidence to guide clinical practice.

Immediately, the results of this study would impact the current NeuroRecovery Network (NRN). If LT provided earlier after injury significantly improved walking capability, inclusion criteria would change for persons eligible for this program. We believe this would also change eligibility for other clinical trials as well as other clinically based activity-based rehabilitation programs.

Attachment 13: Military Relevance Statement

This study is applicable to the health care of military personnel both directly and indirectly. Several VA SCI Services are actively involved with the study centers, and they will be actively recruiting veterans to participate in this Phase II clinical trial. Military personnel served by the Walter Reed Army Medical Center will be eligible for enrollment in this study and we will support the implementation of an NRN site. Indirectly, as this study intends to improve our understanding and treatment of SCI, veterans and current members of the military who have a SCI will benefit from these advances.

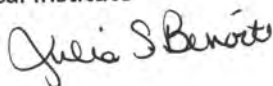
November 20, 2011

To: Robert G. Grossman, M.D.

Professor and Chairman, Department of Neurosurgery

The Methodist Hospital Neurological Institute

From: Julia Sanders Benoit, B.S., M.S.



Doctoral Candidate in Biostatistics

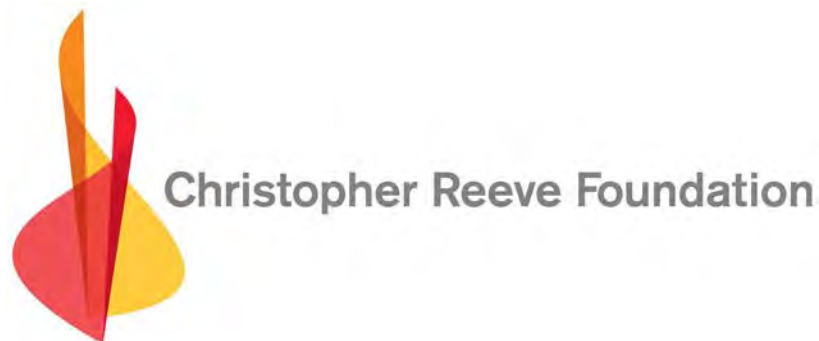
Division of Biostatistics

Subj: Nested New Investigator Phase II trial of BWSLT – NACTN/NRN

Statement of Professional Goals

My professional goals are to enter into an academic career as a clinical trialist in the design, planning, conduct, and analysis of clinical trials. I am currently a doctoral candidate (PhD) in the Division of Biostatistics in the University of Texas School of Public Health. My minor area of concentration is Epidemiology. My dissertation research focuses on modeling longitudinal outcome data which may potentially be misclassified that can describe the dynamic characteristics of change over time in disease severity and allows for possible misclassification of stage of disease based on at least two latent variables. My ambition for this research is to estimate the probability of misclassification and to develop the statistical methodology to identify determinants of disease stage changes over time.

The opportunity to become a nested new investigator on a multi-site spinal cord injury rehabilitation clinical trial is a perfect fit for me. Although I have gained invaluable experience working in a brain trauma injury clinical trial (Effects of Erythropoietin on Vascular Dysfunction and Anemia in Traumatic Brain Injury), I am ready to be challenged further with multiple site clinical trial repeated measures outcome data and the potential for applying my statistical research directly to the outcomes of proposed Phase IIb locomotor randomized clinical trial. In addition, the mentoring in this program provided by the faculty of the Clinical Coordinating Center and the Data Analysis Center on the epidemiology of spinal cord injury and the historical and current understandings and approaches to the design of spinal cord clinical trials will provide me with a substantial foundation to further my commitment and competitiveness for pursuing an academic career in spinal cord research.



North American Clinical Trials Network Governance Manual

The *North American Clinical Trials Network (NACTN) Governance Manual* has been written, reviewed, and/or revised in its entirety as of August 2011. These policies and procedures have been developed by the Christopher Reeve Foundation. The Executive Committee is responsible for their implementation.

Robert G. Grossman, MD, Network Principal Investigator

Date

Michael G. Fehlings, MD, PhD, Executive Committee Member

Date

Ralph F. Frankowski, PhD, Executive Committee Member

Date

Susan J. Harkema, PhD, Executive Committee Member

Date

NACTN Site Principal Investigator

Date

POLICY DESCRIPTION: Executive Committee Policy	
SCOPE: NACTN Principal Investigator and Site Principal Investigators	
PURPOSE: To define the purpose and structure of the Executive Committee	
POLICY: Membership of the Executive Committee • The Executive Committee is formed by the NACTN Principal Investigator. • The committee will be comprised of the NACTN Principal Investigator and a minimum of two NACTN Site Principal Investigators. Goals of the Executive Committee • To provide governance and address long-term issues critical to the goals and objectives of NACTN. Responsibilities of the Executive Committee • To oversee the governance of NACTN • To ensure the execution of the goals and objectives of NACTN • To oversee adherence to the policies and procedures of NACTN • To establish Standing Committees	
REFERENCES:	
EFFECTIVE DATE: March 2010	REPLACES POLICY DATED:

POLICY DESCRIPTION: Review of the <i>North American Clinical Trials Network Governance Manual</i>	
SCOPE: North American Clinical Trials Network (NACTN)	
PURPOSE: The <i>North American Clinical Trials Network Governance Manual</i> shall serve as a readily available resource to all members of NACTN.	
POLICY: The Executive Committee will maintain the <i>North American Clinical Trials Network Governance Manual</i> through writing, reviewing, and revising all policies and procedures in collaboration with the funding agencies. This manual shall be reviewed annually. Additions, revisions, and deletions to the <i>North American Clinical Trials Governance Manual</i> may be made at any time during the year to facilitate effective operations as deemed appropriate.	
PROCEDURE: The Executive Committee shall be responsible for communicating on a timely basis all new policies, revisions, and changes to the Site Principal Investigators (PI), as well as other collaborating individuals. The Site Principal Investigators will be responsible for communication with their respective team members of new policies, revisions, and changes to the manual. It shall be the responsibility of all NACTN team members to be knowledgeable about the <i>North American Clinical Trials Network Governance Manual</i> and to keep abreast of changes as they occur by communicating with their Site Principal Investigators.	
REFERENCES:	
EFFECTIVE DATE: March 2010	REPLACES POLICY DATED:

POLICY DESCRIPTION: Review of the <i>North American Clinical Trials Network Policy and Procedure Manual</i>	
SCOPE: North American Clinical Trials Network Site Principal Investigators, Clinical Research Coordinators.	
PURPOSE: The <i>North American Clinical Trials Network Policy and Procedure Manual</i> shall serve as a readily available resource to all team members.	
POLICY: The Executive Committee will maintain the <i>North American Clinical Trials Network Policy and Procedure Manual</i> through writing, reviewing, and revising all policies and procedures in collaboration with the NACTN Site Principal Investigators. This manual shall be reviewed annually. Additions, revisions, and deletions to the <i>North American Clinical Trials Network Policy and Procedure Manual</i> may be made at any time during the year to facilitate effective operations.	
PROCEDURE: The Executive Committee shall be responsible for communicating on a timely basis all new policies, revisions, and changes to the Site Principal Investigators, as well as other collaborating individuals. The Site Principal Investigators will be responsible for bilateral communication with their respective team members. It shall be the responsibility of all NACTN team members to be knowledgeable about the <i>North American Clinical Trials Network Policy and Procedure Manual</i> and to keep abreast of changes as they occur. Changes to the <i>North American Clinical Trials Network Policy and Procedure Manual</i> may be made as follows: 1. Changes shall be initiated and discussed through the NACTN Conference Call system. The Site Principal Investigator initiating the change shall form a committee of at least one other Site Principal Investigator. The initiating Site Principal Investigator will be designated the Committee Chairperson. The Chairperson will write the original draft of the proposed Policy and Procedure in collaboration with the committee members. The committee members will be responsible for seeking input from their respective Sites and reporting progress on the committee activity at each Committee Conference Call. The Committee will reach a final consensus on the change of policy or procedure. The Committee Chairperson will disseminate the final draft to the Site Principal Investigators two weeks prior to the conference call requesting approval. 2. Any changes to the <i>North American Clinical Trials Network Policy and Procedure Manual</i> must be approved by more than 75% of the present Network Principal Investigator and Site Principal Investigators only by vote on the scheduled monthly Site Principal Investigator calls. A quorum of at least 80% of the Site Principal Investigators must be in attendance for a vote to occur. If there is not a quorum the vote will be rescheduled for the next Site Principal Investigators conference call.	
REFERENCES:	
EFFECTIVE DATE: March 2010	REPLACES POLICY DATED:

