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14. ABSTRACT 666 acutely injured spinal cord subjects have been enrolled in the NACTN data registry and enrollment is ongoing at all nine clinical centers. NACTN has (i) completed a Phase 1 safety study of the neuroprotective drug Riluzole and a manuscript detailing the results has been accepted for publication in the Journal of Neurotrauma; (ii) formed a partnership with AOSpine North America and AOSpine International to conduct a Phase 1/111 clinical trial of Riluzole, expected to begin enrollment later this year; (iii) published 17 papers in the NACTN/AOSNA Focus Issue on Spinal Cord Injury, Journal of Neurosurgery: Spine, Volume 17 September 2012; online at (http://thejns.org/toc/spisup/17/1); (iv) adopted and revised several times a Governance Manual to regulate network activities, deliberations and decision-making; (v) transitioned to an Electronic Data Capture (EDC) system through Systemax's ITW, a medical records and data collection web application with a data center; (vi) entered into data sharing and research partnerships with AOSpine Int'l and EM-SCI. NACTN's Data Committee developed extensive new policies and procedures related to internal and external use of data, publications and authorship. The Treatment Strategy Selection Committee met quarterly to review the spinal cord injury pipeline and identify therapeutics for NACTN to test; it also tapped new members who bring value-added expertise to the Committee. Publications continue to emerge from its Neurological Outcomes Assessment awards. NACTN and NeuroRecovery Network principals teamed up for an instructional course at the 2013 ASIA annual meeting.					
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INTRODUCTION:

Spinal cord injuries are catastrophic to the patient, family members, and society at large. Estimated lifetime care costs vary based on severity of injury (and age at injury). Expenses for a C1-C4 quadriplegic injured at age 25 are estimated to be \$4.37 million and for a paraplegic injured at 25, approximately \$2.1 million. That December 2010 figure does not include indirect costs such as lost wages, fringe benefits and productivity, which are estimated to approach \$66,626 (2010 dollars) annually per patient (2). Annually, paralysis and SCI cost an approximate \$40.5 billion, which is a 317% increase from estimated costs in 1998. (Cahill et al, 2009) What none of these figures adequately capture however is the enormous personal human toll taken on the injured, their families, communities and the larger society.

The field of spinal cord research continues to burgeon with academic laboratories dedicated fulltime to pursuit of strategies to repair the damaged spinal cord. In the case of the Reeve Foundation alone, its International Research Consortium on Spinal Cord Injury has given rise to more than 30 new independent spinal cord labs headed by former Consortium Associates (graduate and postdoctoral students). The federal website clinicaltrials.gov lists 531 spinal cord clinical studies (recruiting, active – not recruiting, unknown, completed). There are now biotech and pharmaceutical companies with portfolios that include spinal cord; among these are Novartis, BioAxone BioSciences, NeuralStem Inc., Acorda Therapeutics, StemCells Inc., Asubio Pharmaceuticals and InVivo Therapeutics.

Human clinical trials are underway across international sites. In January of this year, Neuralstem announced it had received FDA approved by the FDA to begin a Phase I safety trial of its neural stem cell line NSI-566 in patients with chronic spinal cord injury. That same month at Jackson Memorial Hospital in Miami, FL, doctors at The Miami Project to Cure Paralysis enrolled their first subject into a Schwann cell transplantation safety study. In early June, StemCells, Inc. announced that its Phase I/II clinical trial for chronic spinal cord injury had received approval from Health Canada to expand the study to Canadian sites (as of this writing, none have yet been announced). To-date, four patients have been enrolled at the Balgrist Hospital trial site in Zurich. In March 2013, a team of Miami investigators published results of a study in the journal *Spinal Cord* exploring the efficacy of modest hypothermia as an in 35 acute patients (Dididze et al, 2013). And in the *Journal of Neurotrauma* (2012) Wilson et al describe a new model based on motor function at admission and early imaging studies – all within three days of injury - may allow clinicians to better identify likely outcomes at one year (important for decision-making about the best candidates for clinical trials, for new therapies that may emerge and longer term lifestyle and caregiving issues). A recent Lancet publication (Freund et al) reports on the use of MRI to track the degeneration in the cord above the injury. The investigators show this happens earlier than expected and that there is a direct correlation between more tissue loss and less recovery. A commentary to the journal article, “Will imaging biomarkers transform spinal cord injury trials?” which was published simultaneously and was co-authored by NACTN investigator Michael Fehlings, helps frame the Lancet study.

Knowledge about the normal and injured cord continues to expand exponentially. Within the last two years alone, there have been publications that speak to neutralizing one part of the inhibitory scar (Petrosyan et al, 2013); identification of interneurons responsible for grasping (Bui et al, 2013); regeneration and functional recovery (Thuret et al, 2012); restoration of bladder function (Lee et al, 2013) (follow-on work to the 2011 Alilain et al publication on regeneration of respiratory pathways); transplantation of olfactory ensheathing glia (Tabakow et al, 2013); transformation of umbilical blood cells into cells that look and act remarkably like neurons - they transmit electrical impulses, a sign that they are mature and functional (Giorgetti et al, 2012); the potential salutary effect of Docosahexaenoic acid (DHA) in chronic spinal cord injury (Holly et al, 2012); the relationship between new growth cone assembly and regeneration (Bradke et al, 2012); and a combinatorial approach to repair (Zhao et al, 2013).

Interest in spinal cord translation is keener than ever and Reeve’s two clinical research networks made important contributions on that front during the past year. The NeuroRecovery Network published eleven peer-

reviewed studies in the September 2012 issue of the *Archives of Physical Medicine & Rehabilitation*. The North American Clinical Trials Network published 17 peer reviewed papers in a special supplement to the September 2012 issue of the *Journal of Neurosurgery: Spine*.

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. There are presently nine NACTN clinical centers and Coordinating, Data Management and Pharmacology Centers.

BODY: The following tasks have been addressed during the contract period July 19, 2012 – July 18, 2013:

1. Conduct a Phase I safety study of Riluzole. Local IRB approvals are in place at all sites. We anticipate sufficient data on safety and neurological outcome data to set the stage for a Phase 2 trial.

Riluzole is a neuroprotective drug whose 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. Riluzole has been shown to be highly effective in limiting traumatic damage to the spinal cord in laboratory studies (Schwartz et al 2001, 2002; Liu et al 2011). Riluzole is currently used in clinical practice for treatment of amyotrophic lateral sclerosis.

A phase 1 trial of Riluzole was undertaken to investigate its therapeutic potential in SCI. The Phase I trial included 36 patients with traumatic acute spinal cord injury from C4 to T12. Most patients were male (83 percent) and had a cervical injury (78 percent). All were treated within 12 hours of injury. Riluzole, 50 mg, was administered enterally (tablet form) every 12 hours for 14 days. At the successful conclusion of the Riluzole safety study, NACTN did an exhaustive analysis of the data in preparation for a Phase 2 efficacy study and publication of the Phase 1 results.

<http://www.clinicaltrials.gov/ct2/show/NCT00876889?term=spinal+cord+injury+AND+riluzole&rank=1>

In our August 19, 2012 annual report (W81XWH-10-2-0042), we provided extensive details on the results of the Phase 1 study titled *Safety and Pharmacokinetics of Riluzole in Patients with Traumatic Acute Spinal Cord Injury*. Dr. Grossman received notification on July 6, 2013 that the Journal of Neurotrauma had accepted NACTN's Phase 1 manuscript, "A Prospective Multicenter Phase 1 Matched Comparison Group Trial of Safety, Pharmacokinetics, and Preliminary Efficacy of Riluzole in Patients with Traumatic Spinal Cord Injury," for publication. He exercised the Liebert Open Option on behalf of NACTN, which means that the paper will be made free online immediately upon publication. (Attachment A)

Planning for a Phase 2 Riluzole clinical trial: In our August 19, 2012 annual report, we also included a lengthy update on planning for the follow-on efficacy study. The Phase II/III trial – called RISCIS, for Riluzole in Spinal Cord Injury Study – will include 350 patients with cervical injuries, the group that seems to benefit most from the drug, at as many as 20 clinical centers. The trial is being undertaken as collaboration between NACTN and AOSpine (North America - AOSNA) and (International - AOSI). AOSNA is a registered, not-for profit 501(c) (3) foundation which is focused on research and education related to spinal conditions. AOSI is an association of spine surgeons, orthopedic surgeons, neurosurgeons, academics, researchers, and other spine care professionals focused on improving the quality of medical services provided to spinal patients through education, research, documentation and communication.

The RISCIS partnership between the two AOSpine entities and NACTN plays to the strengths of both groups. NACTN brings strong expertise in spinal cord injury, prospective data collection, outcome measures,

pharmacology and the recent experience of having run the Phase I trial of Riluzole in acute spinal cord injury. AOSNA brings a strong, complementary clinical research network with an in-house CRO which has considerable expertise in running multi-center trials, including the recent examination of Riluzole in non-traumatic spinal cord injury (CSM Protect Study). This partnership could not have been forged without the longtime support the Department of Defense has provided to the Reeve Foundation for NACTN.

As detailed extensively in our August 19 2012 annual report, representatives from the Reeve Foundation, NACTN and AOSpine International and North America met July 6-7, 2012 in Houston to begin refining a draft Phase II/III protocol and identifying next steps for implementation of the clinical trial. There was also considerable discussion directed at codifying the (administrative, funding, clinical and scientific) roles and responsibilities of NACTN and AOSpine principals.

The Phase II/III protocol was finalized and locked December 21, 2012 and a copy was attached to our Y3 Q2 report submitted February 1, 2013. The "Pharmacology of Riluzole in Patients with Acute Traumatic SCI" protocol, an addendum to "A Multi-Center, Randomized, Placebo-Controlled, Double-Blinded, Trial of Efficacy and Safety of Riluzole in Acute Spinal Cord Injury" protocol has been written and is appended as **Attachment B**.

Presently, a RISCIS framework agreement has been drafted and is under discussion by representatives of the partners (**Attachment C, DRAFT as of 7/18/2013**). At the same time, a budget detailing the shared and "local" costs of the study is in preparation but it remains a work-in-progress. The Rick Hansen Foundation has not yet made a decision about whether to become a RISCIS partner but a commitment to do so would favorably impact the budget by reducing each partner's shared costs. Central costs of the study to which NACTN will contribute include but are not necessarily limited to project management; database servers, administration, training and clinical data management per site; trial insurance; investigational drug and other supplies; DSMB, safety officer. "Local" costs paid fully by NACTN include annual grants to the clinical sites for study coordinator(s) and other RISCIS-related expenses; site monitoring; and all costs associated with the Phase II/III pharmacological study.

Once finalized, the framework agreement and budget will govern all aspects of the RISCIS trial.

2. Participation by NACTN sites in the Novartis clinical trial of the monoclonal antibody to Nogo.

Martin Schwab, PhD, University of Zurich, advised Dr. Grossman that no decision will be made as to whether or not Novartis will take the ATI-355 anti-Nogo antibody to a POC trial until early fall when Ricardo Dolmetsch, PhD, Associate Professor, Neurobiology at Stanford University, will become the new global head of neuroscience research at Novartis. NACTN continues to express interest in participating in that study, presuming the corporate decision is made to move forward with it.

3. Expansion of NACTN to new military hospitals. San Antonio Military Medical Center – Brooke Army Medical Center/Wilford Hall Medical Center (BAMC), Tripler Army Medical Center, and/or Landstuhl Regional Medical Center (LRMC), are candidate sites:

Brooke Army Medical Center (BAMC) formally joined NACTN in January 2012. As noted in quarterly updates and the #0042 2012 annual report (submitted August 17, 2012), the site received DOD approval July 12, 2012 to screen and enroll patients into the NACTN data registry. Dr. Robert Marsh, the initial BAMC NACTN Principal Investigator, has been replaced for the current 2013 contract year by Joseph K. Hobbs, MD (**Attachment D**). Unfortunately, as noted in several of the most recent DOD reports, continued expansion to other military hospitals has been stalled due to funding limitations.

4. Characterize the Biomechanical, Anatomical and Neurological Differences between Military and Civilian Injuries and Differences in their Outcomes

A list of patients who fit the SCI criteria and information about their medical treatment through the initial echelons of combat casualty care has been obtained with required permissions from the Joint Theater Trauma Registry (JTTR). While this data will have its own limitations based on the data collection capabilities at the different phases of each conflict, Dr. Rosner and his team hope that it will provide a general overview of best management options for spinal column injuries in the wounded warrior. Additional data will be collected from WRNMMC medical records of patients admitted between the dates 1 January 2003 to 23 March 2008. This review of records for wounded service members with SCI from the place of injury to the definitive treatment facility will more fully describe the military medical treatment for SCI sustained during the OIF/OEF conflicts. The timing and type of surgical intervention and stabilization options of the spine as well as assessment of the pattern of spine care in the military setting compared to civilian settings will be explored. Intervention variations based on penetrating vs blast injuries will also be evaluated to assess for possible treatment variations and injury patterns.

Dr. Rosner has identified an individual to assist with collection of the retrospective data and he will be added as an associate investigator on the protocol. The estimated timeline includes 3-4 months for data collection, 3 months for analysis, 3 months for manuscript preparation/submission (brief narrative of the project previously sent). The data is pre-merge and the WRNMMC NACTN team anticipates a possible initial hurdle to obtain full access to WRAMC (old) records, but they believe it is doable.

5. Neurological Outcomes Assessment (NOA) Task Force – an international Task Force was set up to develop, test and validate sensitive outcome measures to detect incremental improvements in human clinical trials.

The following summarizes status of the NOA contracts issued in conjunction with #0361 and #0042 contracts:

- Peter Ellaway, PhD, Imperial College London (NOA1-2010-PE) for “Validation of the electrical perceptual threshold test as a quantitative assessment of cutaneous sensory function for spinal cord injury trials.” The article emerging from this project, “Reliability of the electrical perceptual threshold and Semmes-Weinstein monofilament tests of cutaneous sensibility” was published in Spinal Cord (2013) 51, 120-125 and was appended to our April 18, 2013 Y3 Q3 narrative report.
- Michael Fehlings, MD, PhD, University Health Network (University of Toronto) (NOA5-2011-MF) for “The use of MRI characteristics to predict long-term functional and neurological outcomes after acute spinal cord injury.” The article emerging from this project, “A Clinical Prediction Model for Long-Term Functional Outcome after Traumatic Spinal Cord Injury Based on Acute Clinical and Imaging Factors,” was published in the Journal of Neurotrauma v29 i13 August 28, 2012 and was submitted with our #0042 July 18, 2012 annual report.
- 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.” Final reports for both awards were included with our January 18, 2013 Y3 Q2 narrative report and Dr. Krassioukov’s ISCOS abstract (London, September 3-5, 2012) was also submitted.
- Susan Harkema, PhD, University of Louisville (NOA4-2010-SH) for “Brain/Motor Control-EMG measures.” An article emerging from the project, “Quantitative and sensitive assessment of neurophysiological status after human spinal cord injury,” was published in J Neurosurgery: Spine September 2012, v17, as part of the NACTN/AOSNA Focus Issue on Spinal Cord Injury.

6. Ongoing validation of the Graded Refined Assessment of Strength, Sensibility and Prehension (GRASSP) test and further development of computerized measurement of force generated by the isometric contraction of muscles (Quantitative Motor Assessment Device – QMAD; PRIME). Funding would facilitate bringing QMAD into clinical practice with a portable force-transducer device with output recorded on a handheld PC to monitor and track return of motor function.

A new publication emerging from the GRASSP project is nearing publication in *Neurorehabilitation and Neural Repair*: "Defining the Role of Sensation, Strength, and Prehension for Upper Limb Function in Cervical Spinal Cord Injury." A prepublication copy of the manuscript is appended. ([Attachment E](#))

Prior to Gerard E. Francisco, MD, Chief Medical Officer at TIRR Memorial Hermann and Chair, Department of Physical Medicine and Rehabilitation, The University of Texas Medical School, Houston, and his research team initiating subject data collection of the PRIME, test runs with two SCI patients were initiated at TIRR Memorial Hermann. Problems were identified related to hardware, software and to the set-up. The research team and engineers from OrthoIntrinsic have worked closely to correct the issues. Additionally, therapy coordinators have been identified for assisting with recruitment. Four SCI subjects have been screened for enrollment. Amendments to the protocol have been approved to expand enrollment of subjects with stroke with acute, subacute and chronic stage. Data collection is planned to be completed by September 2013 and data analysis by the end of 2013.

7. Continued enrollment of acutely injured SCI patients into the NACTN Data Registry.

The NACTN 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 and Phase II clinical trials of emerging neuroprotective and neuroregenerative therapies, particularly those that can be administered in the very early stages of injury. 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 traumatic 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.

Currently there are nine clinical centers participating in the registry and as of 08/01/2013, 666 patients had been enrolled into the NACTN SCI Registry.

Registry Data Profile

Tables in [Attachment F](#) provide a profile of SCI cases currently in the registry database. As of 08/01/2013, clinical coordinators at the NACTN clinical sites had screened 1166 SCI patients for registry eligibility. Informed Consent to record prospective standardized acute care treatment data and follow-up data for up to one-year after acute care discharge was given by 666 patients (Table 1). Of these, acute care treatment records for 600 patients are currently in the registry research database with an additional 66 patient records pending entry into the electronic data entry system. The following text summarizes selected demographic, treatment, and outcome information for 568 patients with complete inpatient discharge data.

The majority of registry cases are male (81%) and white (71%). The median age at injury is 45 years; approximately 81% of the 564 registry cases are 20 to 65 years-of-age and 14% are older than 65 (Table 2).

Table 3 lists the circumstances of SCI injuries. The leading circumstances of injury were falls (37%) and motor vehicle accidents (29%). Recreation including sports injuries accounted for (11%). Diving was responsible for 60% of all sports injuries. Civilian assaults accounted for 36 cases (6%) of all SCI injuries.

Military personnel accounted for 16 (3%) of all SCI injuries. Of these, 15 were SCI injuries transferred from Landstuhl (Germany) Regional Medical Center to Walter Reed Army Medical Center (WRAMC). Five of these 15 cases were penetrating bullet wound injuries; seven were classified as blast (IED) injuries; one the result of a helicopter crash, and one due to an accidental fall. Fourteen Landstuhl cases were transferred to WRAMC within 2 to 9 days of injury and one case transferred 18 days after injury. The lone stateside military case was a SCI injury due to a surfing accident, and this case was transferred to WRAMC 15 days after injury from a civilian hospital in Virginia Beach, VA.

Approximately 58% of civilian SCI patients arrived by EMS directly from the site of injury to a NACTN center with a median arrival time of approximately one hour. Of patients transferred from intermediate hospitals the median arrival time post-injury at a NACTN center was 10 hours.

The distribution of AIS severity of patients with a first AIS within seven days of injury is given in Table 4; AIS A (33%), AIS B (10%), AIS C (12%), AIS D (24%), AIS E (7%). Approximately 14% of the 564 patients did not have initial AIS recorded within 7 days of injury.

Of the 568 cases, 38% had no reported complications or intercurrent events during acute care whereas 61% had at least one mild, moderate or severe complication (Table 5). Of the total number of complications ascertained during acute care (1,657) and reported in Table 6, pulmonary, infections, hematologic, and cardiac complications accounted for 75% of all complications. Table 6 also reports the number of patients accounting for each type of complication. For example, 201 patients experienced 393 pulmonary complications giving an incidence rate of 201/568 (35.4%) for pulmonary complications. Incidence rates for each type of complication are given in the last column of Table 6.

The vast majority of SCI injuries were blunt injuries (80%) or crushing injuries (14%), but 5% were penetrating SCI injuries, primarily bullet injuries. Of the 568 patients, 74% sustained cervical injuries and 20% thoracic injuries (Table 7).

Surgical and corticosteroid treatments are summarized in Tables 8 and 9. Of patients evaluated as AIS A through AIS D within seven days of injury 92% were surgically treated whereas 50% of AIS E patients were surgically treated. Approximately 50% of AIS A through AIS D patients received corticosteroid treatment. The distribution of steroid use by first AIS grade is given in Table 9.

Length of acute care hospitalization and discharge status is summarized in Table 10. For 568 SCI patients, approximately 45% had a length of hospital stay exceeding two weeks. Nearly three quarters of the SCI patients were discharged to a rehabilitation hospital (73%) and 6% were transitioned to either long-term acute care or a nursing home. Rehabilitation was initiated for 85% of the patients prior to discharge from acute care.

Table 11 contrasts the AIS grades at admission to AIS grades at hospital discharge for 472 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 compares AIS grades at admission to AIS grades at six months post-injury for 254 patients. Substantial improvement in outcomes at six months was seen at all AIS grades.

Summary

Important milestones were achieved by the registry. With more than 600 cases entered into the NACTN database, the registry has demonstrated that is feasible to acquire prospective standardized research quality clinical data on incident traumatic SCI patients. The NACTN registry research database has provided the main substance for the papers published in the Journal of Neurosurgery - Spine September 20, Volume 17, Special Supplement on SCI clinical translation, and also provided the data needed to plan and implement the Phase I trial of Riluzole.

The NACTN registry has been recognized as national and international resource for SCI research and has been invited by AOSpine International to become a research partner in the AOSpine International project, "AOSpine Knowledge Forum database merge: an overall description of the SCI patient population and related outcomes". NACTN will contribute a subset of approximately 300 anonymized civilian SCI cases to this project.

As detailed in our Y2 annual report submitted 8/17/2012, the NACTN registry data collection system has transitioned from paper submission of data to an electronic data capture (EDC) system. During the past nine months, the University of Louisville registry personnel have been refining and improving the EDC system – its use is codified in the ITW section of NACTN's Manual of Operations ([Attachment G](#)), which was revised 4/16/13. The transition to EDC has removed many data entry errors at the time of entry, rather than at the time of submission to the data center. Error checking and integrity of the data can be done in a more timely fashion, if not almost instantaneously. These improvements to the database will result in more accurate and complete data furthering the goals of the NACTN Registry.

The original goal to enroll 500 patients in the registry has been surpassed with the 666 subjects enrolled at this time.

Electronic Data Capture: as detailed in our Y2 annual report submitted 8/17/2012, NACTN effectively transitioned to an Electronic Data Capture (EDC) system in September 2012 through Systemax's ITW, a medical records and data collection web application with a data center. ITW is used also for the Reeve Foundation's NeuroRecovery Network database; use of the same EDC system by both clinical networks has important research implications downstream.

8. Continued analysis of data for publications and presentations.

As noted in our October 18, 2012 Y2 Q1 narrative report, the NACTN/AOSNA Focus Issue on Spinal Cord Injury, supplement to the *Journal of Neurosurgery: Spine*, Volume 17, was published September 1, 2012, in print and online at (<http://thejns.org/toc/spisup/17/1>). The 17 papers, which identify and evaluate different kinds of spinal cord trauma, detail the incidence and severity of acute complications after SCI, summarize evidence on the predictors of neurological outcomes and prognoses in patients with cervical and thoracic injury and discuss graded assessments to better define the scope and extend of injury, were an important infusion of new information for the field. Some of the papers were based on NACTN's prospective data registry; others discussed original clinical studies; and others still examined NACTN as an organic clinical research network and focused on its organization and decision-making processes for choosing potential therapeutics for evaluation. The J Neurosurgery Special Supplement was submitted as an attachment with our October 18th quarterly report.

As reported above (1), the results of the NACTN Riluzole Phase 1 safety study will be published in the Journal of Neurotrauma: "A Prospective Multicenter Phase 1 Matched Comparison Group Trial of Safety, Pharmacokinetics, and Preliminary Efficacy of Riluzole in Patients with Traumatic Spinal Cord Injury."

The January 18, 2013 Y3 Q2 narrative on this award provided an accounting of work of NACTN's Data Committee, which developed new policies for data integrity and dissemination and manuscript authorship. Those policies were approved by the Executive Committee on January 14, 2013 and presented to the other NACTN Principal Investigators at their monthly meeting on January 16, 2013. Accordingly, the Governance Manual was updated to include the newly approved data policies and procedures, which were submitted as an attachment to the January 18th report.

9. Creation of NACTN governing board, executive committee, a committee structure, and a manual of policies and procedures to codify governance.

As detailed at different times in our narrative reports, the NACTN Governance Manual has been periodically revised to reflect the Network's evolving needs. Revisions included addition of a policy on Confidentiality to engender an environment of collegiality and trust to allow for the open, honest and professional exchange of ideas and the orderly and rigorous pursuit of NACTN-related activities. There were also multiple changes to policies related to Requirements of Individual Sites, Informed Consent and Contracts and Reporting to insure more rigor and accountability in NACTN's operations and activities. Finally, as noted above at (7), new policies

intended to insure data integrity and initiate an orderly step-wise process for access to and dissemination of data were developed and incorporated into the Governance Manual. A copy of the current version (v3, May 2013) is appended as Attachment H.

10. Policies and procedures to solicit and choose promising new therapies from academia and pharma for testing and creation of committee, including basic scientists for this purpose.

The Treatment Strategy Selection Committee 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. Under the leadership of Charles Tator, MD, PhD, the Committee convenes quarterly by teleconference. At its last meeting on May 13, 2013, the Committee agreed to extend invitations to individuals whose expertise would be valuable to the group's deliberations; three are non-NACTN members:

- i. Arnold Snider, vice chairman, Reeve Foundation Board of Directors
- ii. Armin Curt, MD, professor and chairman, Spinal Cord Injury Center, University of Zurich, University Hospital Balgrist; Dr. Curt is the PI on the ongoing Phase 1 Stem Cells Inc. spinal cord clinical trial
- iii. Graham Creasey, MD, Department of Neurosurgery, Stanford University and Spinal Cord Injury Service, VA Palo Alto Health Care System.

Susan Harkema, PhD, NACTN co-PI, University of Louisville; Principal Investigator Reeve NeuroRecovery Network, was also invited to participate.

These four have all agreed to join the Committee. Additionally, Naomi Kleitman, PhD, formerly program director NINDS repair and plasticity – spinal cord injury, recently resigned her position there to take up new responsibilities at a private foundation and at that time tendered her resignation from the NACTN Treatment Strategy Selection Committee. Dr. Tator will invite her successor, when appointed, to take Dr. Kleitman's place.

11. Continued cooperation with other SCI organizations

NACTN and STASCIS: Reference (4) above and the resulting publication that emerged from a NOA project and the merged NACTN/STASCIS databases: "A Clinical Prediction Model for Long-Term Functional outcome after Traumatic Spinal Cord Injury Based on Acute Clinical and Imaging Factors, Jefferson R. Wilson, Robert G. Grossman, Ralph F. Frankowski, Alexander Kiss, Aileen M. Davis, Abhaya V. Kulkarni, James S. Harrop, Bizhan Aarabi, Alexander Vaccaro, Charles H. Tator, Marcel Dvorak, Christopher I. Shaffrey, Susan Harkema, James D. Guest and Michael G. Fehlings, JNeurotrauma 29:1-9 September 1, 2012

NACTN and EM-SCI: NACTN's DMC NACTN has had access to the European Multicenter Study about Spinal Cord Injury (EM-SCI) data registry (SCI cases from 18 clinical sites in Europe), located at the University of Zurich Balgrist Hospital. The initial EM-SCI / NACTN collaborative project was development of a new method of quantifying neurological outcomes of patients stratified by level of injury. The lead investigators were Drs. Grossman and Burau from NACTN and Armin Curt, MD, Balgrist. Regretfully, we must report that Dr. Burau, who was the driver behind this project, passed away several months ago after a long illness sidelined him in the year prior to his death. Drs. Frankowski and Grossman are meeting this month with Leif Peterson, a biostatistician at The Methodist Hospital Research Institute with an appointment at UT School of Public Health, to discuss mining the NACTN database. They are committed to moving forward at this time with development of a new method to quantify neurological outcomes by level of injury.

NACTN and the NeuroRecovery Network (NRN): In November 2012, Toronto Rehabilitation Institute joined the NRN and as of this writing, is poised to begin patient enrollment. As reported in earlier narratives, seeds for them to join were sown during the March 2011 Toronto meeting of NACTN and NRN principal investigators, which was underwritten by DOD funds. There are now four NACTN sites with corresponding NRN centers (Houston, Louisville, Philadelphia and Toronto) and an unparalleled opportunity for expanded spinal cord injury trialing that covers acute injury through rehabilitation. The new NRN brochure is appended as Attachment I.

NACTN and NRN investigators joined forces to present an instructional course at the annual May 2013 ASIA meeting titled “North American Clinical Trials Network (NACTN) and the NeuroRecovery Network (NRN): Advancing SCI Research and Translation of Evidence into Practice.” The power point presentation is appended at Attachment J.

NACTN and AOSpine International: The Data Providing Agreement between AOSpine International and the Reeve Foundation on behalf of NACTN was submitted with our October 18, 2012 Q1 Y3 report. At that time we anticipated similar data sharing agreements between AOSpine International and the Rick Hansen Foundation and EM-SCI. Unfortunately after months of failed attempts to implement agreements with these two organizations, the decision has been made to move forward with merging the NACTN/STASCIS (Surgical Timing in Acute Spinal Cord Injury Study)/AOSpine International anonymized data. Many of NACTN’s investigators will attend the Association for Collaborative Spine Research annual meeting in Chicago at the end of July and they will meet separately to decide how best to move forward with analysis of the combined databases.

Administrative Core:

- The Reeve Foundation submitted a FY12 JWMRP application on June 26, 2012 and as a consequence was invited to prepare a BAA2012 proposal. This was submitted September 4, 2012. Notification of a new award (W81XWH-13-2-0040, effective date May 1, 2013) was received April 24, 2013.
- Award notification and the availability of funding for the next two years meant the Foundation could finally issue 2013 contracts to all NACTN centers, some of which had been operating without contracts or funding since January 1, 2013.
- A No Cost Extension (NCE) through December 31, 2013 for W81XWH-10-2-0042 was submitted June 4, 2012. As of this writing, we are awaiting disposition of the request. If favorable, it would allow us to reallocate uncommitted/unexpended funds and supplement the #0040 award, which was considerably less (\$2,000,000 for two years) than the present contract.
- We are preparing to submit an application for a FY2013 DOD JWMRP award to continue the research being performed under the current #0042 and new #0040 awards. Dr. Grossman received the letter of invitation on June 24th.

Key Research Accomplishments:

- 1) Successful completion of NACTN’s first network-wide clinical trial, a Phase 1 safety study of the neuroprotective drug Riluzole in acute SCI and acceptance of the manuscript reporting on the results
- 2) Effective 7/18/13, 666 acutely injured subjects enrolled into NACTN’s registry database
- 3) Publication of 11 NACTN papers in the Journal of Neurosurgery: Spine September 20, Volume 17, NACTN/AOSpine NA Focus Issue on Spinal Cord Injury
- 4) Effective September 2012, transition to an Electronic Data Capture (EDC) system through Systemax’s ITW, a medical records and data collection web application with a data center. ITW is used also for the Reeve Foundation’s NeuroRecovery Network database; use of the same EDC system by both clinical networks has important research implications downstream.
- 5) Merges of NACTN data registry with STASCIS and EM-SCI databases; launch of discrete projects related to both merges. STASCIS merge resulted in the development and publication of a new clinical prediction model based on motor function at admission and early imaging studies – all within three days of injury – that may allow clinicians to better identify likely outcomes at one year. It will no doubt help those who are newly injured but it will also guide decision-making for picking the best candidates for clinical trials, for therapies that may emerge, and for longer term lifestyle and caregiving issues.
- 6) Data Providing Agreement between Reeve Foundation and AOSpine International and the merge of those databases in combination with that of that STASCIS database. Formulation of research questions to be addressed
- 7) Finalization of RISCIS Phase II/III protocol, which was locked on December 21, 2012

- 8) Finalization of the RISCIS II/III pharmacology protocol, A Multi-Center, Randomized, Placebo-Controlled, Double-Blinded, Trial of Efficacy and Safety of Riluzole in Acute Spinal Cord Injury - Pharmacology of Riluzole in Patients with Acute Traumatic SCI

Reportable Outcomes:

- A Clinical Prediction Model for Long-Term Functional outcome after Traumatic Spinal Cord Injury Based on Acute Clinical and Imaging Factors, Jefferson R. Wilson, Robert G. Grossman, Ralph F. Frankowski, Alexander Kiss, Aileen M. Davis, Abhaya V. Kulkarni, James S. Harrop, Bizhan Aarabi, Alexander Vaccaro, Charles H. Tator, Marcel Dvorak, Christopher I. Shaffrey, Susan Harkema, James D. Guest and Michael G. Fehlings, JNeurotrauma 29:1-9 September 1, 2012
- Journal of Neurosurgery: Spine September 20, Volume 17, NACTN/AOSpine NA Focus Issue on Spinal Cord Injury
- Joint NACTN/NRN presentation, ASIA “North American Clinical Trials Network (NACTN) and the NeuroRecovery Network (NRN): Advancing SCI Research and Translation of Evidence into Practice”
- Reliability of the electrical perceptual threshold and Semmes-Weinstein monofilament tests of cutaneous sensibility, Peter Ellaway, Maria Catley, Spinal Cord (2013) 51, 120-125
- Defining the Role of Sensation, Strength, and Prehension for Upper Limb Function in Cervical Spinal Cord Injury, Sukhvinder Kalsi-Ryan, PhD, Dorcas Beaton, PhD, Armin Curt, MD, Susan Duff, EdD, PhD, Depeng Jiang, Milos R. Popovic, PhD, PEng, Claudia Rudhe, MScOT, Michael G. Fehlings, MD, PHD, and Molly C. Verrier, MHSc, Neurorehabilitation and Neural Repair
- A Prospective Multicenter Phase 1 Matched Comparison Group Trial of Safety, Pharmacokinetics, and Preliminary Efficacy of Riluzole in Patients with Traumatic Spinal Cord Injury, Robert G. Grossman, Michael G. Fehlings, Ralph F. Frankowski, Keith D. Burau, Diana S.L. Chow, Charles Tator, Angela Teng, Elizabeth G. Toups, James S. Harrop, Bizhan Aarabi, Christopher I. Shaffrey, Michele M. Johnson, Susan J. Harkema, Maxwell Boakye, James D. Guest and Jefferson R. Wilson, Journal of Neurotrauma

Conclusion:

At the three-year mark of DOD award W81XWH-10-2-0042, NACTN has accomplished the key SOW tasks. It successfully concluded a Phase 1 study of the neuroprotective drug Riluzole and the results will be published shortly in the Journal of Neurotrauma. It has contributed to the Novartis Phase 1 ATI-355 clinical trial and the STASCIS study, brought Brook Army Medical Center into the network, funded several projects to develop new, more sensitive outcome measures and continued to support the development and validation of both GRASSP and PRIME. It has surpassed its goal of enrolling 500 acutely injured patients into the data registry and published 11 papers in the September 2012 Journal of Neurosurgery: Spine Supplement Issue. It has forged working relationships and collaboration agreements with similar international clinical research networks, has created a committee-based organization and established policies and procedures that are codified in its Governance Manual.

Most importantly, NACTN and AOSpine North America, together with AOSpine International, are partnering on a Phase II/III clinical trial to examine the both safety and efficacy of Riluzole. Called RISCIS (Riluzole in Spinal Cord Injury Study), the trial represents a watershed moment of sorts by creating a new model for sharing the challenges and expenses of translational human studies. In the end, if Riluzole does show effectiveness and continued safety, NACTN will have achieved significant return on investment for the Department of Defense and the network, DOD and the Reeve Foundation will have identified a therapy for a devastating condition that as of this writing has no proven effective treatment.

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Attachments

Attachment A	Journal of Neurotrauma, “A Prospective Multicenter Phase 1 Matched Comparison Group Trial of Safety, Pharmacokinetics, and Preliminary Efficacy of Riluzole in Patients with Traumatic Spinal Cord Injury”
Attachment B	Protocol, Pharmacology of Riluzole in Patients with Acute Traumatic SCI
Attachment C	RISCIS Framework, Draft
Attachment D	Hobbs Curriculum Vita
Attachment E	Preprint: Neurorehabilitation and Neural Repair, “Defining the Role of Sensation, Strength, and Prehension for Upper Limb Function in Cervical Spinal Cord Injury”
Attachment F	Data Tables
Attachment G	ITW Manual of Operations
Attachment H	NACTN Governance Manual
Attachment I	NeuroRecovery Network Brochure
Attachment J	ASIA NACTN/NRN Presentation

A Prospective, Multicenter, Phase I Matched-Comparison Group Trial of Safety, Pharmacokinetics, and Preliminary Efficacy of Riluzole in Patients with Traumatic Spinal Cord Injury

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Abstract

A prospective, multicenter phase I trial was undertaken by the North American Clinical Trials Network (NACTN) to investigate the pharmacokinetics and safety of, as well as obtain pilot data on, the effects of riluzole on neurological outcome in acute spinal cord injury (SCI). Thirty-six patients, with ASIA impairment grades A–C (28 cervical and 8 thoracic) were enrolled at 6 NACTN sites between April 2010 and June 2011. Patients received 50 mg of riluzole PO/NG twice-daily, within 12 h of SCI, for 14 days. Peak and trough plasma concentrations were quantified on days 3 and 14. Peak plasma concentration ($C_{\max}$) and systemic exposure to riluzole varied significantly between patients. On the same dose basis, $C_{\max}$ did not reach levels comparable to those in patients with amyotrophic lateral sclerosis. Riluzole plasma levels were significantly higher on day 3 than on day 14, resulting from a lower clearance and a smaller volume of distribution on day 3. Rates of medical complications, adverse events, and progression of neurological status were evaluated by comparison with matched patients in the NACTN SCI Registry. Medical complications in riluzole-treated patients occurred with incidences similar to those in patients in the comparison group. Mild-to-moderate increase in liver enzyme and bilirubin levels were found in 14–70% of patients for different enzymes. Three patients had borderline severe elevations of enzymes. No patient had elevated bilirubin on day 14 of administration of riluzole. There were no serious adverse events related to riluzole and no deaths. The mean motor score of 24 cervical injury riluzole-treated patients gained 31.2 points from admission to 90 days, compared to 15.7 points for 26 registry patients, a 15.5-point difference ($p=0.021$). Patients with cervical injuries treated with riluzole had more-robust conversions of impairment grades to higher grades than the comparison group.

Key words: clinical trial; neuroprotection; riluzole; spinal cord injury

Introduction

THERE IS CURRENTLY no neuroprotective therapy that has emerged as a standard of care after traumatic spinal cord injury (SCI). After a traumatic injury, the spinal cord undergoes a prolonged series of biological processes of reaction and repair.