POLICY DESCRIPTION: Distribution of the Manuals	
SCOPE: North American Clinical Trials Network Site Principal Investigators, Clinical Research Coordinators.	
PURPOSE: Provide all team members with appropriate access to the <i>North American Clinical Trials Network Governance Manual</i> and the <i>North American Clinical Trials Network Policy and Procedure Manual</i> .	
POLICY: The <i>North American Clinical Trials Network Governance Manual</i> and the <i>North American Clinical Trials Network Policy and Procedure Manual</i> shall be available at a central location at all NACTN Sites and on the NACTN FTP site.	
PROCEDURE: The <i>North American Clinical Trials Network Governance Manual</i> and the <i>North American Clinical Trials Network Policy and Procedure Manual</i> shall be distributed annually to Site Principal Investigators, Clinical Research Nurses, and Study Coordinators.	
REFERENCES:	
EFFECTIVE DATE: March 2010	REPLACES POLICY DATED:

POLICY DESCRIPTION: Mission Statement	
SCOPE: North American Clinical Trials Network Site Principal Investigators, Clinical Research Coordinators.	
PURPOSE: To define the Mission Statement for the North American Clinical Trials Network.	
POLICY: To assess potential therapies for spinal cord injury and test the most promising in clinical trials.	
MISSION: NACTN's mission is to carry out clinical trials of the comparative effectiveness of new therapies for spinal cord injury using an established consortium of neurosurgery departments at university-affiliated civilian medical center hospitals and military hospitals with medical, nursing and rehabilitation personnel who are skilled in the evaluation and management of spinal cord injury.	
REFERENCES:	
EFFECTIVE DATE: March 2010	REPLACES POLICY DATED:

POLICY DESCRIPTION: Goals of the North American Clinical Trials Network	
SCOPE: North American Clinical Trials Network Principal Investigators, Site Principal Investigators, Clinical Research Coordinators.	
PURPOSE: The goals of NACTN are to: 1. Test promising therapies for spinal cord injury in rigorous clinical trials that are designed to ensure interpretable, meaningful data and safety for the patients undergoing treatment. 2. Develop and maintain a comprehensive data registry of acutely injured patients who are admitted to NACTN sites. Information will be collected on the natural course of spinal cord injuries (SCI) and treatment through the first 12 months post-injury. 3. Analyze and publish/present NACTN data to inform, enrich and help shape the field at large. 4. Develop, test and validate sensitive outcome measures to detect incremental improvements in human clinical trials (Neurological Outcomes Assessment [NOA] initiative), including GRASSP and PRIME. 5. Continue to strategically expand NACTN to new civilian and military hospitals. 6. Provide training and support for personnel and technical resources needed to conduct trials of therapy effectively and efficiently. 7. Maintain a network of sites that provide standardized care to their spinal cord patient populations through the training and monitoring of personnel. 8. Work collaboratively with other national/international clinical networks and consortia as appropriate.	
REFERENCES:	
EFFECTIVE DATE: August 2011	REPLACES POLICY DATED: March 2010

POLICY DESCRIPTION: Objectives of the North American Clinical Trials Network	
SCOPE: North American Clinical Trials Network Principal Investigators and Site Principal Investigators, Clinical Research Coordinators.	
PURPOSE: The objectives of NACTN are to: 1. Develop a network of leading-edge centers to facilitate the rational testing of promising therapies for SCI and provide and maintain a consistent level and quality of care across centers through training, meetings and continuous information exchanges for and among NACTN PIs, study coordinators and other personnel. 2. Develop a mechanism to rigorously solicit and assess potential therapies and prioritize interventions to be tested. 3. Maintain and monitor a comprehensive data registry that includes data from all NACTN sites on the natural twelve-month course of recovery of all enrolled patients. Specific data includes baseline SCI clinical assessment, treatment course, hospital discharge summary, incidence of complications and standardized follow-up examinations. 4. Facilitate and guide NOA research/activities focused on the autonomic, motor, sensory-pain and quality of life instruments identified by the NOA Task Force as its phase-one priority. 5. Institutionalize mechanisms to access, analyze and disseminate data through publications and presentations. 6. Establish NACTN as a resource for the field at large, helping to set standards of care and best clinical practices. 7. Work closely with NACTN's Department of Defense (DOD) colleagues to expand into military and Veterans Administration (VA) hospitals.	
REFERENCES:	
EFFECTIVE DATE: March 2010	REPLACES POLICY DATED:

POLICY DESCRIPTION: NACTN Confidentiality	
SCOPE: North American Clinical Trials Network Principal Investigators and Site Principal Investigators, Clinical Research Coordinators, Other NACTN Personnel.	
PURPOSE: To engender an environment of collegiality and trust that will facilitate the effective pursuit of NACTN's mission through open, honest and professional exchanges of ideas and the orderly and rigorous pursuit of NACTN-related activities.	
POLICY: 1. NACTN expects and requires all Principal Investigators, Site Principal Investigators, Clinical Research Coordinators and other NACTN personnel to keep confidential any sensitive or proprietary information belonging to NACTN which has not been released to the public domain or to other select Third Parties. Such information includes but shall not be limited to unpublished data, deliberations of NACTN's Executive, Standing and Ad Hoc Committees, NACTN manuals, case report forms, protocols and other organizing and research documents. 2. Exceptions to this Confidentiality Policy can be made through ad hoc approval of NACTN's Executive Committee. 3. The term Third Party refers to any individual or group other than those defined in the Scope of this Policy.	
REFERENCES:	
EFFECTIVE DATE: August 2011	REPLACES POLICY DATED:

North American Clinical Trials Network

Table of Organization

POLICY DESCRIPTION: General Requirements of the Individual Sites	
SCOPE: North American Clinical Trials Network Principal Investigators, Clinical Research Coordinators.	
PURPOSE: To define the general requirements of the individual North American Clinical Trials Network Sites.	
POLICY: The NACTN Sites will: 1. Provide newest advanced clinical care to maximize the natural course of recovery of function and health for acutely injured patients enrolled in the NACTN data registry. Implement the procedures and protocols recommended by the network Site PIs that support this outcome. 2. Work closely with NACTN's Coordinating Center to ensure full and timely compliance with all local and DOD IRB and other regulatory requirements. 3. Respond in timely fashion to all Reeve Foundation requests/deadlines/deliverables to ensure continued funding from DOD. 4. Screen acutely injured patients arriving at NACTN sites and enroll into the NACTN data registry. Follow each enrolled patient for 12 months, or as long as clinically appropriate, collecting and submitting to the Data Management Center (DMC) data on sequential neurological examinations, the radiological characteristics of the injury to the spinal cord and the vertebral column and detailed medical information about complications, etc. 5. Provide a clinical environment that encourages open communication between the patient, family and the NACTN clinical staff to facilitate enrollment of patients into the data registry and the requisite twelve-month follow-up, or as long as clinically appropriate. 6. Maintain a highly-trained staff that can properly evaluate patient status, record all relevant data and submit accurate data to the DMC. Coordinate, develop, submit and approval of the protocol and its subsequent amendments. Maintain regulatory binders. 7. Ensure the confidentiality of NACTN data and provide complete patient data to the DMC in a timely manner following established procedures. 8. Maintain accurate and complete study records and source documents that will be made available to representatives of the US Army Medical Research and Materiel Command (USAMRMC) as part of its responsibility to protect human research subjects. 9. Collaborate and share data with other Sites to continually assess and improve the delivery of care, data collection and follow-up and therapeutic clinical trialing within and by NACTN. a. Ensure that Site PIs, study coordinators and other relevant NACTN personnel participate in periodic meetings, webinars and/or telephone conference calls organized for training, planning, trial initiation and/or other purposes.	
REFERENCES:	
EFFECTIVE DATE: August 2011	REPLACES POLICY DATED: March 2010