Therapies have been directed toward limiting the damage to the spinal cord and enhancing repair at each stage of the process. The general categories of therapy have been neuroprotection to limit the secondary injury that occurs after acute trauma, modulating the inflammatory response to injury, modifying the glial and fibroblastic scar that blocks regrowth of axons, and stimulating regrowth

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and repair of damaged axons and providing substrates to guide axons and bridge gaps. Substantial repair of SCI will probably require the application of a series of therapies, each directed toward a particular phase of the reactive and reparative processes.

Early within the secondary injury cascade, the initial trauma force, in combination with subsequent ischemic changes, leads to neuronal membrane dysfunction, which includes the constitutive activation of voltage-gated sodium ion channels.¹⁻³ This pathologic continuous activation causes a marked increase in intracellular sodium levels and leads to an influx of calcium ions through the sodium-calcium exchange pump.^{4,5} Rises in intracellular calcium concentration then lead to the extracellular release of toxic levels of the excitatory neurotransmitter glutamate.⁶ The combination of these events leads to increased regional cellular death as a result of ionic imbalance, formation of reactive oxidative ions, intracellular energy failure, cytotoxic edema formation, and glutamatergic excitotoxicity.

Riluzole, a sodium-channel blocking medication, which is U.S. Food and Drug Administration (FDA) approved for the treatment of amyotrophic lateral sclerosis (ALS),⁷ has been shown to improve the outcome of SCI in preclinical studies.^{8,9} Twelve preclinical studies of riluzole efficacy in acute rodent models of SCI, published between 1996 and 2011, have recently been summarized in a review article on neuroprotective drug therapy and SCI.¹⁰ In comparison to control animals, riluzole-treated animals exhibited reduced tissue cavitation and better preservation of white matter, motor neurons, mitochondrial function, somatosensory-evoked potentials, and locomotor scores in different studies.¹⁰ Recent work evaluating the timing of riluzole administration in rats revealed that treatment initiated at both 1 and 3 h postinjury resulted in improved neurobehavioral outcomes as well as tissue-preserving effects.¹¹ The presence of a well-defined target mechanism and demonstration of beneficial effects in pre-clinical studies, combined with its tolerability in the ALS population, make riluzole an attractive candidate for evaluation to treat acute human SCI.¹² With this background, a phase I prospective, matched-comparison group trial of the pharmacokinetics (PK), safety, and preliminary efficacy of riluzole as a neuroprotective agent in acute traumatic SCI was carried out with the following goals to:

1. Test the feasibility of a trial of a therapy that must be administered within 12 h of acute traumatic SCI.
2. Study the PK and pharmacodynamics of riluzole in SCI.
3. Obtain data on the safety of riluzole in SCI using a matched cohort group for comparison.
4. Obtain exploratory pilot data on the effects of riluzole on measures of neurological outcome after SCI using a matched cohort group for comparison.
5. Relate the pharmacology of riluzole in SCI to safety and outcome measures.

Methods

Organization of the trial by the North American Clinical Trials Network

The trial was registered with ClinicalTrials.gov (identifier: NCT00876889). Planned enrollment of 36 patients was conducted between April 12, 2010 and June 20, 2011 at six clinical centers of the North American Clinical Trials Network (NACTN) for Treatment of Spinal Cord Injury (Table 1). NACTN is a consortium of clinical centers composed of neurosurgery department faculty and staff caring for SCI patients at university-affiliated hospitals, a coordinating center, a data management center and a pharmaco-

TABLE 1. TRIAL SITES

<i>Trial sites</i>	<i>Principal investigators</i>
Thomas Jefferson University, Philadelphia	James S. Harrop, MD
University of Maryland, Baltimore	Bizhan Aarabi, MD
University of Virginia, Charlottesville	Christopher I. Shaffrey, MD
University of Texas Health Science Center, Houston	Michele M. Johnson, MD
University of Louisville, Louisville	Susan J. Harkema, PhD Maxwell Boakye, MD
University of Toronto, Toronto	Michael G. Fehlings, MD, PhD Charles H. Tator, MD, PhD

logical center. Each NACTN clinical center has one or two principal investigators and a study coordinator who is a physician or a clinical research nurse. NACTN was established in 2005 with the support of the Christopher Reeve Foundation, which is its sponsoring organization.^{13,14} The Telemedicine and Advanced Technology Research Center (TATRC), United States Army Medical Research and Materiel Command (USAMRMC), has supported NACTN since 2006. Partial grant support for this trial was also received from AOSpine, which helped to facilitate the trial design and initial logistics of trial implementation.

Trial design: Riluzole treatment cohort and eligibility criteria

The trial was a multi-site, single-arm, open-label-treatment pilot study with an enrollment goal of 36 patients. Eligibility criteria are given in Table 2. A detailed description of the trial design has been

TABLE 2. ELIGIBILITY CRITERIA

Inclusion criteria
Age ≥ 18 and ≤ 70 years
Written informed consent by patient or legally authorized representative to participate in the study
No other life-threatening injury
Nonpenetrating spinal cord injury at neurologic level from C4 to T11
ASIA Impairment Scale grade A, B, or C
No cognitive impairment that would preclude an informed consent, including moderate or severe traumatic brain injury
Initial dose of riluzole within 12 h of injury
Exclusion criteria
Hypersensitivity to riluzole or any of its components
Unable to receive riluzole orally or by nasogastric tube
History of liver or kidney disease (e.g., hepatitis A, B, or C or cirrhosis)
A recent history of regular substance abuse (illicit drugs or alcohol)
Unconscious
Penetrating spinal cord injury
Pregnancy as established by urine pregnancy test
Currently involved in another spinal cord injury research study
Has a mental disorder or other illness, which, in the view of the site investigator, would preclude accurate medical and neurological evaluation
Unable to commit to the follow-up schedule
Is a prisoner
Unable to converse, read, and write in English at the elementary-school level

published previously.¹⁵ The sample size of this safety study was established in advance and was based on complication rates observed in NACTN registry data¹³ and discussed below. The incidence rates of complications were expected to range from 0.15 to 0.30 in patients not treated with riluzole. Using a one-sided exact binomial test with a type I error rate of 5%, a case series of 36 patients receiving riluzole was projected to have approximate power of 0.80–0.99 to detect doubling of the complication rate in the riluzole case series.

Comparison group: North American Clinical Trials Network Spinal Cord Injury Registry group

As a phase I trial, the study did not have a concurrent control group of patients who did not receive riluzole, but who otherwise received the same standard of care treatment as the riluzole cohort. In lieu of a concurrent control group with which to compare the safety and neurological outcome data for the riluzole cohort, a comparison group was formed of 36 SCI patients who had received standard-of-care treatment at the NACTN clinical centers, whose records were in the NACTN SCI Registry. The NACTN SCI Registry contains information about the clinical courses of 594 SCI patients admitted to the NACTN clinical centers from October 2005 through November 2012, who consented to having data on their injury recorded in an institutional review board (IRB)- and human research protection office (HRPO)-approved data registry. Information was collected prospectively under the following headings: demographic data; medical history; initial clinical status; Glasgow Coma Score (GCS); Abbreviated Injury Score; International Standards For Neurological Classification of Spinal Cord Injury (ISNCSCI) motor, sensory, and impairment scores; type of neurological injury; type of bony injury; imaging of cord and canal diameters on computed tomography, magnetic resonance imaging, or myelogram; traction-reduction; medical therapy; surgical therapy; complications, including cardiac, pulmonary, hematological, gastrointestinal (GI), genitourinary (GU); infectious; skin; and neuropsychiatric.¹⁴

Data from 36 registry patients meeting the eligibility criteria for the riluzole patients were matched with the 36 patients treated with riluzole. Criteria for registry cases included admission to a NACTN center within 12 h of injury, American Spinal Injury Association (ASIA) Impairment Scale (AIS) grade A, B, or C at admission, cervical or thoracic injury, nonpenetrating SCI at neurological level from C4 to C11, and GCS >13. Registry cervical and thoracic cases were then matched by AIS grade to the riluzole patients' neurological level of injury, gender, and age. This hierarchy of matching was the method adopted to select among multiple matches. All matching was blinded to outcome measures in the registry and riluzole groups. Thirty (83%) of the 36 registry patients were drawn from five of the six NACTN sites trialing riluzole in the present study.

Determination of riluzole dose and dosing schedule

Riluzole (50 mg; Rilutek[®]; Sanofi-Aventis, Bridgewater, NJ) was administered every 12 h orally or by nasogastric tube, starting within 12 h of injury for 28 doses.

The riluzole dose was determined by using human data and by scaling from animal data.¹⁶ From the human data, the most conservative approach was used, based on the FDA-approved dose for ALS patients. In dose-ranging studies of riluzole in ALS that used doses of 50, 100, and 200 mg/day, a daily dose of 50 mg twice-daily (b.i.d.) of riluzole was confirmed to have the best benefit-to-risk ratio.¹⁷

From animal data, the human equivalent dose (HED) was allometrically scaled from the animal dose (6 mg/kg b.i.d.) in female Wistar rats (weight, 250–300 g) and was calculated with the equation from FDA Guidance for Industry (2005)¹⁸:

$$\begin{aligned}\text{HED} &= \text{Animal Dose (mg/kg)} \times (\text{animal wt/human wt in kg})^{0.33} \\ &= (6 \text{ mg/kg bid}) \times (0.25 \text{ kg}/70\text{kg})^{0.33} \\ &= 0.92 \text{ mg/kg bid} = 64.2 \text{ mg}/70 \text{ kg b.i.d.}\end{aligned}$$

The trial dose of 50 mg b.i.d. was set conservatively below the HED of 64.2 mg b.i.d., scaled from the effective, safe animal dose of 6 mg/kg b.i.d.¹¹ and in concordance with the dose of 50 mg b.i.d. that achieved the best safety and efficacy balance in ALS patients.¹⁷

The time window of 12 h after injury for administration of riluzole is in concordance with a study of delayed postinjury administration of riluzole in a preclinical model of moderate cervical SCI.¹¹ Riluzole treatment at 1 h and at 3 h postinjury both provided locomotor improvement. Differences in metabolic rate and time course of appearance of inflammatory biomarkers in rodents and humans suggest that pathological changes in SCI peak 4–6 times more rapidly in rat than in human SCI, making 12 h a reasonable exploratory time window for a phase I trial of riluzole.¹¹ The mean time and standard deviation (SD) of SCI patients receiving the first dose of riluzole in the present study was 8.7 ± 2.2 h.

Pharmacology of riluzole in spinal cord injury patients

The PK of riluzole in the 36 patients in the present study have been published in detail.¹⁶ Plasma samples for PK study were collected 1–2 h predose and 2 h postdose for trough and peak concentrations, respectively, on days 3 and 14 after the initial dose. Findings that are pertinent to the phase I clinical trial are given below in the Results section of this report.

Patient care protocol

Patients received care for SCI as described in the *Guidelines for the Management of Acute Cervical Spine and Spinal Cord Injuries*.¹⁹ Treatment included rapid ventilatory, cardiovascular and nutritional support, reduction of vertebral subluxations, surgical decompression of the spinal cord and vertebral stabilization, and prophylactic measures to prevent deep vein thrombosis (DVT) using leg compression devices and/or anticoagulation with heparin or low molecular weight heparin. Administration of corticosteroids, generally methylprednisolone (MPSS), was in accord with the policies of the admitting center. Thirty-nine percent of the riluzole and 58% of the registry patients received MPSS.

Schedule of events and data collection

Table 3 shows the schedule of events for the study, the riluzole dosing schedule, and the clinical and laboratory data that were collected on admission to the study, during acute hospitalization, and at 42 ± 7 , 90 ± 10 , and 180 ± 14 days.

Screening and admission to the study

SCI patients examined in the emergency department (ED) within 12 h of injury were screened for eligibility and had the study explained to them and to legally authorized representatives, if present. Consenting individuals were then enrolled in the trial. Time of enrollment was taken as the time of admission to the study, and the measurements referred to in the tables as admission data were made at this time, before receiving riluzole. For the purpose of recording and tracking riluzole administration, the day on which the first dose of riluzole was given was designated as day 1 of the study.

Data collection

Data were collected prospectively, daily when required by the protocol, by NACTN clinical coordinators working together with the principal investigators of each clinical site. Data were recorded

TABLE 3. SCHEDULE OF EVENTS

	Screening (<12 hrs. from injury) Enrollment/ Admission	Treatment Period														Post Treatment		Follow-up			
		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	Day/C	Acute	Day 42	Day 90	Day 180	Unscheduled F/U
Chart Review	X																				
Enrollment/Trial Admission	X																				
Informed Consent Form	X																				
Signed Identification Data	X																				
Medical History/SCI Data	X																				
ISNCSCI Examination	X																				
Clinical Blood Draw/Liver	X																				
Function Tests																					
Pharmacology Blood Draw	X																				
Medications																					
Riluzole Administration	X																				
Adverse Events/Complications																					
Discharge Data																					
BPI Short Form																					
SCIM version 1																					

on 16 case-report forms, throughout the course of the acute care hospitalization of the patients and at the follow-up visits made in the rehabilitation hospital or at the clinical center. The following data were collected:

1. Prehospitalization demographic data, past medical history, preinjury medication use, circumstances and time of injury, and time of arrival to the ED of the admitting NACTN hospital.
2. Evaluation of the medical condition of the patient.
3. Measurement of neurological status with ISNCSCI motor and sensory and AIS examinations.²⁰ Evaluations were repeated on days 3 and 14 of acute hospitalization, before and after spinal surgery, and at the 42-, 90-, and 180-day examinations. The Spinal Cord Independence Measure (SCIM)²¹ was performed at 90 and 180 days.
4. Details of the medical and surgical therapy received.
5. Hematology and blood chemistries, including liver function tests, were drawn on admission to the study and on days 3, 7, 10, and 14 and when medically indicated at 42, 90, and 180 days.
6. Medical complications and serious adverse events (SAEs) were assessed by NACTN principal investigators by observation of the patients with input of the clinical coordinators as well as medical and nursing staff. Categorization and severity level of complications were determined by the principal investigators using the criteria described in an analysis of the incidence and severity of acute complications after SCI, based on data from the NACTN SCI Registry.²²

All data were submitted to the data management center and were subjected to multiple manual and electronic data quality-control procedures.

Compliance with regulatory requirements

1. Approval of the protocol by the HRPO of the Department of Defense (DoD).
2. Harmonization of the IRB requirements of each center with requirements of the HRPO; final approval of the harmonized protocol and the informed consent form by each IRB.
3. Appointment of a central trial medical monitor, a physiatrist at a university unaffiliated with any of the centers, who received reports of all SAEs.
4. Appointment of a local medical monitor at each clinical center who received reports of adverse events at that center.

Training of personnel and trial initiation meeting

Two training meetings were held at the Frazier Rehab Institute for the principal investigators and study coordinators, reviewing in detail the study protocol, the *Guidelines for the Management of Acute Cervical Spine and Spinal Cord Injuries*¹⁹ and in performing ASIA examinations on individuals with SCI under the guidance of skilled instructors.

A trial initiation meeting of all investigators and coordinators was held at The Methodist Hospital Coordinating Center, including a 2-day review of the protocol, the schedule of events, the rules and procedures for reporting adverse events, and stopping rules.

Site monitoring

NACTN's study monitor conducted on-site visits to the clinical centers and reviewed case report forms, source documentation, and on-site regulatory binders to ensure regulatory and protocol compliance with Good Clinical Practices.

Statistical analysis

Admission characteristics of riluzole and registry patients were compared using two-sample independent *t*-tests and two-sample chi-square methods or Fisher's exact test, as appropriate, for categorical data. Chi-square methods were also used to compare the incidence of medical complications between the two groups. Total motor scores for riluzole and registry patients stratified by impairment grade at admission were analyzed using the permutation test for independent samples, with motor scores as the raw observations. The permutation test makes no assumptions about the shapes of the underlying distributions or dispersions of motor scores and is particularly effective for skewed data. Permutation tests were computed using StatXact 8 with Cytel Studio software (Cytel Inc., Cambridge, MA).

Box plots were used to compare distributions of 90- and 180-day gains in total motor score and pin-prick sensory scores for the riluzole and registry groups. Box plots show the middle 50% of the data by a box that extends from the 25th to the 75th percentile and tails (whiskers) that contain at least 99% of the data and markers that indicate any outlying data values. Sample medians are shown within each box. Box plots are labeled for ease in interpretation and comparison. All graphics and other statistical tests were computed using StatCorp (2009) Stata statistical software (Release 11; StataCorp LP, College Station, TX).

Results

The enrollment goal of the study was fulfilled. Thirty-six patients with acute traumatic injury to the spinal cord (ages, 18–69),

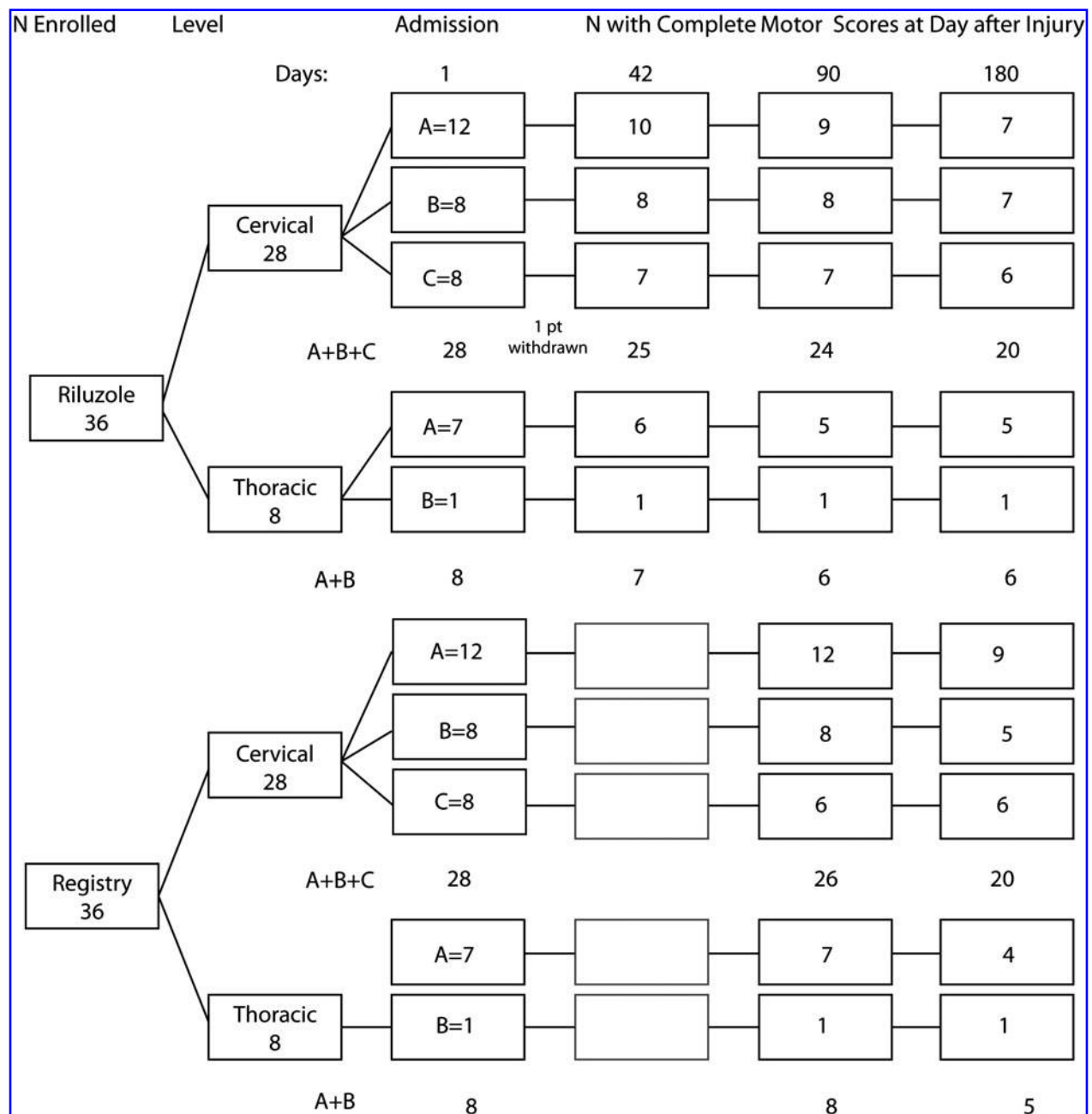


FIG. 1. Patient flow diagram of numbers of riluzole and registry patients available with complete motor scores on admission and at 42, 90, and 180 days.

impairment grades A–C, with levels of injury (lowest normal motor level) C4–T11, were enrolled at six NACTN clinical center hospitals between April 12, 2010 and June 20, 2011 and received riluzole enterally within 12 h of injury at a dose of 50 mg every 12 h for a total of 28 doses.

Cervical and thoracic injuries—riluzole and registry cohorts: Impairment grade on admission, demographics, cause of injury, hours to admission to emergency department and surgery, and corticosteroid administration

Figure 1 provides an overview of patient flow for safety and neurological outcome data, stratified by cervical and thoracic sites of injury and impairment grade. There were no statistically significant differences in demographics or clinical variables for the riluzole and registry patient groups (Table 4). Table 4 shows that

28 (78%) injuries in the riluzole cohort were cervical and 8 (22%) were thoracic.

Patients in the registry cohort were selected to match the numbers of cervical and thoracic injuries, neurological levels of injury, and impairment scale grades of the patients in the riluzole cohort. Distribution of impairment grades for both the riluzole and the registry cohorts was 19A, 9B, and 8C. Thirty (83%) patients were male and 6 (17%) were female in the riluzole cohort. The gender ratio was nearly identical in the registry cohort. The mean age was 41.3 years for patients with cervical injuries and 45.4 for patients with thoracic injuries, with a range of 18–69 in the riluzole cohort. The mean age for the cervical injuries in the registry cohort was 40.8 years. The causes of injury were predominantly motor vehicle accidents ($N=20$) and falls ($N=9$) in the riluzole cohort; the causes in the registry cohort were similar. Mean hours from injury to ED were 3.0 ± 1.8 for riluzole patients with cervical injuries and 2.5 ± 2.3 for registry patients.

TABLE 4. CERVICAL AND THORACIC INJURIES: DEMOGRAPHICS AND CLINICAL VARIABLES ON ADMISSION TO STUDY IN RILUZOLE AND REGISTRY PATIENTS

Variable	Riluzole Cervical N=28	Registry Cervical N=28	p value	Riluzole Thoracic N=8	Registry Thoracic N=8
AIS					
A	12	12		7	7
B	8	8		1	1
C	8	8		0	0
Total	28	28	Matched	8	8
Age in years	41.3 ± 17.4	40.8 ± 14.4	0.91	45.4 ± 16.4	30.4 ± 17.7
Gender					
Male	24	23		6	8
Female	4	5		2	0
Total	28	28	1.00	8	8
Cause					
Motor vehicle accident	13	8		7	6
Fall	8	11		1	2
Sports	5	8		0	0
Assault	2	1		0	0
Total	28	28	0.52	8	8
Hours to hospital ED	3.0 ± 1.8	2.4 ± 2.3	0.28	3.6 ± 1.7	2.7 ± 2.9
Surgery					
Yes	25	28		8	8
No	3	0		0	0
Total	28	28	0.24	8	8
Hours to surgery					
6–12	14	11		1	2
12–24	7	9		3	2
24–48	3	3		4	3
>48	1	5		0	1
Total	25	28	0.42	8	8
Body mass index	26.4 ± 4.1	27.0 ± 4.2	0.59	28.1 ± 4.3	26.1 ± 1.9
Surgical approach					
Anterior	4	7		0	1
Posterior	7	10		5	7
Both	14	11		3	0
Total	25	28	0.52	8	8
Corticosteroids					
Yes	10	17		4	4
No	18	11		4	4
Total	28	28	0.11	8	8

AIS, American Spinal Injury Association Impairment Scale; ED, emergency department.

Thirty-three (92%) of the riluzole patients underwent early surgery for spinal cord decompression and vertebral column stabilization, 42% within 6–12 h of injury, and another 28% in 12–24 h. Three of the cervical injuries did not undergo surgery. Median hours from injury to surgical decompression and stabilization were 11.3 h for cervical injuries and 23.6 for thoracic injuries for the riluzole cohort and were similar for the registry cohort. Surgical approaches were anterior (4; 12%), posterior (12; 36%), and both (17; 51%) for the riluzole cohort and were similar for the registry group.

Corticosteroids were administered at the time of admission to 39% of the riluzole cohort and 58% of the registry group.

The mean duration of initial hospitalization of the riluzole cohort was 17 days (range, 5–41). Thirty-five patients were discharged to a rehabilitation hospital and 1 to a nursing facility. The mean duration of hospitalization for the registry cohort was 23 days.

The leading pre-existing medical conditions in the riluzole cohort were hypertension (10 patients) and diabetes mellitus (5 patients) and were similar in the registry cohort.

Neurological levels of injury for cervical and thoracic patients receiving riluzole and for registry patients are shown in Table 5.

TABLE 5. CERVICAL AND THORACIC INJURIES: RILUZOLE AND REGISTRY PATIENTS: NEUROLOGICAL LEVELS OF INJURY

Level of injury	N (%)	% of cervical
<i>Riluzole cervical N=28</i>		
C4	13 (36.1)	46.4
C5	7 (19.4)	25.0
C6	7 (19.4)	25.0
C8	1 (2.8)	3.6
Total cervical	28 (77.8)	(100)
Level of injury	N (%)	% of thoracic
<i>Riluzole thoracic N=8</i>		
T1	2 (5.6)	25.0
T2	2 (5.6)	25.0
T6	1 (2.8)	12.5
T9	1 (2.8)	12.5
T11	2 (5.5)	25.0
Total thoracic	8 (22.2)	(100)
Total cervical and thoracic	36 (100)	
Level of injury	N (%)	% of cervical
<i>Registry cervical N=28</i>		
C4	11 (30.6)	39.3
C5	10 (27.8)	35.7
C6	6 (16.7)	21.4
C8	1 (2.8)	3.6
Total cervical	28 (77.8)	(100)
Level of injury	N (%)	% of thoracic
<i>Registry thoracic N=8</i>		
T1	3 (8.3)	37.5
T6	2 (5.5)	25.0
T10	1 (2.8)	12.5
T11	1 (2.8)	12.5
T12	1 (5.5)	12.5
Total thoracic	8 (22.2)	(100)
Total cervical and thoracic	36 (100)	

For the patients with cervical injuries in the riluzole cohort, C4-level injuries predominated ($N=13$; 46% of cervical injuries), followed by C5 and C6 ($N=7$; 25% each) and C8 ($N=1$; 4%). Among the thoracic injuries, 4 (50%) were high thoracic, at T1 and T2, respectively, 2 (25%) were mid-thoracic, at T6 and T9, and 2 were low thoracic, at T11. Seven of the eight thoracic injuries were impairment grade A on admission and one was B. Levels of injury were similar for riluzole and registry patients.

Distribution of impairment grades on admission for each level of injury for patients receiving riluzole is shown in Table 6. Distribution was similar for registry patients.

Time to riluzole administration and number of doses received

The mean time to the first dose of riluzole was 8.7 h for the riluzole cohort ($n=36$) as a whole (Table 7). Thirty-five patients completed the study. The goal of administering 28 doses of riluzole was reached in 71% of these 35 patients; an additional 26% received 27 doses and 3% received 26 doses.

Patient withdrawal

One patient was withdrawn on the seventh day of receiving riluzole when his liver function tests showed a moderate elevation of gamma-glutamyl transpeptidase (GGT). This patient was a 69-year-old man with previous comorbidities of emphysema and hypertension. He had sustained a C4 injury in a fall (impairment grade C). He developed respiratory failure on day 2 and pneumonia on day 4. GGT was normal on admission and on day 4, but had risen to $4.6\times$ the upper limit of normal (ULN) on day 7. He was receiving medications that can impair liver function. Riluzole was stopped as a precautionary measure to prevent possible liver damage. GGT fell to a mildly elevated level on day 10. Impairment grade was C at 90 days postinjury and GGT was normal.

Pharmacokinetics of riluzole in spinal cord injury patients

A detailed report of the PK of riluzole in the patients in this study has been published.¹⁶ The following will summarize the key data that are of pertinence to the current report. Riluzole PK were evaluated in 33 patients on day 3 and in 32 patients on day 14, as

TABLE 6. CERVICAL INJURIES: RILUZOLE AND REGISTRY PATIENTS: NEUROLOGICAL LEVEL AND DISTRIBUTION OF IMPAIRMENT GRADES ON ADMISSION

Level	A	B	C	Total
<i>Riluzole: impairment grade</i>				
C4	5	4	4	13
C5	2	3	2	7
C6	4	1	2	7
C8	1	0	0	1
Total	12	8	8	28
<i>Registry: impairment grade</i>				
C4	5	4	2	11
C5	2	3	5	10
C6	4	1	1	6
C8	1	0	0	1
Total	12	8	8	28

TABLE 7. CERVICAL AND THORACIC INJURIES: TIME TO RILUZOLE ADMINISTRATION

Time window	Minimum (h)	25th percentile (h)	Median/mean (h) (SD)	75 th percentile (h)	Maximum (h)
Injury to admission N=36	0.7	1.5	2.3/3.0 (1.8)	4.2	7.0
Injury to riluzole N=36	3.7	6.9	8.5/8.7 (2.2)	10.6	12.1

SD, standard deviation.

both C_{peak} and C_{trough} samples of patients were collected and quantifiable. The plasma concentration and the systemic exposure to riluzole (area under the plasma-concentration curve; AUC_{0-12}) varied significantly among patients. Maximum concentration (C_{max}) ranged from 24 to 409 ng/mL (mean, 129 ± 14 ; standard error [SE]) on days 3 and 9 to 317 ng/mL (mean, 77 ± 14 ; SE) on day 14.

The PK of riluzole— C_{max} , C_{min} , AUC_{0-12} , clearance (CL), and volume of distribution (V)—changed during the acute and subacute phases of SCI during the 14 days of administration, a phenomenon consistently observed in all patients at all clinical sites. Mean C_{max} , C_{min} , and AUC_{0-12} (129 ng/mL, 46 ng/mL, and 982 ng*h/mL, respectively) were significantly higher on day 3 than on day 14 (77 ng/mL, 19 ng/mL, and 521 ng*h/mL, respectively), resulting from lower CL (50 vs. 106 L/h) and a smaller V (557 vs. 1298 L) on day 3.¹⁶

Safety: Medical complications and serious adverse events

SCI patients have a high incidence of physiological disturbances and medical complications occurring acutely after injury as documented in a recent publication of data from the NACTN SCI Registry.²² Using the definitions of severe and moderate complications described in that article, the incidence of complications occurring within 30 days of injury was determined. Table 8 shows medical complications and SAEs tabulated both by frequency of occurrence of specific types of complications (e.g., infection and pulmonary) and by the number of individuals sustaining one or more complication. Complications reported as SAEs are marked with a superscript b.

Table 9 shows the number of patients in the riluzole and registry groups who sustained at least 1 complication involving one or more of the seven organs or systems by which complications were classified and the incidences of these complications. There was no significant difference between the two groups.

The frequency of specific types of severe and moderate complications, expressed as a percentage of the total number of complications, was also compared to that reported in 315 patients in the NACTN SCI Registry.²² For riluzole versus registry, the comparisons were the following: infection, including pneumonia (26 vs. 22%); pulmonary, including pulmonary embolism, respiratory failure, lobar collapse, atelectasis, and pneumothorax (23 vs. 27%); hematological, including DVT, anemia, thrombocytopenia, and coagulopathy (12 vs. 15%); cardiac, including asystole, bradycardia, arrhythmia, and shock (7 vs. 13%); neurological/psychiatric, including neuropathic pain and depression and anxiety (15 vs. 7%); GI/GU, including bleeding and bowel obstruction (11 vs. 9%); and skin, including pressure sores (8 vs. 7%).

There were no SAEs attributable to riluzole. There were no deaths.

TABLE 8. CERVICAL AND THORACIC INJURIES: RILUZOLE PATIENTS^a

Complications	No. of complications
Infection: 19 complications (14 patients)	
Urinary tract infection	10
Pneumonia	5
Staphylococcal infection of skin	2
Sepsis ^b	1
Infectious diarrhea	1
Pulmonary: 17 complications (11 patients)	
Respiratory failure	7
Lobar collapse/atelectasis	3
Pneumothorax	2
Acute respiratory distress syndrome ^b	2
Pleural effusion	1
Bronchial obstruction mucus plug, syncope ^b	1
Pulmonary embolus ^b	1
Neurological/psychiatric: 11 complications (10 patients)	
Neuropathic pain	4
Depression	3
Anxiety	2
Agitation	1
Elevation of sensory level ^b	1
Hematological: 9 complications (7 patients)	
Deep venous thrombosis ^b	3
Thrombocytopenia	2
Neutropenia	1
Coagulopathy	1
Thrombophlebitis	1
Severe anemia	1
Gastrointestinal: 7 complications (5 patients)	
Prolonged nausea/vomiting	3
Rectal hemorrhage ^b	1
Dysphagia	1
Anal fistula	1
Bowel obstruction ^b	1
Skin: 6 complications (4 patients)	
Pressure-damaged skin areas other than sacral	3
Sacral decubiti	2
Rash: allergic reaction	1
Cardiovascular: 5 complications (5 patients)	
Prolonged arrhythmia	2
Asystolic episode ^b	1
Prolonged bradycardia (<50 bpm)	1
Prolonged shock (BP <80 mmHg)	1

^aSeventy-four severe and moderate medical complications and 12 serious adverse events within 30 days of admission in 36 patients.

^bReported as a serious adverse event (total, N=12).

bpm, beats per minute; BP, blood pressure.

TABLE 9. CERVICAL AND THORACIC INJURIES: RILUZOLE AND REGISTRY PATIENTS: INCIDENCE OF MEDICAL COMPLICATIONS AND *P* VALUES OF DIFFERENCES

System/category	Riluzole N=36		Registry N=36		p value*
	Patients ^a	Incidence ^b	Patients ^a	Incidence ^b	
Infection	14	0.389	13	0.361	0.81
Pulmonary	11	0.306	16	0.444	0.22
Neuropsychiatric	10	0.278	8	0.222	0.59
Hematological	7	0.194	9	0.250	0.57
Cardiovascular	5	0.139	11	0.306	0.09
GI/GU	5	0.139	9	0.250	0.19
Skin	4	0.111	3	0.083	0.69

^aNumber of patients with at least one complication of the specified system.

^bIncidence of complications within 30 days of injury.

*Pearson's chi-square test for comparing two proportions.

GI, gastrointestinal; GU, genitourinary.

Safety: Elevation of liver enzymes and bilirubin above the upper limit of normal

Liver enzymes and bilirubin were monitored on admission and during administration of riluzole. On admission, elevated levels of different liver enzymes and bilirubin were found in 9–37% of patients. Thirteen percent of patients had mild ($>ULN$ to $2.5\times ULN$) or moderate (>2.5 – $5\times ULN$) elevations of alanine transferase (ALT), 37% had mild or moderate elevations of aspartate transaminase (AST), 11% had mild elevations of GGT, and 9% had mild elevations of bilirubin (Table 10; Fig. 2). Some patients had elevation of a single enzyme, whereas others had two or three enzymes elevated.

During administration of riluzole, liver enzymes and bilirubin were monitored on days 3, 7, 10, and 14. Incidence of elevation of enzyme levels increased during administration of riluzole, with increasing frequency in the second week of administration. Seventy percent of patients had mild or moderate elevations of ALT and

63% of AST on at least one of the days of testing. One patient had a borderline severe elevation of ALT ($6\times ULN$; (severe defined as >5 – $20\times ULN$). Another patient had a borderline severe elevation of AST ($5.5\times ULN$). These elevations returned to normal at 3 and 6 months. Fifty-three percent of patients had mild or moderate elevations of GGT, and 1 patient had a borderline severe elevation of GGT ($7\times ULN$). Seventeen percent had mild or moderate elevations of alkaline phosphatase (ALP). Fourteen percent had mild or moderate elevation of bilirubin (Table 10; Fig. 2).

No patient had elevated bilirubin on day 14, the last day of administration of riluzole. The appearance of an increased level of a liver enzyme was not necessarily followed by a progressive increase in the level of that enzyme. In many cases, the elevated concentration had returned to a normal level at the next date of testing. The elevation of one enzyme was not necessarily linked to the elevation of another enzyme.

No relationship was found between the C_{max} of riluzole and liver enzyme levels.

Neurological outcome

Neurological outcome was assessed with ISNCSCI total motor score progression, sensory score progression, impairment grade conversion, and SCIM. Each measure was assessed separately for cervical and thoracic injury cohorts and stratified by impairment grades A, B, and C.

Cervical injuries: Progression of motor scores from admission to 42, 90, and 180 days

A flow diagram of the subgroups of the riluzole and registry cohorts, stratified as described above and the number of patients with complete ISNCSCI motor data available for comparison on the specified days after injury, is shown in Figure 1.

After withdrawal of 1 patient (C4 level of injury impairment grade C, see above, "Patient withdrawal"), there were 27 with cervical injuries available for measurement of motor scores. The impairment grades and numbers of these patients were A-12, B-8, and C-7. Motor score outcomes in the riluzole-treated cohort were compared with those in a matched cohort of patients drawn from the NACTN SCI Registry (Table 4). The progression of the total motor scores from admission to 42 days for the riluzole cohort, and to 90 and 180 days for the riluzole and registry cohorts, is shown in Table 11 and illustrated graphically in Figure 3. Table 11 shows the

TABLE 10. CERVICAL AND THORACIC INJURIES: LIVER ENZYME AND BILIRUBIN ELEVATIONS AT ADMISSION AND DURING RILUZOLE ADMINISTRATION^a

	ALT N (%)	AST N (%)	ALP N (%)	GGT N (%)	Bilirubin N (%)
Admission before riluzole					
Normal	27 (87)	20 (62)	32 (100)	25 (89)	29 (91)
Mild ^b	3 (10)	8 (25)	0 (0)	3 (11)	3 (9)
Moderate ^c	1 (3)	4 (12)	0 (0)	0 (0)	0 (0)
Severe ^d	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Total	31 (100)	32 (100)	32 (100)	28 (100)	32 (100)
While receiving riluzole					
Normal	10 (28)	12 (33)	30 (83)	15 (44)	31 (86)
Mild ^b	15 (42)	16 (44)	5 (14)	13 (38)	4 (11)
Moderate ^c	10 (28)	7 (19)	1 (3)	5 (15)	1 (3)
Severe ^d	1 (3)	1 (3)	0 (0)	1 (3)	0 (0)
Total	36 (100)	36 (100)	36 (100)	34 (100)	36 (100)

^aSee Figure 2.

^bMild: $>ULN$ to $2.5\times ULN$.

^cModerate: >2.5 – $5\times ULN$.

^dSevere: >5 – $20\times ULN$.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transpeptidase; ULN, upper limit of normal.

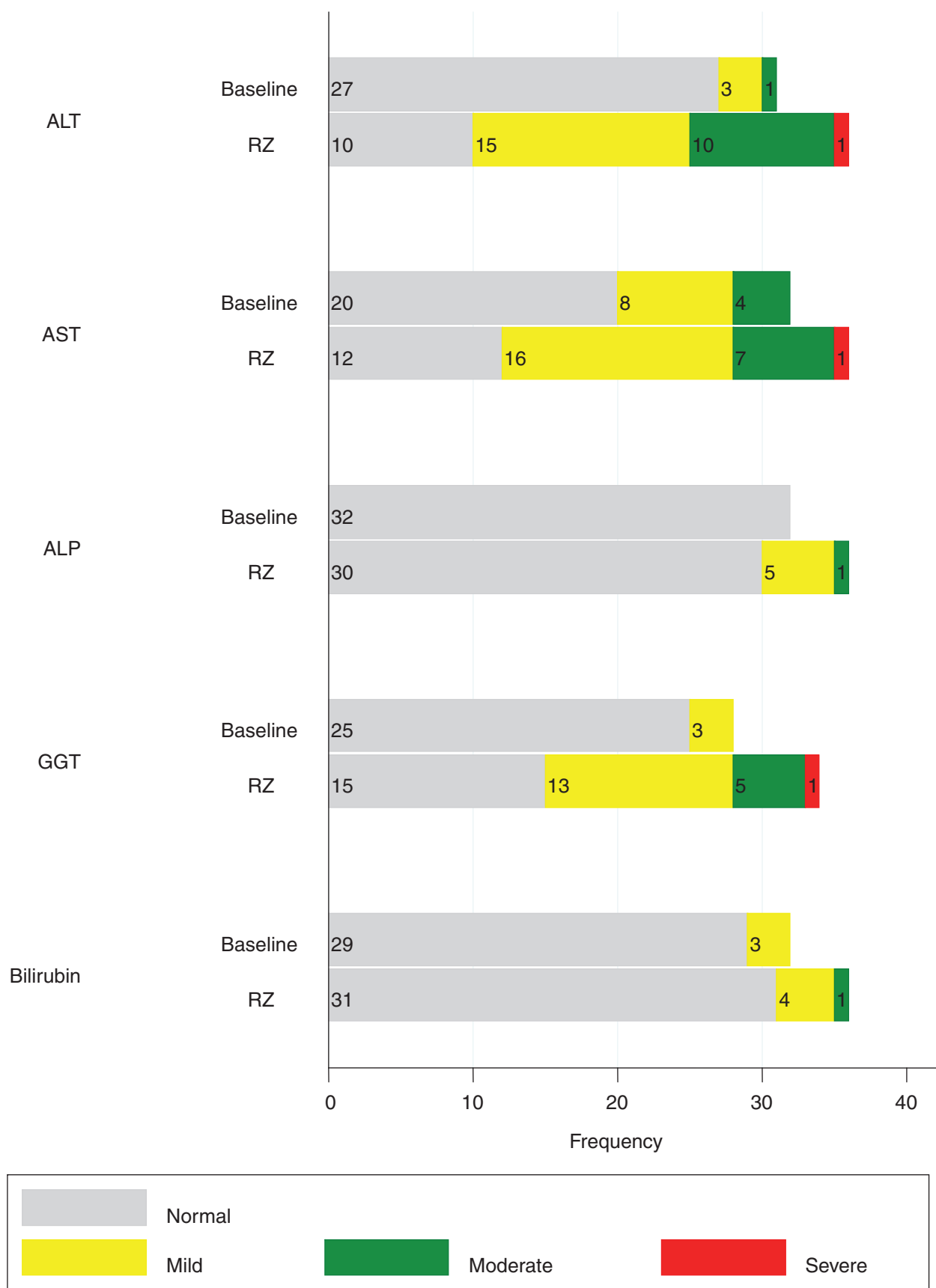


FIG. 2. Cervical and thoracic injuries: frequency of normal and elevated liver enzymes and bilirubin. See Table 10. ALT, alanine transferase; AST, aspartate transamine; ALP, alkaline phosphatase; GGT, gamma-glutamyl transpeptidase; RZ, riluzole.

TABLE 11. CERVICAL INJURIES: RILUZOLE AND REGISTRY PATIENTS

Admission	N	Riluzole			Registry	
		Admission ^a mean (SD)	42-day mean (SD)		Admission ^d mean (SD)	90-day mean (SD)
A	10	16.8 (15.9)	24.0 (16.1)			
B	8	16.4 (10.1)	44.5 (25.6)			
C	7	30.3 (23.0)	64.4 (28.1)			
All	25	20.4 (17.2)	41.9 (27.8)			
Admission to 90 days	N	Admission ^b mean (SD)	90-day mean (SD)	N	Admission ^d mean (SD)	90-day mean (SD)
A	9	14.6 (9.3)	27.3 (26.3)	12	21.6 (14.2)	31.9 (19.9)
B	8	16.4 (10.1)	55.4 (28.1)	8	19.9 (9.2)	31.0 (22.9)
C	7	30.3 (23.0)	76.1 (18.8)	6	36.7 (13.0)	68.8 (18.1)
All	24	19.7 (15.7)	50.9 (31.5)	26	24.5 (13.9)	40.2 (25.4)
Admission to 180 days	N	Admission ^c mean (SD)	180-day mean (SD)	N	Admission ^e mean (SD)	180-day mean (SD)
A	7	16.1 (8.7)	31.4 (29.6)	9	23.3 (13.8)	34.8 (20.8)
B	7	14.6 (9.4)	60.3 (24.6)	5	22.4 (11.1)	46.6 (32.5)
C	6	32.0 (24.5)	81.8 (23.9)	6	33.0 (13.9)	84.0 (12.3)
All	20	20.4 (16.6)	56.6 (32.5)	20	26.0 (13.4)	52.5 (30.3)

Sample size, mean, and standard deviation of motor scores at 42, 90, and 180 days are stratified by admission impairment grade (see Fig. 3). See consort diagram, Figure 1, and graph, Figure 3.

^aIncludes 25 riluzole patients with both an admission and 42-day motor score.

^bIncludes 24 riluzole patients with both an admission and 90-day motor score.

^cIncludes 20 riluzole patients with both an admission and 180-day motor score.

^dIncludes 26 registry patients with both an admission and 90-day motor score.

^eIncludes 20 registry patients with both an admission and 180-day motor score.

SD, standard deviation.

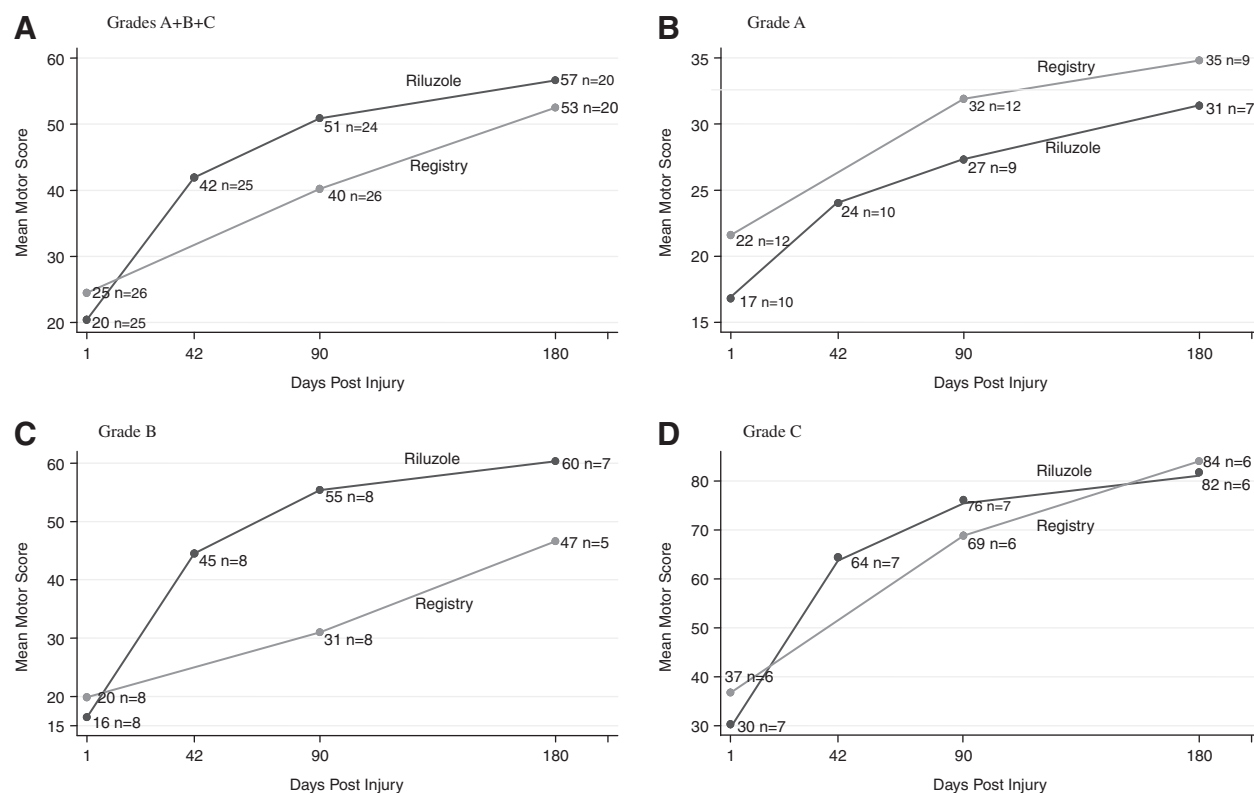


FIG. 3. Cervical injuries: riluzole and registry patients. Progression of mean total motor score (and *n* patients available) at admission and 42, 90, and 180 days, stratified by admission impairment grade. (A) All grades. (B) Grade A. (C) Grade B. (D) Grade C. See Table 11.

TABLE 12. CERVICAL INJURIES: RILUZOLE AND REGISTRY PATIENTS: MOTOR SCORE MEAN CHANGES FROM ADMISSION TO 90 DAYS AND FROM ADMISSION TO 180 DAYS

Admission AIS	N	Riluzole			Registry			Riluzole: registry difference mean	p value*
		90-day change mean (SD)		N	90-day change mean (SD)		N		
A	9	12.7 (20.7)		12	10.3 (17.1)		12	2.4	0.787
B	8	39.0 (28.7)		8	11.1 (17.4)		8	27.9	0.037
C	7	45.8 (16.0)		7	32.1 (19.3)		6	13.7	0.194
All ^a	24	31.2 (26.2)		27	15.7 (19.3)		26	15.5	0.021

Admission AIS	N	180-day change mean (SD)			180-day change mean (SD)			Riluzole: registry difference mean	p value*
		180-day change mean (SD)		N	180-day change mean (SD)		N		
A	7	15.3 (9.3)		7	11.4 (17.2)		9	3.9	0.715
B	7	45.7 (10.8)		5	24.2 (24.8)		5	21.5	0.208
C	6	49.8 (8.4)		5	51.0 (9.7)		6	-1.2	0.911
All ^b	20	36.3 (28.5)		18	26.5 (24.0)		20	9.8	0.248

^aIncludes all cases with both an admission and 90-day total motor score.

^bIncludes all cases with both an admission and 180-day total motor score.

*Exact *p* values based on the nonparametric permutation test for two independent samples.

AIS, American Spinal Injury Association (ASIA) Impairment Scale; SD, standard deviation.

absolute motor scores at admission and at 90 and 180 days, stratified by impairment grade on admission and for the cohort as a whole. Table 12 shows the *change* in scores from admission to 90 and to 180 days, stratified by impairment grade on admission and for the cohort as a whole.

Table 11 (upper panel) presents the progression of the mean total motor score for 25 riluzole patients with cervical injuries from admission to 42 days postinjury. The table includes only patients with admission and 42-day scores. Patients are stratified by impairment grades A, B, and C and by A+B+C, that is, the entire group taken as a whole (all).

Ten patients (admission impairment grade A) progressed from an admission mean motor score of 16.8 to 24.0 at 42 days, gaining 7.2 points and achieving 76% of the score of 31.4 reached at 180 days by 7 of these patients, as shown in the lowest panel of the table.

Eight patients (admission impairment grade B and motor score of 16.4) progressed to a score of 44.5 at 42 days, a gain of 28.1 points and achieved 74% of the score of 60.3 reached at 180 days by 7 of these patients.

Seven patients (admission impairment grade C and motor score of 30.3) progressed to a score of 64.4, a gain of 34.1 points, and achieved 79% of the score of 81.8 reached at 180 days by 6 of these patients.

For all grades, the group of 25 riluzole patients had a mean admission motor score of 20.4, progressed to a score of 41.9 at 42 days, a gain of 21.5 points, and achieved 74% of the score of 56.6 reached at 180 days by 20 of these patients, as shown in the lowest panel of the table.

The progression of motor scores to 90 and to 180 days for riluzole patients and registry patients, stratified by impairment grades, is shown in the middle and lowest panels, respectively, of Table 11 and is displayed graphically in Figure 3.

Table 11 (middle panel) compares the motor scores for 24 riluzole and 26 registry patients at 90 days postinjury, stratified by impairment grade. The table includes only patients with motor scores for those dates. Data for both the riluzole and registry groups, each taken as a whole (all), are shown in the lowest row of the panel and are displayed graphically in Figure 3A. For the 90-day comparison, the scores on admission were 19.7 for the riluzole cohort and 24.5 for the registry cohort. At 90 days, the riluzole

cohort had progressed to a score of 50.9 and the registry cohort to a score of 40.2.

The lowest panel shows the scores at 180 days. At 180 days, the motor score for all patients was 56.6 for 20 riluzole patients and 52.5 for 20 registry patients.

The greatest gains in mean motor score occurred in grade B patients. The score of riluzole B patients went from 16.4 on admission to 55.4 at 90 days. At 180 days, the score of 7 riluzole B patients went from 14.6 to 60.3 (a 4.13-fold gain). The gain in bilateral lower extremity motor score (LEMS) exceeded that of the bilateral upper extremity motor score (UEMS). The gain in LEMS for 8 patients from admission to 90 days was 25.9 points and for UEMS, 13.1 points. The gain in LEMS for 7 patients from admission to 180 days was 29 points and for UEMS, 14.9 points.

The next-greatest gains were for C-grade patients, with a 2.45-fold gain at 90 days and 2.56-fold gain at 180 days. Grade A patients had the lowest gains (1.86-fold at 90 days and 1.95-fold at 180 days).

Table 12 presents the *change* of motor score and the riluzole cohort-registry cohort difference in the gain of scores and *p* values. The data are stratified by impairment grades and for the cohort as a whole for patients with admission and 90-day scores and patients with admission and 180-day scores.

For grade A patients, the riluzole-registry mean difference at 90 days was 2.4 points ($p=0.787$); for grade B patients, 27.9 ($p=0.037$); for grade C patients, 13.7 ($p=0.194$). For the entire cohort, the difference was 15.5 (significant at $p=0.021$). The score for the grade B patients contributed the largest effect toward the significance value for the entire group.

At 180 days, the riluzole-registry difference for grade B patients was 21.5 ($p=0.208$) and for grade C patients, -1.2 ($p=0.911$). For all patients, the difference was 9.8 ($p=0.248$).

Figure 4 presents a box-plot comparison of the gains in motor scores from admission to 90 days for 24 riluzole patients and for 26 registry patients, as well as for 20 patients of each group at 180 days. Box plots show the median gain and the 75th and 25th percentiles and the maximum and minimum values for both groups. The median is used rather than the mean because the data are skewed toward higher motor score values, and thus a mean does not adequately locate the center of the data. This is particularly true for the 90-day gains. At 90 days, the median value was 23.5 for the

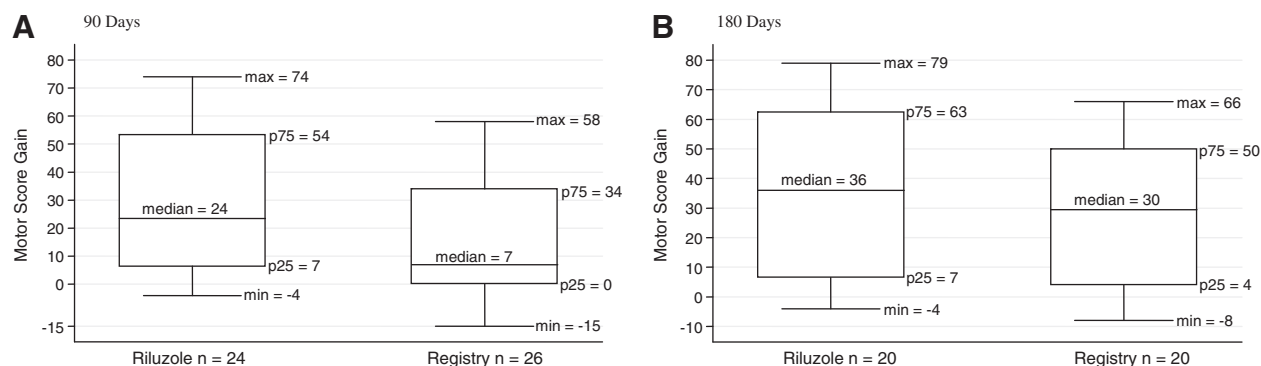


FIG. 4. Cervical injuries: riluzole and registry patients. Box plots of gains in total motor score. (A) 90 days. (B) 180 days. max, min, maximal and minimal scores encompassing at least 99% of the data; p25, p75, 25th and 75th percentiles.

riluzole group and 7 for the registry group. At 180 days, the median value was 36 for the riluzole patients and 29.5 for the registry patients. The distribution of the data indicates more robust motor outcome in the riluzole patients.

No relationship was found between gain in motor score and time from injury to administration of riluzole.

No differences were found in outcome motor scores between the 14 patients (cervical and thoracic) who received both MPSS and riluzole and patients who received only riluzole.

Cervical injuries: Progression of sensory scores

Pin-prick scores were available at 90 days for 24 riluzole patients and for 23 registry patients, as well as at 180 days for 20 riluzole and 15 registry patients. Box plots of gain in pin-prick scores for riluzole and for registry patients at 90 and 180 days are shown in Figure 5 as an example of the changes that were observed for both light touch and for pin-prick sensation. Pin-prick scores were 10 points higher for the riluzole patients than for the registry patients at 90 days and 9 points higher at 180 days for the riluzole patients than for the registry patients, but the differences in gains were not significant. The results for light touch were similar.

Cervical injuries: conversion of impairment grades at 90 days and at 180 days

Table 13 shows the change in impairment grades from admission to 90 days for 27 patients with cervical injuries and 26 matched

registry patients. Of 12 grade A riluzole patients, 6 (50%) remained at A, 3 (25%) converted to B, 2 (17%) went to C, and 1 (8%) to D. In contrast, of 12 grade A registry patients, 9 (75%) remained at A and 1 (8%) each converted to B, C, and D.

Of 8 grade B riluzole patients, 1 remained at B, 3 converted to C, and 4 converted to D. In contrast, of 8 grade B registry patients, 4 (50%) remained at B, 3 (38%) converted to C, and 1 (12%) converted to D.

Of 7 grade C riluzole patients, 1 remained at C (14%), 5 (72%) converted to D, and 1 (14%) converted to E. In contrast, of 5 registry patients, 3 (60%) remained at C and 2 (40%) converted to D.

Table 14 shows conversions at 180 days for 20 patients in the riluzole cohort and 20 in the registry cohort with impairment data. The percentage of patients that converted to a more functional grade continued to be higher in the riluzole than in the registry cohort. The greatest positive effect was in grade B patients.

Cervical injuries: Spinal Cord Independence Measure

SCIM scores were available at 180 days for 20 riluzole patients and for 14 registry patients. There was no significant difference in the total score for the entire riluzole cohort, in comparison to the registry cohort. Seven B grade patients, however, had a 17.8-point mean advantage over 5 grade B registry patients.

Thoracic injuries

There were 8 thoracic injuries: 7 grade A and 1 grade B. At 180 days, the group exhibited a mean gain of 3 points in total motor

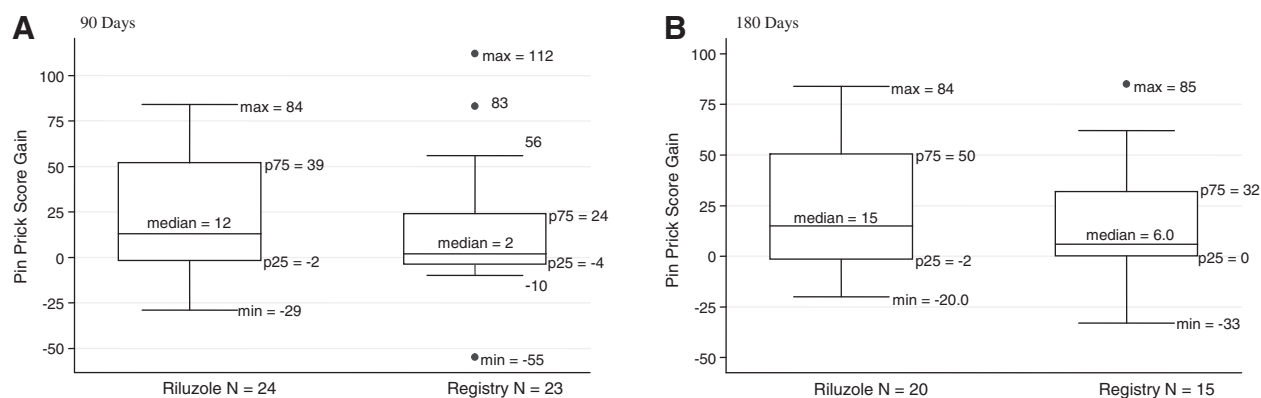


FIG. 5. Cervical injuries: riluzole and registry patients. Box plots of gains in pin-prick scores, all grades. (A) 90 days. (B) 180 days. max, min, maximal and minimal scores encompassing at least 99% of the data; *max, *min, outlying values; p25, p75, 25th and 75th percentiles.

TABLE 13. CERVICAL INJURIES: RILUZOLE AND REGISTRY PATIENTS

<i>Riluzole</i>						
<i>Admission</i>		<i>90 days</i>				
<i>Grade</i>	<i>N=27</i>	<i>A</i> <i>N (%)</i>	<i>B</i> <i>N (%)</i>	<i>C</i> <i>N (%)</i>	<i>D</i> <i>N (%)</i>	<i>E</i> <i>N (%)</i>
A	12	6 (50)	3 (25)	2 (17)	1 (8)	
B	8		1 (13)	3 (37)	4 (50)	
C	7			1 (14)	5 (72)	1 (14)
<i>Registry</i>						
<i>Admission</i>		<i>90 days</i>				
<i>Grade</i>	<i>N=26</i>	<i>A</i> <i>N (%)</i>	<i>B</i> <i>N (%)</i>	<i>C</i> <i>N (%)</i>	<i>D</i> <i>N (%)</i>	<i>E</i> <i>N (%)</i>
A	12	9 (75)	1 (8)	1 (8)	1 (8)	
B	8		4 (50)	3 (38)	1 (12)	
C	6			3 (50)	3 (50)	

Conversions of impairment grades at 90 days.

score and a 5.2-point gain in pin-prick score. Three of the 7 grade A patients converted to a more functional grade; 2 of the 7 matched registry grade A patients converted to a more functional grade.

Discussion

Feasibility of riluzole as an acutely administered therapy for spinal cord injury

The study demonstrates that it is feasible to screen, consent, and enroll SCI patients in a clinical trial of drug therapy, obtain laboratory and radiological data, and start pharmacological therapy within 12 h of injury. This finding should provide encouragement for further trials of therapies that must be applied very rapidly after SCI.

TABLE 14. CERVICAL INJURIES: RILUZOLE AND REGISTRY PATIENTS

<i>Riluzole</i>						
<i>Admission</i>		<i>180 days</i>				
<i>Grades</i>	<i>N=20</i>	<i>A</i> <i>N (%)</i>	<i>B</i> <i>N (%)</i>	<i>C</i> <i>N (%)</i>	<i>D</i> <i>N (%)</i>	<i>E</i> <i>N (%)</i>
A	7	5 (71)	1 (14)	0 (0)	1 (14)	0 (0)
B	7			2 (29)	5 (71)	0 (0)
C	6			1 (17)	4 (64)	1 (17)
<i>Registry</i>						
<i>Admission</i>		<i>180 days</i>				
<i>Grades</i>	<i>N=20</i>	<i>A</i> <i>N (%)</i>	<i>B</i> <i>N (%)</i>	<i>C</i> <i>N (%)</i>	<i>D</i> <i>N (%)</i>	<i>E</i> <i>N (%)</i>
A	9	7 (78)	1 (11)	0 (0)	1 (11)	0 (0)
B	5		2 (40)	1 (20)	2 (40)	0 (0)
C	6			0 (0)	6 (100)	0 (0)

Conversions of impairment grades at 180 days.

Demographic and neurological characteristics of the riluzole cohort

The patients enrolled in the present trial were representative of the population of SCI admitted to NACTN center hospitals in the distribution of injuries between cervical and thoracic locations and in the distribution of their impairment grades. Cervical injuries comprised 78% of the patients in the present study (Table 5), and the ratio of cervical to thoracic injuries and their impairment grades were similar in the NACTN SCI Registry. Therefore, there does not appear to be selection bias of patients for the present trial.

Pharmacology of riluzole in spinal cord injury

It would be expected that for riluzole to have a therapeutic effect, a threshold level of blood-plasma concentration must be reached and that there is a therapeutic range of concentrations.

An aim of the present study was to determine whether an association could be observed between blood-plasma levels of riluzole and motor outcome scores, with the object of determining a therapeutic blood-plasma level of riluzole. The previously published report of the pharmacology of riluzole in the patients in this phase I trial indicated that on day 3 of administration, there was a 17-fold difference in maximal concentration of riluzole between the lowest and highest values (24–409 ng/mL) in different patients. The cause of the variability in blood levels is likely to be, in part, the result of differences in absorption of riluzole from the gut¹⁶ and, in part, from variability in individual body mass index (Table 4). An attempt was made to correlate C_{max} and gain in motor and sensory scores for all cervical injury patients as a group and for A, B, and C subgroups. No significant correlation was found. However, there was a positive correlation for grade B patients when extreme, outlying motor score and C_{max} values were censored. It is possible that the low levels of plasma concentration of riluzole, in some patients, did not reach a threshold for efficacy. Considering the multiple factors that determine neurological outcome, it may be difficult to achieve a correlation. Further analysis will be undertaken in a phase II study with a larger number of patients in an attempt to validate a therapeutic effect and determine a therapeutic range of plasma concentration. If a therapeutic effect and range can be established, monitoring of plasma levels and adjustment of the enteral dose would be a rational approach to therapy.

The previous publication of the pharmacology of riluzole in SCI reported on the finding of an increase in the clearance and distribution of riluzole between the 3rd and 14th days of administration that resulted in a lower plasma concentration on day 14. This finding indicates that the changing physiology of the SCI patient can affect the metabolism of drugs and emphasizes the importance of monitoring changes in drug metabolism in SCI clinical trials for evaluating safety and efficacy data. It is also another factor that suggests the possible utility of monitoring blood levels of riluzole to adjust dosage.

Safety of riluzole in spinal cord injury: Medical complications and serious adverse events

The primary aim of the phase I trial was to determine the incidence of medical complications and SAEs in SCI patients receiving riluzole. The incidence and types of complications were similar in the riluzole patients and in the comparison registry group and in the larger NACTN SCI Registry.²² There were no SAEs attributable to riluzole and no deaths. In the NACTN SCI Registry, mortality in 126 patients with impairment grade A was 8.7% (11 patients). The

leading causes of death were cardiac ($n=4$), pulmonary ($n=4$), and multi-organ failure ($n=2$). If the same mortality rate occurred among the 19 grade A patients in the present trial, an average mortality of 1.65 patients would be expected.

Safety: Effects on liver enzymes

Elevations of ALT and of AST are considered to be indicators of drug-induced damage to liver cells. Elevation of GGT is a less-specific indicator of drug-induced damage to the liver. Elevation of ALP is considered to be primarily an indicator of obstruction of the bile duct. Elevation of liver enzymes has been reported in patients with ALS undergoing treatment with riluzole.¹⁷ Elevation of liver enzymes has been reported to occur acutely in patients with SCI²³ and in animal models of SCI, possibly resulting from impairment of blood flow to the liver.^{24,25} In the present study, riluzole administration in SCI patients was associated with a mild to moderate elevation of blood levels of ALT, AST, GGT, ALP, and bilirubin, to a varying degree for each of these markers of liver function. Elevations of ALT, AST, and GGT that reached the lower levels of a severe elevation ($>5-20 \times \text{ULN}$) occurred on one occasion in each of 1 patient for each of these enzymes. Enzyme elevations were transient and bilirubin levels were normal on the last day of riluzole administration. Mild and moderate elevation of ALT and AST in SCI patients, as reported by Shepard and Bracken,²³ was confirmed to occur within the first day of injury before administration of riluzole.

Neurological outcomes: Cervical injuries, motor scores

As a phase I trial whose primary aims were determining the PK and safety of riluzole, and without a concomitant control group, the trial was not designed or powered to detect significant changes in neurological outcome. Nevertheless, a trend was observed of a more robust outcome in riluzole-treated patients.

Comparison can be made with the results of the recently published phase II placebo-controlled, randomized trial of minocycline in acute SCI.²⁶ Minocycline administration was associated with a 14-point gain in motor score over placebo, and motor score recovery substantially reached a plateau after 3 months. In the present phase I trial, a gain of 15.5 points was found for the riluzole group of 24 patients over the comparison registry group of 26 patients. It is difficult to precisely determine the comparability of the minocycline and the riluzole treatment groups and of the registry comparison and the placebo control group with respect to the anatomical levels of injury, distribution of impairment scores, and numbers of patients. Putting the question of comparability aside, Figure 3 of the minocycline article, showing graphs of motor gains of minocycline and placebo patients, shows, for minocycline patients, a gain from admission to 190 days of approximately 28 points, and for placebo, a gain of approximately 14 points. This gain is comparable to the gain at 180 days in the present phase I riluzole trial of 31.2 points for 24 riluzole patients and of 15.7 points for 26 registry patients.

In the minocycline trial in patients with cervical injuries, LEMS had greater gains than UEMS. In the present study, the same observation was made for grade B patients with cervical injuries who received riluzole.

Comparison of gains in UEMS can also be made with a recent report of the extent of spontaneous motor recovery after traumatic cervical sensorimotor complete SCI.²⁷ Analysis of the Sygen trial and the European Multi-Center Study about SCI (EM-SCI) databases found a 10–11-point gain in UEMS at 1 year. The riluzole

grade B patients, not as severely impaired as grade A patients, achieved a UEMS gain of 14.9 points at 180 days and a LEMS gain of 29 points.

Cervical injuries: Progression of sensory scores

In the minocycline trial, cervical motor-incomplete patients had pin-prick scores that were 14 points greater than placebo patients.²⁶ In the riluzole patients, complete and incomplete injuries in the present study had, at 180 days, a gain of 9 points over the registry patients.

Cervical injuries: conversion of impairment grades

The most robust conversions were exhibited by grade B patients. At 90 days, 87% of 8 grade B riluzole patients converted to a more functional grade, compared to 50% of 8 grade B registry patients. At 180 days, all 7 (100%) of grade B riluzole patients had progressed to a more functional grade, compared to 3 (60%) of 5 registry patients.

These findings can be compared to data in the recent publication of motor recovery of cervical SCI from the National Spinal Cord Injury Statistical Center (NSCISC) database. For grade B patients, from a baseline of 7 days or less, to 1 year, 34% remained at grade B and 67% converted to C (30%) and D (37%).²⁸

Conversions of grade A patients were not as robust, and rates for riluzole and registry patients were comparable to those reported in the EM-SCI database: For grade A patients assessed within 2 weeks of injury with a final assessment at 1 year, 32% converted to a more functional grade.²⁹ These figures are in agreement with the NSCISC database figure of 30% conversion at 1 year²⁸ and correspond in the present phase I study to the conversion rate for 7 grade A riluzole patients of 29% at 180 days.

It should be noted, in making comparisons with these two studies,^{28,29} that their baseline measurements were made within 1 week of injury in one study and within 2 weeks in the other. In the present study, baseline assessment of impairment grade was made within 12 h of injury. It is well recognized that within such a group of patients, spontaneous improvement may occur rapidly, which would result in a different classification of some of the patients in the group if the assessment had been made at 72 h. However, the registry group was also assessed within 12 h and should be an appropriate comparison group.

Cervical injuries: The Spinal Cord Independence Measure

At 180 days, there was no significant difference between the SCIM scores of the riluzole and registry groups, although there was a trend for better scores for grade B patients.

Improvement in functional outcome is, of course, the desired goal of therapy. Further detailed study of SCIM and other functional outcome measures in a phase II trial is warranted.

Thoracic injuries

The 8 thoracic injuries in the present study were all motor complete. On admission, 1 patient had sacral sensation. There was minimal improvement of motor and sensory score in this group of patients. A recent report of the neurological outcomes of 399 thoracic complete patients in the EM-SCI database found minimal motor and sensory improvement in this group of severely injured patients.³⁰ Motor improvement occurred predominantly in patients with low thoracic injury. There were only two such individuals in

the present riluzole study. Therefore, a therapeutic effect of riluzole might be detected in a larger number of low thoracic injuries and in patients who are grade B or C.

Limitations of the study

The trial was open label and the patients and examiners were aware of the treatment, factors that might result in a positive bias for riluzole treatment.

The outcomes of the patients receiving riluzole were compared with a recent historical group of patients in the NACTN SCI registry and not with a contemporaneous control group, as would occur in a phase II trial. However, the comparison registry group used to evaluate outcomes was treated at NACTN hospitals operating under the same standard-of-care protocol, and many riluzole and registry patients were evaluated by the same clinical teams, which may have reduced the variability of scoring of outcome measures.

Factors other than treatment with riluzole may have influenced neurological outcome. The very short time from injury to ED admission and supportive medical care and from injury to surgical decompression and stabilization for both the riluzole and registry patients may have had a therapeutic effect, when compared to historical studies performed at earlier times, when the incidence of decompression or stabilization surgery was not as great or carried out as urgently.

The number of patients was small, particularly when stratified by impairment scores. As commonly observed in longitudinal studies of acute SCI, the number of patients available for examination decreased as patients completed inpatient rehabilitation and returned to their homes or to a care facility far from a NACTN center. Despite strenuous efforts to obtain data from all patients unable to return to a center for examination, 3 of the 27 cervical injury patients who completed the 14-day course of riluzole treatment were unavailable for examination at 90 days, and an additional 4 were unavailable at 180 days, leaving 24 riluzole patients for analysis at 90 days and 20 at 180 days. The variability of neurological outcomes of SCI patients is great, particularly of grade C patients, and in a small sample, even 1 or 2 patients with extreme scores can bias the results.

Conclusion

Riluzole administered enterally within 12 h of SCI was well tolerated. There were no SAEs attributable to riluzole. Bearing in mind the limitations of the study, the exploratory pilot data suggest that riluzole may have a beneficial effect on motor outcome in cervical SCI that was manifest at 90 days postinjury. Improvement in lower extremity motor score appeared to be the primary effect. Further study of the PK, safety, and effects of riluzole on neurological outcome in acute traumatic SCI will be carried out in a phase II trial.

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Author Disclosure Statement

No competing financial interests exist.

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Addendum to “A Multi-Center, Randomized, Placebo-Controlled, Double-Blinded, Trial of Efficacy and Safety of Riluzole in Acute Spinal Cord Injury”

Pharmacology of Riluzole in Patients with Acute Traumatic SCI

Goals of Riluzole Pharmacological Study

To obtain information about pharmacokinetics (PK) and pharmacodynamics (PD) of riluzole and relate that information to toxicity and efficacy outcomes. The pharmacological component of the phase 2/3 study is a continuation of the pharmacological component of the phase 1 trial which has been published (Chow et al., 2012). The findings of the phase 1 pharmacological study are as follows:

Riluzole pharmacokinetics was evaluable in 33 patients on day 3 and in 32 patients on day 14, as both C_{peak} and C_{trough} samples of the patient were collected and quantifiable. The plasma concentration and the systemic exposure to riluzole (area under the plasma concentration curve, AUC_{0-12}) varied significantly among patients. Maximum concentration (C_{max}) ranged from 24 to 409 ng/ml (mean 129 ± 14 ng/ml, SE) on day 3 and 9 to 317 ng/ml (mean 77 ± 14 ng/ml SE) on day 14.

The pharmacokinetics of riluzole - C_{max} , C_{min} , AUC_{0-12} , clearance (CL/F) and volume of distribution (V/F), normalized by the bioavailability, changed during the acute and subacute phases of SCI during the 14 days of administration, a phenomenon consistently observed in all patients at all clinical sites. Mean C_{max} , C_{min} and AUC_{0-12} (129 ng/ml, 46 ng/ml and 982 ng *hr/ml, respectively) were significantly higher on day 3 than on day 14 (77 ng/ml, 19 ng/ml and 521 ng *hr/ml, respectively), resulting from lower CL/F (50 L/hr vs 106 L/hr) and a smaller V/F (557 L vs 1298 L) on day 3. This finding indicates that the changing physiology of the SCI patient during the acute – subacute phase of injury can affect the metabolism of drugs and emphasizes the importance of monitoring changes in drug metabolism in SCI clinical trials for evaluating safety and efficacy data.

Specific Aims

1. To determine the individual peak and trough concentrations of riluzole after a loading dose of 100 mg BID for the first 2 doses followed by 26 doses of 50 mg twice daily by enteral administration.
2. To derive individual and population pharmacokinetic parameters of half-life ($t_{1/2}$), systemic exposure ($AUC_{0 \rightarrow 12}$), volume of distribution (V/F) and clearance (CL/F) by one-compartment model, using WinNonlin and NONMEM software, respectively.