POLICY DESCRIPTION: Equipment and Facility Requirements for the Individual Sites	
SCOPE: North American Clinical Trials Network Site Principal Investigators, Clinical Research Coordinators.	
PURPOSE: To define the equipment and facility requirements for the individual sites.	
POLICY: Each Site shall provide the following: 1. Appropriate space and state-of-the-art equipment to examine, treat and test patients and maintain the requisite clinical records. 2. Appropriate equipment to collect patient data and transmit it to the DMC according to established procedures.	
REFERENCES:	
EFFECTIVE DATE: March 2010	REPLACES POLICY DATED:

POLICY DESCRIPTION: Clinical Operations	
SCOPE: North American Clinical Trials Network Site Principal Investigators, Clinical Research Coordinators.	
PURPOSE: To define the framework for clinical operations for the Network Sites.	
POLICY: 1. NACTN clinical operations are defined with specificity in the Manual of Operations (June 2011, Version 5), including (i) Acute Care (data collection, patient screening, data registry enrollment/submission procedures, participant log, correction request form), (ii) Data Collection Forms (AIS, APACHE II), and (iii) Follow-Up (ASIA, FIM, SCIM, WISCI II, Withdrawal of Consent, Lost to Follow-Up). 2. The final protocol for a NACTN clinical trial will detail clinical operations for that study.	
REFERENCES:	
EFFECTIVE DATE: August 2011	REPLACES POLICY DATED: March 2010

POLICY DESCRIPTION: Ethics, Rights, and Responsibilities	
SCOPE: North American Clinical Trials Network Site Principal Investigators, Clinical Research Coordinators.	
PURPOSE: To define the Policies and Procedures for Patient Rights and Responsibilities as they apply to the NACTN Sites.	
POLICY: Each NACTN site will follow the Patient Rights and Responsibilities of its respective facility.	
REFERENCES:	
EFFECTIVE DATE: March 2010	REPLACES POLICY DATED:

POLICY DESCRIPTION: Informed Consent	
SCOPE: North American Clinical Trials Network Site Principal Investigators, Clinical Research Coordinators.	
PURPOSE: To define the process by which informed patient consents will be obtained.	
POLICY: Appropriate signed informed consent form will be obtained from the patient if awake, alert and able to provide informed consent prior to participating in NACTN research; if the patient is unable to provide his/her signature, his/her Legally Authorized Representative (LAR) may do so. This will be done through signing an Informed Consent Form approved by the Site's IRB and the Department of Defense's Office of Research Protections (ORP), Human Research Protection Office (HRPO). If a patient or his/her representative chooses not to sign the Informed Consent Form, this will not prevent the patient from receiving the standard of care at that facility.	
PROCEDURE: 1. All key NACTN personnel administering the Informed Consent must have current Human Subject Protection Certification on record, Medical License, signed and dated CV and Financial Conflict of Interest for clinical trials. 2. All study procedures will commence only after the informed consent form is signed. A copy of the informed consent will be given to the patient and /or LAR. 3. If the patient chooses not to sign an Informed Consent Form, he/she will continue to receive the standard of care at the NACTN site; however his/her data will not be entered into the data registry maintained at the NACTN Data Management Center located at the University of Houston-School of Public Health, Houston, Texas. Additional details about informed consent forms are maintained in the NACTN Manual of Operations (June 2011, Version 5).	
REFERENCES:	
EFFECTIVE DATE: August 2011	REPLACES POLICY DATED: March 2010

POLICY DESCRIPTION: Performance Improvement	
SCOPE: North American Clinical Trials Network Site Principal Investigators, Clinical Research Coordinators.	
PURPOSE: NACTN is committed to participating in the respective facility's Performance Improvement Program and the data collection process for NACTN.	
POLICY: Consistent with the objectives of the program, NACTN will identify and pursue opportunities for improvement with the goal of delivering the best possible patient care and designing and implementing rigorous and safe clinical trials of potential new SCI therapies. NACTN will follow the Guidelines for Good Clinical Practice and FDA and DOD regulations.	
PROCEDURE: Each facility will work with their respective locations to implement the appropriate performance improvement activities.	
EFFECTIVE DATE: August 2011	REPLACES POLICY DATED: March 2010

POLICY DESCRIPTION: Job Descriptions	
SCOPE: North American Clinical Trials Network Site Principal Investigators, Clinical Research Coordinators.	
PURPOSE: To define the job descriptions for the North American Clinical Trials Network Sites.	
POLICY: Each NACTN site shall have individuals identified to meet the following roles and responsibilities. <u>Site PI</u> – Responsible for the overall operation of the site as required by the <i>NACTN Policy and Procedure Manual</i> and for the communication and sharing of ideas, concepts and data among site personnel and the larger NACTN network. Site PI is responsible for overseeing the IRB and informed consent processes, and annual narrative and financial reports to the Reeve Foundation. He or she is expected to participate fully in the governance and/or committee organization of NACTN. <u>Clinical Research Coordinator</u> – Minimum of one clinician responsible for assessing a patient’s capacity to consent to the research protocol, obtaining consent, enrolling subjects, performing neurological examinations, collecting/transmitting accurate data, coordinating follow-up, maintaining regulatory documentation, etc. Must be a licensed clinician: a physician, nurse, physical therapist, or other licensed clinician.	
REFERENCES:	
EFFECTIVE DATE: March 2010	REPLACES POLICY DATED:

POLICY DESCRIPTION: Funding of the NACTN Grant	
SCOPE: North American Clinical Trials Network Site Principal Investigators, Clinical Research Coordinators.	
PURPOSE: To define the policies and procedures for funding of the NACTN grant.	
POLICY: Continued funding will be dependent upon the Site Principal Investigator and his or her site meeting their obligations as detailed in the <i>NACTN Governance Manual</i> , and continued funding from the Department of Defense.	
REFERENCES:	
EFFECTIVE DATE: March 2010	REPLACES POLICY DATED:

POLICY DESCRIPTION: Contracts and Reporting	
SCOPE: North American Clinical Trials Network Site Principal Investigators, Clinical Research Coordinators.	
PURPOSE: To define the contract and reporting process for North American Clinical Trials Network Sites.	
POLICY: Site PIs are responsible for ensuring institutional and USAMRMC ORP HRPO approvals for implementation of NACTN studies and for timely completion of all progress and financial reports as required by the Reeve Foundation and DOD. PIs are also required to meet any and all ad hoc requests from The Methodist Hospital Coordinating Center and/or Reeve Foundation related to effective and timely pursuit of the NACTN mission. PIs and Coordinators will follow DOD reporting obligations. ▪ Major modifications to the research protocol and any modifications that could potentially increase risk to subjects must be submitted to the USAMRMC ORP HRPO for approval prior to implementation. All other amendments must be submitted with the continuing review report to the HRPO for acceptance. ▪ All unanticipated problems involving risks to subjects or others, serious adverse events related to study participation, and deaths related to study participation must be reported promptly to the HRPO. ▪ Any deviation to the subject protocol that affects the safety or rights of the subject and/or integrity of the study data must be reported promptly to the HRPO. ▪ All modifications, deviations, unanticipated problems, adverse events, and deaths must also be reported at the time of continuing review of the protocol. ▪ A copy of the continuing review report approved by the local IRB must be submitted to the HRPO as soon as possible after receipt of approval. ▪ In addition, the current version of the protocol and consent form must be submitted along with the continuing review report and the local IRB approval notice for continuation of the protocol. ▪ The final study report submitted to the local IRB, including a copy of any acknowledgement documentation and any supporting documents must be submitted to the HRPO as soon as all documents become available. ▪ Final narrative and financial annual reports are required to be submitted to the Reeve Foundation on a timely basis, as provided for in each site's research award contract. Payments on the current research contract will not be made until final reports for the previous contract have been submitted to the Foundation.	
REFERENCES:	
EFFECTIVE DATE: August 2011	REPLACES POLICY DATED: March 2010

POLICY DESCRIPTION: Categories for Use of the NACTN Grant	
SCOPE: North American Clinical Trials Network Principal Investigators, Clinical Research Coordinators.	
PURPOSE: To define the appropriate uses of the NACTN grant	
POLICY: - Grant funds should be used solely to support the goals of NACTN. The categories for use of the NACTN grant funds are listed below. Personnel: salary support for those individuals designated specifically for NACTN functions, including but not necessarily limited to - Site PI (up to 10% effort) - Clinical Research Nurse - Study Coordinator - Other Personnel Equipment: NACTN approved equipment. Travel: expenses related to attendance at NACTN related meetings and/or training sessions. From time to time Reeve Foundation may provide reimbursement for meeting-related expenses <u>but all NACTN annual budgets should include a travel allocation.</u> Supplies: includes small items required to implement the registry and NACTN clinical trials. Other: including the cost of acquiring, maintaining and reporting data for NACTN functions. Any items in this category must be carefully documented. Indirects: maximum 10% of the direct costs (total of Personnel, Equipment, Travel, Supplies, and Other categories). The total of direct and indirect costs cannot exceed the total grant amount. - NACTN grant funds shall <u>not</u> be used: - To support other studies conducted at each site that are not NACTN-related - For travel that is not NACTN-related - For equipment purchases that are not used for NACTN research - To support the salaries of personnel who are not NACTN members	
REFERENCES:	
EFFECTIVE DATE: March 2010	REPLACES POLICY DATED:

POLICY DESCRIPTION: Media Services and Public Relations	
SCOPE: North American Clinical Trials Network Principal Investigators, Clinical Research Coordinators.	
PURPOSE: To provide guidelines for promoting the North American Clinical Trials Network Sites	
POLICY: NACTN Sites are encouraged to promote their programs and facilities in their respective local regions. However, all mention of NACTN and/or the Christopher Reeve Foundation must be reviewed with the Reeve Foundation prior to dissemination of the information. NACTN sites are expected to use the Reeve Foundation North American Clinical Trials Network registered mark for any and all publication and/or display purposes. Contact Maggie Goldberg, who can be reached at the Christopher Reeve Foundation at 1.800.225.0292, or mgoldberg@christopherreeve.org. The following information must appear on all presentations and publications (contract number is available from the Christopher Reeve Foundation): The North American Clinical Trials Network has been and/or is supported by the Christopher Reeve Foundation and U.S. Army Medical Research and Material Command under Contracts No. W81XWH-07-1-0361 and No. W81XWH10-02-0042.	
REFERENCES:	
EFFECTIVE DATE: August 2011	REPLACES POLICY DATED: March 2010

POLICY DESCRIPTION: Role of Consultants	
SCOPE: North American Clinical Trials Network Principal Investigators, Clinical Research Coordinators.	
PURPOSE: To provide guidelines for the role of consultants in the North American Clinical Trials Network	
POLICY: Consultants may be retained by the Executive Committee to provide guidance and advice in their area of expertise NACTN Consultants may: • Join any NACTN committee, including manuscript committees • Chair and vote in NACTN committees • Initiate an ad hoc committee with the approval of a Site Principal Investigator • Join Site Principal Investigators conference calls as appropriate as non-voting participants • Attend meetings and training sessions as appropriate • Be acknowledged as an NACTN member Consultants to NACTN are considered network members for the purposes of data dissemination and publication practices.	
REFERENCES:	
EFFECTIVE DATE: March 2010	REPLACES POLICY DATED:

POLICY DESCRIPTION: Standing Committee Policy	
SCOPE: North American Clinical Trials Network Site Principal Investigators, Clinical Research Coordinators	
PURPOSE: To define the purpose and structure of Standing Committees	
POLICY: Membership of the Standing Committees The committee will be comprised of a minimum of two NACTN Site PIs. • Standing committees are formed by the Executive Committee to address long-term issues critical to the goals and objectives of NACTN. • The Executive Committee identifies a need, defines the purpose, and appoints a chair. • Together, the Executive Committee and Chair define the minimum membership requirements. • The Chair forms the committees from NACTN members. • Any NACTN member may join a standing committee. The intent is for NACTN members who are most interested and have the most background and knowledge in an area propose the relevant policies and procedures. • The committee develops policies and procedures to meet the established goals, which are presented to the site PIs for approval. The committee chair is responsible for making sure there are agendas and minutes for every meeting. All documents (including agendas and minutes) must be uploaded to the NACTN FTP site.	
REFERENCES:	
EFFECTIVE DATE: March 2010	REPLACES POLICY DATED:

POLICY DESCRIPTION: Standing Committee – Data Management

SCOPE: North American Clinical Trials Network Principal Investigators, Clinical Research Coordinators.

PURPOSE:

To establish a Data Management Committee to provide supervision for the data integrity process and provide outcome measure understanding.

Membership of the Data Management Committee

- The committee will be comprised of a minimum of two NACTN members with expertise in data collection, management, analyses, dissemination and publications.

Goals of the Data Management Committee

- Facilitate the dissemination, publication and presentation of data collected by NACTN.
- Ensure the integrity of any publications or presentations that use NACTN data.
- Develop policies for data dissemination which comply with IRB requirements for the protection of personal health information and access to publicly supported databases.
- Standardization of outcome measurement and data collection across NACTN sites.
- Reducing the occurrence of user input errors in the database.
- Streamline and modify data fields in database to reflect scientific analyses of appropriate outcome measures without redundancy of testing.
- Evaluate and prioritize proposed changes to the database from the point of view of usability as well as ensuring that the data is sufficient for scientific analysis.
- Institutionalize a process to govern data registry queries.
- Ensure ongoing feedback to all NACTN Site PIs about the database changes.

Responsibilities of the Data Management Committee

- To develop policies and procedures to meet the goals outlined above.
- Discuss outcome data collection procedures across sites to determine consistency for purposes of data integrity with all other outcome committees.
- Review data and current literature and consult with other committees to determine the most optimal outcomes measures to measure performance without having redundancy of testing.
- Discuss database errors that emerge from data extractions with the site representatives and assist in the development of strategies to disseminate resolutions.
- Identify and propose changes to the database based on requests from the committee and from the sites that optimize data entry as well as ensuring that the data is sufficiently detailed for scientific analysis and interpretation.
- To oversee the creation and maintenance of a syllabus.

- To develop and update policies and procedures to meet the goals outlined above.