3. To correlate pharmacokinetics and pharmacodynamics of riluzole in patients by the correlation of the riluzole concentrations or $AUC_{0 \rightarrow 12}$ with laboratory measures including AST, ALT, WBC count, and the incidence of adverse events, as well as with efficacy scores, namely, ISNCSCI motor, sensory and impairment scores and SCIM.
4. To determine if an exposure/response relationship can be established between the plasma levels of riluzole and improvement in neurological outcome with the object of determining a therapeutic plasma level of riluzole.

Patient Recruitment

A goal of obtaining PK data on approximately 60 patients will be adequate for correlating PK measurements with efficacy measures, building on the pharmacological data acquired in 33 patients in the phase 1 trial.

Methods

The following methods were successfully used in the phase 1 safety trial of riluzole (Chow et al., 2012).

Sampling schedules for blood plasma

1. Blank control (pre-treatment <12-hr from injury): at least 5 ml of plasma obtained from blood collected before the administration of riluzole. To obtain 5 ml of plasma, draw three blood samples, each 4 ml draw-volume, in Na⁺ Heparin vacutainers. Centrifuge in lab within 5-10 minutes at 2,700g for 10 minutes to separate plasma from whole blood. Transfer the plasma samples from the 3 tubes to an Eppendorf tube to make up at least 5 ml of plasma.
2. Blood samples for determinations of peak and trough concentrations:

On days 3 and 14, blood samples will be taken for the trough (pre-riluzole dose) and peak (2 hours post-riluzole dose) concentrations, respectively. One blood sample (4 ml) draw volume will be drawn before the riluzole dose is given and another blood sample (4 ml) draw volume will be drawn at 2 hr post dose. The research staff will record the time of dosing with riluzole and the exact sampling time for all blood samples.
3. Storage and shipping of samples for analysis:

Plasma samples will be stored at -80°C (or at least as low as -20°C) prior to the shipment with dry ice to: Dr. Diana S-L. Chow at 1441 Moursund Street, University of Houston College of Pharmacy at Texas Medical Center.

Samples from each site will be shipped in complete sets of 5 samples for each patient collected over 14 days. The plasma samples Dr. Chow receives will be labeled with a

patient trial number stripped of patient identifiers. The 5 specimen samples should be labeled as follows:

1. Blank control (pre-treatment <12 hr from injury)
2. Trough D3
3. Peak D3
4. Trough D14
5. Peak D14

Note the date collected in mm/dd/yy format and time of collection in military 24 hour format. Dr. Chow cannot link any individual sample to any individual patient.

Plasma samples not used for analysis will be stored at -80°C until completion of the study. After completion of the study the samples will be discarded following the protocol used at the College of Pharmacy, University of Houston.

Samples will be collected from patients receiving riluzole and patients receiving placebo for the purpose of maintaining blinding.

Schedule of Plasma Sample Collection

	Baseline < 12hr of injury	Day 3		Day 14	
	Trough¹	Trough	Peak²	Trough	Peak
Total Blood draw	12 ml	4 ml	4 ml	4 ml	4 ml
Na+ Heparin vacutainer	(3) 4 ml	4 ml	4 ml	4 ml	4 ml
Plasma obtained	5 ml	2 ml	2 ml	2 ml	2 ml

¹Trough – pre-riluzole dose

²Peak – draw 2 hours post-riluzole dose

CSF samples

The assay developed is also capable of quantifying the riluzole concentration in CSF, whenever a sample is available. CSF withdrawal is indicated if there is a suspicion of meningitis, if there is a need for myelography or if there are other medical indications.

CSF samples will be stored at -80°C (or at least as low as -20°C) prior to the shipment with dry ice to Dr. Diana S-L. Chow at 1441 Moursund Street, University of Houston, College of

Pharmacy at Texas Medical Center. Samples from each site will be shipped for each patient collected over time. The amounts of CSF samples will be 5 cc or less. The CSF samples Dr. Chow receives will be labeled with a patient trial number stripped of patient identifiers and contain the following information: CSF, subject ID #, date collected in mm/dd/yy format, and time collected in military 24 hour time. Dr. Chow cannot link any individual sample to any individual patient.

Any CSF not used for analysis will be stored at -80°C until completion of the study. After completion of the study the samples will be discarded following the procedure used at the College of Pharmacy for disposal of nontoxic materials.

Pharmacokinetic analysis and modeling

Individual and population pharmacokinetic parameters of half-life ($t_{1/2}$), systemic exposure ($AUC_{0 \rightarrow 12}$), volume of distribution (V/F) and clearance (CL/F) will be derived, using WinNonlin and NONMEM software, respectively. The area under the plasma concentration–time curve will be calculated over a 12 hour period, expressed as per kilogram of body weight ($AUC_{0 \rightarrow 12}/kg$), and used as a measure of total riluzole systemic exposure.

Statistical analysis

The impacts of age, gender, smoking history, and concomitant medications on the plasma concentration of riluzole and pharmacokinetics parameters will be evaluated with covariate models using NONMEM analysis.

Relationships between plasma concentrations and $AUC_{0 \rightarrow 12}/kg$ with AST, ALT and WBC count will be determined with linear regression analysis.

The correlations between plasma concentrations and $AUC_{0 \rightarrow 12}/kg$ with the occurrence of adverse events and efficacy measurements of neurological outcome will be determined with logistic regression analysis.

Interim analysis of pharmacokinetics will be carried out at the time of the interim analysis of the study as a whole.

FRAMEWORK AGREEMENT

Among **AOSpine International**
Stettbachstrasse 6
CH-8600 Dübendorf, Switzerland
(hereinafter referred to as "AOSI")

and **AOSpine North America**
1700 Russell Road
Paoli, PA 19301, US
(hereinafter referred to as "AOSNA")

and **Christopher and Dana Reeve Foundation**
636 Morris Turnpike
Suite 3A
Short Hills, NJ 07078, US
hereinafter referred to as "CDRF")

regarding the realization of the clinical trial "Riluzole in Spinal Cord Injury Study (RISCIS)".

AOSI, AOSNA and CDRF may be referred to hereinafter individually as a "Party" or collectively as "Parties".

WITNESSETH:

- Whereas** AOSI is an association, focused on improving the quality of medical services provided to spine patients through education, research, documentation, and communication;
- Whereas** AOSNA is a nonprofit organization dedicated to the advancement of patient care, in orthopaedic, craniomaxillofacial and veterinary surgery; its mission is to improve the care of patients with musculo-skeletal injuries and their sequelae in North America, through education and research in the principles, practice and results of treatment;
- Whereas** CDRF is dedicated to curing spinal cord injury by funding innovative research, and improving the quality of life for people living with paralysis through grants, information and advocacy;
- Whereas** the Parties intend to realize the clinical trial "A Multi-Center, Randomized, Placebo-Controlled, Double-Blinded, Trial of Efficacy and Safety of Riluzole in Acute Spinal Cord Injury", in short: "Riluzole in Spinal Cord Injury Study (RISCIS)" (referred to hereinafter as „Trial"), at several study sites, by planning the Trial conjointly, but performing it by each Party individually at own study sites (referred to hereinafter as "Project");
- Whereas** the Parties shall enter into a framework agreement in order to regulate the shared rights and duties (referred to hereinafter as "Framework Agreement").

Therefore, for valuable consideration and intending to be legally bound, the Parties agree to the following.

Article 1 – Shared Rights and Duties of the Parties

1. The Parties shall be entitled or obliged in particular
 - a) to plan the Trial and to establish the Protocol conjointly;
 - b) to provide the Trial Product and to bear its costs;
 - c) to delegate a member to the Operational Board and to support the performance of the Project;
 - d) to obtain rights at the results of the Trial;
 - e) to co-operate at publications and to be author of publications;

- f) to provide financial support for the Project as indicated in Appendix 2;
 - g) to bear the costs of the own study sites;
 - h) to collaborate at the Project free of charge;
 - i) to contract a trial insurance;
 - j) to meet the duties of this Framework Agreement;
 - k) to decide on the acceptance of new co-operating partners;
 - l) ...
2. The aforementioned duties and rights are regulated in detail in this Framework Agreement.

Article 2 – Duties and Rights of each Party

1. Each Party shall be entitled or obliged in particular
- a) to perform the Trial at its own study sites according to the Rules of Good Clinical Practice and the Protocol as attached hereto as Appendix 1 and to monitor the Trial at its own study sites;
 - b) to define the number of study sites and the estimated number of Trial Subjects, after consultation of and in accordance with the Operational Board (details being regulated in Appendix 3);
 - c) to recruit the Trial Subjects for the own study sites, to apply for the necessary approvals and to regulate potential reimbursement for the Trail Subjects;
 - d) to take over the responsibility for the performance of the Trial at its own study sites and to bear the corresponding costs, as defined in Appendix 2 as “Individual Costs”;
 - e) in the event of an early termination, to contribute to the Shared Costs in the amount which has been defined as appropriate by the Operational Board according to art. 3 paragraph 5 of this Framework Agreement;
 - f) to accept decisions taking by the majority of the Operational Board;
 - g) to notify adverse events to the national authority according to the applicable national law and to notify at the same time the Data Safety Monitoring Board (DSMB);
 - h) ...

2. CDRF shall be entitled to perform the Trial according to a modified, Department of Defense compliant protocol.
3. The aforementioned duties and rights shall be regulated in detail in the Sites Agreements, agreed upon between each Party and its own study sites (referred to in the Framework Agreement as "Site Agreements").

Article 3 – Funding of the Project

1. The Parties shall bear the costs for the realization of the Project, as defined in Appendix 2 as Shared Costs, conjointly.
2. The proportion of each Party and the deadlines for paying are defined in Appendix 2. The percentage or share to be contributed by each Party shall be calculated according to the ratio between the number of study sites, each Party has, and the total number of study sites.
3. The payments have to be transferred to the following account:

Name and address account holder	
Name and address banking institution	
Bank account	
Bank identification code	
SWIFT / BIC	
IBAN	
Project number	

4. In the event that the Trial is terminated earlier, the payments shall be limited at a pro-rata amount. Contributions which go beyond this amount and have already been transferred, but have not yet been used, shall be refunded to the concerned Party or Parties.
5. In the event that one of the Parties terminates this Framework Agreement earlier, this Party has to contribute its proportion at the Shared Costs according to Appendix 2 as far as it is necessary in order to proceed with the Project. The Operational Board shall decide which proportion is appropriate.
6. Payments shall be made by each Party per fixed date of payment.

Article 4 – Operational Board

1. The Parties shall establish an Operational Board. The Operational Board shall consist of one member of each Party, the Principal Investigator and the Co-Principal Investigator. Each member of the Operational Board shall have equal rights. For the rest, the Operational Board shall constitute itself by its own.
2. The Operational Board shall in particular:
 - a) ensure the administrative and scientific realization of the Project and take all decisions which have to be taken in this context; the decisions shall be taken by the majority of all members of the Operational Board;
 - b) decide on the proceeding in the event of not foreseen incidences such as insufficient recruitment of Trial Subjects, higher costs than expected, bad quality of the results and the like;
 - c) designate AOSNA as Principal Sponsor in the sense of Good Clinical Practice;
 - d) contract a study insurance which covers all study sites of all Parties and all Trial Subjects;
 - e) define the proceeding with the results and the rights on the results, including filing of patent applications and the like;
 - f) draft and release publications;
 - g) decide on the admitting of new co-operation partners and ensure that they sign this Framework Agreement as well;
 - h) establish an account in order to transfer the Shared Costs;
 - i) decide on the proportion a Party has to pay in the event of an early termination of this Framework Agreement by this Party;
 - j) ...

Article 5 – Confidential Information

1. All information, data, documents and other related information received by each Party from the other Party under this Framework Agreement ("Confidential Information") is and shall be considered throughout, and for five (5) years after the termination of this Framework Agreement, as confidential, except for information which:

- a) at the time of disclosure is or becomes part of the public domain through no breach or fault of one of the Parties or its employees or agents;
 - b) at the time of disclosure by one of the Parties is in the other Party's lawful possession as evidenced by the concerned Party's written records;
 - c) the Party receives from a third party which has the right to disclose such information and which did not obtain such information in violation of the other Party's rights;
 - d) is required by law or by the competent authorities as part of fulfillment of their responsibilities;
 - e) was discovered or developed by the concerned Party independently of the present Framework Agreement.
2. Each Party shall hold Confidential Information in strict confidence and shall disclose Confidential Information to its employees or agents only on a need-to-know basis. Each Party shall ensure and shall be responsible that such employees or agents shall be bound and obligated by provisions of confidentiality identical to the Party's own confidentiality obligations hereunder.

Article 6 – Data Ownership and Intellectual Property Rights

a) Data Ownership

1. Any and all know-how, inventions, improvements and discoveries, whether patentable or not ("Intellectual Property"), and developed and/or reduced to practice by one of the Parties independently of this Framework Agreement shall be owned exclusively by the respective Party.
2. Any raw data and results, including accompanying documentation, generated or arising in the performance of the Project (referred to hereinafter as "Knowledge"), discovered, developed and/or reduced to practice by one of the Parties under this Framework Agreement, shall be owned by all Parties. The Party discovering, developing and/or reducing to practice Knowledge shall disclose and transfer it as quick as possible to the other Parties free of charge. Such Knowledge may be used by each Party at its free disposal for its internal operations as well as its internal and external teaching purposes. Such Knowledge may be used for other disclosures and/or publications only according to **Article 7** of this Framework Agreement and together with the other Parties, or with the other Parties' written agreement for individual use.

3. Each Party shall retain ownership of all original case report forms (CRF) and medical records and data that result from the Trial from its own study sites (according to site agreements).

b) Intellectual Property Protection

1. The Parties shall file together an application for, and take steps to obtain and maintain Intellectual Property Protection, in any country and related to any Knowledge discovered, developed and/or reduced to practice jointly by the Parties under this Framework Agreement and in connection with the Project. Each Party shall be entitled to be indicated as inventor in a potential patent. The Operational Board shall agree upon the individual persons of each Party to be indicated as inventors.
2. Each Party may, at its discretion and as far as applicable, but in coordination with the other Parties, file an application for, and take steps to obtain and maintain Intellectual Property Protection in any country and related to sub-analyses performed by this Party.

c) Licensing, commercial exploitation and future collaboration

1. The Parties shall negotiate – as the case may be and in due course – on licenses, commercial exploitation and/or future collaboration between the Parties and/or third parties.

Article 7 – Publications

1. The Parties shall install a body in order to handle all issues in the framework of publications (“Publication Board”) and designate one member from each Party as well as the Principal Investigator and the Co-Principal Investigator as members of the Publication Board.
2. The members of the Publication Board shall elaborate rules for the Publication Board (“Rules”). They shall define in these Rules in particular, but not limited, the procedure for publications on the Trial, the guidelines for authors, the selection of authors and the order, according to which the authors are listed at the beginning of the publication. This order shall depend in particular, but not limited, on the number of Trial Subjects, completeness of data, contribution to the drafting of the manuscript and further contribution to the publications.

3. The Publication Board shall be in charge of evaluating manuscripts for publications as proposed by authors. It shall publish own reports as considered appropriate.
4. The Publication Board shall ensure that publications are delayed for up to ninety (90) days in the event that the Operational Board or one of the Parties wants to secure Intellectual Property Protection of Knowledge that would otherwise become publicly known by said publication or disclosure.
5. The Publication Board shall ensure that the Parties financial support is indicated in an appropriate manner in any oral presentation, publication, paper and/or further communication.
6. Each Party shall be entitled to submit an own publication if the Publication Board has failed to submit a publication within six (6) months after completion of the Project. Each Party and/or the Publication Board shall provide the other Party the necessary Knowledge and results upon its request within due time.
7. Neither Party nor the Publication Board shall be entitled to use the name, mark or symbol of one of the Parties without the prior written consent of the concerned Party.

Article 8 – Insurance

1. The Parties shall contract a study insurance which covers all damages in all Trial Subjects at all study sites that may occur due to the participation in the Trial. The costs for such insurance shall be borne by all Parties conjointly and to same proportions.

Article 9 – Responsibilities and Liability

1. The Parties shall be responsible conjointly for the realization of the Project.
2. Each Party shall be liable to the other Parties for liabilities, damages, losses or expenses which arise for the other Parties by reason of a breach of this Framework Agreement, or as a result of misconduct, negligence, willful tortuous, or criminal action by the fallible Party, its employees or persons mandated by this Party. In this event, the fallible Party shall the other Parties and all personnel involved in the realization of the Project indemnify, defend, release and hold harmless against any liability, damage, loss or expense (including reasonable attorney's fees and expenses of litigation) incurred by or imposed upon the other Parties and/or the said personnel as a result of any claim, suit, action, demand or judgment related to its behavior.

3. Each Party shall be responsible for the performance of the Trial in its study sites and each Party shall be liable to the Trial Subjects at its own study sites for injuries suffered by a Trial Subject participating in the Trial, and resulting from the administration, use or application of Trial Product during the Trial.
4. Each Party shall reimburse the costs of extra unanticipated tests, treatments, and hospitalizations of Trial Subjects in its own study sites required as a result of adverse events which have resulted from the Trial Product administered, used or applied during the Trial.

Article 10 – Term and Termination

1. This Agreement shall enter into force following its signature by the Parties and end automatically after completion of the realization of the Project.
2. Each Party may terminate this Framework Agreement by written notice sixty (60) days in advance if
 - a) this Party does not obtain IRB approval or other necessary approvals within the period of time defined in the Site Agreement;
 - b) this Party does not enroll any Trial Subjects into the Trial within the period of time defined in the Site Agreement after receiving final approval from the IRB and the national health authorities;
 - c) an investigator at one of its study sites is no longer able to meet his contractual obligations and no acceptable substitute Investigator can be found within thirty (30) days after the first investigator's incapacity has occurred;
 - d) this Party negligently fails to perform or performs negligently any material work in accordance with this Framework Agreement and such failure continues for thirty (30) days after receipt of written notice from the other Parties;
 - e) this Party is or becomes unable to recruit the number of Trial Subjects according to Appendix 3 or at least a sufficient number within the period of time defined in the site agreement; ...
4. In the event of a termination according to art. 10 paragraph 2 of this Framework Agreement, the terminating Party has to ensure that the realization of the Project is guaranteed from the financial point of view and this Party has to transfer the proportion of the Shared Costs defined according to art. 3 paragraph 5 of this Framework Agreement.
5. Each Party may terminate this Framework Agreement with immediate effect if the IRB, competent health authority, Investigator and/or Principal

Sponsor recognize that any safety concerns necessitate discontinuation of the Trial.

6. The following provisions shall survive the termination of this Framework Agreement: Articles 5, 6 and 7.

Article 11 – Governing Law and Venue

1. This Agreement shall be governed by, and construed in accordance with, the substantive laws of
2. Venue shall be

Article 12 – General Terms

1. Neither Party shall be entitled to assign or otherwise transfer their rights and duties under this Framework Agreement in whole or in part to any third party without the prior written consent of the other Parties.
2. This Framework Agreement together with its Appendices sets forth the entire agreement between the Parties and supersedes all previous agreements regarding the subject matter hereof. This Framework Agreement may be extended, renewed or otherwise amended by the mutual written consent of the Parties.
3. In case of inconsistencies between this Framework Agreement and the Protocol, this Framework Agreement shall prevail.
4. If any provision of this Framework Agreement is found to be invalid or unenforceable, the invalidity or unenforceability of such provision shall not affect the other provisions of this Framework Agreement, and all provisions not affected shall remain in full force and effect. The Parties shall attempt to replace the invalid or unenforceable provision taking into account the sense and the objectives of this Framework Agreement.
5. The Parties shall act as independent parties hereunder and not as employees nor agents of any other Party.
6. No Party shall be liable for delay or failure to perform its duties under this Framework Agreement due to *force majeure*, provided such Party promptly gives the other Parties written notice claiming *force majeure* and uses its best efforts to eliminate the effect of such *force majeure*. *Force majeure* means any unforeseeable and insurmountable event beyond the reasonable control of the Party affected thereby. If the period of delay or failure extends for more than three (3) months, any Party shall have the right to terminate this Framework Agreement upon

written notice at any time after expiration of said three (3) month period.

7. Any disputes arising out of or relating to this Framework Agreement that cannot be resolved in good faith discussions among the Parties within 30 days shall be submitted to arbitration in accordance with the Swiss Rules of International Arbitration of the Swiss Chambers of Commerce in force on the date when the Notice of Arbitration is submitted in accordance with these Rules. The number of arbitrators shall be one. The seat of the arbitration shall be in Zurich, Switzerland, and the arbitral proceedings shall be in English. All notices by one Party to another in connection with any arbitration shall be in writing.
8. All notices to the Parties pursuant to this Framework Agreement, other than regular business correspondence, shall be sent in writing by registered letter or international courier to the addresses of the Parties as indicated below or to another address indicated in writing by the Party in question.

To AOSI
AOSpine International

Att. Peter Langer
Research Manager
Stettbachstrasse 6
CH-8600 Dübendorf
Switzerland
Tel: +41 44 200 24 68

To AOSNA
[Name and address]

To CDRF
[Name and address]

In Witness Whereof, the Parties hereto have caused this Framework Agreement to be executed in triplicate by their duly authorized representatives.

AOSpine International

Place and Date _____

[insert Name and Function]

AOSpine North America

Place and Date _____

[insert Name and Function] _____

**Christopher and Dana Reeve
Foundation**

Place and Date _____

[insert Name and Function] _____

* * * * *

Appendix 1: Protocol

Appendix 2: Definition of Shared Costs and Individual Costs and Payment
Schedule

Appendix 3: Estimated number of Study Sites and Trial Subjects per Party

Appendix 1: Protocol

Appendix 2: Definition of Shared Costs and Individual Costs and Payment Schedule

1. The Shared Costs include the costs for:
study insurance, study product, remote monitoring, database management, statistics, administrative costs for the performance of the Project (such as meetings, consultant services, assessments and the like according to decisions of the Operational Board), ...
2. The Individual Costs include the costs for:
the performance of the Trial at the local study sites, potential reimbursements for Trial Subjects, ...
3. The Parties shall contribute to the Shared Costs for the Project as follows:
 - a) AOSI: _____
 - b) AOSNA: _____
 - c) CDRF: _____
4. The Shared Costs shall be transferred to the account indicated in Art. 3.2 as follows:
 - a) The percentage of ... at ...
 - b) The percentage of ... at ...
 - c) The percentage of ... at ...
 - d) ...
5. Each Party shall bear its Individual Costs by its own.

Appendix 3: Estimated number of Study Sites and Trial Subjects per Party

1. The Parties estimate the number of Study Sites as follows:
 - a) AOSI: 4 centers at the maximum
 - b) AOSNA: 6 centers
 - c) CDRF: 4-6 centers
2. The Parties estimate the overall number of Trial Subjects per Party to be included in the Trial as follows:
 - a) AOSI:
 - b) AOSNA:
 - c) CDRF:
3. The Operational Board may discuss and evaluate modifications in the estimated numbers by its own or upon request of one Party. The definition of modified numbers shall be subject to the consent of all Parties.

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Defining the Role of Sensation, Strength, and Prehension for Upper Limb Function in Cervical Spinal Cord Injury

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Abstract

Background. Upper limb function plays a significant role in enhancing independence for individuals with tetraplegia. However, there is limited knowledge about the specific input of sensorimotor deficits on upper limb function. Thus the theoretical framework designed to develop the Graded Redefined Assessment of Strength Sensibility and Prehension (GRASSP) was used as a hypothetical model to analyze the impact of impairment on function. **Objective.** To define the association of impairment (sensation, strength, and prehension measured by the GRASSP) to upper limb function as defined by functional measures (Capabilities of Upper Extremity Questionnaire, Spinal Cord Independence Measure). **Methods.** A hypothetical model representing relationships by applying structural equation modeling was used to estimate the effect of the impairment domains in GRASSP on upper limb function. Data collected on 72 chronic individuals with tetraplegia was used to test the hypothetical model. **Results.** Structural equation modeling confirmed strong associations between sensation, strength, and prehension with upper limb function, and determined 72% of the variance in “sensorimotor upper limb function” was explained by the model. Statistics *if fit* showed the data did fit the hypothesized model. Sensation and strength influence upper limb function directly and indirectly with prehension as the mediator. **Conclusions.** The GRASSP is a sensitive diagnostic tool in distinguishing the relative contribution of strength, sensation and prehension to function. Thus, the impact of interventions on specific domains of impairment and related contribution on clinical recovery of the upper limb can be detailed to optimize rehabilitation programs.

Keywords

tetraplegia, upper limb, hand, function, impairment

Introduction

Upper limb function is integral to independence for individuals with traumatic tetraplegia; therefore, restoration of upper limb function is of great significance to this population.¹ The extent of recovery has a direct bearing on the functional independence of an individual.^{2–7}

However, the relationship between impairment and functional status is not well established^{8,9} and a greater understanding of impairment and its role in upper limb function could provide valuable information to support clinical decision making,¹⁰ such as treatment selection, prescription, and understanding the specific effects of interventions.

Development of the Graded Redefined Assessment of Strength Sensibility and Prehension (GRASSP) incorporated the specific impairment domains: sensation, strength, and prehension,^{11,12} which we hypothesized to contribute to upper

limb function. It was conceptualized in the theoretical framework designed prior to the development of the GRASSP¹¹

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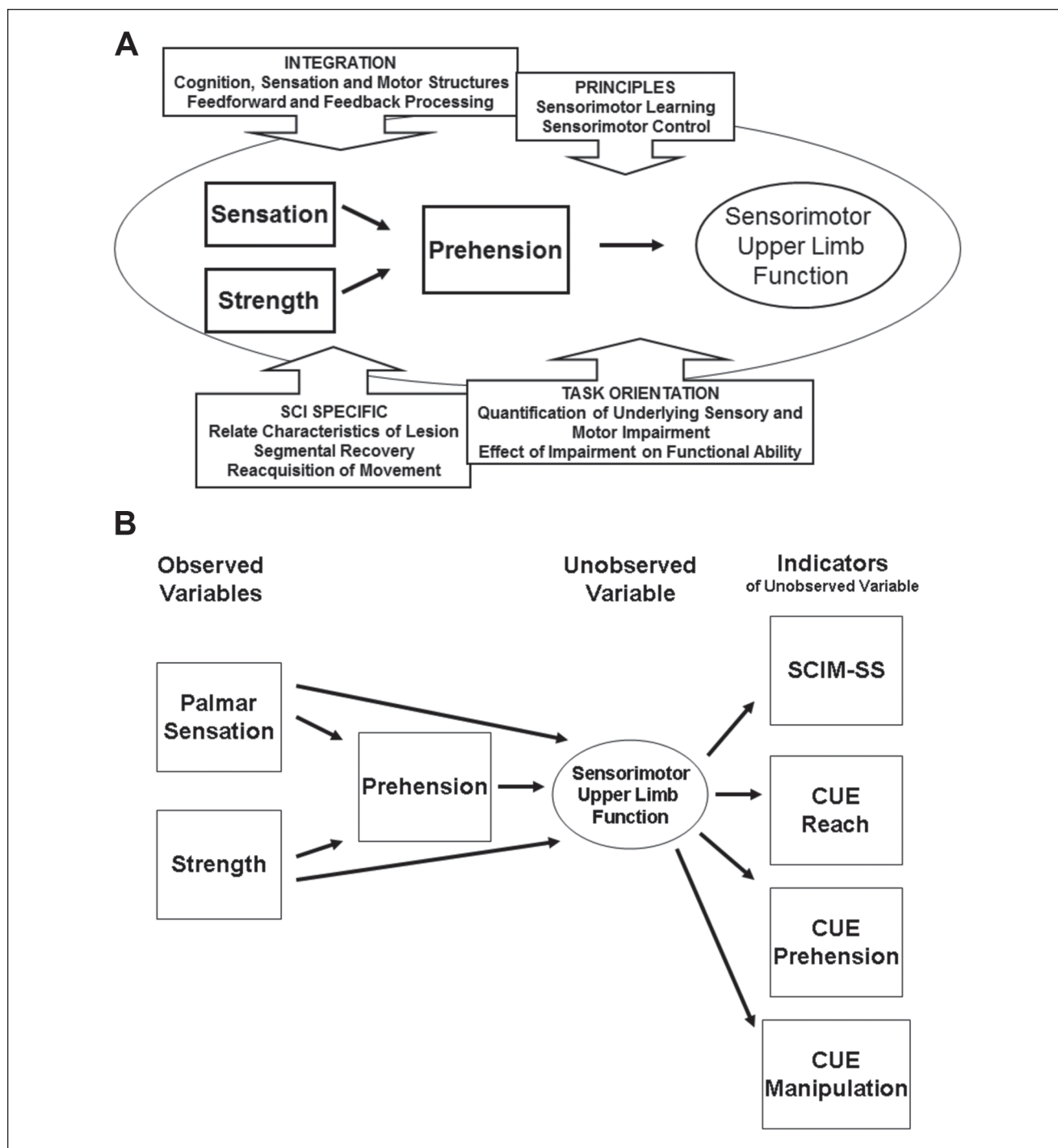


Figure 1. (A) Theoretical framework and (B) hypothetical model.

Abbreviations: SCIM-SS, Spinal Cord Independence Measure Self-Care Subscale; CUE, Capabilities of Upper Extremity Questionnaire.

(Figure 1) that all 3 domains play a role in upper limb function. However, the contribution of each component was unknown and where the intermediate relationships (integration) existed among impairment domains was not fully understood. Motor strength and its relationship to function is

often documented,¹³ but the distinct effects of sensation on function and upper limb recovery specific to tetraplegia remain underreported. The GRASSP falls into the International Classification of Functioning, Disability, and Health category of body structures and function. Although,

prehension would typically fall into the activity category; the tasks are measured by “how” they are performed rather than “if” the tasks are performed and defines innervation to a greater extent. Thus, the developers consider the GRASSP to be an impairment measure. Sensorimotor upper limb function was defined as the construct for the GRASSP, and a theoretical framework (Figure 1A) was designed to guide development of the measure. The framework incorporated the concepts of motor control and motor learning theory,¹⁴ which involve the interactions of the function (task), the individual, and the environment.¹⁵ Task performance, which depends on integrated systems of sensation, motor, and cognition, was also incorporated. An integrated (prehension) component was added to assess how sensory and motor impairments contribute to an integrated function; this issue becomes increasingly important during the recovery process. When scoring is directed toward the quality and performance of movement (noting how the grasp is produced) more so than the ability alone (task performed or not), the results indicate which neurological elements are intact and or recovering.¹¹ The combination of the 3 domains is one of the novel qualities of the GRASSP and has not yet been presented in any previous upper limb measures.¹⁶ The domains of GRASSP characterize the upper limb specifically, which allows clinicians and researchers to elucidate some of the endogenous recovery mechanisms related to hand function and to determine specifically the effects of interventions. Thus, GRASSP will be invaluable in establishing efficacy in new trials and translating emerging mechanisms of hand function from bench to [bed](#).

Two previous articles have reported on the development¹¹ and psychometric properties¹² of the GRASSP. The analysis in this article is conducted using the same data collected in the validation study. However, the aim here is to confirm the hypothesized relationships between the domains defined in the theoretical framework and measure with this cohort of data.

Specifically, the objective of this analysis was to determine the association between the impairment domains (sensation, motor, and prehension) and the construct of “sensorimotor upper limb function”¹¹ by testing the hypothetical model (based on the theoretical framework). The purpose of this analysis is to establish further insight into what GRASSP subtest scores define individually and collectively. For clinicians and researchers administering the GRASSP, these findings can define the change of impairment and how it affects function clinically. Furthermore, the elements of impairment that are influenced by mechanisms of recovery and interventions can also be identified using GRASSP.

Methods

Data were collected as part of the GRASSP validation study¹² where methods, data collection, and description of

the sample are available. This article represents a second analysis performed with elements of the original data set collected for reliability and validity. Analysis was conducted with SPSS 17.0 and M-Plus 5.2.

Outcome Measures

The GRASSP is a multidomain impairment measure specific to the upper limb for individuals with tetraplegia. It consists of 5 subtests, palmar sensation and dorsal sensation measured by Semmes Weinstein Monofilaments, Strength of 10 arm and hand muscles measured by traditional motor grading, prehension activity, and performance measured by observation of grasping and task acquisition. Further details of the development, theoretical framework, and content are available in 3 published articles.^{11,12,16} The Spinal Cord Independence Measure (SCIM)¹⁷ is a global measure of performance specific for individuals with spinal cord injury (SCI), used to define the function and independence of the sample in this study. Interrater reliability is greater than .8 when assessed by agreement statistics for most SCIM items, and intraclass correlation coefficient for the total score is .94.¹⁸ Concurrent validity of the SCIM with the Functional Independence Measure (FIM) is .79.¹⁸ Within the SCIM, there are 3 subscales (self-care, respiration and sphincter management, and mobility) and in this analysis the SCIM self-care subscale (SCIM-SS) was used as one of the representations of upper limb function. The SCIM-SS includes items solely related to the use of the upper limb; therefore, comparison between the GRASSP subtests are made with the SCIM-SS, rather than the total SCIM score. Subscales of the SCIM are reliable and useful quantitative representations of the specific constructs of independence in SCI.¹⁹⁻²¹

The Capabilities of Upper Extremity Questionnaire (CUE) is a subjective questionnaire that determines one’s perception of functional ability. The questions asked are related to one’s perception of how difficult a task may be. The CUE is embedded with questions that fall into the three components of upper limb function reaching tasks, prehension tasks, and manipulation tasks, scores for each task are added for a total CUE score. Psychometric properties of the CUE have been reported as .92 (Cronbach’s α) and .74 (Pearson correlation coefficient) for concurrent validity with the FIM.²² GRASSP, SCIM, and CUE results collected during the same visit were extracted from the data set for the analysis of impairment and “upper limb function.”

Analytic Plan

During the development of the theoretical framework (hypothetical model, Figure 1A and B) we anticipated there would be a positive relationship between the impairment domains and upper limb function, specifically; strength would play a stronger role than sensation in upper limb

Table 1. GRASSP Scoring Details Included in This Analysis (Subtest and Item Scores and Ranges).

Subtest	Each Item	Number of Items in Subtest	Subtest Total Score Range	Score Ranges and Score Spinal Cord Levels Represented
Palmar sensation	0-4	3	0-12	0-4—C6 5-8—C7 9-12—C8
Strength	0-5	10	0-50	0-10—C5 11-15—C6 16-25—C7 26-40—C8 41-50—T1
Prehension performance	0-5	6	0-30	0-5—C5-C7 6-10—C5-C7 11-15—C5-C7 16-20—C5-T1 21-25—C5-T1 26-30—C5-T1

Abbreviation: GRASSP, Graded Redefined Assessment of Strength Sensibility and Prehension.

function. Structural equation modeling (SEM) was selected as the method for analysis to test the hypothetical model, because it is a more robust method to analyze data. SEM has a specific sample size adequacy test based on the number of parameters being estimated in the model, thus we estimated only one parameter, the latent trait which could be managed with our data set ($n = 72$).

Structural equation modeling is a general approach to multivariate data analysis, used to study complex relationships among variables. It is used to describe directed dependencies among a set of variables and provides an opportunity to test models with multiple dependent variables and provides a value of both direct and indirect effects of all variables. SEM is a confirmatory technique that confirms a specified model^{23,24}; our hypothetical model was based on the theoretical framework (Figure 1A). In SEM, a latent trait variable is defined and predicted by dependent variables²⁵; in the case of our model, “sensorimotor upper limb function” was the latent trait. The independent variables used were the palmar sensation subtest total score, the strength subtest total score, and prehension performance subtest total score, right side data only (see Table 1). Dorsal sensation and qualitative prehension are the remaining 2 subtests and were not used in the analysis as they are not as relevant to function as the selected 3 variables.¹¹ The SCIM-SS and CUE were the indicators of the latent trait. The data were then run through the model to determine how well the data fit the hypothesized model. The fit of the model is known as the “goodness of fit.”^{24,25} Statistics of fit determine how well the specified model (hypothesis) fits the actual data. A χ^2 test is conducted to evaluate the overall model fit, which assesses the magnitude of discrepancy between the sample and fitted covariance matrices. A large

χ^2 with an insignificant value (where $P < .05$ is considered significant) indicates a good fit of the model. The χ^2 , although not the most rigorous index of fit, is used and often accompanied by other indices. The root mean square error of approximation (RMSEA) evaluates how well the model fits the population’s covariance and is sensitive to the number of estimated parameters in the model. A value less than .10 indicates a good fit. The RMSEA is used when the number of estimated parameters is low in the case of this model, only one parameter is estimated. The standardized root mean square residual (SRMR) is the square root of the difference between the residuals of the sample covariance matrix and the hypothesized covariance model. A value of less than .09 indicates a good fit. The SRMR is used when there are varying ranges of scales among indicators, which is the case in the model tested. The comparative fit index (CFI) accounts for the sample size, all latent variables are uncorrelated and compared to the sample covariance matrix with the null model. The Tucker–Lewis index (TLI) of fit is used when a small sample size is being analyzed and can point out a poor fit when other indices are pointing to a good fit. A value greater than .96 indicates a good fit for both of these indices. The CFI considers the small sample size and the TLI considers simple models. Thus, the selection of indices was specific to the model hypothesized.^{25,26} All hypotheses were examined simultaneously by specifying one structural equation model (Figure 1B). One latent variable of “sensorimotor upper limb function” was incorporated which brought several benefits to the measurement of variables in this model, hence the accuracy of its structural relations.²³

Figure 1B defines the hypothetical model for which SEM was conducted to determine the relationship of

Table 2. Demographics Based on ISNCSCI Single Neurological Level (n = 72).