REFERENCES:	
EFFECTIVE DATE: August 2011	REPLACES POLICY DATED: March 2010

POLICY DESCRIPTION: Standing Committee – Treatment Strategy Selection	
SCOPE: North American Clinical Trials Network Principal Investigators, Clinical Research Coordinators.	
PURPOSE: To establish a Treatment Strategy Selection Committee to solicit and/or otherwise identify potential new SCI therapeutics; review the animal and preclinical data and formulate a recommendation to the Executive Committee as to whether or not NACTN should consider testing a particular intervention in clinical trial..	
Membership of the Treatment Strategy Selection Committee - The committee will be comprised of a minimum of two site PIs with particular knowledge of translational research and clinical trials in SCI. Additionally, the committee would invite basic scientists to participate ad hoc, depending on the therapies under consideration Goals of the Clinical Trials Committee - Establish a mechanism by which to identify and evaluate potential therapies for NACTN to test in clinical trials, including from within NACTN but also from academia and pharma. - Utilize non-NACTN expertise by reaching out to appropriately qualified investigators in basic and translational science to provide input regarding prospective therapeutics. Responsibilities of the Clinical Trials Committee - To review and summarize the evidence to support the new intervention - To identify inclusion/exclusion criteria for the new intervention - To draft or oversee medical and therapy protocols for the new intervention - To appoint and oversee ad hoc committees to assist with achieving the goals - To interface with the Executive Committee, Site Directors, the Reeve Foundation, and/or the DOD as needed	
REFERENCES:	
EFFECTIVE DATE: August 2011	REPLACES POLICY DATED: March 2010

POLICY DESCRIPTION: Standing Committee – Neurological Outcome Assessments (NOA)	
SCOPE: North American Clinical Trials Network Principal Investigators, Clinical Research Coordinators.	
PURPOSE: To establish a Neurological Outcome Assessments Committee to guide the development, testing and validation of sensitive and reliable outcome measures (Motor, Autonomic, Sensory and Pain, Quality of Life) to detect incremental improvements in patients such as improvements in neurological level and/or quantitative measures for ASIA A/B/C.	
Membership of NOA: • Designated experts in the following areas: ○ Autonomic dysfunction ○ Motor recovery ○ Quality of life ○ Sensory function and pain Goals of NOA: • Assess currently available measures with respect to quantification, objectivity, sensitivity, reliability, validity • Assess viable measurements under development • Prioritize measurements to be targeted for utilization and/or development • Develop plans of action for instruments targeted • Facilitate partnerships with other academic and industry representatives to facilitate and expedite development of improved outcome instruments Responsibilities of NOA: • Provide leadership to the international panel of experts assembled to develop, test and validate new outcome measures • Work closely with the Reeve Foundation to insure financial support for NOA activities, including funding through DOD and other suitable entities • Ensure publication of newly developed outcome instruments, as appropriate • Spearhead the translation of newly developed outcome instruments from the lab to NACTN's clinical sites, including but not limited to appropriate training initiatives to ensure standardization across all sites	
REFERENCES:	
EFFECTIVE DATE: March 2010	REPLACES POLICY DATED:

POLICY DESCRIPTION: Ad Hoc Committee Policy	
SCOPE: North American Clinical Trials Network Site Principal Investigators, Clinical Research Coordinators	
PURPOSE: To define the purpose and structure of Ad Hoc Committees	
POLICY: • Ad hoc committees are formed for short-term projects to meet the goals and objectives of NACTN. • The purposes of an ad hoc committee are: - o To address a specific objective or goal of a standing committee - o To initiate a change in the NACTN Policies and Procedures - o To provide structure to research projects from project development, to data analyses and publication - o Other special projects • Ad hoc committees are formed by any NACTN member • Any NACTN member may join an ad hoc committee • An ad hoc committee must include a minimum of two site PIs. The initiating member is the Chair of the ad hoc committee. • The committee chair is responsible for making sure there are agendas and minutes for every meeting. Either the chair can do this, or these tasks can be delegated to the committee members. All documents (including agendas and minutes) must be uploaded to the NACTN FTP site.	
REFERENCES:	
EFFECTIVE DATE: March 2010	REPLACES POLICY DATED:

POLICY DESCRIPTION: Hiring and Training of Personnel	
SCOPE: North American Clinical Trials Network Principal Investigator and Site Principal Investigators	
PURPOSE: To define the qualifications required when hiring and training key personnel	
POLICY: • It is the responsibility of the Site Principal Investigators to hire a skilled, qualified Clinical Research Nurse/Study Coordinator to perform clinical tasks (i.e. assessment of patient's ability to consent, obtain consent, enroll subjects, perform neurological examinations, collect /transmit accurate data, coordinate follow-up visits, maintain regulatory documentation, etc). • The Site Principal Investigator is responsible for ensuring that staff members and new personnel are trained on the study protocol and are instructed on how to collect data and complete the case report forms.	
REFERENCES:	
EFFECTIVE DATE: March 2010	REPLACES POLICY DATED:

POLICY DESCRIPTION: NACTN Conference Calls	
SCOPE: North American Clinical Trials Network Principal Investigators, Clinical Research Coordinators.	
PURPOSE: To facilitate regular communication among and between NACTN sites and team members.	
• NACTN’s Coordinating Center will organize monthly conference calls for all NACTN members and distribute an agenda in advance of each call. • All sites must be represented on conference calls. Ideally, the lead Clinical Research Nurse/Study Coordinator will participate on each call. If he or she is not able to participate, then it is his or her responsibility to have at least one key team member on the conference call to represent the site and to communicate discussions. • Agendas and minutes will be written and distributed to all NACTN members for their files and to be referenced as appropriate. All agendas and minutes will also be uploaded to the NACTN FTP site.	
REFERENCES:	
EFFECTIVE DATE: August 2011	REPLACES POLICY DATED: March 2010

POLICY DESCRIPTION: IRB Regulatory Process	
SCOPE: North American Clinical Trials Network Principal Investigators, Clinical Research Coordinators.	
PURPOSE: To define the regulatory process	
POLICY: • Research IRB protocols are initially generated by the Coordinating Center with approval from the TMH Coordinating Center IRB and USAMRMC HRPO ORP. These Master Research Protocols are then distributed to the sites for local IRB approval. Site IRB approval letters, ICFs, IRB application, site addendums and any other supportive documents that the site IRB reviewed, must then be sent to the Coordinating Center for submission to the DOD HRPO ORP for review and approval. • Proposed modifications to the existing IRB research protocol must first be reviewed by the Coordinating Center. ○ If the Coordinating Center deems that the modification is minor according to DOD regulations, then the site will forward the change request to the site's local IRB. All amendments must be submitted to the Coordinating Center in real time after IRB approval and with the continuing review approval from the HRPO. ○ If the Coordinating Center deems that the modification is major or could potentially increase risk to subjects, the modification must receive local IRB approval, and then be submitted by the Coordinating Center for USAMRMC ORP HRPO approval prior to implementation. • All local IRB and DOD letters of approval must be maintained in the regulatory site binder and sent to the Coordinating Center for its regulatory files.	
REFERENCES:	
EFFECTIVE DATE: August 2011	REPLACES POLICY DATED: March 2010



NACTN/ Building Infrastructure to Accelerate Transfer of Basic Research in Spinal Cord Injury (SCI) to Clinical Practice

Robert G. Grossman, MD

Chairman, Department of Neurosurgery

Co-Director, The Neurological Institute

The Methodist Hospital, Houston

01-July-2010 – 30-June-2011

Research Period: 05-May-2007 – 18-July-2012

Type of Funding: CSI/Gap/OCO/JPC 6

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Military relevant issue to be solved

What problem are you addressing?

- Improving the outcome of traumatic injury to the spinal cord
- Overcoming the barriers to bringing basic discoveries in neuroprotection and regeneration to clinical trials and practice
- Addressing the outstanding problems in conducting SCI trials:
 1. Organization of a multicenter network of hospitals with SCI expertise
 2. Creating a database of the natural history of SCI recovery from the acute through the chronic phase of repair and recovery
 3. Developing sensitive quantitative measures of motor, sensory and autonomic outcome
 4. Developing surrogate measures of outcome, particularly MRI of the spinal cord
 5. Evaluating basic discoveries for clinical translation
- Addressing the problem of delivering a neuroprotective therapy that can be given orally on the battlefield soon after injury – Phase 1 trial of Riluzole (See slides 5-11)



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Solution

The North American Clinical Trials Network (NACTN) for Treatment of Spinal Cord Injury

Nine Clinical Centers, a Pharmacological Center and a Data Management Center

Clinical Centers

1. **The Methodist Hospital, Houston**
Principal Investigator, Robert G. Grossman, M.D.
Project Manager, Elizabeth Touns, M.S., R.N., CCRP
2. **The University of Toronto, Toronto**
Michael Fehlings, M.D., Ph.D., Charles Tator, M.D., Ph.D.
3. **The University of Texas-Memorial Hermann Hospital, Houston**
Michele Johnson, M.D.
4. **The University of Virginia Hospital, Charlottesville**
Christopher I. Shaffrey, M.D.
5. **The University of Louisville, Louisville**
Maxwell Boakye, M.D., Susan Harkema, Ph.D.,
6. **University of Maryland, Baltimore**
Bizhan Aarabi, M.D.
7. **University of Miami, Miami**
James D. Guest, M.D., Ph.D.
8. **Thomas Jefferson University, Philadelphia**
James Harrop, M.D.
9. **Walter Reed Army Medical Center, Washington DC**
Michael Rosner, M.D.



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Solution

The North American Clinical Trials Network (NACTN) for Treatment of Spinal Cord Injury

- **Pharmacological Center**
University of Houston, College of Pharmacy
Diana Chow, Ph.D.
- **Data Management and Statistical Coordinating Center**
University of Texas School of Public Health – Data Management and
Statistical Coordinating Center
Ralph Frankowski, Ph.D.
Keith Burau, Ph.D.
- **NACTN Committees: Executive; Data Management; Neurological
Outcome Assessment (NOA); Treatment Strategy Selection;
Publications**



Project Description

Phase 1 Trial of Riluzole as a Neuroprotective Agent for Acute SCI

A major goal was reached this year with the completion of enrollment of the planned number of 36 patients in the Phase 1 Riluzole trial

Riluzole Mechanisms of Neuroprotection

1. Block of persistent, slowly inactivating sodium current (iNaP) channels, reducing influx of sodium and calcium into damaged neurons
2. Up-regulation of glutamate transporter 1 (GLT-1) in astrocytes reducing glutamate excitotoxicity
3. Amplification of heat shock factor 1 (HSF1) molecular chaperone

Preliminary Findings

1. Pharmacological analysis : Therapeutic plasma levels of Riluzole were achieved
2. Safety: The rate of SCI related complications in the Riluzole group was similar to that in a control group of matched patients from the NACTN registry. No Riluzole related serious adverse events (SAEs) (Slide 10)
3. Neurological Outcome: Comparison of the ASIA Impairment Scores (AIS) on admission and at 3 month examinations of the Riluzole treated patients with a control group of matched patients from the NACTN registry shows a trend towards greater improvement in the Riluzole treated patients (Slide 11). The number of treated patients is small; other factors such as early surgical decompression and stabilization are being analyzed. Confirmation with a larger number of patients is indicated.

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Project Description

Phase 1 Trial of Riluzole as a Neuroprotective Agent for Acute SCI

Protocol

Inclusion Criteria

- Age: 18-70
- Gender: male and female
- Neurological Level of Injury: C4-T12
- AISA Impairment Score (AIS): A, B or C
- Patient able to receive Riluzole within 12 hours of injury

Administration of Riluzole

Time window: First dose within 12 hours of injury

Dose: 50 mg

Route: Oral or Nasogastric tube

Frequency: q 12 hours

Duration: 28 doses (14 days)

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Project Description

Riluzole Phase 1 Trial - Schedule of Events

	Screening <12 hrs, from injury	Treatment Period														Post Treat.	Follow-up			
	Baseline	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	D/C Acute	6 wk F/U	3 Mo F/U	6 Mo F/U	Unschedul ed F/U
Chart Review																				
Recruit																				
Informed Consent Form																				
Case ID Data Identification																				
Medical History & Injury Detail																				
ASIA Exam																				
Clinical Blood Draw																				
Blood Plasma Draw																				
SCI Treatment Detail/Data																				
Medications																				
Riluzole Admin.																				
AE/SAE Complication																				
Surgery Data																				
BPI (Short Form)**																				
SCIM **																				
CSF Riluzole ***																				

***Blood plasma collected twice on day 3 and day 14; before Riluzole administration (Trough) and 2 hours after Riluzole administration (Peak).**

****Brief Pain Index (BPI Short Form) and Spinal Cord Independence measure (SCIM) recorded at 6 week, 3 month, 6 month and unscheduled visits.**

*****CSF test for determination of Riluzole concentration any day when CSF withdrawal is clinically indicated.**



Project Description

Phase 1 Trial of Riluzole as a Neuroprotective Agent for Acute SCI

DEMOGRAPHICS AND CHARACTERISTICS OF INJURY

Enrollment initiated 4/12/10 - completed 6/20/11 N = 36

Analysis of the first 31 patients enrolled

Demographics

Gender	N (%)	Age	Minimum	25 %	Median	75 th %	Maximum
Male	27 (87%)		18 yrs	22 yrs	37 yrs	56 yrs	69 yrs
Female	4 (13%)						

Cause of SCI

Cause	MVA	Falls	Diving	Cycle	Assault
	14 (44%)	8 (28%)	4 (12%)	3 (10%)	2 (6%)

Injury Level & Severity Grades A, B, C (column percents)

Injury Level	A	B	C	Total
Cervical	9 (60%)	8 (100%)	7 (100%)	24 (77%)
Thoracic	7 (40%)	0	0	7 (23%)
Total	15	8	7	31 (100%)



Project Description

Phase 1 Trial of Riluzole as a Neuroprotective Agent for Acute SCI THERAPY

Time from Injury to Admission and to Administration of Riluzole. N = 31 patients

Time	Minimum	25 %	Median	75 %	Maximum
Injury to Admission	0.7 hrs	1.5 hrs	2.3 hrs	4.2 hrs	7.0 hrs
Injury to Riluzole	3.7 hrs	7.1 hrs	8.5 hrs	10.6 hrs	12.1 hrs

Surgery by AIS Severity (Grades A, B, C)

Surgery	A	B	C	Total
Posterior	5 (33%)	2 (25%)	4 (50%)	11 (35%)
Anterior	1 (7%)	0	2 (25%)	3 (10%)
Both	8 (53%)	5 (63%)	1 (13%)	14 (45%)
None	1 (7%)	1 (13%)	1 (13%)	3 (10%)
Total	15	8	8	31 (100%)

Time from Injury to surgery; Riluzole Patients N=28 (3 patients had no surgery)

Time	Minimum	25 th %	Median	75 th %	Maximum
Injury to Surgery	6.4 hrs	8.8 hrs	12.8 hrs	23.6 hrs	213 hrs

NACTN Registry Data (Historical control from NACTN hospitals 2005-2011)

Time from injury to Surgery AIS A, B, C Patients admitted within 12 hrs of injury. N = 128

Time	Minimum	25 th %	Median	75 th %	Maximum
Injury to Surgery	3.4 hrs	9.2 hrs	17.3 hrs	41 hrs	736 hrs



Project Description

Phase 1 Trial of Riluzole as a Neuroprotective Agent for Acute SCI

Safety

Analysis of 31 patients. Admission to Acute Care Discharge 4/12/10 – 6/20/11

Incidence of severe complications by AIS Severity for 31 Riluzole Patients

Severe Complications	AIS A Severity N (column %)	AIS B Severity N (column %)	AIS C Severity N (column %)	Total N (column %)
Yes	5 (33.3%)	1 (12.5%)	3 (37.5%)	9 (29.0%)
No	10	7	5	22
Total	15	8	8	31

Incidence of Severe Complications by AIS Severity for 137 NACTN Registry Patients

Severe Complications	AIS A Severity N (column %)	AIS B Severity N (column %)	AIS C Severity N (column %)	Total N (column %)
Yes	26 (30.2%)	6 (20.7%)	0 (0.0%)	32 (23.4%)
No	60	23	22	105
Total	86	29	22	137

Relative Risk of Severe Complication by type for 31 Riluzole Patients compared to 137 NACTN Registry Patients

Complication	Riluzole Incidence N (% incidence)	Registry Incidence N (% incidence)	Risk Ratio	95% Confidence Interval	P-value
All	9 (29.0%)	32 (23.4%)	1.24	(0.66, 2.33)	0.496
Pulmonary	4 (12.9%)	19 (13.9%)	0.93	(0.34, 2.54)	1.000
Cardiac	3 (9.68%)	9 (6.57%)	1.47	(0.42, 5.12)	0.465
Hematological	3 (9.68%)	2 (1.46%)	6.63	(1.15, 38.0)	0.044
GI/GU	2 (6.45%)	3 (2.19%)	2.95	(0.51, 16.9)	0.230
Infection	1 (3.22%)	12 (8.76%)	0.37	(0.5, 2.73)	0.466
Neurological	1 (3.22%)	3 (2.19%)	1.47	(0.16, 13.7)	0.561