Single Neurological Level	n (%)
C2	8 (11)
C3	5 (7)
C4	25 (35)
C5	13 (18)
C6	18 (25)
C7	3 (4)
C8	1 (1)

Abbreviation: ISNCSCI, International Standards for Neurological Classification of Spinal Cord Injury.²⁹

impairment to upper limb function. In SEM, it is necessary to establish a latent trait variable otherwise known as an unobserved value, which is estimated by observed variables. In this model, the latent trait variable was “sensorimotor upper limb function,” which was indicated by the SCIM-SS and the CUE component (reach, prehension, manipulation) scores. In SEM it is more reliable to have at least 3 variables to estimate the latent trait²⁶; therefore, the CUE was split into the 3 components (reach, prehension, manipulation) that represent upper limb function.^{15,27}

Results

Sample

The data used in this analysis included a multicenter/multinational cross-sectional sample. The total sample consisted of 72 individuals with chronic tetraplegia ranging from 6 months to 20 years postinjury. Distribution of the sample according to the International Standards of Neurological Classification in Spinal Cord Injury (ISNCSCI)^{28,29} is defined in Table 2. Approximately 52.5% of the individuals presented with the C6-C7 motor levels whereas approximately 66% presented with C4-C6 sensory levels. According to AIS (American Spinal Injury Association Impairment Scale) classification, 39% (n = 28) of the sample were deemed to be AIS A complete, and 61% (B 25%, n = 18; C 19%, n = 14; D 17%, n = 12) of the sample as AIS B, C, or D incomplete.^{28,29} Complete details of the sample are available in the article that reports validation of the GRASSP.¹²

Structural equation modeling rendered the strength of association between impairment, function and the latent trait variable of sensorimotor upper limb function. Figure 2 shows the SEM results for the hypothetical model, which presents the effect of impairment on sensorimotor upper limb function. The SEM results show a very good fit of the model to the data; the model explained 72% of the variance in “sensorimotor upper limb function.” The very high value of R^2 was substantiated by the goodness-of-fit indices. The

goodness-of-fit indices were greater than the accepted thresholds ($\chi^2 = 14.3$, $P = .11$; CFI = .99, TLI = .97, and RMSEA = .09, SRMR = .02), which implies that the R^2 value is reliable and the relationship among variables are also reliable. Prehension has a significant positive effect on upper limb function and strength and palmar sensation both have a direct and indirect effect through prehension on upper limb function.

Based on the SEM, palmar sensation showed a direct and indirect relationship to upper limb function. (Note: Each arrow represents the strength of the association that it illustrates, in the case of this model arrow values can be added if consecutive on the left of the latent trait.) The relationship mediated through prehension is larger ($0.19 + 0.32$) than the direct relationship (0.31); but both direct and indirect relationships are statistically significant. Strength also showed a direct and indirect relationship to upper limb function. The relationship mediated through prehension is larger ($0.68 + 0.31$) than the direct relationship to upper limb function, but both direct and indirect relationships are statistically significant. Therefore, sensorimotor upper limb function can be predicted by palmar sensation and strength through prehension. The values on the right of the latent trait 0.89, 0.80, 0.92, 0.93) simply confirm that sensorimotor upper limb function is adequately estimated by the variables used. The values are very high and significant, which would be expected as the SCIM and CUE are functionally relevant tests and the construct of “sensorimotor upper limb function” is well defined by impairments that are functionally relevant. Essentially, changes in strength and sensation are most likely to have an effect on upper limb function when associated with improvement in prehension.

Discussion

This is the first assessment tool to reveal the importance of separate domains in integrated functions and will assist in understanding the impact of emerging mechanisms of recovery for hand function and specific rehabilitation interventions. In summary, this analysis has contributed to the body of knowledge that provides information to confirm that the GRASSP version 1.0 is useful and relevant in a clinical and research setting.

Significance of Findings

The development process of GRASSP version 1.0 has consisted of many stages, one of which was the design of the theoretical framework (Figure 1A). The framework guided the process of item generation. This analysis confirms that the design of the measure and the elements incorporated in GRASSP do capture what they were intended to—core and integrated elements of impairment to define with greater

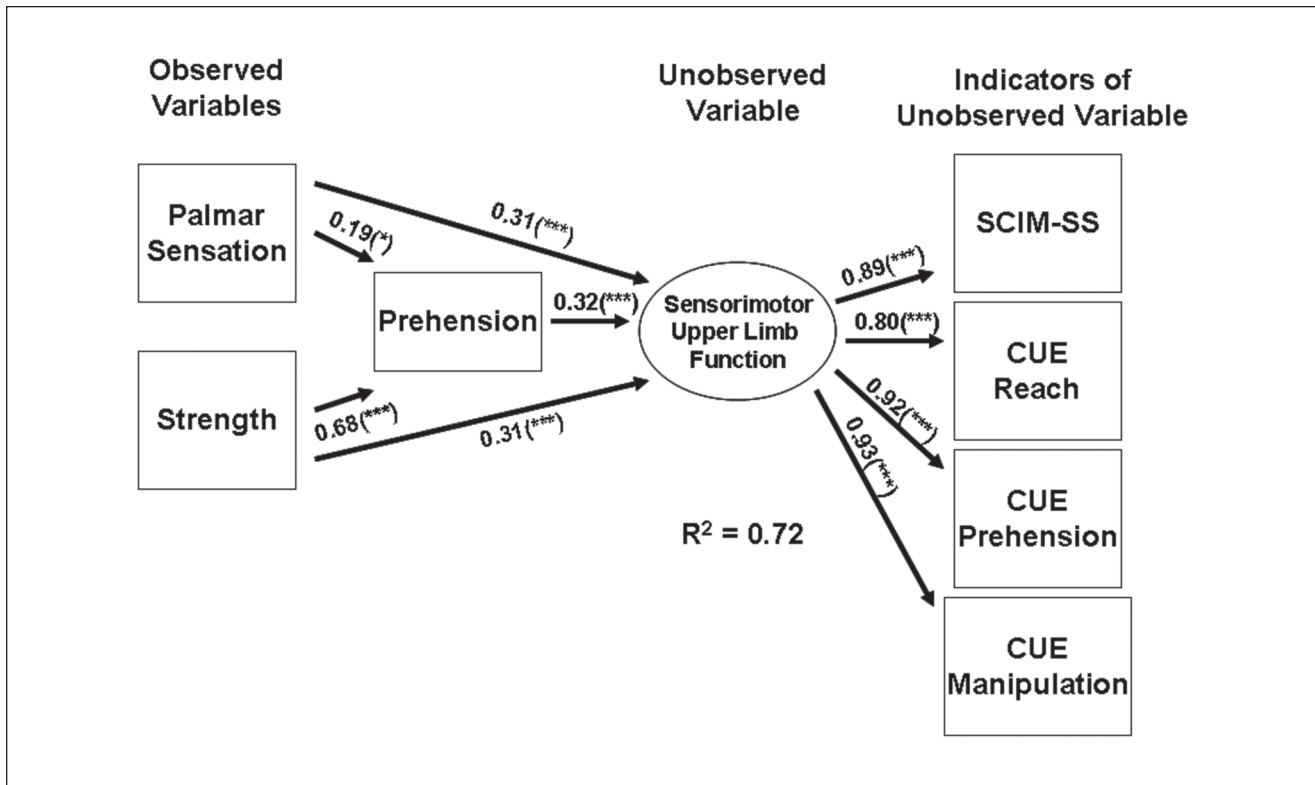


Figure 2. Structural equation modeling results for the hypothetical model.

Abbreviations: SCIM-SS, Spinal Cord Independence Measure Self-Care Subscale; CUE, Capabilities of Upper Extremity Questionnaire.

* $P < .05$; ** $P < .01$; *** $P < .001$.

sensitivity upper limb function. Thus, this analysis confirms the adequacy of the framework and design of the assessment tool.

Significance of Sensory Testing of the Hand in Tetraplegia

Second, this analysis establishes the importance of sensory testing in the hand for individuals with tetraplegia to establish status at baseline, over the course of recovery and to define the relationship of impairment to function. Sensation is reported to have a significant impact on prehension and manipulation.^{15,30,31} The recovery of sensation after peripheral hand injury is considered to be fundamental for the return of function.^{31,32}

Preliminary evidence has shown improvements in sensation when measured by Semmes Weinstein Monofilaments after a 3-week intensive massed practice and somatosensory stimulation protocol for individuals with tetraplegia. Overall hand function was most improved for individuals receiving massed practice and somatosensory stimulation, versus just massed practice or somatosensory stimulation, or conservative management alone.³³⁻³⁵ Apart from this work there is very little reference to the significance of

measuring hand sensation in tetraplegia in the field of SCI. Some developers of tests have commented on the additional benefit sensory testing would provide in elucidating functional ability^{31,36}; however, they have not incorporated sensation or been able to show its significance. Thus, this work has shown within the confines of what GRASSP measures that the role of sensation is significant for the assessment of individuals with tetraplegia as it plays a role in defining not only impairment but also function.

Core and Integrated Impairment

Third, this work confirms that sensation, strength, and prehension play a distinct role in upper limb function as hypothesized by the theoretical framework. At the outset, we assumed it was important to measure all 3 domains of impairment to reflect function accurately. However, the magnitude of the relationships was unknown. We anticipated that there was an intermediate relationship where strength and sensation would influence prehension, and prehension would then have an association with upper limb function. So far there is little evidence available to define the relationship between sensation and strength on upper limb function in tetraplegia. Furthermore, changes in

impairment do not have a uniform impact on clinical recovery between individuals, thus the assessment of the strength and sensation should be accompanied by the assessment of prehension to understand recovery on an individual basis.

This analysis defines for the field how the GRASSP allows us to distinguish the contribution of strength, sensation, and prehension to upper limb function. Understanding the contribution of strength and sensation is important in clinical studies to distinguish and better understand the effect of interventions, which is now possible with GRASSP. The GRASSP has the potential not only to inform as to whether the prehension is changing but also what elements contribute to the change, thus allowing the developers of new hand function therapies to establish efficacy and also understand the integration of the core elements of impairment. The GRASSP will enable us to see what impairment (sensation or strength) is most affected by a therapy further informing us of the benefits of new treatments. Furthermore, it can inform the administrator whether change in sensation has an effect on hand and arm function.

Evidence for Therapeutic Interventions

Some of the most basic and important functions for humans occur by way of prehensile ability.³⁰ With restoration of hand function as the focus in certain labs,^{33-35,37,38} the significance of components of prehension and the best possible ways to enhance prehension are paramount. This analysis provides us with some insights into this. SEM substantiates that sensation and strength are relatively equal in their effect on upper limb function. The relationships of sensation and strength mediated through prehension show that strength is a stronger factor. These relationships of upper limb function mediated through prehension support the concept of rehabilitation processes incorporating the use of functional tasks, specifically prehension retraining protocols. Therefore, it is of importance that recovery of sensation on the palmar surface of the hand be enhanced after SCI. Targeted sensory retraining of the hand within a functional paradigm (task-specific prehension) may be necessary to refine functional ability during the rehabilitation phase. In this analysis, it is noted that having good sensation indirectly impacts upper limb and hand function. Therapies need to be applied so that the palmar surface of the hand is stimulated, to promote activity optimizing sensory activity leading to recovery. Furthermore, interventions targeted toward recovering motor function must be applied within a functional context, with varying degrees of force generation and sequencing of muscle activation.

Limitations

This particular analysis was conducted with a cross section of data collected on individuals with chronic tetraplegia.

Thus, the findings established with this set of data are likely not to be recreated with a more acute sample of data. In fact, the authors are interested to see the differences between the 2 groups, which is a proposed future analysis. Sample size was not a shortcoming of this work; however, to repeat the analysis on a second cohort would be optimal to confirm the defined relationships. Furthermore, the opportunity to conduct SEM with additional independent variables would allow the authors to define additional associations and relationships, which could help develop a greater understanding of the interrelationships of impairment, function, and quality of life.

Conclusion

In conclusion, the GRASSP assesses impairment in 3 domains. During the development of the GRASSP, the theoretical framework guided item generation to be anatomically, neurophysiologically, and functionally relevant.¹¹ The GRASSP was intended to distinguish the contributions of sensation and strength to function and does so effectively. This analysis confirms that all 3 domains are relevant in the assessment of impairment of the upper limb post-cervical SCI. Such measures are needed to better understand what and where treatments achieve improvements. The SEM confirms the concepts and components of the construct particularly the domains and their individual and integrative importance.

Quantifying impairment more precisely has enabled the investigators to establish the magnitude of the relationships and integration of palmar sensation, upper limb strength, and prehension to upper limb function. In the future, using the SEM approach across the recovery period could assist in determining the magnitude of impairment change that will lead to different levels of functional change. The next steps will be to test the degree of these relationships and integration during the course of recovery.

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Appendix F
North American Clinical Trials Network

SCI Data Registry Summary
08/01/2013

Table 1. Registry Screening and Enrollment

Status	Number	Percent Total
Screened	1166	
Enrolled	666	57.1%
In Database	600	90.1%
Pending	66	9.9%

Table 2. Patient Demographics

Characteristic	Number (N=568)	Percent
Gender		
Male	459	80.8
Female	109	19.2
Age (yrs)		
< 20	28	4.9
20-65	461	81.2
>65	79	13.9
Race		
White	405	71.3
Nonwhite	163	28.7

Table 3. Circumstances of Injury

Circumstance	Number (N=568)	Percent
Fall	210	37.0
MVA	167	29.4
Recreation	60	10.6
Motorcycle	54	9.5
Assault	36	6.3
Other/Unk	25	4.4
Military ¹	16	2.8

¹- See text for circumstance details

Table 4. Severity of Neurological Deficit
Initial AIS Grade Within 7 days of injury

AIS Grade	Number	Percent
A	189	33.3
B	59	10.4
C	66	11.6
D	138	24.3
E	38	6.7
not available	78	13.7
TOTAL	568	

Table 5. Incidence of Complications

Complications	SCI Cases (N=568)	Percent
None	218	38.4
1	77	13.6
2	56	9.9
3	49	8.6
4+	168	29.6

**Table 6. Acute Care Complications
Type, Frequency, and Incidence**

Complication	Frequency N=1657 (%)	Number of patients	Incidence Rate (N= 568 cases)
Pulmonary	393 (23.7)	201	35.4
Infection	354 (21.4)	199	35.0
Hematology	242 (14.6)	152	26.8
Cardiac	251 (15.1)	156	27.5
Neuropsychiatric	122 (7.4)	104	18.3
GI/GU	143 (8.6)	104	18.3
Skin	145 (8.8)	100	17.6
Failure of stabilization	7 (0.4)	7	1.2

Incidence rates = (# of patients with the complication type)/568

Table 7. Injury Type and SCI Region

Characteristic	Number (N=568)	Percent
Injury Type		
Blunt	452	79.6
Crush	77	13.6
Penetrating	28	4.9
Other	11	1.9
Injury Region¹		
Cervical	418	73.6
Thoracic	111	19.5
Lumbar/Sacral	36	6.3
SCIWORA	3	0.5

¹Highest level report when injury involved multiple levels

Table 8. Surgical by AIS Grade

AIS ¹ Severity	Number of Patients ² (N=566)				Total
	Posterior (%)	Anterior (%)	Both (%)	None (%)	
A	102 (54.0)	43 (22.8)	31 (16.4)	13 (6.9)	189
B	29 (49.2)	18 (30.5)	8 (13.6)	4 (6.8)	59
C	40 (60.6)	17 (25.8)	4 (6.1)	4 (6.1)	65
D	52 (37.7)	54 (39.1)	16 (11.6)	16 (11.6)	138
E	15 (39.5)	3 (7.9)	1 (2.6)	18 (47.4)	37
Unknown	40 (51.3)	20 (25.6)	6 (7.7)	12 (15.4)	78
Total	278	155	66	67	566

¹ First AIS obtained within 7 days of injury.² Excludes two patients with unknown surgeryTable 9. Steroid Use by Severity of Neurological Deficit
Initial AIS Grade Within 7 days of Injury

AIS Grade	Steroids (N=568)			N
	Yes (%)	No (%)	Unkn (%)	
A	50.3	49.2	0.5	189
B	55.9	40.7	3.4	59
C	50.0	50.0	0	66
D	47.8	52.2	0	138
E	13.2	86.8	0	38
Unkn	30.8	65.4	3.8	78

Table 10. Hospital Stay and Acute Care Discharge

Hospital Length of Stay	Number (N=568)	Percent
<8 days	137	24.1
8-14	177	31.1
15-21	94	16.5
>21	160	28.2
Discharge Status		
Rehab Hospital	413	72.7
Home Care	100	17.6
Nursing Home	16	2.8
Long-Term Care	16	2.8
In-Hospital Death	15	2.6
Other	8	1.4

Table 11. AIS security Conversion
Admission versus Acute Care Discharge

AIS ¹ Admit	AIS ² Discharge					Patients
	A	B	C	D	E	
A	87.9%	7.5%	4.0%	0.6%	0	174
B	12.1%	58.6%	24.1%	5.2%	0	58
C	1.5%	3%	59.1%	34.8%	1.5%	66
D	0.7%	0	2.9%	89.1%	7.3%	137
E	0	0	0	5.4%	94.6%	37
Patients	162	49	64	151	46	472

¹First AIS obtained within 7 days of injury: excludes cases with AIS unknown within 7 days of Injury

²AIS within 14 days of discharge from acute care: excludes cases with AIS unknown at discharge

Table 12. AIS Severity Conversion
Admission versus Six-Month Follow-up

AIS ¹ Admit	Six Month AIS ²					Patients
	A	B	C	D	E	
A	74%	15.6%	6.3%	4.2%	0	96
B	13.3%	26.7%	30%	23.3%	6.7%	30
C	2.8%	2.8%	11.1%	63.9%	19.4%	36
D	0	0	1.3%	59.7%	39%	77
E	0	0	0	0	100%	15
Patients	76	24	20	80	54	254

¹First AIS obtained within 7 days of injury: excludes cases with AIS unknown within 7 days of Injury

²AIS obtained 4 to 8 months post-injury

ITW

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Introduction

ITW is a software application used by NACTN to collect data from chart reviews. ITW maintains separate databases for each site that can be accessed only from that site.

ITW Security

Data entered into ITW resides at Peak 10 – a professionally managed data center. Security is maintained with key card, pin code and biometrics. The servers are in a locked cabinet and monitored 24/7 with surveillance cameras. Firewalls are monitored 24/7. Access to the server is blocked except for traffic originating from behind the center's individual Firewall. All traffic is encrypted. The data residing in storage is encrypted. External backups are encrypted.

There is a data extraction process which allows for the extraction of de-identified data from any or all of the centers for analysis. A Data Integrity Policy governs this process.

How CrossIQ works

We could use any PHI for the CrossIQ index, but the United States Social Security Number and Canadian Insurance Identification number is the most constant and known by the patient. Similar social numbers are used in most other countries.

The social security number is encrypted and hashed using the SHA-2 method.

1. The treating institution can see the PHI for the patient. ITW only allows the treating institution to see the information on their patients. This is accomplished by data encryption methods and network identification. The only computers able to access the institution's data in ITW have to be within the hospital's network; thus meeting the same tests for HIPAA security. In addition, the data transmitted to and from ITW is encrypted using AES128 so that as the data passes through public network switches, it is unreadable and unusable. These methods are standards for the computer industry.
2. Since the treating Institution can 'know' PHI, we can use a piece of it to 'test' to see if the patient has been entered into the research 'network'. The logical and most reliable piece of PHI is the Social Security Number. It is ONLY used as a test, and can be removed by the institution if they choose to not keep it in ITW.
3. The number is sent to the indexing server in CrossIQ using AES transmission encryption and is then converted to hashed number. Because the hash encryption method is so strong and asynchronous it is impossible to 'reverse' the number.
4. This would normally be enough, but CrossIQ takes one more step and creates a Globally Unique Identifier (GUID) that is sent back to the institution. The GUID is a 32-character hexadecimal string and is the identifying CrossIQ number and literally cannot be reverse engineered.
5. Additional Institutions treating the patient will make the same test. If the test is positive, CrossIQ will pass back the correct number or create a new one if the test is negative. This method will leave their information totally in their control without divulging PHI.

Notable Facts

- The Social Security Number is not the only PHI held in ITW. That is why Systemax treats all data in ITW as PHI regardless of its nature.
- The data from the treating institution will be able to maintain the integrity of the data even if the patient enters treatment under different episode numbers.
- Research will be able to track and use data far into the future for reasons they may not know now.

CrossIQ Research Study Integrity

After the CrossIQ index is established it is necessary for the treating facility to identify the patient as a consented participant in a study. The responsibility for this identification is still kept with the persons entrusted with the patient's PHI.

This additional step allows the research data manager to identify which patients have consented to be a part of certain studies. Thus, the data manager will only send information to the study researcher from patients that have given their consent. This will all take place without identifying the patient.

Getting Started

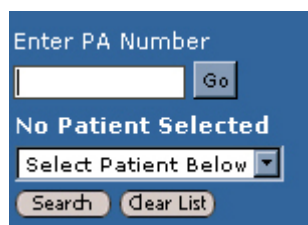
The NACTN database is hosted by the JHSMH ITW web server at: <http://172.20.202.80:####/>. Each site has its own 4 digit code. For best results, use Internet Explorer version 6.0 and higher.

To log in, enter your username and password on the log in screen.



The screenshot shows a web browser window with a blue header bar containing the text "Neuro Recovery Network". Below the header, on a light orange background, is the instruction "Enter your Username and Password to logon...". There are two text input fields: the first is labeled "User Name:" and the second is labeled "Password:". Below these fields is a button labeled "Continue..".

Everything in ITW is keyed to a specific patient, so to get started, choose the patient by entering the Patient ID (PA) number into the text field in the left-hand menu, and click on "Go" or use the search button to search for a specific patient.



The screenshot shows a blue sidebar menu. At the top, it says "Enter PA Number". Below this is a text input field followed by a "Go" button. Further down, the text "No Patient Selected" is displayed. Below that is a dropdown menu with the text "Select Patient Below". At the bottom of the sidebar are two buttons: "Search" and "Clear List".

Registering a New Patient

The screenshot displays the 'Episode Maintenance' form within a web application. On the left, a blue sidebar contains a navigation menu with 'Episode Maintenance' selected. The main form area is divided into several sections. The top section includes fields for 'EPNum:', 'MRNum:', 'PANum:', 'Last Name:', 'First Name:', 'Middle Name:', 'Address:', and 'County:'. The middle section contains 'Test Case:', 'SSN:', 'DOB:', 'Phone:', 'email:', 'Race:', 'Gender:', 'Marital Status:', 'Height:', and 'Weight:'. The bottom section includes 'Admin Date:', 'Admin Time:', 'Status:', 'Room:', 'Primary Insurer:', 'Insurer #2:', 'Insurer #3:', 'Medicare #:', 'Medicaid #:', 'Attending Phys:', 'Admitting Phys:', 'Referring Phys:', 'Consulting Phys:', 'Total Revenue:', 'DC Date:', 'DC Time:', and a 'Discharge' button. An 'Add' button is located at the bottom right of the form.

1. From the main ITW page, select Episode Maintenance from the blue bar on the left.
2. Enter the patient's MRNum and PANum using your site specific instructions. The PANum will not be used by the NACTN data center, but is required by the programming. You can enter the NACTN identification number or a separate identifier from your site as desired.
3. At a minimum you must enter the patient's date of birth, race, and gender. Anything else entered on this form will not be extracted to the data center.
4. Click add.

CrossIQ Registration

Every NACTN Patient must have a CrossIQ number in order for the data to be extracted to the data center. This is accomplished by entering the patient's social security number. This is the only reliable way to track patients across multiple sites and multiple programs.

OPPT Frazier Systemax,PT

Enter PA Number
 Go

TESTPATIENT024, BILL
DOB: 8/14/1980
PANUM: 999999024
MRNUM: 9999024

Select Patient Below
Search Clear List

You have 16 extraction errors

Main Reports Utilities

Today
Face Sheet
OP PT
Patient Information
Insurance
Pre-Admission
Intake Questionnaire
Multi-Discipline Eval
ASIA
Physician
Patient Charges
History/Environment
Physician Notes
Mile Markers
Research
CrossIQ Register
Patient Programs
Program Overview
Data Correction

Logout

CrossIQ Registration

Patient: TESTPATIENT024, BILL
Social: 999999999
Status: Not Registered
QIndexID:

The Social for this patient is invalid.
Please enter a valid Social:

Social:

Register this Patient...

1. Click on the folder next to Research to access the CrossIQ menu.
2. Click on CrossIQ Register. This screen can allow for the social security number to be entered and submitted to the CrossIQ system without storing the number in your site specific ITW. If you would like the social security number stored in ITW you may enter it in the appropriate field on the Episode Maintenance form.
3. Enter the patient's social security number in the box provided and click on **Register this Patient**. If the patient requests, you can turn the screen to the patient to enter his or her social security number.

Heather Tolle

Enter PA Number Go

TESTPATIENT, heather
 DOB: 5/5/1955
 PANUM: 555555555
 MRNUM: 999999019

Select Patient Below

Main Reports Utilities

- Physical Therapy
- ASIA
- Documents
- NRN Financial
- Episode Maintenance
 - CrossIQ Register
 - Patient Programs
 - Program Overview
- Phys Maintenance
- Payor Maintenance
- User Maintenance

CrossIQ Registration

Patient: TESTPATIENT, John
 Social:
 Status: Not Registered
 QIndexID:

The Social for this patient is invalid.
 Please enter a valid Social:
 Social:

 **I certify that this a true Social Security Number, Canadian Insurance Number or other ID issued to a non-resident.**
 444-44-4444

4. You will be asked to personally certify that the number entered is infact the social security number of the patient. If you certify that the number is the patient's real social security number, click continue.
5. You will then be given the opportunity to register the patient in different programs.

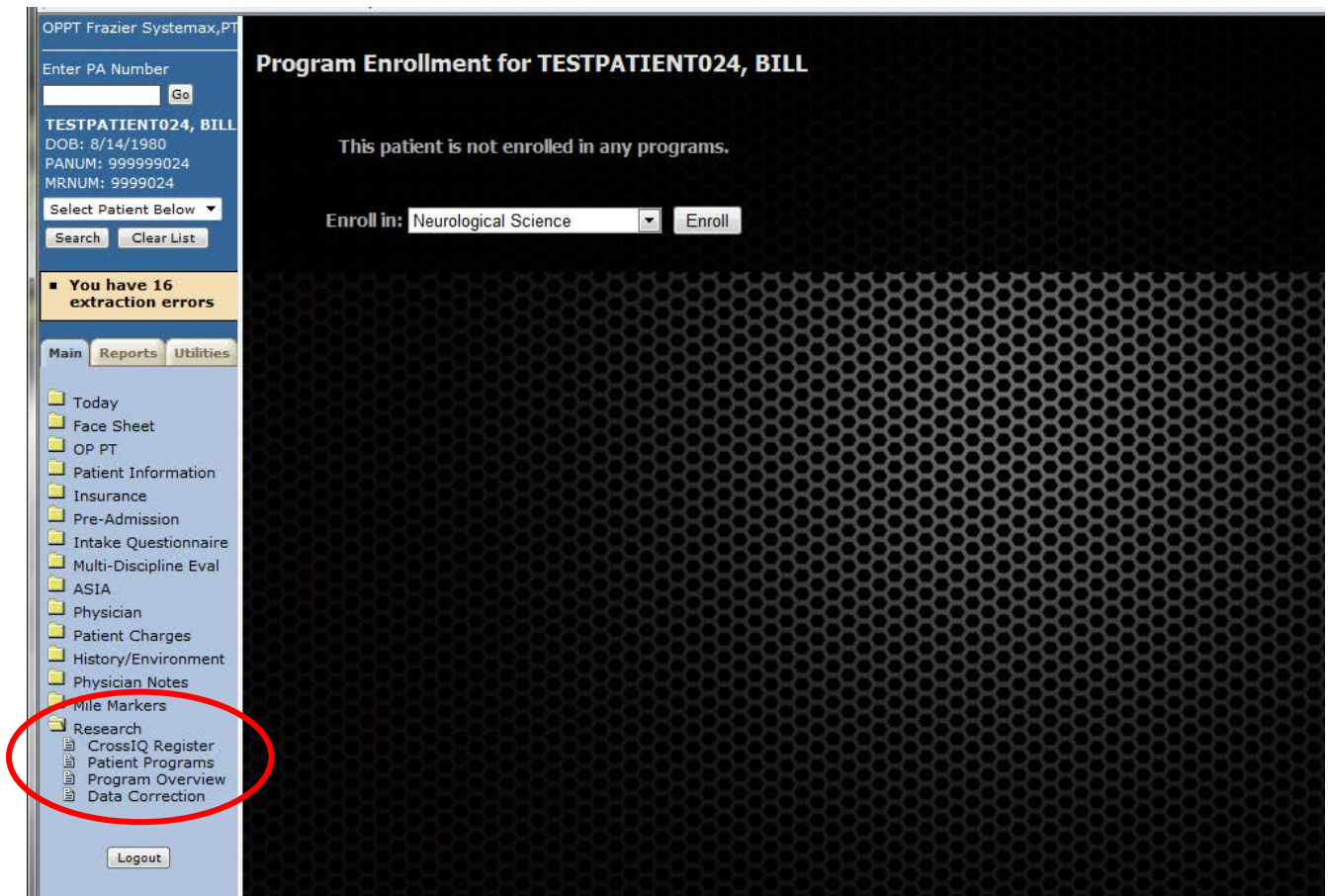
Country Specific ID Numbers

For patients that are not US citizens and do not have social security numbers, the following country given ID numbers should be used. If you have any additional quesitons, please contact Heather Tolle at the data center.

Country	ID Number
Australia	Tax File Number
Canada	Social Insurance Number
Mexico	Social Security Number
South Africa	Person Identification Number

Selecting a Patient Program

A patient program must be selected to identify the data during the extraction process. Immediately after registering the patient with CrossIQ you will be taken to the program enrollment screen. You may make changes to the enrolled programs for the patient at a later date by clicking on the folder icon next to Research and selecting Patient Programs.



1. To get to the program enrollment screen- click on the folder icon next to Research at the left and Patient Programs will now appear.
2. Click on the down arrow by the Enroll in drop box to see all the programs available.
3. Select the program/study/registry that the patient has consented to participate in and click Enroll.

Program Enrollment for TESTPATIENT024, BILL

Interested

Neurological Science

Enroll in Another Program:
Spinal Cord area ▼

Neurological Science

Status: Interested ▼

External Research #:

Extended Consent: ☐

Consent Withdrawn:

Enrollment Periods [Add New](#)

Begin Date	End Date	
		Delete

Global Questions **Program Questions** **Services**

Question	Answer	Notes
Neuro science question 1 ?		
Neuro science question 2 ?	Select... ▼	
Neuro science question 3 ?	☐	
Neuro science question 4 ?		

4. Enter the NACTN patient ID in the External Research# field. The ID should be entered in the format siteID-patient ID. Example- 005-0063.
5. For currently enrolled NACTN participants, only a Begin Date is required and should be the same date as the patient's consent. When the patient is finished with the registry follow ups, an End Date should be entered. No other information is needed at this time.
6. Click Save Changes

Program Enrollment for TESTPATIENT024, BILL

Interested

Neurological Science
#123456
10/24/2012 - current

Spinal Cord area

Enroll in Another Program:
Area 51

Enroll

Spinal Cord area

Status: Interested

External Research #:

Extended Consent: ☐

Consent Withdrawn:

Enrollment Periods [Add New](#)

Begin Date:

End Date:

Delete

Save Changes

Global Questions Program Questions Services

Question	Answer	Notes
Describe injury ?		

Update Answers

When a patient is enrolled in multiple programs, the one highlighted in green will show the details on the right side of the screen.

Entering an Evaluation

All data collected during the standardized follow up schedule except the ASIA must be entered into eval forms in ITW, NACTN's electronic data collection system.

There are five types of forms in ITW:

- NACTN Main Evaluation- includes demographics, clinical evaluation, traction, orthosis, surgery summary, and Hospital summary.
- FIM, SCIM, WISCI II- includes the FIM, SCIM, WISCI II, and Form 13 Liver enzymes.
- Acute Care Complications- Includes all complications, Cardiac, pulmonary, hematology, GI/GU, infections, skin, failure of stabilization, neuropsychiatric.
- STASCIS (Surgery)- Imaging, injury, Anterior surgery, posterior surgery.
- Follow Up Issues- Withdraw/Lost, follow-up complications.

Once you open one of these groups, you must fill out all of the required forms. Blanks are not allowed in ITW forms. If something wasn't tested, put NT in the field (it stands for Not Tested). It must be entered exactly like this (NT with no spaces or punctuation, both letters uppercase, no other text allowed) so it isn't considered an error that has to be corrected.

The screenshot shows the ITW system interface with the 'Eval' tab selected. On the left is a 'Feet/Meter Converter' and a tree view of evaluation categories. On the right is the 'Evaluation (10/27/2011 12:51:33 PM)' form. The form has sections for Session Information, Health, Subjective, Pain, Vital signs sitting at rest, and Orthostatic Test, Supine. Each section has a list of items, each with an 'NT' button to its left. A red circle highlights the 'NT' button next to the 'Health' section, with an arrow pointing to it from the text 'NT Buttons'.

If no data will be entered on an entire form, click the **NT** button (coming soon) to the left of the form name in ITW, and NT will automatically be entered in every field in that form. If you click the **NT** button when the measurements are required, you must open the form and explain in the comments field why the test was not done.

Accessing Eval Menu

The screenshot displays the NACTN ITW interface. On the left, a blue sidebar contains the user name 'Heather Tolle' and a 'Plan' button. Below this is a section for 'Testpatient008, Bill' with fields for DOB, PANUM, and MRNUM, and a 'Select Patient Below' dropdown. A 'Search' button and a 'Clear List' button are also present. The sidebar has tabs for 'Main', 'Reports', and 'Utilities'. Under 'Main', a list of folders is shown: 'Physical Therapy', 'ASIA', 'Documents', 'NRN Financial', 'Medications', 'Episode Maintenance', 'Phys Maintenance', 'Payor Maintenance', 'User Maintenance', and 'Research'. The 'ASIA' folder is circled in red. The main content area has a yellow background. At the top, the 'Eval' menu is circled in red. Below it, there are three sections: 'NRN', 'NACTN', and 'Neurosurgery'. Each section has a 'Select' dropdown and an 'Add' button. The 'NRN' section has a table with columns 'Date', 'Name', and 'Closed'. The 'NACTN' section has a table with columns 'Date', 'Name', and 'Closed'. The 'Neurosurgery' section has a table with columns 'Date', 'Name', and 'Closed'. The 'ASIA' folder in the sidebar is circled in red. The 'Eval' menu in the top bar is circled in red. The 'Add' button next to the 'NACTN' dropdown is circled in red.

Heather Tolle

Enter PA Number
 Go

Testpatient008, Bill
DOB: 5/5/1955
PANUM: 999999008
MRNUM: 888888
Select Patient Below
Search Clear List

Main Reports Utilities

Physical Therapy
ASIA
Documents
NRN Financial
Medications
Episode Maintenance
Phys Maintenance
Payor Maintenance
User Maintenance
Research

Logout

Plan

Eval

NRN Select Add

Date	Name	Closed
1/3/13 4:30 PM	Evaluation	
12/11/12 11:11 AM	Evaluation	
2/26/07 2:45 PM	Evaluation	

NACTN Select Add

Date	Name	Closed
4/16/13 2:41 PM	NACTN Main Evaluation	
4/15/13 9:21 AM	Follow Up Issues	
4/12/13 4:42 PM	Follow Up Issues	
2/26/13 4:25 PM	FIM, SCIM, WISC II, Liver enzyme panel	
2/25/13 10:03 AM	STASCIS	

Neurosurgery Select Add

No evals have been added yet.

(1) Eval in top menu bar. Click to access the Evals.

(2) Dropdown box next to the “Add” button. Use to add a new Eval, select whether you are adding an Evaluation (all required forms except ASIA and QOL) or a Quality of Life CHART Interview (just CHART forms). Once you have selected, click on “Add”.

(3) ASIA forms. Click on ASIA in the blue bar on the left of the screen to enter ASIA data

NACTN Evaluation

The screenshot displays the NACTN Evaluation interface. On the left, a comprehensive folder menu (labeled 4) lists various forms available for selection. On the right, a list of required forms (labeled 5) is shown, each with an 'NT' button (labeled 6) next to it. At the top right, a 'Sign' button (labeled 7) is visible. The interface is titled 'Evaluation (1/6/2011 3:59:21 PM)' and includes a 'Feet/Meter Converter' at the top left.

(4) The comprehensive folder menu is located on the left, listing all forms available.

(5) The required NACTN forms are listed on the right side of the screen. All forms can also be accessed using the comprehensive folder menu on the left side of your screen.

(6) NT Buttons. If you click on the NT button next to a form on the list of required forms, every response in that form will be changed to NT. The red flag next to the form changes to a plus sign once you enter data into that form. Like any other form, you can open it and if you choose to, you can change one or more responses from NT to a different value.

(7) Sign button- **Every eval must be signed before it is extracted.** Once you have entered all data for an eval, the eval must be signed. To make corrections to data in signed evals, please see the heading “Making Corrections to ITW” in this section.

Eval Form

The screenshot shows the 'Eval' form interface. On the left is a sidebar with a 'Feet/Meter Converter' button and a list of assessment categories: Session Information, Health, Subjective, Pain, Vital signs sitting at rest, Orthostatic Test, Tone, Strength, Weight, Harness, Step training evaluation, Phase, Cognition, Memory, Communication, Balance, Functional Mobility, Posture, Gait, Step Activity Monitor, Sensation, ROM, Coordination, Wheelchair, Additional Data, and Developmental Assessment. The main area has tabs for 'Plan' and 'Sessions'. Below the 'Plan' tab, a 'Back' button is circled in red with a red '8' next to it. The 'Sessions' tab shows a session ID '71154'. The title is 'Functional Mobility, 6 Minute Walk Test, Initial Device, Distance'. Below this is a red asterisk and the text '*Required Information'. To the right, 'Previous Measurement:' is shown with a date/time dropdown set to '7/27/2011 10:51:00 AM' and a 'View Last 10 Entries' button. A red arrow points from a red '9' to the 'Update' button at the top of the form, which is also circled in red. The form contains fields for 'Priority' (checkbox), 'Fxnal Obj Finding' (checkbox), 'Distance in meters' (text input), 'Assistive Device' (dropdown), 'Contact guard provided' (dropdown), and a 'Comments' text area. A 'Delete' button is at the bottom right. Another 'Update' button at the bottom of the form is also circled in red.

(8) To return to the Eval screen without saving your changes, click on “Back.”

(9) To save your data and return to the Eval screen, click on “Update”.

Form Level Validation

Data entered in the NACTN eval forms in ITW will be verified against an acceptable format for that data when the update button is clicked. Below is the ASIA neurological level form. The Right Neurological Sensory Level says unknown, which is incorrect, only a vertebral level is accepted in this field. When the update button is clicked on this form a warning window pops up saying "Rt Neuro sensory level must be a vertebrae" and you won't be able to save this form and move to the rest of the eval until the seconds field satisfies the format requirement.