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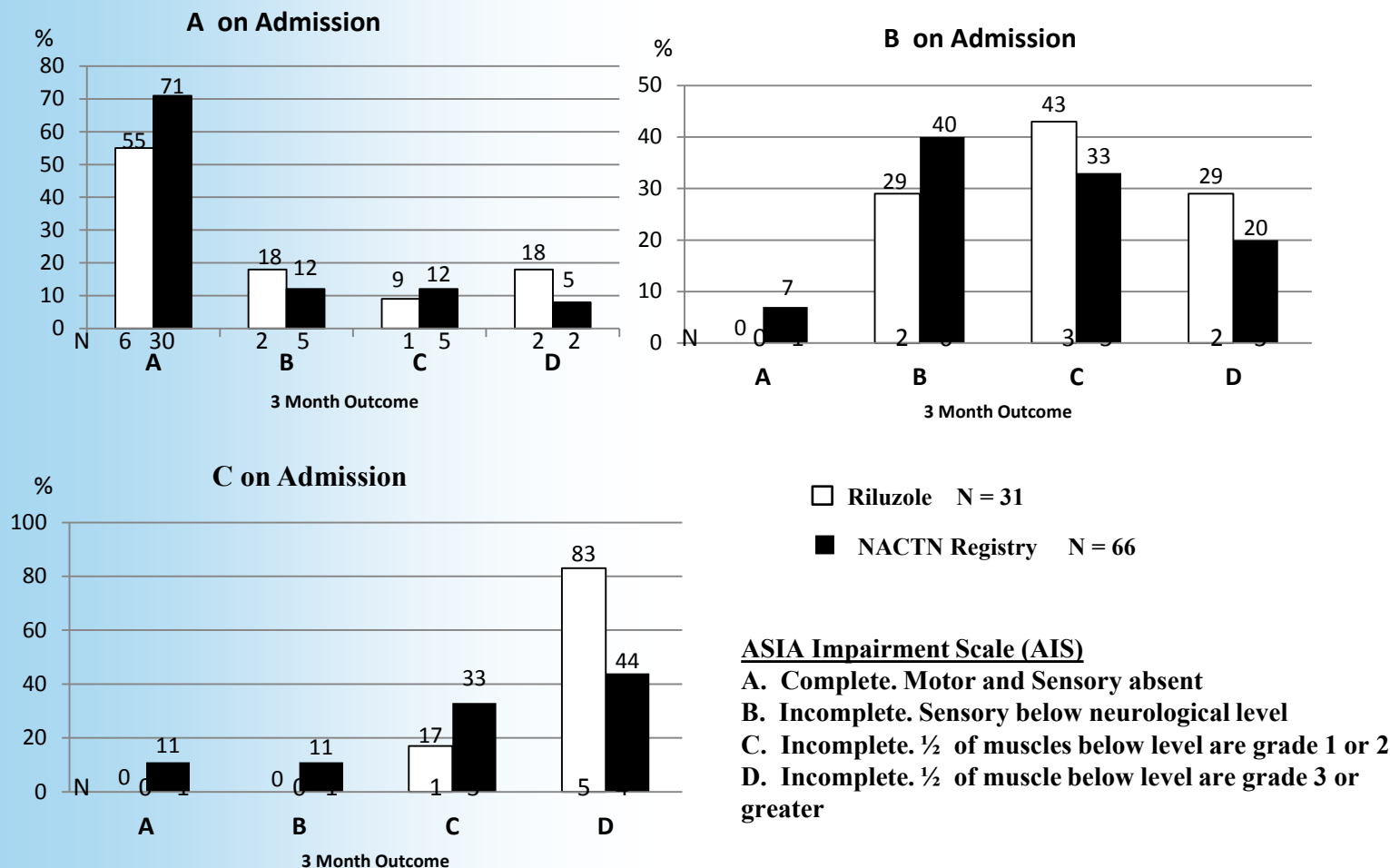
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Project Description

Phase 1 Trial of Riluzole as a Neuroprotective Agent for Acute SCI

Neurological Outcome

Admission AIS Score and AIS Outcome at 3 Months and Comparison with NACTN Registry Patients





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Validation Strategy

What is your validation strategy?

- Detailed analysis is underway of the Phase 1 Riluzole trial by Drs. Ralph Frankowski and Keith Bureau of the Data Management Center, Dr. Diana Chow of the Pharmacological Center, Dr. Grossman of the Coordinating Center and the NACTN PIs. Comparisons of adverse events and neurological outcomes are being made with the outcomes of the 488 SCI patients admitted to the NACTN hospitals 2006-2011 who are enrolled in the NACTN registry.

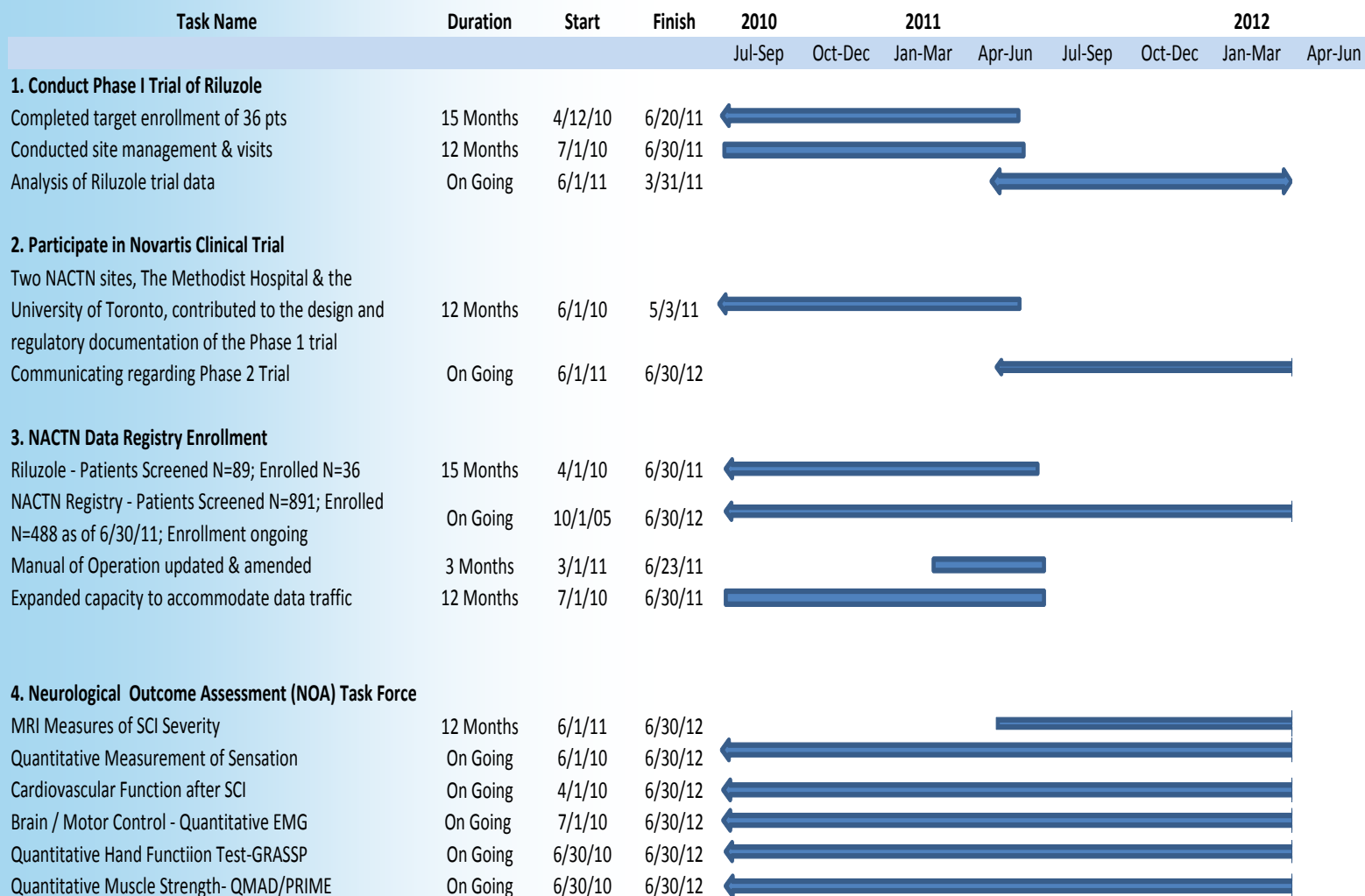
Additional comparisons are being made with the data base of the Surgical Treatment of Acute SCI study (STASCIS) of over 400 patients and with the data base of the European Multicenter Study about SCI (EM-SCI) with over 1800 patients.