The screenshot shows a web form titled "Neurological Level" with a yellow background. At the top left is a "Back" button. Below the title is an "Update" button. The form contains several input fields: "Voluntary anal contraction" (dropdown menu set to "No"), "Any anal sensation" (dropdown menu set to "No"), "Rt Neuro sensory level" (text input field containing "unknown"), "Lt Neuro sensory level" (empty text input field), "Rt Motor level" (empty text input field), "Lt Motor level" (empty text input field), "Single" (empty text input field), "ASIA in" (empty text input field), "Any no" (empty text input field), "Compli" (empty text input field), and "ZPP Rt" (empty text input field). A modal dialog box titled "Message from webpage" is overlaid on the form. It contains a yellow warning triangle icon and the text: "Please correct the following error(s). Rt Neuro sensory level must be a vertebrae C2-8, T1-12,...S45)". There is an "OK" button at the bottom right of the dialog box.

Note: This system only picks up on the formatting of entered data, it will not prevent the entry of other errors or blanks.

Form Level Validation Troubleshooting:

When you can't determine why an entry isn't being accepted by the system, **make sure that there are no spaces before or after the entry.**

Re-read the error message to make sure you're looking at the correct field and you understand the desired format for that field.

Common mistakes:

Format type	Incorrect entry	Correct entry	Reasoning
Date	2/9/11	02/09/2011	All dates must have a 2 digit month, 2 digit day, and 4 digit year separated by slashes
Injury level (Vertebral level(s) of fracture and Onset level(s) no fracture)	C4-6	C4-C6	Vertebral levels must have one letter and one number, the only exception is S4-5
Medication dose	45mg	45	Medication doses are measured in mg, so only the number is needed
Oxygen Saturation	98%	98	O2 saturation is measured in percentages, so you only need to enter the number, not the percent sign.
Time	15;31;44	15:31:44	Colons should be used in time entries rather than semi-colons, but thanks for using military format and including seconds

If you encounter any other problems preventing you from proceeding with the eval, please contact the data headquarters immediately.

Signing Evals

NACTN		Select	Add
Date	Name	Closed	
4/30/13 2:41 PM	NACTN Main Evaluation		
4/17/13 11:03 AM	STASCIS		
4/17/13 11:03 AM	NACTN Main Evaluation		
4/1/13 1:25 PM	STASCIS		
2/22/13 3:03 PM	Follow Up Issues	X	
2/22/13 3:03 PM	STASCIS	X	
2/22/13 3:03 PM	NACTN Main Evaluation	X	
2/13/13 10:11 AM	NACTN Main Evaluation	X	
9/19/12 4:12 PM	FIM, SCIM, WISCI II	X	
8/23/12 10:05 AM	Acute Care Complications	X	
8/23/12 10:04 AM	NACTN Main Evaluation	X	

An eval will appear as one line with a date and eval name under the main eval tab in ITW. Each eval must be signed before the data will get extracted to the data center. From the screen above you can immediately tell which evals have been signed and which have not based on the presence of an x in the closed column. The evals for this patients that occurred in April 2013 have not been signed, but the evals before that month have been signed.

After you've entered all the data necessary on an eval, you sign it by clicking the sign button at the top of the forms. You'll be asked to enter your ITW password. Once the password is entered, click submit.

Heather Tolle

Enter PA Number

Testpatient004, Bill
DOB: 5/5/1955
PANUM: 999999004
MRNUM: 444444

Select Patient Below ▼

Main Reports Utilities

- Physical Therapy
- ASIA
- Documents
- NRN Financial
- Medications
- Episode Maintenance
- Phys Maintenance
- Payor Maintenance
- User Maintenance
- Research

Eval

NACTN Main Evaluation (4/30/2013 2:41:19 PM)
Signed by Heather Tolle

Patient Information

- Personal
- Medical History

Circumstances of Injury

- Circumstances of Injury & Evac Details

Clinical evaluation on arrival

- Initial measures
- Glasgow Coma Score (GCS)
- Steroid information

Spinal Surgery

- Summary
- Intraoperative Complications
- Post Operative Bracing
- Listhesis surgical reduction

Non-Operative Treatment of SCI

- Traction

Once the eval is signed, you'll be taken to a screen that only shows those forms added to the eval. The name of the person that signed the eval will appear at the top of the eval. No changes can be made in ITW to evals that are signed. Any changes to data must be made through the CrossIQ system.

Creating Documents for Printing

If you would like to print an ITW form for any reason, right-click on the form and selecting 'print'

The screenshot shows a web-based form titled "Health, Current Medications". At the top, there is a red asterisk followed by "Required Information". To the right, "Previous Measurement:" is followed by a dropdown menu showing "10/27/2011 12:52:00 PM". Below this are "Update" and "View Last 10 Entries" buttons. The form contains several input fields: "Priority" (checkbox), "Fxnal Obj Finding" (checkbox), "Medication Changes after admit" (dropdown), "Information Obtained from" (dropdown), and a series of rows for "Medication", "Dose (in mg)", and "Times a day". A right-click context menu is open over the form, showing options like "Back", "Forward", "Save Background As...", "Set as Background", "Copy Background", "Select All", "Paste", "Blog with Windows Live", "E-mail with Windows Live", "Translate with Live Search", "All Accelerators", "Create Shortcut", "Add to Favorites...", "View Source", "Encoding", "Print..." (highlighted), "Print Preview...", "Refresh", and "Export to Microsoft Excel".

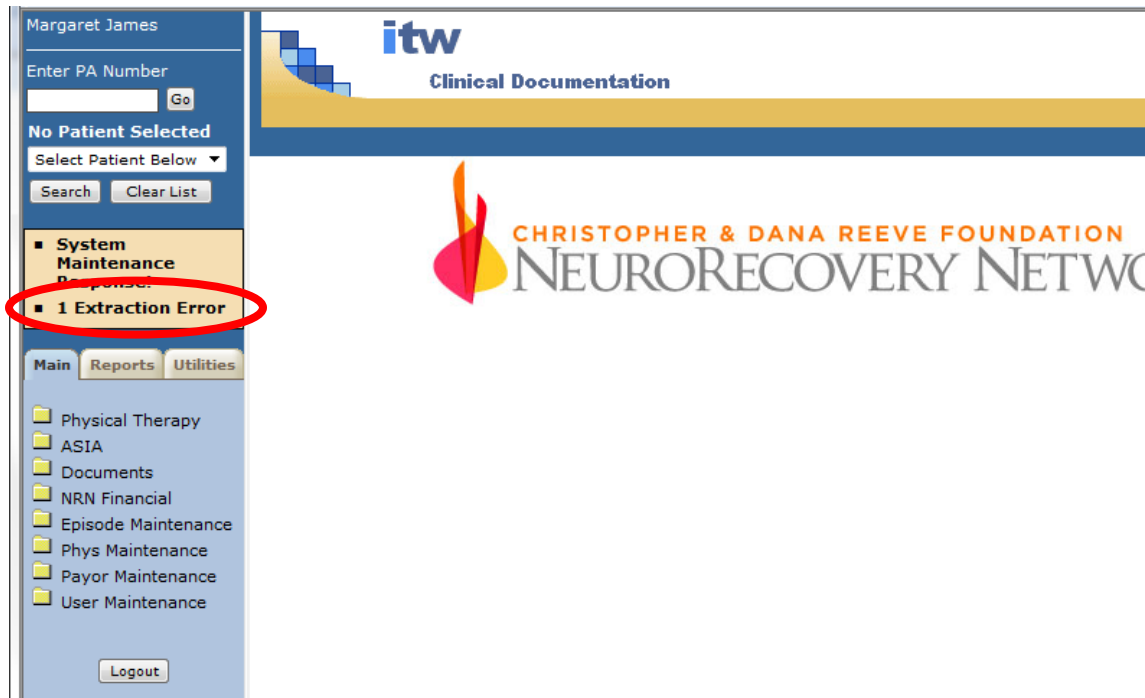
The screenshot shows a "Print" dialog box with two tabs: "General" and "Options". The "General" tab is selected. It contains a "Print frames" section with a preview of a document and three radio button options: "As laid out on screen", "Only the selected frame" (which is selected), and "All frames individually". Below this are two checkboxes: "Print all linked documents" and "Print table of links". At the bottom are "Print", "Cancel", and "Apply" buttons.

You may need to change the options on your printer to print only the selected frame, consult your printer's manual for instructions.

Making Corrections in ITW

CrossIQ allows for an error correction process within ITW. When there are errors in the extracted data, a notification will appear on the left side of the ITW main screen. An account/patient does not have to be active to see this alert.

All corrections of extracted data entered on an eval or ASIA must be done using the CrossIQ system.



Click on the notification of an extraction error. Data managers will have 2 extraction error notifications. One that says you have X extraction errors, and one saying your site has X extraction errors. Clicking on the link that says your site has X errors will give you access to all the errors at your site, while clicking on the other link will only give access to the errors that were entered under your login.

Margaret James

Enter PA Number

No Patient Selected
Select Patient Below

■ System Maintenance Response!

■ 1 Extraction Error

Main

Reports

Utilities

Physical Therapy

ASIA

Documents

NRN Financial

Problems with Extracted Data

Problems Awaiting Correction

View

Error Message: May not be blank - Enter NT if Not Tested or Enter correct value.

Error Value:

Evaluation - Evaluation (10/18/2011) - Step Activity Monitor - Number of steps first day

Recent Corrections Awaiting Approval

You currently have no corrections awaiting approval.

Click the View link to the left of the name in the Problems awaiting correction section.

Michelle Feltz

Enter PA Number

Test, Bill
 DOB:
 PANUM: 999999007
 MRNUM: 777777

Main Reports Utilities

Financial
 CrossIQ Worklists
 Applications
 Facility Errors

Extracted Data Correction

Evaluation - 10/8/2010 11:38:00 AM
 NRN, Evaluation, Balance, Overground Standing

'Minutes' Please explain the large difference between this outcome and past overground standing outcomes.

Original Value: 0

Correction Form

Minutes

Seconds 5-9

Assistive Device None

Comments

If you cannot correct this error, please explain:

Field open for editing

Error explanation box. Used to communicate with Heather, not for correcting errors.

There will only be one field available to change. If you need to change a field that isn't available, see the following section of this manual on opening fields to edit.

If you're unable to correct an error for whatever reason, explain why in the error explanation box provided.

Once you've entered the corrected data point, or comments indicating that the change cannot be made, click the Update Extracted Value button.

Note that the patient's name is a link to load the account in the menu, and the Evaluation name/date is a link to open and view the document. The Error description is displayed in yellow.

Margaret James

Enter PA Number

No Patient Selected

Select Patient Below

System Maintenance Response!

Main

Reports

Utilities

Physical Therapy

ASIA

Documents

NRN Financial

Problems with Extracted Data

Problems Awaiting Correction

You currently have no problems awaiting correction.

Recent Corrections Awaiting Approval

View		Evaluation - Evaluation (10/18/2011) - Step Activity Monitor - Number of steps first day
Error Message:		May not be blank - Enter NT if Not Tested or Enter correct value.
Error Value:		
Corrected Value:		NT

Once corrected, the change will show in the Problems Awaiting Approval section. To see the corrected value you can click on View to the left of the error.

The problems awaiting corrections and recent corrections awaiting approval list can also be viewed through Reports tab > CrossIQ Worklists folder > Facility Errors link, but only by administrators.

Opening a New Field for Corrections

The CrossIQ error correction system only allows a field which is suspected of being in error to be corrected. In order to change data in a field that does not have an error, the data correction area must be used.

Only evals that were completed within the last 2 months will be immediately available for correction. Any corrections on older evals must be approved by the data center.

The screenshot shows the OPPT Frazier Systemax,PT interface. On the left is a sidebar with a search bar for PA Number, patient details for TESTPATIENT024, BILL (DOB: 8/14/1980, PANUM: 999999024, MRNUM: 9999024), and a notification of 16 extraction errors. Below this is a navigation menu with folders like Today, Face Sheet, OP PT, Patient Information, Insurance, Pre-Admission, Intake Questionnaire, Multi-Discipline Eval, ASIA, Physician, Patient Charges, History/Environment, Physician Notes, Mile Markers, and Research. The Research folder is expanded, showing sub-items: CrossIQ Register, Patient Programs, Program Overview, and Data Correction. The main area is titled 'Research Data Correction' and 'TESTPATIENT024, BILL'. It features an 'Information Type' dropdown menu with options: Select..., Select..., Evaluations (highlighted), and Interventions. A 'Logout' button is at the bottom of the sidebar.

1. Go to the Research folder > Data Correction,
2. Select Evaluations or Interventions, depending on which one you need to make a correction to. NACTN doesn't use interventions, so only the evaluations section will be needed.
3. Click View beside the form to be changed.

Research Data Correction

KHALast, MAGfirst

Information Type: Evaluations

Select Evaluation: 12/26/2006 - ASIA

Select Form:

View	
View	Rt Motor,OT
View	Rt Light Touch,OT
View	Lt Light Touch,OT
View	Lt Pin Prick,OT
View	Rt Pin Prick,OT
View	Lt Motor,OT
View	ICH Scale,OT
View	Physician,Documentation
View	Rt Light Touch,MD
View	Rt Pin Prick,MD
View	Lt Light Touch,MD
View	Lt Pin Prick,MD
View	Rt Pin Prick,PT
View	Lt Light Touch,PT
View	Rt Light Touch,PT
View	Rt Motor,PT
View	Lt Pin Prick,PT
View	Lt Motor,PT

Rt Light Touch,OT		
C2	1	Change Requested
C3	1	Request Change
C4	1	Request Change
C5	1	Request Change
C6	1	Request Change
C7	2	Request Change
C8	2	Change Requested
T1	2	Request Change
Comments		Not Extracted

4. Click the “Request Change” button beside the value to be edited.
 - a. If the field requested to change is on an eval that is less than 2 months old, you’ll see a Change button that takes you to the correction form where you can change the value requested.
 - b. If the field is on an eval that is more than 2 months old the change must be approved by the data center. The request change button will then show Change Requested. Once the data center approves the change that field will appear in the list of site errors and will not have an error description.
 - c. If the field is not extracted by the data center, rather than a request change button, there will be a message saying not extracted. These fields are never seen by the data center.
 - d. If the field has been locked by the data center, changes are not permitted on the eval. The word Locked will appear where the Request Change button is. Contact the data center if you feel you must change a field on this eval.

OPPT Frazier
Systemax,PT

Enter PA Number

KHALast, MAGfirst
 DOB: 11/14/1952
 PANUM: 10881779
 MRNUM: 55783

Select Patient Below

You have 16 extraction errors

Main Reports Utilities

- Today
- Face Sheet
- OP PT
- Patient Information
- Insurance
- Pre-Admission
- Intake Questionnaire
- Multi-Discipline Eval
- ASIA
- Physician
- Patient Charges
- History/Environment
- Physician Notes
- Mile Markers
- Research
 - CrossIQ Register
 - Patient Programs
 - Program Overview
 - Data Correction

Extracted Data Correction

KHALast, MAGfirst
 ASIA - 9/3/2009 3:04:00 PM
 InP PT, ASIA, C2 - T1, OT

'C6 (Wrist extensors)'

Original Value:

Correction Form

C5 (Elbow flexors)

C6 (Wrist extensors)

C7 (Elbow extensors)

C8 (Finger flexors)

T1 (Finger abductors)

Comments

3

0

1

2

3

4

5

5*

NT

If you cannot correct this error, please explain:

After clicking the Change button if available, the form to be edited is shown. The value to be corrected is available for change now. Once the correction is made, click Update Extracted Value. At this point, you are returned to the "Problems with Extracted Data" page for further changes. This is the same list viewed if you click the alert on the menu "You have X extraction errors."

The name on this page is a link that will make the account active in the menu if necessary.

Changing Your Password in ITW

1. Click on “Utilities” tab
2. Click on “Maintenance”
3. Click on “Password”
4. Enter and confirm new password

Resetting Passwords in ITW for Other Staff

1. Log on with administrative permissions
2. Click on “Utilities” tab
3. Click on yellow folder – “Supervisor Utilities”
4. Click on “Password Reset”
5. Type in User Name
6. The password will reset to “password”
7. Have staff log on with “password” and they will then be prompted to change their password

Marking an Episode as a Test Case

This can be used when a second episode is accidentally entered for a patient. This should be rare.

1. Load the Patient
2. Under Episode Maintenance click the Test Case check box in the upper right corner.



Christopher Reeve Foundation

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

Christopher I. Shaffrey, MD, Executive Committee Member

Date

Robert Marsh, MD, 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: <i>Review of the 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: March 2010	REPLACES POLICY DATED:

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 (July 2007, 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: March 2010	REPLACES POLICY DATED:

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: March 2010	REPLACES POLICY DATED:

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: March 2010	REPLACES POLICY DATED:

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 the 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: March 2010	REPLACES POLICY DATED:

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: Data Integrity Overview	
SCOPE: North American Clinical Trials Network (NACTN) PI's, administrators and clinical team members	
PURPOSE: To provide a framework for the Data Integrity Process for the North American Clinical Trials Network (NACTN)	
PROCEDURE: <u>Data Integrity Manual:</u> With the assistance of the NACTN Data Manager, the DIDO Committee will develop and maintain a Data Integrity Manual, which will include, at minimum: • A listing of all variables currently examined in the data integrity process • Methods used for data reduction (checking of entered raw data vs. summary scores) to ensure data integrity • A list of all error conditions for each variable. <u>Data Syllabus:</u> The DIDO Committee and NACTN Data Manager will develop and maintain a Data Syllabus to be distributed with data disseminations. The syllabus will include details about the history of NACTN, its goals, and details on interpreting all variables ever collected by NACTN. <u>Frequency of Extraction/Data Integrity Reviews:</u> At the current time, extractions are performed manually by Systemax on a monthly basis. <u>Integrity of Data:</u> As soon as a new extraction is received, all data collected since the previous extraction will be checked as described in the Data Reduction to Ensure Data Integrity policy below and the Data Integrity Manual.	
REFERENCES:	
EFFECTIVE DATE: January 2013	APPROVAL DATE: January 14, 2013
APPROVED BY: Executive Committee	REPLACES POLICY DATED:

POLICY DESCRIPTION: Data Reduction to Ensure Data Integrity	
SCOPE: North American Clinical Trials Network (NACTN) PI's, administrators and clinical team members	
PURPOSE: To describe the methods used during data reduction to ensure integrity of data collected in the North American Clinical Trials Network (NACTN)	
PROCEDURE: Whenever data are extracted, all data are checked as follows: <u>The Data Integrity Process:</u> • Data is run through an automated program that checks each variable for a standard format and automatically flags several errors as described in the data integrity manual. These errors include formatting discrepancies, logical errors, and missing data points. • Several Data points are manually checked to verify correct documentation and coding. • Potential errors in the data are separated by site and documented in a detailed error report sent to each site clinical coordinator, and data manager no later than 5 business days after the data dissemination. • Sites are given 7 business days after receiving the error report to make any necessary corrections to the data. • Data Management will track errors to identify recurring errors to distribute to site PIs.	
REFERENCES:	
EFFECTIVE DATE: January 2013	APPROVAL DATE: January 14, 2013
APPROVED BY: Executive Committee	REPLACES POLICY DATED:

POLICY DESCRIPTION: Dissemination of Data – INTERNAL

SCOPE: North American Clinical Trials Network (NACTN) PI's, administrators and clinical team members

PURPOSE:

To define who may have access to NACTN data for the purpose of data analysis and/or publication and to define the requirements and process for dissemination of data.

POLICY:

All Executive Committee members will review and approve all proposals requesting access to the NACTN data.

PROCEDURE:

For the purpose of this procedure, internal is defined as all members and former members of NACTN and their designees as approved by the Executive Committee. External is defined as anyone not associated with NACTN.

Internal applicants requesting data from the database shall submit a standardized form available from the host site data manager. Internal applicants requesting data from only their individual site must specify this in the special requests section of the application.

Applicants will submit a data request form which includes:

- a 500 word abstract which describes the purpose, specific aims, hypotheses, relevant evidence and relevance to the NACTN mission
- Identification of the data to be extracted from the database using the appropriate ITW form numbers.
- Signed statement assuring:
 - accuracy of provided information on the form
 - agreement that data will be released solely to the requestor
 - compliance with home institution IRB policies
 - compliance with waiver statement

Internal applicants may request data from their own NACTN site with the approval of their site PI, as indicated by their signature on the form. A request for data from multiple NACTN sites must be approved by that site's PI, as well as one other site PI or Executive Committee member.

Once this preliminary approval is received, the data request form is submitted to the NACTN database manager, who will disseminate it electronically to the NACTN Executive Committee members.

Approval or disapproval of the request for data from all NACTN sites must be by majority of all Executive Committee members. The decision may be based on the following criteria:

- Soundness of the scientific theory
- Redundancy of requests
- Relevance to the NACTN mission
- Availability and accuracy of data

If the request is denied by a majority of the Executive Committee members, a member of the Data Integrity and Dissemination Oversight committee (DIDO) will prepare a letter to the applicant explaining the reason for denial. The letter will be provided to the NACTN database manager for distribution to the applicant.

If the Executive Committee members approve the request, the form is sent to the database manager who will perform additional integrity checks on the data.

The disseminated data integrity process:

- Disseminated data must be extracted a minimum of two times from the site of origin to assure any corrections made to the data are reflected in the dissemination.
- Disseminated data must go through the Data Reduction to Ensure Data Integrity procedure above which checks the data against possible errors listed in the data integrity manual.
- Any data points which remain in error are removed from the dissemination.
- The DIDO committee will oversee the integrity of disseminations.

Once the approvals and integrity checks are complete, the database manager will query the de-identified data and forward it solely to the requestor in the requested format. If DIDO determines that the data quality is insufficient for release (i.e. missing data, high incidence of errors), the database manager will notify the requestor and NACTN PIs as well as the Executive Committee. All PIs will be notified of the data request denial during the monthly conference call. Release of approved data or denial of requests must be completed in a timely manner.

Data management will keep a record of what data have been released, to whom, and when. This information must be available for review by members of NACTN, and should be disseminated annually.

All request forms will be entered into a database that can be searched by request to the NACTN database manager.

Video distributed in professional presentations and publications to demonstrate NACTN procedures will fall under the data dissemination policy. Video of NACTN patients or procedures distributed for the press will fall under the Media Services & Public Relations Policy.

REFERENCES:

EFFECTIVE DATE: January 2013

APPROVAL DATE: January 14, 2013

APPROVED BY: Executive Committee

REPLACES POLICY DATED:

POLICY DESCRIPTION: Dissemination of Data – EXTERNAL

SCOPE: North American Clinical Trials Network (NACTN) PI's, administrators and clinical team members

PURPOSE:

To define who may have access to NACTN data for the purpose of data analysis and/or publication and to define the requirements and process for dissemination of data.

POLICY:

Executive Committee members will review and approve all proposals requesting access to NACTN data.

PROCEDURE:

For the purpose of this procedure, internal is defined as all members and former members of NACTN and their designees as approved by the PIs. External is defined as anyone not associated with NACTN.

External applicants requesting data from the database shall submit a standardized form available from the host site data manager. External applicants will submit a data request form which includes:

- a 500 word abstract which describes the purpose, specific aims, hypotheses, relevant evidence and relevance to the NACTN mission
- Identification of the data to be extracted from the database using the appropriate ITW form numbers
- Demonstration of the applicant's qualifications to complete the analysis (such as a current curriculum vitae/resume or NIH biosketch)
- Signed statement assuring:
 - accuracy of provided information on the form
 - agreement that data will be released solely to the requestor
 - compliance with home institution IRB policies
 - compliance with waiver statement

External applicants may not request NACTN data that is 3 years old or less unless provisions are made by NACTN's Executive Committee.

Approval or disapproval of the request must be by majority of all NACTN Executive Committee members. The decision may be based on the following criteria:

- Soundness of the scientific theory
- Redundancy of requests
- Relevance to the NACTN mission
- Availability and accuracy of data

If the request is denied by a majority of Executive Committee members, a member of the Data Integrity and Dissemination Oversight Committee (DIDO) will prepare a letter to the applicant explaining the reason for denial. The letter will be provided to the NACTN database manager for distribution to the applicant.

If the Executive Committee members approve the request, the form is sent to the database manager who will perform additional integrity checks on the data.

The disseminated data integrity checks:

- Disseminated data must be extracted a minimum of two times from the site of origin to assure any corrections made to the data are reflected in the dissemination.
- Disseminated data must go through the Data Reduction to Ensure Data Integrity procedure above which checks the data against possible errors listed in the data integrity manual.
- Any data points which remain in error are removed from the dissemination.
- The DIDO committee will oversee the integrity of disseminations.

Once the approvals and integrity checks are complete, the database manager will query the de-identified data and forward it solely to the requestor in the requested format. The database manager will notify the NACTN PIs and Executive Committee of the data dissemination. If DIDO determines that the data quality is insufficient for release (i.e. missing data, high incidence of errors), the database manager will notify the requestor and NACTN PIs as well as the Executive Committee. All PIs will be notified of the data request denial during the monthly conference call. Release of approved data or denial of requests must be completed in a timely manner.

External requestors will be charged a nominal fee, as determined by the Executive Committee, to cover expenses. Any questions from external requestors about this data, further clarifications or requests for additional data should be directed to the DIDO committee.

Data management will keep a record of what data have been released, to whom, and when. This information must be available for review by members of NACTN, and should be disseminated annually.

All request forms will be entered into a database that can be searched by request to the NACTN database manager.

Video distributed in professional presentations and publications to demonstrate NACTN procedures will fall under the data dissemination policy. Video of NACTN patients or procedures distributed for the press will fall under the Media Services & Public Relations Policy.

REFERENCES:

EFFECTIVE DATE: January 2013

APPROVAL DATE: January 14, 2013

APPROVED BY: Executive Committee

REPLACES POLICY DATED:

NACTN NATIONAL DATABASE

Data Dissemination Request Form

Name of Requestor:

Title:

Address:

Institutional Affiliation:

Phone Number:

Fax Number:

Official email address:

Requestor affiliated with NACTN

☐ YES

☐ NO

Request data from:

☐ Single NACTN Site

☐ All NACTN Sites

Part I: 500 Word Abstract

Attach a 500 word abstract including your purpose, specific aims, hypotheses, relevant evidence in support of your request and the relevance to the NACTN mission.

☐ The data will be disseminated in a grant proposal. If publication or public dissemination eventually emanates from this dissemination, another dissemination form will be completed and an abstract provided.

Part II: Data Request Form

Fill out the attached form to describe exactly what data you need to fulfill the aims of your abstract. Should this request be approved, indicate how the extracted data should be transmitted to you.

Part III: Qualifications

a. External applicants must attach a current curriculum vitae/resume or NIH biosketch.

b. Does your institution require IRB approval or exemption for this query?

☐ YES

☐ NO

If yes, please attach copies of your institutional IRB approval or exemption for this query.

Part IV: Sign the Following Waiver

All information contained in the attached documents is accurate and current. I understand that approval or disapproval of this request may be based on: soundness of scientific theory; redundancy of requests; relevance to the NACTN mission; availability of data; IRB status; qualifications of the applicant. Should approval be granted, de-identified data will be transmitted solely to me using the method indicated below. A nominal fee may be charged to cover the expenses to extract and transmit the data. If I am a NACTN member, I must follow the Publication of Data Procedure prior to submitting a manuscript for publication which contains NACTN data.

Signature of Applicant

Date

Print Applicant Name

Requested Data: Please list the ITW form numbers containing the data you are requesting. ITW forms and form numbers are available in the NACTN Data Syllabus. If there are any questions, contact Heather Tolle at heathertolle@kentuckyonehealth.org.

Format for Output:

☐ Excel

☐ Comma-delimited ASCII

Demographic Data: All data requests will include all available demographic data. At this time, this includes gender, race, month and year of birth and marital status.

Special Requests:

Instructions:

Submit your request to Heather Tolle at heathertolle@kentuckyonehealth.org, who will distribute it electronically to the PI's and Executive Committee members.

Date submitted: _____

POLICY DESCRIPTION: Presentations Without Data	
SCOPE: North American Clinical Trials Network (NACTN) PI's, administrators and clinical team members	
PURPOSE: To define the requirements and processes for presentations that do not include NACTN data.	
PROCEDURE: This procedure applies to all presentations which do not contain data concerning patients, outcomes or financial records. These presentations will likely fall into one of three types: community outreach, marketing, and education. Presenters must request review from the Executive Committee before making presentations that represent the NACTN which do not contain data concerning patients, outcomes, or financial records. Reviewers have 24 hours to respond to the request, if there is no response it is assumed that approval is granted. Non-data presentation requests will be entered into a centralized database using the attached form. This information must be available for review by members of NACTN, and should be disseminated periodically. If the presenter wants to give the same presentation on a different occasion, a new form must be submitted for the log, not for re-approval, indicating relevant information for the subsequent presentation. Presenters must follow the Media Services and Public Relations procedure in the Governance Section of the Policy and Procedures Manual.	
REFERENCES:	
EFFECTIVE DATE: January 2013	APPROVAL DATE: January 14, 2013
APPROVED BY: Executive Committee	REPLACES POLICY DATED:

POLICY DESCRIPTION: Presentations With Data
SCOPE: North American Clinical Trials Network (NACTN) PI's, administrators and clinical team members
PURPOSE: To define the requirements and process for presentation of NACTN data.
POLICY: Presenters must get approval from an Executive Committee member before making presentations that represent NACTN and contain data concerning patients, outcomes, or financial records.
PROCEDURE: This procedure applies to four types of presentations: community outreach, marketing, education, and scientific. Presentations that represent NACTN and contain data concerning patients, outcomes, or financial records must be approved as follows: The attached form will be used for the submittal and approval of all presentations. An abstract which describes the purpose, specific aims, hypotheses, relevant evidence and relevance to the NACTN mission is required. The presenter must gain the approval of their site PI, as well as an Executive Committee member and one additional site PI. Once the preliminary approvals are gained, the form is submitted to the NACTN database manager who will disseminate it electronically to the NACTN PIs and Executive Committee members for review. Site PIs have 48 hours to respond to the request. If there is no response, it is assumed that there are no comments. For scientific presentations that require abstract submission, the presenter must give notice of intent to the NACTN database manager at least 2 weeks in advance of submitting an abstract for approval to an Executive Committee member and a site PI. This notice must include a timeframe for when the abstract will be received for review. The Executive Committee member and site PI will make every effort to be available during the specified timeframe. If an Executive Committee member or a site PI is unavailable, and the deadline is such that the presenter cannot wait until the PI is available, then the presenter will need to get the approval of another site PI. Once the preliminary approvals are gained, the form is submitted to the NACTN database manager who will disseminate it electronically to the NACTN PIs and Executive Committee members for review. Site PIs have 48 hours to respond to the request. If there is no response, it is assumed that there are no comments. For non-scientific presentations, the presenter must gain the approval of their site PI, as well as an Executive Committee member and one additional site PI. If an Executive Committee member or site PI is unavailable, an additional site PI must approve the presentation. Once the preliminary approvals are gained, the form is submitted to the NACTN database manager, who will disseminate the request electronically to the NACTN PIs and Executive Committee members for review. Site PIs have 48 hours to respond to the request. If there is no response, it is assumed that there are no comments. If the presenter wants to give the same presentation on a different occasion, a new form must be submitted for the log, not for re-approval, indicating relevant information for the subsequent

presentation.	
REFERENCES:	
EFFECTIVE DATE: January 2013	APPROVAL DATE: January 14, 2013
APPROVED BY: Executive Committee	REPLACES POLICY DATED:

North American Clinical Trials Network (NACTN)
Dissemination Record
Presentations

Please complete a separate form for each presentation on NACTN that will be made by the staff who work anywhere within your SITE

NAME OF THIS SITE : _____

1. **Presenter:**

(Last)

(First)

(Middle Initial)
2. **Co-Presenters/Authors** (if applicable):
 - a.

(Last)

(First)

(Middle Initial)
 - b.

(Last)

(First)

(Middle Initial)
 - c.

(Last)

(First)

(Middle Initial)
3. **Title of Presentation:**
4. **Date of Presentation:**
5. **Topic/Subject of Presentation:**
6. **Type of Presentation:**
 - a. ☐ Oral presentation of original study findings
 - b. ☐ Oral teaching presentation - Grand Rounds, case presentation, literature review, etc.
 - c. ☐ Poster presentation of original study findings
 - d. ☐ Poster teaching presentation - Case presentation, literature review, device review, etc.
 - e. ☐ Community outreach
 - f. ☐ Marketing
 - g. ☐ Education
7. Does your presentation/poster involve the use of **data derived from the NACTN Data Set?**

_____yes

_____no
8. Is this **presentation about a project that is funded directly from the NACTN grant?**

_____yes

_____no

9. Is/will the following statement included **in writing** on the poster or during the oral presentation?

“NACTN is funded by the Telemedicine & Advanced Technology Research Center, US Army Medical Research and Materiel Command.”

_____yes _____no

10. Where presentation will take place?

- a. Name of organization, conference, course, workshop, institution where presentation was given (ie Physical Medicine and Rehabilitation Grand Rounds, The Ohio State University):

- b. **Sponsor of the conference**, course, workshop, etc.: (e.g. ACRM, ASIA, University of Pittsburgh PM&R Dept., Rocky Mountain SCI System):

- c. **Location** of Presentation: (e.g. Hospital, facility or university AND City and State):

- d. **Number of Attendees:** _____

11. **Contact person** for questions regarding this presentation:

Name: _____

Telephone: _____

Email address: _____

12. **Please attach a scientific abstract for the poster/presentation if data is being presented.**

13. **Directors who approved this presentation:**

Presenter's Site PI: _____

Executive Committee Member: _____

Additional Site PI: _____

Please return this form to: Heather Tolle at heathertolle@kentuckyonehealth.org

POLICY DESCRIPTION: Publication of Data
SCOPE: North American Clinical Trials Network (NACTN) PI's, administrators and clinical team members.
PURPOSE: To define the requirements and process for publication of NACTN data
POLICY: The entire group of NACTN PIs and Executive Committee members and their designated experts will review the final draft of publications and their associated data analyses prior to submission for publication. The NACTN Executive Committee will vote on approval either during meetings or electronically.
PROCEDURE: Manuscripts which are authored by a member or members of NACTN are considered internal publications. Manuscripts without a member of NACTN as authors are designated external manuscripts. For internal publications, any member of NACTN wishing to prepare a scientific manuscript based on NACTN data will begin by forming an ad hoc committee to write the paper. All members of NACTN are eligible to participate on the ad hoc writing committee. Committee participation requires significant contribution to the design, data analysis and writing of the manuscript. The first action of the ad hoc committee is to appoint a chair and establish a timeline for preparation of the manuscript. This timeline will be stated at the next PIs conference call. Failure to adhere to the timeline may result in the appointment of a new chair of the writing committee for that manuscript. In order to be considered for authorship of approved internal publications, an individual must be on the ad hoc writing committee. The committee will propose a list of authors and designated order, based on the guidelines found in: Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication. <i>Updated February 2006</i> International Committee of Medical Journal Editors The members of the ad hoc committee must reach consensus on both the draft publication and the list of authors. Then, they are submitted to the NACTN database manager, who will disseminate them electronically to the NACTN PIs, Executive Committee and experts. The entire group of NACTN PIs and Executive Committee and designated experts (if so desired) will review the final draft of publications, their associated data analyses, and proposed list of authors prior to submission for publication. The reviewers have the right to ask for clarification of the raw data used as well as the data analysis process, including calculations or transformations of the raw data. Any suggested changes by the reviewers that will not be implemented should be discussed with the individual reviewer.

The reviewers have no more than 2 weeks to provide comments or seek clarification.

After the 2 week review period, each Executive committee member eligible to vote, along with any designated experts, will determine if they are prepared to vote electronically on the manuscript or that discussion with other voters is needed. A single request for discussion will table the vote until after discussion occurs on the next Executive Committee conference call. If there are no requests for discussion, an electronic vote will proceed. Approval of internal manuscripts and author lists requires a consensus vote. All PIs will be notified of manuscript approval during the monthly conference call.

Authors of external manuscripts may submit their paper for review by the NACTN PIs and Executive Committee but are not required to do so. The review process will be the same except that no vote will be given. Any questions or concerns that remain unresolved after the review process of external manuscripts may result in an editorial written by members of NACTN.

REFERENCES:

EFFECTIVE DATE: January 2013

APPROVAL DATE: January 14, 2013

APPROVED BY: Executive Committee

REPLACES POLICY DATED:

II. Ethical Considerations in the Conduct and Reporting of Research

II.A Authorship and Contributorship

II.A.1. Byline Authors

An “author” is generally considered to be someone who has made substantive intellectual contributions to a published study, and biomedical authorship continues to have important academic, social, and financial implications. (1) In the past, readers were rarely provided with information about contributions to studies from those listed as authors and in acknowledgments. (2) Some journals now request and publish information about the contributions of each person named as having participated in a submitted study, at least for original research. Editors are strongly encouraged to develop and implement a contributorship policy, as well as a policy on identifying who is responsible for the integrity of the work as a whole.

While contributorship and guarantorship policies obviously remove much of the ambiguity surrounding contributions, it leaves unresolved the question of the quantity and quality of contribution that qualify for authorship. The International Committee of Medical Journal Editors has recommended the following criteria for authorship; these criteria are still appropriate for those journals that distinguish authors from other contributors.

- Authorship credit should be based on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3.
- When a large, multi-center group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript (3). These individuals should fully meet the criteria for authorship defined above and editors will ask these individuals to complete journal-specific author and conflict of interest disclosure forms. When submitting a group author manuscript, the corresponding author should clearly indicate the preferred citation and should clearly identify all individual authors as well as the group name. Journals will generally list other members of the group in the acknowledgements. The National Library of Medicine indexes the group name and the names of individuals the group has identified as being directly responsible for the manuscript.
- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.

- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

Some journals now also request that one or more authors, referred to as “guarantors,” be identified as the persons who take responsibility for the integrity of the work as a whole, from inception to published article, and publish that information.

Increasingly, authorship of multi-center trials is attributed to a group. All members of the group who are named as authors should fully meet the above criteria for authorship.

The order of authorship on the byline should be a joint decision of the co-authors. Authors should be prepared to explain the order in which authors are listed.

II.A.2. Contributors Listed in Acknowledgments

All contributors who do not meet the criteria for authorship should be listed in an acknowledgments section. Examples of those who might be acknowledged include a person who provided purely technical help, writing assistance, or a department chair who provided only general support. Editors should ask authors to disclose whether they had writing assistance and to identify the entity that paid for this assistance. Financial and material support should also be acknowledged.

Groups of persons who have contributed materially to the paper but whose contributions do not justify authorship may be listed under a heading such as “clinical investigators” or “participating investigators,” and their function or contribution should be described—for example, “served as scientific advisors,” “critically reviewed the study proposal,” “collected data,” or “provided and cared for study patients.”

Because readers may infer their endorsement of the data and conclusions, all persons must give written permission to be acknowledged.

II.B Editorship

II.B.1. The Role of the Editor

The editor of a journal is the person responsible for its entire content. Owners and editors of medical journals have a common endeavor—the publication of a reliable and readable journal, produced with due respect for the stated aims of the journal and for costs. The functions of owners and editors, however, are different. Owners have the right to appoint and dismiss editors and to make important business decisions in which editors should be involved to the fullest extent possible. Editors must have full authority for determining the editorial content of the journal. This concept of editorial freedom should be resolutely

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: ○ To address a specific objective or goal of a standing committee ○ To initiate a change in the NACTN Policies and Procedures ○ To provide structure to research projects from project development, to data analyses and publication ○ 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: March 2010	REPLACES POLICY DATED:

Today's Care. Tomorrow's Cure.



The **NeuroRecovery Network (NRN)** is a cooperative network of cutting-edge rehabilitation centers designed to provide and develop therapies to promote functional recovery and improve the health and quality of life for people living with paralysis. Funded by the Christopher & Dana Reeve Foundation through a cooperative agreement with the Centers for Disease Control and Prevention (Award No. 1U59DD000338), the NRN translates the latest scientific advances into effective, activity-based rehabilitation treatments.

Each center is staffed with a group of dedicated professionals who have received specialized training in order to deliver the NRN's therapies. The staff includes center directors, physicians, administrative and clinical supervisors, data managers, physical therapists, occupational therapists and rehab technicians.

What is Locomotor Training?

Locomotor Training (LT) is the method of physical therapy currently deployed by the NRN. In LT sessions, the body of the paralyzed patient is suspended in a harness over a treadmill, while specially trained therapists move his legs to simulate walking. As the patient regains function, improvements in sitting, standing, reaching, grasping or walking occur.

LT derives from recent advances in scientific understanding about neural plasticity (the ability of the neurons in the nervous system to develop new connections and “learn” new functions) and the role the spinal cord plays in controlling stepping and standing. LT works to “awaken” dormant neural pathways by repetitively stimulating the muscles and nerves in the lower body – allowing

patients whose lower bodies may appear partially or completely disconnected from input from the brain to regain motor abilities and achieve rehabilitation goals.

Data Collection Information

Participants in the NRN become part of a network-wide database that is collecting comprehensive medical information about the progress of each patient. By collecting and analyzing this information, the NRN is able to accurately measure program outcomes. Recent findings from this program evaluation were published in the September 2012 issue of the *Archives of Physical Medicine and Rehabilitation* and provide guidance for clinical decision-making.

In addition to Locomotor Training, NeuroRecovery Network participants work on sitting and balance exercises.



Patients' Frequently Asked Questions

(applicable to NeuroRecovery Network Rehab Centers only)

Who qualifies to participate in the NeuroRecovery Network?

At the present time, the Locomotor Training program is open to individuals with complete or incomplete cervical or thoracic spinal cord injury who have some muscle tone in their legs and lesion above T12.

What steps does one have to take to receive treatment in the NRN?

Patients must have a referral from a physician to receive this therapy. All potential patients must be seen by the NRN physician and physical therapists at the NRN facility, to be screened for any complicating medical issues that would make this therapy inappropriate. Following this evaluation, if deemed appropriate for this therapy, a plan of treatment will be established.

How long will the course of therapy take?

The average person receives the therapy for three to four months, and will undergo a minimum of 60 sessions. Each patient is re-evaluated every 20 sessions. At that time, the NRN physicians and therapists will make any adjustments needed to the number of days per week the patient receives the therapy and talk about the goals for the next 20 visits.

How much time will each Locomotor Training session take?

Each session generally lasts one and a half hours. When a patient enters the program, he starts five days per week. As he progresses through the phases of recovery, the number of days per week may decline to four days/week and then three days/week.

What is the cost of receiving therapy through the NRN?

Who will pay for it?

NRN sites are committed to working with every patient to secure reimbursement for participating in this program. It is expected that the costs will be covered by the patient's insurance company.

What results can I expect? What long-term improvements to my health will this therapy provide?

A range of results and health improvements are reported in the scientific literature; others are beginning to emerge as we apply this therapy to human patients. What we know is that results will vary from patient to patient. No two NRN patients will respond in exactly the same way, nor is each patient likely to experience the entire range of possible changes and improvements. This therapy may contribute to improved cardiovascular and pulmonary function and blood flow to the arms and legs. In some patients, it may boost the healing potential of the skin, help increase bone density, and improve bladder function. Functional results among NRN patients have ranged from improved trunk stability to recovery of standing and stepping ability.

For Frequently Asked Questions about community-based facilities, please visit **ChristopherReeve.org/NRN**



The NeuroRecovery Network provides activity-based therapies to individuals living with paralysis with the goal of improved function, health, independence and quality of life.



636 Morris Turnpike, Suite 3A | Short Hills, NJ 07078 | (800) 225-0292 | ChristopherReeve.org

NeuroRecovery Network

NRN Director:

Susan Harkema, PhD, Department of Neurological Surgery
Kentucky Spinal Cord Injury Research Center, University of Louisville

NRN Leadership Team:

Andrea Behrman, PhD, PT, Department of Neurological Surgery
Kentucky Spinal Cord Injury Research Center, University of Louisville
Mary Schmidt Read, PT, DPT, MS, Magee Rehabilitation Hospital
Elizabeth Ardolino, Assistant Professor, University of St. Augustine
Karey McDowell MS, CTRS, CPT, Supervisor—Community Fitness and Wellness, Frazier Rehab Institute
Carrie Shogren, OTR/L|Senior Occupational Therapist, Courage Center

Rehabilitation Centers

For information about enrollment, please contact each center:

Craig Hospital, Englewood, CO

Candy Tefertiller, ctefertiller@craighospital.org

Frazier Rehab Institute, Louisville, KY

Kim Atkinson, kimberlyatkinson@kentuckyonehealth.org

Kessler Medical Rehabilitation Research and Education Center

Kessler Institute for Rehabilitation, West Orange, NJ

Gail Forrest, PhD, gforrest@kesslerfoundation.org

Magee Rehabilitation Hospital, Philadelphia, PA

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Ohio State University Medical Center—Dodd Hall, Columbus, OH

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Shepherd Center, Atlanta, GA

Keith Tansey, MD, PhD, keith_tansey@shepherd.org

The Institute for Rehabilitation and Research, Houston, TX

Heather Taylor, PhD, Heather.Taylor@memorialhermann.org

Toronto Rehabilitation Institute, Toronto, ON

Chris Alappat, chris.alappat@uhn.ca

Community Fitness and Wellness Facilities

Courage Center, Minneapolis, MN

Jeanne Olson, jeanne.olson@couragecenter.org

Frazier Rehab Institute—Community Fitness and Wellness Facility, Louisville, KY

Karey McDowell, kareymcdowell@kentuckyonehealth.org

Neuroworx, South Jordan, UT

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NextStep Fitness, Lawndale, CA

Janne Kouri, management@nextstepfitness.org

NextSteps Chicago, Willow Springs, IL

Jon O'Connor, Director, nextstepschicago@gmail.com





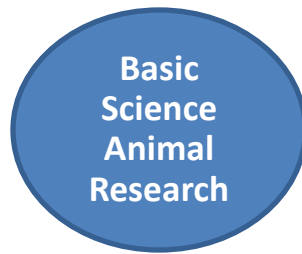
KENTUCKY
**SPINAL CORD
INJURY**
RESEARCH
CENTER

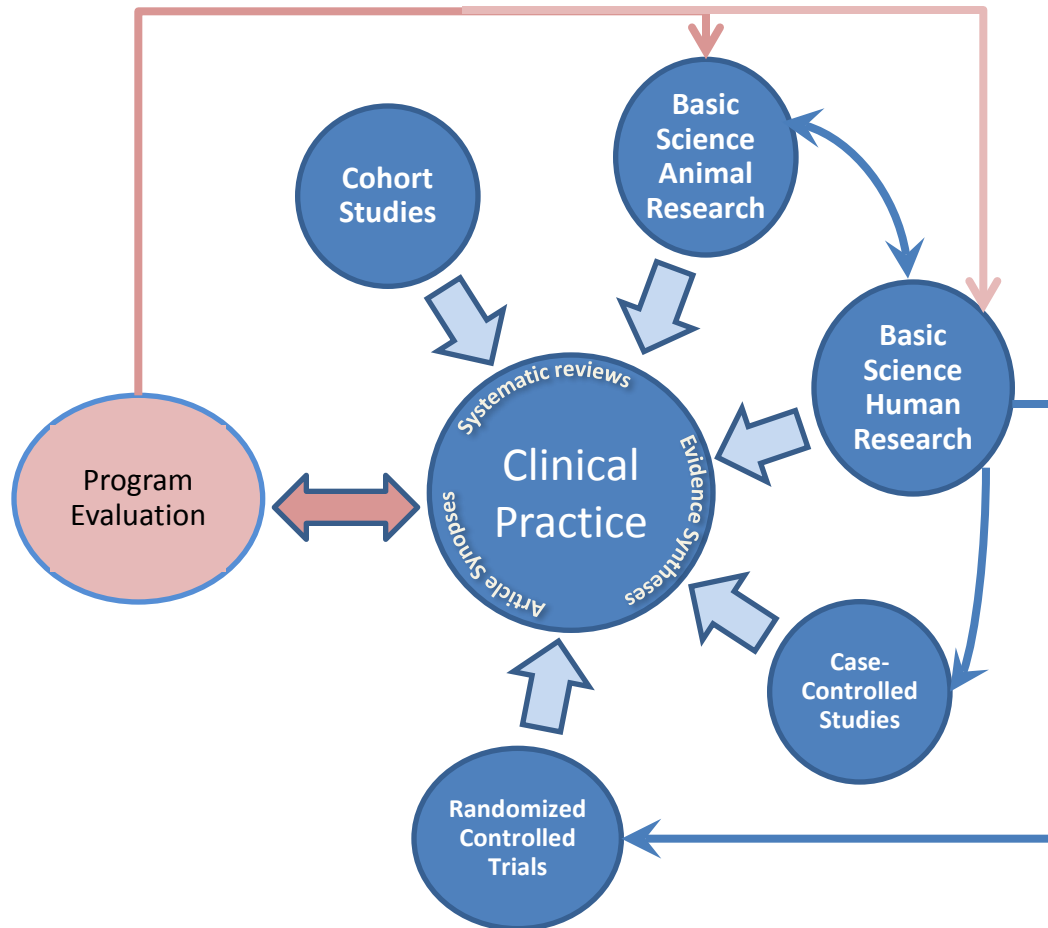
UNIVERSITY of LOUISVILLE



Frazier Rehab Institute
KentuckyOne Health™









CHRISTOPHER & DANA REEVE FOUNDATION

NORTH AMERICAN CLINICAL TRIALS NETWORK



Coordinating Center

PI: Robert Grossman
Elizabeth Touns
Jerika Acosta
Tanisha Bernhardt



PI: Michele Johnson
Martha Powner
Christopher Riley
Fusun Kiran



PI: Michael Fehlings
Charles Tator
Yuliay Petrenko
Sukhvinder Kalsi-Ryan
Jefferson Wilson



PI: Christopher Shaffrey
John Jane Sr.
Justin Smith
Daniel Chernavsky
Cherly Haner
Elizabeth Yount



PI: Maxwell Boakye
PI: Susan Harkema
Jonathan Hodes



PI: Bizhan Aarabi
Christina (Charlene) Aldrich
Dana Beam
Kaloal Booker



PI: Michael Rosner
Vicki Miskovsky



PI: James Guest
Marina Dididze
Christopher Gilbert



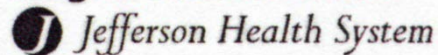
Thomas
Jefferson
University

PI: James Harrop
Melissa Witt
John Furlong
Beth Thwaites



Brooke Army Medical Center
PI: Robert A. Marsh
Shalece Kofford Barrow
Aida Paredes

Magee Rehabilitation



Philadelphia, PA

Director:

Mary Schmidt Read, PT, DPT, MS

Physician:

Guy Fried, MD

Administrator:

Mary Schmidt Read, PT, DPT, MS

Clinical Supervisor:

Liz Watson

Data Manager:

Alice Kennedy

Rehabilitation Centers



Louisville, KY

Director:

Kim Atkinson, PT, NCS

Physician:

Steve Williams, MD

Administrator:

Kim Atkinson PT, NCS

Clinical Supervisor:

James Ochsner, PT

Data Manager:

Carolyn Tipton



Houston, TX

Director:

Heather Taylor, PhD

Administrator:

Rhonda Abbott, PT, MS

Physicians:

Jeff Berliner, MD

Lisa Wenzel, MD

Clinical Supervisor:

Marcie Kern, PT

Data Manager:

Michelle Feltz



Shepherd Center

Atlanta, GA

Director:

Keith Tansey, MD, PhD

Physician:

Anna Elmers, MD

Administrator:

Paula Ackerman

Clinical Supervisor:

Brian Holliday, DPT

Data Manager:

Jason Tidwell



West Orange, NJ

Director:

Gail Forrest, PhD

Administrator:

Pat Judd, PT, MHA, MS

Physicians:

Steven Kirshblum, MD

Monifa Brooks, MD

Clinical Supervisor:

Buffy Wojciehowski, PT

Data Manager:

Ryan Lamb



Columbus, OH

Director:

D. Michele Basso, EdD, PT

Administrator:

Physician:

W. Jerry Mysiw, MD

Clinical Supervisor:

Carol Eskay, MPT

Data Manager:

Mike Young



Caring exclusively for patients with spinal cord and brain injuries.

Denver, CO

Director:

Candy Tefertiller

Administrator:

Candy Tefertiller

Physician:

Thomas Balazy

Clinical Supervisor:

Meghan Joyce

Data Manager:

Taylor Martinez



Toronto, ON, CA

Director:

Heather Flett

Administrator:

Joanne Zee

Physician:

Mark Bayley

Clinical Supervisor:

Chris Alappat

Data Manager:

Molly Verrier

For a list of all team members, please visit <http://louisville.edu/medschool/neurosurgery/harkema/nrn>

The extraordinary vision, compassion and dedication of Christopher and Dana Reeve made the NeuroRecovery Network possible.

This program is funded by the Christopher and Dana Reeve Foundation through Grant/Cooperative Agreement Number U10.CC0220379 between the Reeve Foundation and the Centers for Disease Control and Prevention (CDC)

UNIVERSITY OF LOUISVILLE

KENTUCKY SPINAL CORD INJURY RESEARCH CENTER



Community Fitness and Wellness Facilities



Louisville, KY

Director: Karey McDowell, MS,CTRS, CPT
Administrator:
Karey McDowell, MS,CTRS, CPT
Facility Supervisor: Doug McCoy, BS
Data Manager: Kevin Richardson



Los Angeles, CA

Director: Janne Kouri, BBA
Administrator: Christel Mitrovich, BS, MS
Facility Supervisor: Christel Mitrovich, BS, MS
Data Manager: Joel Wenger



Chicago, IL

Director: Jon O'Connor, BS
Administrators: Jon O'Connor, BS
Mike Keenum, PT
Facility Supervisor: Sakina Valika, PT, DPT
Data Manager: Tim Davis



South Jordan, UT

Director: Jan Black, MS, PT
Administrator: Dale Hull, MD
Facility Supervisor: Jan Black, MS, PT
Data Manager: Shana Black, Ashley Beyeler



Minneapolis, MN

Director: Jeanne Olson, PT, : MBA
Administrator: Karen Peterson, PTA
Facility Supervisor: Carrie Shogren
Data Manager: Andy Rapacz

For a list of all team members, please visit <http://louisville.edu/medschool/neurosurgery/harkema/nrn>

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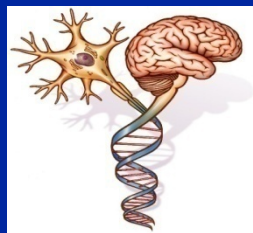
North American Clinical Trials Network for the Treatment of Spinal Cord Injury: Goals and Progress

Jefferson R. Wilson MD

Michael G. Fehlings MD PhD FRCSC FACS

Division of Neurosurgery, Institute of Medical Sciences
University Health Network, University of Toronto

American Spinal Injury Association annual meeting
Chicago, IL
May 8, 2013



Neurosurgery



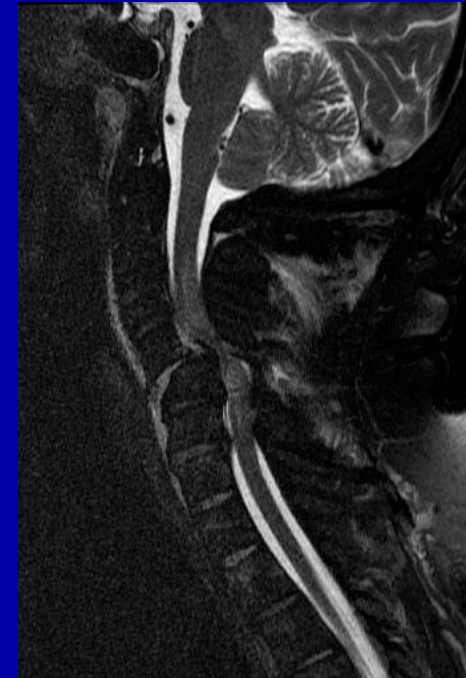
www.uhn.on.ca/programs/spine

Disclosures

- Post-Doctoral Fellowship support from:
 - Christopher and Dana Reeve Foundation
 - Cervical Spine Research Society

Case Vignette: The Clinical Dilemma

- 39-year-old man
- Dove into shallow water at 7:30 am
- Complete cervical spinal cord injury
- Initial resuscitation & stabilization then transferred to our unit in a hard cervical collar
- On arrival: C4 level ASIA-A complete cervical spinal cord injury



How can we optimize patients' long-term recovery in the acute setting ?

Objectives

- 1) Discuss the origins, structure and key goals of NACTN
- 2) Discuss work related to the NACTN prospective SCI registry
- 3) Discuss NACTN as a setting for therapeutic clinical trials
 - Riluzole phase I/IIa Trial

History of NACTN

- Established in 2004
- Consists of:
 - 10 clinical centers
 - Data management center (University of Texas)
 - Pharmacological center (University of Houston)
- Only standing Clinical Trials Network for SCI in North America
- Established with support of the Christopher and Dana Reeve Foundation and US DOD



U.S. DEPARTMENT OF DEFENSE

Mission of NACTN

- To bring basic discoveries in neuroprotection and regeneration to clinical trials and practice
- To maintain a prospective SCI data registry to probe a variety of questions related to the acute management and natural history of SCI patients

NACTN: People and Centers

- Principle Investigator
 - Dr Robert Grossman
 - Methodist Hospital,
Houston
- Clinical Trials Manager
 - Elizabeth Toups
 - Methodist Hospital,
Houston



Clinical Centers

- 1. The Methodist Hospital, Houston**
Principal Investigator (NACTN), Robert G. Grossman, M.D.
- 2. The University of Toronto, Toronto**
Michael Fehlings (Riluzole), 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**
Susan Harkema, PhD., Maxwell Boakye MD
- 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**
Michael Rosner, M.D.
- 10. Brooke Army Medical Center, San Antonio**
Robert March M.D. Ph.D.

NACTN: People and Centers

- Management Center
 - University of Texas School of Public Health
 - Ralph Frankowski PhD
 - Keith Burau PhD
- Pharmacological Center
 - University of Houston, College of Pharmacy
 - Diana Chow PhD

NACTN Committees

- Data Management
- Neurological Outcome Assessment
- Publications
- Strategy Selection

Prospective NACTN SCI Registry

- Data registry maintained concurrently with clinical trial Enrollment
- Projects arising from NACTN Registry
 - Acute Complications
 - Clinical-Radiological Prediction Model
 - Defining the impact of Age on outcomes
 - Imaging repository

Prospective NACTN SCI Registry

- Approximately 550 patients enrolled
- Acute Data Elements
 - Demographics, ISNCSCI exam, medical treatments, surgery, complications
- Long-term Follow-up Data
 - ISNCSCI exam, chronic complications, SCIM, FIM, WISCI

Baseline Characteristics

Characteristic	No. (%)
sex	
M	387 (79.8)
F	98 (20.2)
age in yrs†	
<20	31 (6.4)
20–65	390 (80.4)
>65	64 (13.2)
race	
white	363 (74.8)
other	122 (25.2)
circumstance of injury	
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	11 (2.3)
injury type	
closed	459 (94.7)
penetrating	19 (3.9)
other	7 (1.4)
injury region	
cervical	367 (75.7)
thoracic	88 (18.1)
lumbar/sacral	27 (5.6)
SCIWORA	3 (0.6)

Acute AIS grade by Surgical Approach

AIS Grade*	No. of Patients				
	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
not obtained	30	15	15	15	75
total	197	111	93	48	449

Hospital Stay and Disposition

Parameter	No. (%)
hospital LOS (days)	
<8	128 (26.4)
8–14	141 (29.1)
15–21	79 (16.3)
>21	137 (28.2)
discharge status	
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)

* LOS = length of stay; rehab = rehabilitation.

Approximately 90% of patients enrolled have follow-up data available at 3, 6 or 12 months

AIS conversion at hospital discharge

Initial AIS Grade*	AIS Grade at Discharge†					Total
	A	B	C	D	E	
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
total	122	51	53	123	10	359

* Grade obtained within 7 days of injury.

† Grade obtained within 14 days of acute care discharge.

SCIM indoor mobility at 6 or 12 mos.

AIS Grade*	No. (%)		Total
	Able to Walk Independently	Unable to Walk Independently	
A	1 (1.3)	77 (98.7)	78
B	2 (5.7)	33 (94.3)	35
C	7 (22.6)	24 (77.4)	31
D	48 (49.0)	50 (51.0)	98
E	18 (100.0)	0 (0)	18
total	76 (61)	184 (39)	260

* First grade obtained within 7 days of injury.

Prospective NACTN SCI Registry

- Projects arising from NACTN Registry
 - Acute Complications
 - Clinico-radiographic prediction model
 - Defining the role of age of clinical outcomes
 - Imaging Repository

Incidence and severity of acute complications after spinal cord injury

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AND JAMES S. HARROP, M.D.¹⁰

- Majority of existing focus on sub-acute or chronic complications
- Objective: Characterize the profile and severity of acute SCI complications

No. of Complications	No. of Patients (%)
0	133 (42.2)
1	37 (11.7)
2	22 (7.0)
3	28 (8.9)
≥4	95 (30.2)
total	315 (100.0)

NACTN Registry: Complications

Complications by Organ System

Complication	No. of Complications				No. of Patients (%)
	Severe	Moderate	Mild	Total	
pulmonary	40	150	38	228	121 (38.4)
infectious†	14	137	30	181	112 (35.6)
hematological‡	3	106	22	131	73 (23.2)
cardiac	20	72	19	111	76 (23.8)
GI/GU	10	51	12	73	53 (16.8)
skin	5	45	17	67	49 (15.6)
neuropsychiatric	4	46	15	65	57 (18.1)
total	96	607	153	856	
% total	11.2	70.9	17.9	100	

Incidence of Complications by AIS grade

ASIA Grade	No. of Patients	Patients w/ Complications*	Incidence as % (95% CI)†
A	126	106	84.1 (76.6–90.0)
B	52	32	61.5 (47.0–74.7)
C	46	21	45.7 (30.9–61.0)
D	91	23	25.3 (16.7–35.5)
total	315	182	57.8 (52.1–63.3)

Relative Risk of complications by demographic factors and associated injuries

Baseline Variable	Relative Risk (95% CI)
ASIA grade	
A	3.32 (2.32–4.78)
B	2.43 (1.61–3.68)
C	1.81 (1.12–2.90)
D	referent
SCI	
penetrating	1.49 (1.16–1.92)
not penetrating	referent
GCS score	
≤8	1.43 (1.06–1.92)
9–15	referent
Abbreviated Injury Scale chest score	
>3 (severe/critical)	1.31 (1.08–1.60)
≤3	referent
prior smoking	
yes	1.27 (1.06–1.54)
no	referent
level of SCI	
cervical	1.12 (0.88–1.43)
thoracolumbar	referent
age at injury (yrs)	
≥65	1.11 (0.87–1.41)
<65	referent
comorbidities	
present	1.09 (0.89–1.34)
absent	referent

Predictors of pulmonary complications in blunt traumatic spinal cord injury

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- Isolated evaluation of acute in-hospital pulmonary complications
 - Pneumonia, effusion, PneumoTx, PE, ARDS
- Objectives:
 - To identify combination of predictors
 - Impact on neurological outcome

Predictors of Pulmonary Comps

Potential Risk Factor	No. of Pts	No. w/ PCs	Risk (%)	Unadjusted	
				RR	95% CI (p value)*
demographic data					
sex					
female	23	10	43.5	referent	
male	86	41	47.7	1.1	0.65–1.84 (0.4323)
age, in yrs					
16–25	24	10	41.7	referent	
26–35	18	13	72.2	1.73	1.00–3.01 (0.0480)
36–45	16	6	37.5	0.90	0.41–1.98 (0.5280)
46–55	20	8	40.0	0.96	0.47–1.96 (0.5780)
56–65	23	9	39.1	0.93	0.47–1.88 (0.5479)
>65	8	5	62.5	1.50	0.73–3.07 (0.2699)
mechanism					
MVA	47	19	40.4	referent	
fall	33	14	42.4	1.04	0.62–1.78 (0.5197)
sports	21	14	66.7	1.65	1.04–2.61 (0.0407)
other	8	5	62.5	1.54	0.82–2.93 (0.2177)
neurological level					
L1–S1	8	2	25.0	referent	
T2–12	14	5	35.7	1.43	0.36–5.74 (0.4897)
C5–T1	40	17	42.5	1.66	0.47–5.81 (0.3239)
C2–C4	47	27	57.4	2.30	0.67–7.82 (0.0937)
severity					
adm ASIA motor score					
51–100	33	3	9.1	referent	
25–50	33	14	42.4	4.67	1.48–14.7 (0.0049)
<25	43	34	79.1	8.70	2.92–25.9 (<0.0001)
adm ASIA Impairment Scale grade					
D	32	3	9.4	referent	
C	13	4	30.8	3.28	0.85–12.7 (0.0935)
B	16	7	43.8	4.67	1.39–15.7 (0.0097)
A	48	37	77.1	8.22	2.77–24.4 (<0.0001)

MRI Predictors of Pulm. Comps

Potential Risk Factor	No. of Pts	No. w/ PCs	Risk (%)	Unadjusted	
				RR	95% CI (p value)*
% MCC					
0–20	25	13	52.0	referent	
21–40	48	20	41.7	0.80	0.48–1.33 (0.2759)
41–67	36	18	50.0	0.96	0.58–1.58 (0.5425)
% MSCC					
<0	29	13	44.8	referent	
0–19	31	13	41.9	0.94	0.52–1.67 (0.5137)
20–57	49	25	51.0	1.14	0.70–1.85 (0.6447)
LIL, in mm					
<21	31	10	32.2	referent	
21–40	37	14	37.8	1.17	0.61–2.26 (0.4121)
>40	41	27	65.9	2.04	1.17–3.56 (0.0046)

MCC: Maximum Canal Compromise

MSCC: Maximum Spinal Cord Compression

LIL: Length of Lesion on T2 MRI

Pulmonary Complications and AIS grade conversion

ASIA Impairment Scale Grade	ASIA Impairment Scale Grade					Total	% CR
	A	B	C	D	E		
all pts							
A	31	6	7	4	0	48	35.4
B	2	4	6	3	1	16	62.5
C	1	0	2	8	2	13	77.0
D	0	0	0	20	12	32	37.5
total	34	10	15	35	15	109	34.0
pts w/o PCs during acute care management							
A	7	0	2	2	0	11	36.4
B	1	2	2	3	1	9	66.7
C	0	0	1	6	2	9	88.9
D	0	0	0	19	10	29	34.5
total	8	2	5	30	13	58	31.0
pts w/ PCs during acute care management							
A	24	6	5	2	0	37	35.1
B	1	2	4	0	0	7	57.1
C	1	0	1	2	0	4	50.0
D	0	0	0	1	2	3	66.7
total	26	8	10	5	2	51	37.2

* CR = conversion rate.

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

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- Model Predicting 1-year Functional Outcome for SCI Patients based on acute clinical and MRI features developed/validated
 - Improve clinical communication and trial design
- NACTN and STASCIS data used to create combined dataset (729 Patients)

Predictor Variables

Predictor	Coding
Initial ASIA Impairment Scale (AIS) Grade	AIS grade A=1 AIS grade B=2 AIS grade C=3 AIS grade D=4 AIS grade E= (Not Included)
Initial ASIA Motor Score (AMS)	AMS ≤ 50 = 0 AMS > 50 = 1
Age	Continuous predictor
Spinal MRI Intra-medullary Signal Characteristics	No Signal=0 Signal consistent with spinal cord edema=1 Signal consistent with spinal cord hemorrhage= 2

Outcome of Interest: FIM motor score

SELF-CARE

- A. Eating
- B. Grooming
- C. Bathing
- D. Dressing - Upper Body
- E. Dressing - Lower Body
- F. Toileting

SPHINCTER CONTROL

- G. Bladder Management
- H. Bowel Management

TRANSFERS

- I. Bed, Chair, Wheelchair
- J. Toilet
- K. Tub, Shower

LOCOMOTION

- L. Walk/Wheelchair
- M. Stairs



FIM LEVELS

No Helper

Independent

7 = Complete Independence (Timely, Safely)

6 = Modified Independence (Device)

Helper

Modified Dependence

5 = Supervision (Subject = 100%+)

4 = Minimal Assist (Subject = 75%+)

3 = Moderate Assist (Subject = 50%+)

Complete Dependence

2 = Maximal Assist (Subject = 25%+)

1 = Total Assistance or not testable (Subject < 25%)

Constructed Linear and Logistic Models

TABLE 3. PARAMETER ESTIMATES FOR MODELS PREDICTING (A) FIM MOTOR SCORE, AND (B) FUNCTIONAL INDEPENDENCE, AT 1-YEAR FOLLOW-UP FROM ORIGINAL SAMPLE AND BOOTSTRAP REPLICATES

<i>Prognostic variable</i>	<i>Parameter estimate</i>	<i>p Value</i>	<i>Bootstrap parameter estimate (95% CI)</i>	
A.				
Intercept	50.28	<0.01	49.73 (49.0,50.5)	
Age	-0.33	<0.01	-0.33 (-0.34,-0.32)	
Admission AMS> 50	9.17	<0.01	9.11 (8.61,9.61)	
Admission AIS grade	12.47	<0.01	12.54 (12.34,12.76)	
MRI signal	-4.83	0.19	-4.65 (-4.91,-4.40)	
<i>Prognostic variable</i>	<i>Parameter estimate</i>	<i>Odds ratio</i>	<i>p Value</i>	<i>Bootstrap parameter estimate (95% CI)</i>
B.				
Intercept	-2.93	-	<0.01	-2.99 (-3.11,-2.87)
Age	-0.03	0.97	<0.01	-0.03 (-0.03,-0.03)
Admission AMS> 50	1.35	3.86	<0.01	1.34 (1.27,1.41)
Admission AIS grade	1.36	3.90	<0.01	1.39 (1.27,1.41)
MRI signal	-0.29	0.75	0.54	-0.30 (-0.34,-0.25)

ASIA, American Spinal Injury Association; AMS, ASIA motor score; MRI, magnetic resonance imaging; 95% CI, 95% confidence interval; AIS, ASIA Impairment Scale; FIM, functional independence measure.

Linear Model R²:
0.52 (0.52, 0.53)

Logistic Model AUC:
0.92 (0.92, 0.93)

Internally Validated Models

$$\text{FIM motor 1-year} = 50.28 - 0.33(\text{Age}) + 9.17(\text{AMS}) + 9.17(\text{AIS grade}) - 4.83(\text{MRI signal})$$

$$\text{Prob. Independence 1-year} = \frac{\exp[-2.93 - 0.03(\text{Age}) + 1.35(\text{AMS}) + 1.36(\text{AIS grade}) - 0.29(\text{MRI Signal})]}{(1 + \exp[-2.93 - 0.03(\text{Age}) + 1.35(\text{AMS}) + 1.36(\text{AIS grade}) - 0.29(\text{MRI Signal})])}$$

Where :

Age: continuous variable > 16

AMS: ASIA Motor Score $\leq 50 = 0$; ASIA Motor Score $> 50 = 1$;

AIS grade: AIS grade A=1; AIS grade B=2; AIS grade C=3; AIS grade D=4;

MRI Signal: No signal change=0; Sig. cons. w/edema=1; Sig. cons. w/hemor=2;

FIG. 2 Predictive model equations (ASIA, American Spinal Injury Association; AMS, ASIA motor score; MRI, magnetic resonance imaging; FIM, functional independence measure; AIS, ASIA Impairment Scale).

Applied Models to theoretical SCI patients

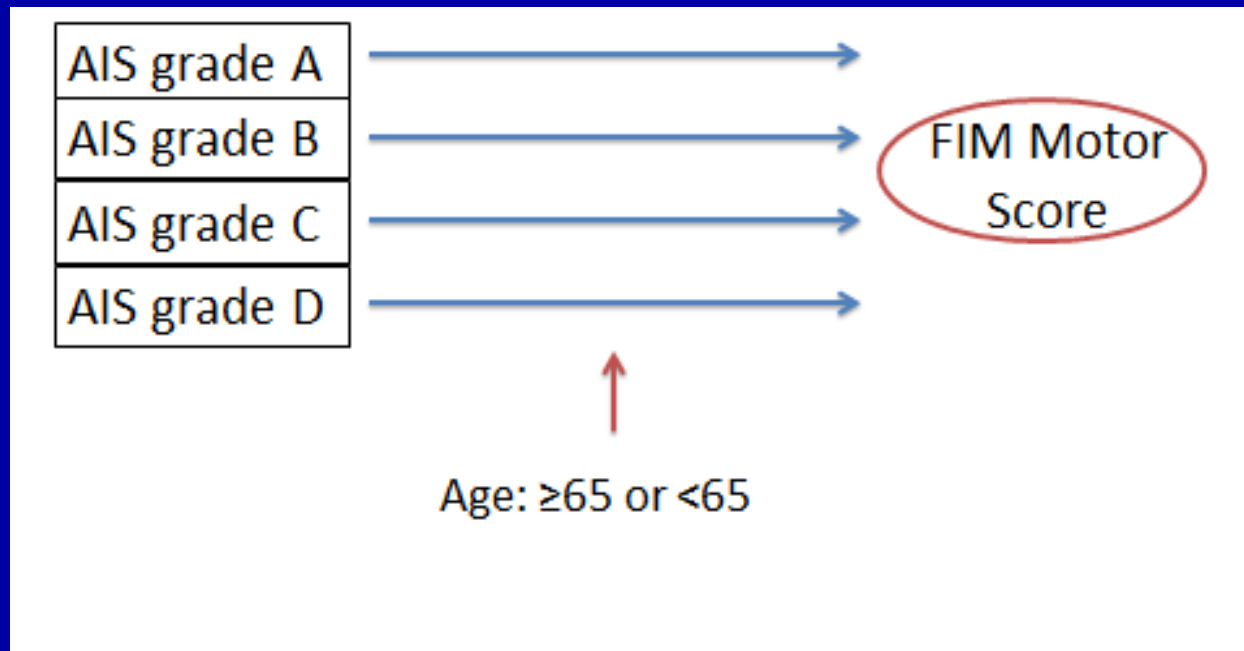
TABLE 4. PREDICTED ESTIMATES FOR FIM MOTOR SCORE AND THE PROBABILITY OF ACHIEVING FUNCTIONAL INDEPENDENCE AT 1-YEAR POST-INJURY FOR A HYPOTHETICAL SET OF SCI PATIENTS

<i>Characteristic</i>	<i>Patient 1</i>	<i>Patient 2</i>	<i>Patient 3</i>	<i>Patient 4</i>	<i>Patient 5</i>	<i>Patient 6</i>
Age (years)	75	75	55	55	25	25
AIS A	Yes	No	Yes	No	No	No
AIS B	No	No	No	No	No	Yes
AIS C	No	No	No	No	Yes	No
AIS D	No	Yes	No	Yes	No	No
AMS > 50	No	Yes	No	Yes	Yes	No
MRI hemorrhage	Yes	No	Yes	No	No	No
MRI edema	No	No	No	No	Yes	Yes
Predicted FIM motor score	28	85	44	91	84	62
Probability of functional independence	0.01	0.83	0.08	0.90	0.72	0.22

ASIA, American Spinal Injury Association; AMS, ASIA motor score; MRI, magnetic resonance imaging; AIS, ASIA Impairment Scale; FIM, functional independence measure.