Pharmacological analysis is being carried out of plasma levels of Riluzole and outcome.



Research/Development Timeline

North American Clinical Trials Network (NACTN)



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Successes to Date

1. **Completion of enrollment of 36 patients in Phase 1 trial of Riluzole as a neuroprotective agent in SCI. No serious adverse effects related to Riluzole (first 31 patients). There is a trend toward improved neurological outcomes.**
2. **Development of sensitive method of measuring Riluzole in plasma. Analysis of pharmacokinetics of Riluzole plasma levels in first 33 patients**
3. **Enrollment of 488 acute SCI patients into NACTN data registry effective July 6, 2011**
4. **Neurological Outcomes Assessment Task Force is developing sensitive quantitative outcome measures:**
 - (a) **MRI measures of SCI, M. Fehlings, MD, PhD, University of Toronto**
 - (b) **Electrical perceptual threshold quantitative measurement of sensation, P. Ellaway, PhD., Imperial College, London**

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Successes to Date Part 2

- (c) Cardiovascular function after SCI, A. Krassioukov, MD, PhD, U British Columbia**
- (d) Brain/motor control – quantitative EMG, S. Harkema, PhD, U Louisville**
- (e) Quantitative Hand Function Test (GRASSP), S. Kalsi-Ryan, PhD, U Toronto**
- (f) Quantitative muscle strength – QMAD/PRIME, R. Grossman, MD, Methodist Hospital**
- (g) Merging NACTN, STASCIS and EM-SCI data bases providing a registry of over 2000 acute SCI and their neurological outcomes**



Challenges

Technical or programmatic

- **Incorporating the quantitative measures of motor, sensory and autonomic functions developed by NOA into the Phase 2 Riluzole trial**
- **Developing the design of the Phase 2 Riluzole trial and determining the size of the control and experimental groups**

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What's Next

- **Complete the safety, neurological outcome and pharmacological analysis of the Phase 1 Riluzole trial, September – December, 2011**
- **Develop protocol for the Phase 2 Riluzole trial**
- **Continue integration of NACTN/STASCIS/EM-SCI data bases to provide a prior data set for the design of the Phase 2 Riluzole trial**
- **Validate NOA quantitative outcome measures and incorporate into the Phase 2 Riluzole trial**
- **Continue enrollment in the NACTN SCI registry**
- **Expansion of NACTN to new military hospitals: San Antonio Military Medical Center (SAMMC). Discussions in September – October with Lt. Col. Randall McCafferty, neurosurgical service**



Compare Competing Solutions

- **NACTN is the only standing, on-going network for conducting clinical trials of new therapy for SCI. It has been developed to evaluate and to be able to carry out the full range of pharmacologic, surgical, regenerative, cellular transplantation and electrical and exercise – induced plasticity therapies presently being planned in investigator initiated and industry studies.**
- **There is a paucity of current SCI trials in the USA. There is one currently on-going industry-sponsored Phase 1 trial of stem-cell transplantation (Geron Corporation).**
- **The Novartis Phase 1 trial of the anti-Nogo antibody, a regenerative therapy, has completed enrollment of 14 patients in Cohort 5 and the data is being analyzed. Two NACTN sites (Toronto and Methodist) contributed to the study design and regulatory process. Novartis has indicated a desire for NACTN participation if they move forward with a Phase 2 trial.**

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Intellectual Property / Publications Deriving from this Project

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- **Acute Complications after Spinal Cord Injury – A Multicenter Prospective Study of the Spectrum. Incidence and Severity: The North American Clinical Trials Network (NACTN) for Treatment of Spinal Cord Injury; Robert G. Grossman, Ralph F. Frankowski, Keith D. Burau, Elizabeth G. Toups, Michele M. Johnson, Michael G. Fehlings, Christopher I. Shaffrey, Susan J. Harkema, Jonathan E. Hodes, Bizhan Aarabi, Michael K. Rosner, James D. Guest, James S. Harrop. *J Neurotrauma*, in review.**
- **The Graded Redefined Assessment of Strength, Sensibility and Prehension (GRASSP): Reliability and Validity; Sukhvinder Kalsi-Ryan, Dorcas Beaton, Armin Curt, Susan Duff, Milos R. Popovic, Claudia Rudhe, Michael G., Fehlings, and Mary C. Verrier, in press *J Neurotrauma*.**
- **ASIA/ISCOS Course I: (Outcome Measures for Acute/Sub-acute Cervical AIS-A SCI during a Phase 2 clinical Trial): GRASSP Version 1.0 Clinical Measure of Upper Limb impairment for individuals with Traumatic Tetraplegia: Psychometrics, Impairment and Relationships to Function; Sukhvinder Kalsi-Ryan BScPT, MSc, PhD, June 6, 2011.**
- **NACTN: Building a Clinical Trials Network for Spinal Cord Injury, Robert G. Grossman, Elizabeth Toups, Ralph Frankowski, Keith Burau, Susan Howley, for the NACTN investigators, included in the book, *Essentials of Spinal Cord Injury*, publisher Thieme, in press.**
- **Data-sharing agreements between NACTN and the University of Zurich, Balgrist University Hospital and a signed Memorandum of Understanding between Reeve Foundation (NACTN) and the Ontario Neurotrauma Foundation to explore establishment of an NRN in Toronto and the addition of St. Michael's and Sunnybrook Hospitals to NACTN.**



Transition/ Business/ Marketing Plan

- **NA at this stage**

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Additional Project Information

**Lab/Company/Group: Christopher Reeve
Foundation**

Principal Investigator: Robert Grossman

Government COR: Ken Curley

Government Project Officer: Jennifer Blumberg

**Contract Instrument: Grant/Cooperative
Agreement**

**Period of Performance: 14-May-2007 – 18-Aug-
2012**

Contract Specialist: Lance Nowell

EDMS# : 3204

Contract #: W81XWH-10-2-0042

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Peter H Ellaway and Maria Catley: Comparison of the Electrical Perceptual Threshold and Semmes-Weinstein Monofilament Tests of Cutaneous Sensibility. In preparation to be submitted to Spinal Cord 2012

Fehlings, MG, Arvin B. The Timing of Surgery in Patients with Central Spinal Cord Injury. J Neurosurg - Spine 2009;10(1):1-2

Michael G. Fehlings, editor and the NACTN investigators: JNeurosurg - Spine 2012 Supplement. Manuscripts submitted

Fehlings MG, Vaccaro A, Wilson JR, Singh A, Cadotte DW, Harrop JS, Aarabi B, Shaffrey C, Dvorak M, Fisher C, Arnold P, Massicotte EM, Lewis S, Rampersaud R., Early versus Delayed Decompression for Traumatic Cervical Spinal Cord Injury: Results from the Surgical Timing in Acute Spinal Cord Injury Study (STASCIS). Accepted "PloS One" January 2012

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