Impact of Age on Outcome after SCI

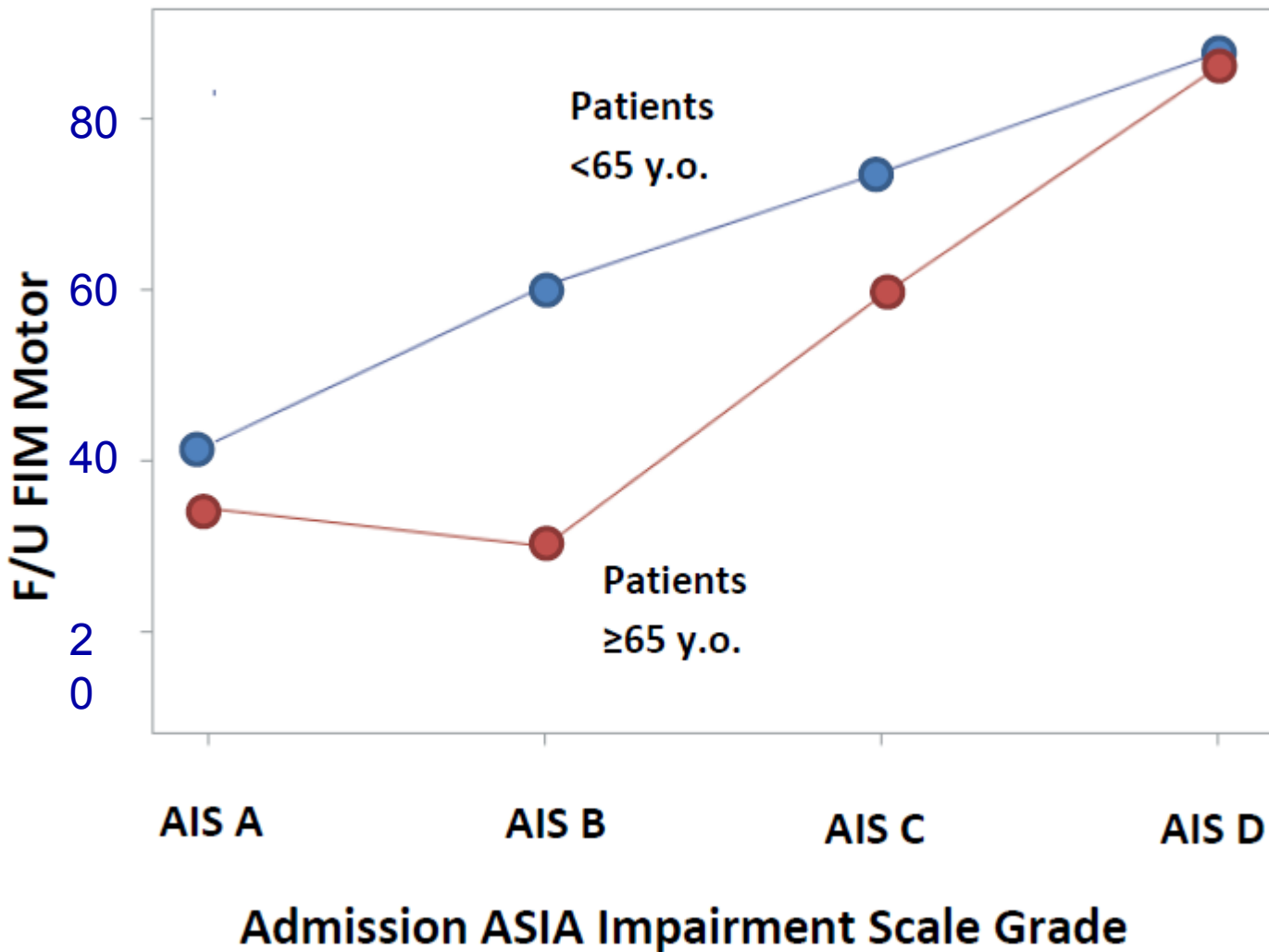
- Evaluate the impact of Age on Neurological and Functional Outcomes using the NACTN and STASCIS dataset
- Evaluate how this effect changes across the spectrum of injury severity



Results: Univariate Analysis

Outcome	Younger	Older	p-value
FIM motor score	64.2($\pm$ 28.0)	54.0($\pm$ 31.7)	P=0.03
ASIA motor score change	24.1($\pm$ 23.4)	20.7($\pm$ 17.2)	P=0.47
AIS grade change			P=0.35
No change	157(54.0%)	16(47.1%)	
1 grade	94(32.3%)	15(44.1%)	
≥ 2 grades	40(13.8%)	3(8.8%)	

Interaction plot: Injury Severity vs. Functional Outcome



Imaging Repository

- Acute and Follow-up CT/MRIs obtained for patients enrolled in prospective registry
 - Used as the subject of several ongoing studies
- Investigating the role of DTI/fMRI

JNS Spine NACTN/AOSNA

October 2012

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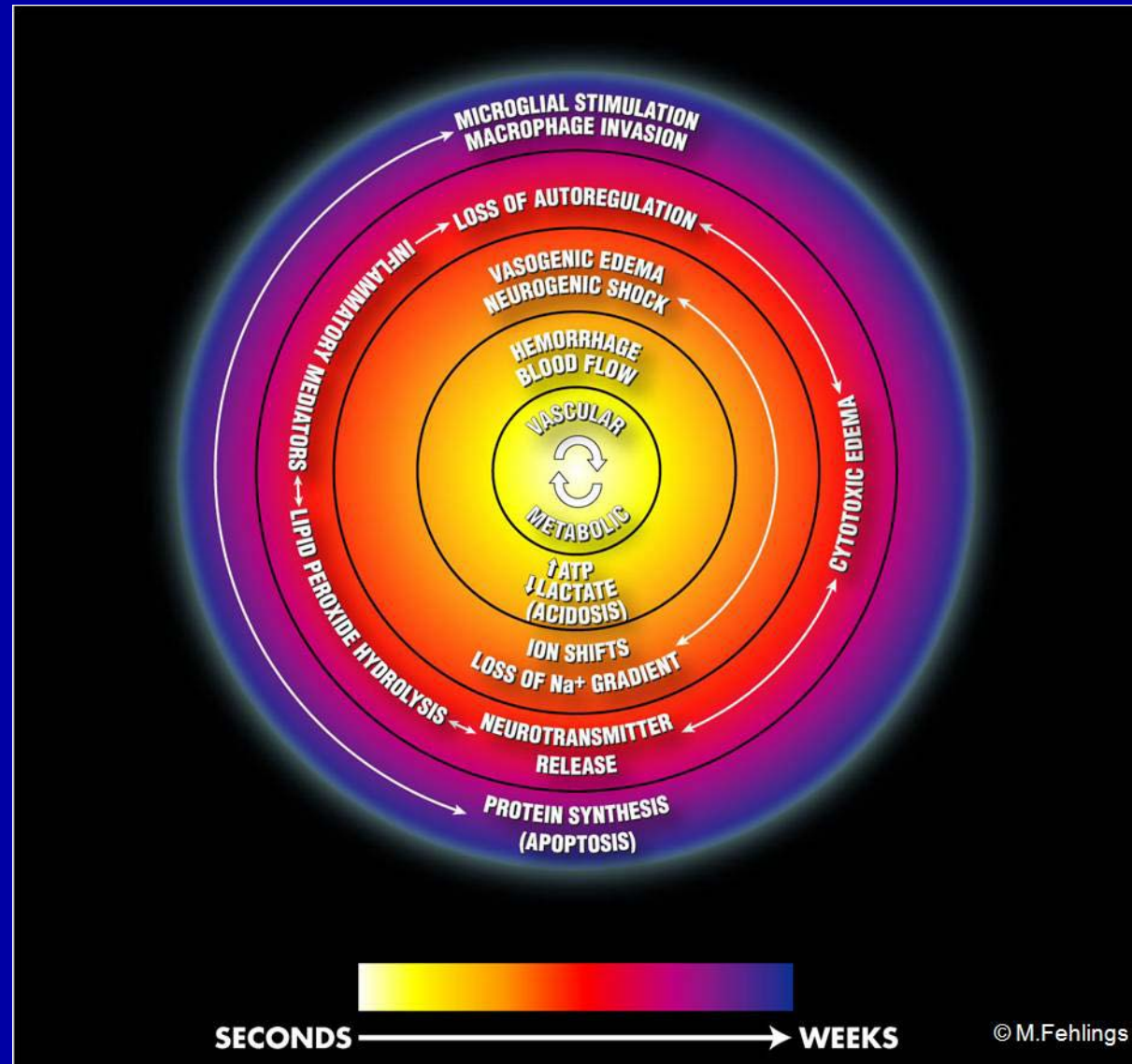
Article Title	Article Type
North American Clinical Trials Network for the Treatment of Spinal Cord Injury: goals and progress	research article
Clinical predictors of neurological outcome, functional status, and survival after traumatic spinal cord injury: a systematic review	systematic review
Quality of life in persons with spinal cord injury: comparisons with other populations	clinical article
Predictors of pulmonary complications in blunt traumatic spinal cord injury	clinical article
Clinical prediction model for acute inpatient complications after traumatic cervical spinal cord injury: a subanalysis from the Surgical Timing in Acute Spinal Cord Injury Study	clinical article
What do we currently know about thoracic spinal cord injury recovery and outcomes? A systematic review	systematic review
Development of the Graded Redefined Assessment of Strength, Sensibility and Prehension (GRASSP): reviewing measurement specific to the upper limb in tetraplegia	clinical article
Quantitative and sensitive assessment of neurophysiological status after human spinal cord injury	clinical article

Article Title	Article Type
Optimization of the decision-making process for the selection of therapeutics to undergo clinical testing for spinal cord injury in the North American Clinical Trials Network	research article
A systematic review of spinal fMRI research: outlining the elements of experimental design	systematic review
Incidence and severity of acute complications after spinal cord injury	clinical article
Pharmacology of riluzole in acute spinal cord injury	research article
Quantitative testing in spinal cord injury: overview of reliability and predictive validity	systematic review
Riluzole for the treatment of acute traumatic spinal cord injury: rationale for and design of the NACTN Phase I clinical trial	research article
Translational potential of preclinical trials of neuroprotection through pharmacotherapy for spinal cord injury	research article

NACTN as a setting for therapeutic clinical trials

- Completed Phase I/IIa Riluzole Trial
- Plans for Phase II/III Trial (RISCIS)

Primary and Secondary Injury Mechanisms after SCI



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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- Benzothiazole anticonvulsant Na⁺ channel blocker
 - Shown in two randomized controlled trials to:
 - ✓ promote increased survival
 - ✓ attenuate neurological dysfunction in patients with amyotrophic lateral sclerosis (ALS), a progressive neurodegenerative disorder characterized by motoneuron and corticospinal tract degeneration
- Potential hepatotoxicity has been noted (Bensimon and Doble, 2004)

Phase I Riluzole Trial

- The primary aim:
 - To develop acute care safety and pharmacokinetic profiles of riluzole in patients who have sustained a traumatic spinal cord injury

- Secondary objectives:
 - 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

Study Design

- Multi-site, single arm active treatment pilot study
- All Patients received Riluzole 50mg NG/PO q12h x 14 days, started within 12 hours of injury
- Target enrollment: 36 subjects
- Primary safety endpoint follow-up period for the pilot study is 3 months
- Neurological outcome assessed after 6 months

Patient Characteristics

Characteristic	Patient Number
Gender:	
Male	30 (83%)
Female	6 (17%)
Mean Age	39 (Min:18, Max:69)
Neurological Level of Injury:	
Cervical	28 (78%)
Thoracic	8 (22%)
ASIA Impairment Scale (AIS) grade:	
AIS grade A	19 (53%)
AIS grade B	9 (25%)
AIS grade C	8 (22%)
Etiology:	
Motor Vehicle Accident	18(50%)
Fall	9(25%)
Sport related	7(19%)
Assault	2 (6%)

Medical and Surgical Treatment

Treatment Variable	N (%)
Mean Time to Surgery	17 hours (Min: 6, Max:214)
Surgery <24 hours:	25 (75%)
Surgical Approach (Decompression and Fusion)	
Anterior	4(11%)
Posterior	12(33%)
Both	17(47%)
Steroids*:	
Yes	14(39%)
No	22(61%)

**NASCIS II 24 hour steroid protocol used

Riluzole Safety: Major Events

System	Serious Adverse Events	N
Pulmonary	Acute Respiratory Distress Syndrome	2
	Pulmonary Embolus	1
	Dyspnea/Hypoxia	1
Infectious	Sepsis	1
Hematologic	Deep Venous Thrombosis	2
Cardiovascular	Asystolic Episode	1
	Syncopal Episode	1
	Internal Carotid Artery Stenosis	1
Gastrointestinal	Rectal Hemorrhage	1
	Partial Bowel Obstruction	1
Enzyme Elevation	Liver Enzyme Elevation Day 7 (4.6 x UNL) *	1

Complications

Comparison between Riluzole and Registry Cohort

	Riluzole N = 36		Registry N = 36		
System/Category	Patients ¹	Incidence ²	Patients ¹	Incidence ²	P-value ³
Infection	14	0.389	13	0.361	0.81
Pulmonary	11	0.306	16	0.444	0.22
Neuropsychiatric	10	0.278	10	0.278	1.00
Hematological	7	0.194	9	0.250	0.57
Cardiovascular	5	0.139	11	0.306	0.09
GI/GU	5	0.139	9	0.250	0.19
Skin	4	0.111	3	0.083	0.69

Cervical Injuries: ASIA Motor Score Recovery

Admission AIS grade	Riluzole	SCI Registry	Riluzole – Registry Difference	P-value
	90 Day Mean (SD)	90 Day Mean (SD)		
AIS A	13 (20.7)	10 (17.0)	+3	0.79
AIS B	39 (28.7)	11 (17.4)	+28	0.04
AIS C	46 (16.0)	32 (19.3)	+14	0.19
All	31 (26.2)	15 (19.3)	+16	0.02
	180 Day Mean (SD)	180 Day Mean (SD)		
AIS A	15 (9.3)	11 (17.2)	+4	0.72
AIS B	46 (10.8)	24 (24.8)	+22	0.21
AIS C	50 (8.4)	51 (9.7)	-1	0.91
All	36 (28.5)	27 (24.0)	+9	0.25

Phase I/IIa Trial: Conclusion

- Have established feasibility of a multicenter trial evaluating Riluzole in traumatic SCI
- Preliminary safety and neurological recovery data appear promising

Next Steps: RISCIS Trial

- Pre-enrollment Stages of Phase III Trial to formally evaluate efficacy of Riluzole in the treatment of SCI
 - Riluzole in Spinal Cord Injury Study (RISCIS)
 - International Multicenter RCT
 - Protocol Finalized
 - Collaborative funding structure involving AOSpine NA, AOSpine International and Christopher and Dana Reeve Foundation

Future Directions for NACTN

- Phase III trial Riluzole
- Evaluation of other therapeutics
- Continued outcomes related research making use of Registry and Imaging Repository

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NACTN



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and the Christopher and Dana Reeve Foundation
grant/cooperative agreement no. U10/CCU220379



- To provide support for the development of specialized centers that provide **standardized** rehabilitation using **activity-based therapy** based on current **scientific and clinical evidence** for people with spinal cord injury and other selected neurological disorders
- To evaluate the effect of rehabilitative interventions formulated from scientific and clinical evidence on function, health, and quality of life
- Translation of research findings into financially feasible clinical practice
- Continuum:
 - Clinical Centers – therapy provided by skilled therapists
 - Community Fitness and Wellness facilities – exercise specialists promoting lifelong health and wellness

Reeve Foundation

Susan P. Howley
 Joseph Canose

NRN Advisory Board:

V. Reggie Edgerton, PhD
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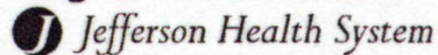
Network Director:

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Co-Directors:

Andrea L. Behrman, PhD, PT
 Mary Schmidt Read, PT, DPT, MS
 Liz Ardolino, PT, PhD
 Karrey McDowell, MS, CTRS, CPT

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Physician:

Guy Fried, MD

Administrator:

Mary Schmidt Read, PT, DPT, MS

Clinical Supervisor:

Liz Watson

Data Manager:

Alice Kennedy

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Steve Williams, MD

Administrator:

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Clinical Supervisor:

James Ochsner, PT

Data Manager:

Carolyn Tipton



Houston, TX

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Lisa Wenzel, MD

Clinical Supervisor:

Marcie Kern, PT

Data Manager:

Michelle Feltz



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Atlanta, GA

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Monifa Brooks, MD

Clinical Supervisor:

Buffy Wojciehowski, PT

Data Manager:

Ryan Lamb



Columbus, OH

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D. Michele Basso, EdD, PT

Administrator:

Physician:

W. Jerry Mysiw, MD

Clinical Supervisor:

Carol Eskay, MPT

Data Manager:

Mike Young



Caring exclusively for patients with spinal cord and brain injuries.

Denver, CO

Director:

Candy Tefertiller

Administrator:

Candy Tefertiller

Physician:

Thomas Balazy

Clinical Supervisor:

Meghan Joyce

Data Manager:

Taylor Martinez



Toronto, ON, CA

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Heather Flett

Administrator:

Joanne Zee

Physician:

Mark Bayley

Clinical Supervisor:

Chris Alappat

Data Manager:

Molly Verrier

For a list of all team members, please visit <http://louisville.edu/medschool/neurosurgery/harkema/nrn>

The extraordinary vision, compassion and dedication of Christopher and Dana Reeve made the NeuroRecovery Network possible.

This program is funded by the Christopher and Dana Reeve Foundation through Grant/Cooperative Agreement Number U10.CC0220379 between the Reeve Foundation and the Centers for Disease Control and Prevention (CDC)

**UNIVERSITY OF
 LOUISVILLE®**

**KENTUCKY SPINAL CORD
 INJURY RESEARCH CENTER**



Community Fitness and Wellness Facilities



Louisville, KY

Director: Karey McDowell, MS,CTRS, CPT
Administrator:
Karey McDowell, MS,CTRS, CPT
Facility Supervisor: Doug McCoy, BS
Data Manager: Kevin Richardson



Los Angeles, CA

Director: Janne Kouri, BBA
Administrator: Christel Mitrovich, BS, MS
Facility Supervisor: Christel Mitrovich, BS, MS
Data Manager: Joel Wenger



Chicago, IL

Director: Jon O'Connor, BS
Administrators: Jon O'Connor, BS
Mike Keenum, PT
Facility Supervisor: Sakina Valika, PT, DPT
Data Manager: Tim Davis



South Jordan, UT

Director: Jan Black, MS, PT
Administrator: Dale Hull, MD
Facility Supervisor: Jan Black, MS, PT
Data Manager: Shana Black, Ashley Beyeler



Minneapolis, MN

Director: Jeanne Olson, PT, : MBA
Administrator: Karen Peterson, PTA
Facility Supervisor: Carrie Shogren
Data Manager: Andy Rapacz

For a list of all team members, please visit <http://louisville.edu/medschool/neurosurgery/harkema/nrn>

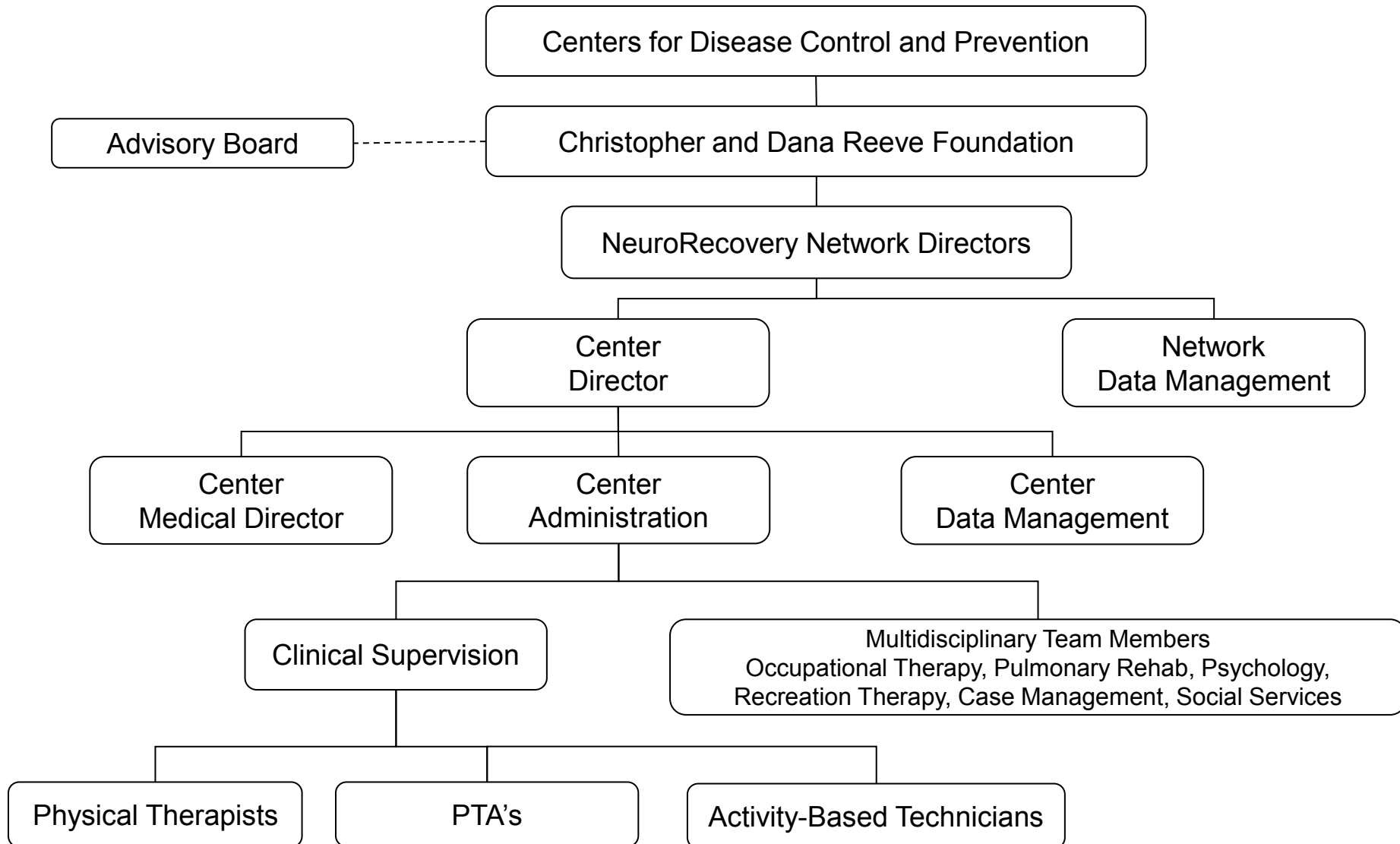
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CHRISTOPHER & DANA REEVE FOUNDATION NEURORECOVERY NETWORK







V. Reggie Edgerton, PhD



Moses V. Chao, PhD



NYU Medical Center
NYU School of Medicine & NYU Hospitals Center



Michael G. Fehlings, MD, PhD



Andrei Krassioukov, MD, PhD



Shelley Sorani, MA
Community Representative
San Francisco, CA



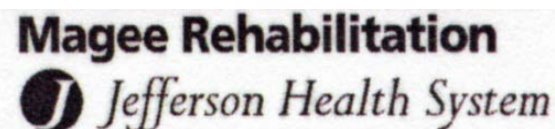
- **First Intervention : Manually Assisted Locomotor Training**
 - Subacute and Chronic Spinal Cord Injury AIS C and D, now including A and B
 - A rehabilitative strategy designed to re-train walking, trunk and upper extremity function
 - Provide sensory cues to re-train neural patterns that will result in effective neurorecovery which translates into enhanced function
 - Integrate “locomotor training principles” throughout the three environments of the BWST training, overground training and community integration



- **Evolving and possible future Initiatives:**

- Health and wellness measurement in areas related to respiratory , autonomic, metabolic, and urodynamic functions
- Upper extremity neurorecovery and function
- Program evaluation of activity based interventions specific to the upper extremity
- Program evaluation of frequency of interventions
- Program evaluation of interventions used with lower motor neuron injuries
- Development of diagnosis specific outcome measures – i.e. ABLE Scale for balance in SCI, and NeuroRecovery Scale for recovery of function in SCI
- Financial reimbursement for activity based interventions

N =	527
Years since injury	2.55 +/- 5; 1 [0.1, 53]
Age	39.17 +/- 17; 39 [3, 86]
Race	
White	74%
Black	17%
Hispanic	5%
Other	4%
AIS	
A	5%
B	5%
C	29%
D	61%
Gender	
Male	76%
Female	24%





N =	239
Years since injury	5.0 +/- 7.64; 2.7 [.1, 53.1]
Age	36.8 +/- 15.6; 36 [6, 83]
Race	
White	74%
Black	8%
Hispanic	6%
Asian	3%
Other	9%
NRS Phase	
1	72%
2	26%
3	2%
Gender	
Male	80%
Female	20%



- **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.* Arch Phys Med Rehabil. 2009 Jul;90(7):1208-17.
- **Marginal Association Measures for Clustered Data.** *Douglas J. Lorenz PhD, Somnath Datta PhD, Susan J. Harkema PhD.* Statistics in Medicine. 2011 Nov 30;30(27):3181–3191.
- **Establishing the NeuroRecovery Network: Multi-site rehabilitation centers that provide activity-based therapies and assessments for neurologic disorders** *Susan J. Harkema, PhD, Mary Schmidt-Read, MS, DPT, Andrea L. Behrman, PhD, PT, Amy Bratta DPT, Sue Ann Sisto PhD, PT, and V. Reggie Edgerton, PhD.* Arch Phys Med Rehabil. 2012 Sept;93(9):1498-1507.
- **Balance and ambulation improvements in individuals with chronic incomplete spinal cord injury using Locomotor Training- based rehabilitation.** *Susan J. Harkema, PhD, Mary Schmidt-Read, MS, DPT, Douglas Lorenz, MA, MSPH, V. Reggie Edgerton, PhD, and Andrea L. Behrman PhD, PT.* Arch Phys Med Rehabil. 2012 Sep;93(9):1508-17.
- **NeuroRecovery Network provides standardization of locomotor training for persons with incomplete spinal cord injury.** *Sarah A Morrison, PT, Gail F Forrest, PhD, Leslie R. VanHiel, MSPT, Michele Davé, DPT, Denise DeLorenzo, PT.* Arch Phys Med Rehabil. 2012 Sep;93(9):1574-7.

- **Assessment of functional improvement without compensation reduces variability of outcome measures after human spinal cord injury.** *Andrea L. Behrman, PhD, PT; Elizabeth Ardolino, PhD, PT; Leslie VanHiel, PT, DScPT; Marcie Kern, PT; Darryn Atkinson, PT; Doug Lorenz, MA; Susan Harkema, PhD.* Arch Phys Med Rehabil. 2012 Sep;93(9):1518-29.
- **Ambulation and balance outcomes measure different aspects of recovery in individuals with chronic incomplete spinal cord injury.** *Gail F. Forrest, PhD, Douglas J. Lorenz, MA, Karen Hutchinson, PhD, Leslie VanHiel, MSPT, D. Michele Basso, EdD, Somnath Datta, PhD, Sue Ann Sisto, PhD, PT, Susan Harkema, PhD.* Arch Phys Med Rehab. 2012 Sep;93(9):1553-64.
- **A dynamic longitudinal evaluation of the utility of the Berg Balance Scale in patients with motor incomplete spinal cord injury.** *Somnath Datta, Ph.D., Douglas J. Lorenz, M.A., M.S.P.H., Susan J. Harkema Ph.D.* Arch Phys Med Rehabil. 2012 Sep;93(9):1565-73.
- **Longitudinal patterns of functional recovery in patients with incomplete spinal cord injury receiving activity-based rehabilitation.** *Douglas J. Lorenz, M.A., Somnath Datta, Ph.D., Susan J. Harkema Ph.D.* Arch Phys Med Rehabil. 2012 Sep;93(9):1541-52.
- **Life Care Planning Projections for Individuals with Motor Incomplete Spinal Cord Injury before and after Locomotor Training Intervention: A Case Series.** *Sarah A. Morrison, PT, Jamie L. Pomeranz, PhD, CRC, CLCP, Nami Yu, MHS, CRC, Mary Schmidt Read, PT, DPT, MS, Sue Ann Sisto, PT, MA, PhD, Andrea L. Behrman, PT, PhD, FAPTA.* J Neurologic Phys Ther, 2012 Sep;36(3):144-53.

- **Relationship between ASIA Examination and Functional Outcomes in the NeuroRecovery Network Locomotor Training Program.** *Jeffrey J. Buehner, MS, PT, Gail Forrest, Ph.D., Mary Schmidt-Read, MS, DPT, Susan White, Ph.D., Keith Tansey, MD, Ph.D., Michele Basso, PT, Ed.D.* Arch Phys Med Rehabil. 2012 Sep;93(9):1530-40.
- **Cardiovascular status of individuals with Incomplete Spinal Cord Injury from seven NeuroRecovery Network rehabilitation centers.** *Sue Ann Sisto, PT, PhD, Douglas Lorenz, PhD, Karen Hutchinson, DPT, PhD, Lisa Wenzel, MD, Susan Harkema, PhD, Andrei Krassioukov, MD, PhD.* Arch Phys Med Rehabil. 2012 Sep;93(9):1578-87.
- **Basic concepts of activity-based interventions for improved recovery of motor function after spinal cord injury.** *Roland Roy, PhD, Susan Harkema, PhD, V. Reggie Edgerton, PhD.* Arch Phys Med Rehabil. 2012 Sep;93(9):1487-97.
- **Locomotor Training: As a treatment of spinal cord injury and in the progression of neurological rehabilitation.** *Susan Harkema, PhD, Jessica Hillyer, PhD, Mary Schmidt Read, PT, DPT, Elizabeth Ardolino, PT, PhD, Sue Ann Sisto, PT, PhD, Andrea Behrman, PT, PhD.* Arch Phys Med Rehabil. 2012 Sep;93(9):1588-97.
- **The ABLE scale: the development and psychometric properties of an outcome measure for the spinal cord injury population,** *Elizabeth Ardolino, PT, PhD, Karen Hutchinson, PT, PhD, G Pinto Zipp, M Clark, Susan Harkema, PhD.* Phys Ther. 2012 Aug;92(8):1046-54.
- **Locomotor training: is translating evidence into practice financially feasible?** *Sarah Morrison PT, Deborah Backus, PT, PhD.* J Neurol Phys Ther. 2007 Jun; 31(2):50-4.



Establishing the NeuroRecovery Network: Multi-site rehabilitation centers that provide activity-based therapies and assessments for neurologic disorders

Susan J. Harkema, PhD, Mary Schmidt-Read, MS, DPT, Andrea L. Behrman, PhD, PT, Amy Bratta DPT, Sue Ann Sisto PhD, PT, and V. Reggie Edgerton, PhD

Highlights:

- Collaborative partnership of basic scientists, clinical scientists, clinicians and administrators
- Program evaluation of standardized clinical model and not a research model – evaluating the effect of locomotor training and other evidence-based rehabilitative interventions in clinical environments
- Opportunity for translation of basic research into clinical practice



Locomotor Training: Is Translating Evidence Into Practice Financially Feasible?

Sarah Morrison, PT and Deborah Backus, PT, PhD

Highlights:

- A specific model of locomotor training delivered through manual BWSTT can be financially feasible in a hospital-based outpatient clinic.
- Clinics should not be discouraged from employing this treatment modality even with the increased staff and equipment required.



NeuroRecovery Network Provides Standardization of Locomotor Training for Persons with Incomplete Spinal Cord Injury

Morrison SA, Forrest G, VanHiel L, Dave M, DeLorenzo D

Highlights:

- Description of a person with a motor incomplete spinal cord injury receiving standardized locomotor training for 100 sessions across two different NRN centers.
- Consistent improvements were shown for walking endurance, walking speed, average and maximal treadmill training speeds, and amount of body weight support necessary throughout the continuum of training.
- The results supported that the NRN standardized protocol provided a mechanism of delivering consistent and reproducible locomotor training across 2 geographically different sites.

Balance and Ambulation Improvements in Individuals With Chronic Incomplete Spinal Cord Injury Using Locomotor Training-Based Rehabilitation," *Arch Phys Med Rehabil*, July 2011

Harkema S. J., Schmidt-Read M, Lorenz D, Edgerton V.R., and Behrman A.L.

Highlights:

- The effects of standardized Locomotor Training on:
1) locomotion (gait speed, distance); 2) balance; and 3) functional gait speed stratifications after **chronic** incomplete SCI.

MAIN OUTCOME MEASURES

6 Minute walk test
10 Meter Walk test
Berg Balance Scale.



Phase I



Initial Training



3 months training



Recovery



Phase III



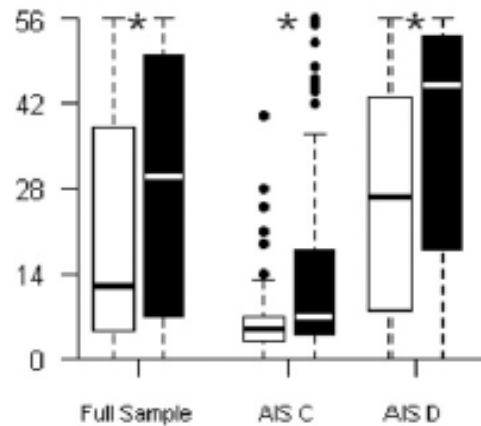
Training



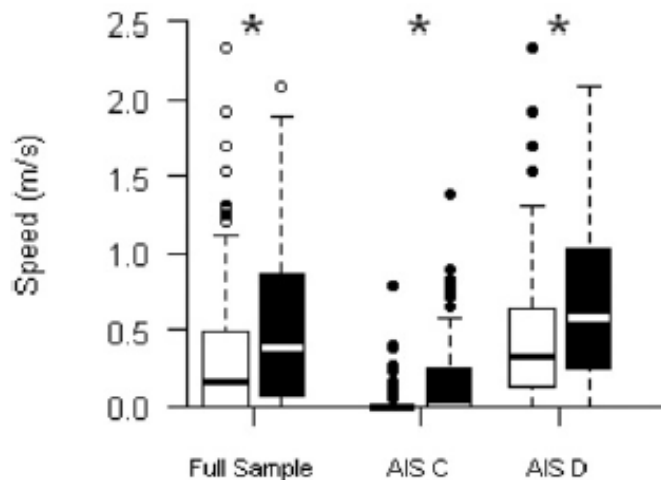
Recovery



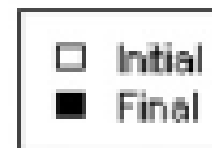
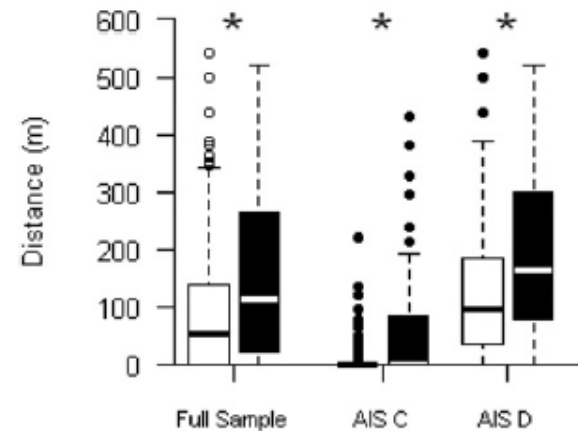
Berg Balance Scale Score



Ten Meter Walk Scores



Six Minute Walk Scores

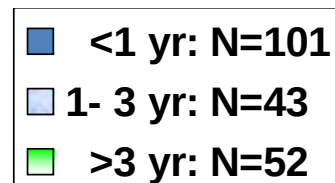
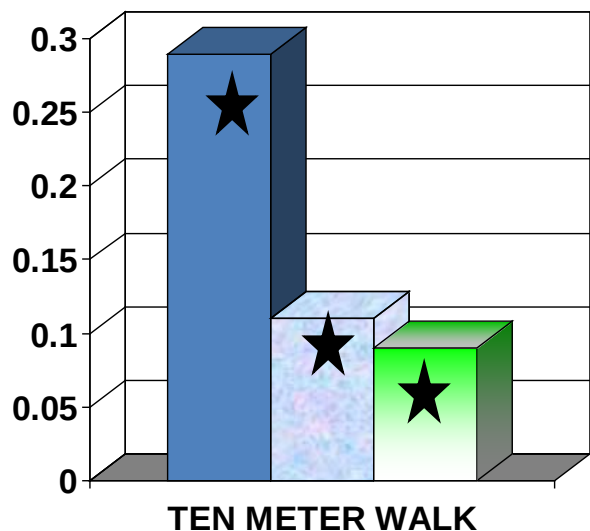
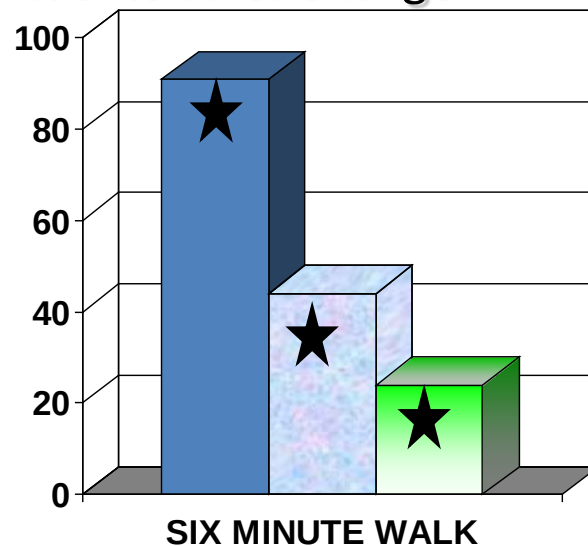
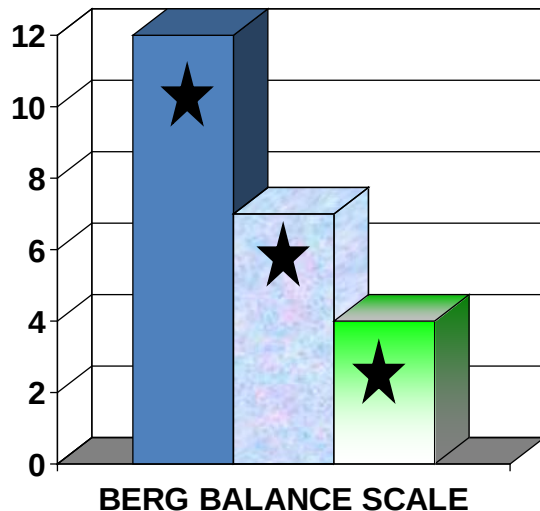


Significant improvement: $P < .001$
Wilcoxon rank-sum test

Effect of Time Since Injury: Initial to Final Change



Absolute Change



★ Significant improvement: $P < .001$
Kruskal-Wallis test

Balance and Ambulation Improvements in Individuals With Chronic Incomplete Spinal Cord Injury Using Locomotor Training-Based Rehabilitation," *Arch Phys Med Rehabil*, July 2011

Harkema S. J. ,Schmidt-Read M, Lorenz D, Edgerton V.R., and Behrman A.L.

Highlights:

- 57% of NRN patients significantly improved on all 3 outcome measures
- 87% improved on at least 1 outcome measure
- 22 people or 12% - **NON Responders**
- Greatest change in first year post injury however significant changes in all three measures for >3 years post injury
- **Results** support real recovery for walking for chronic SCI



Relationship between ASIA exam and functional outcomes in the NeuroRecovery Network locomotor training program

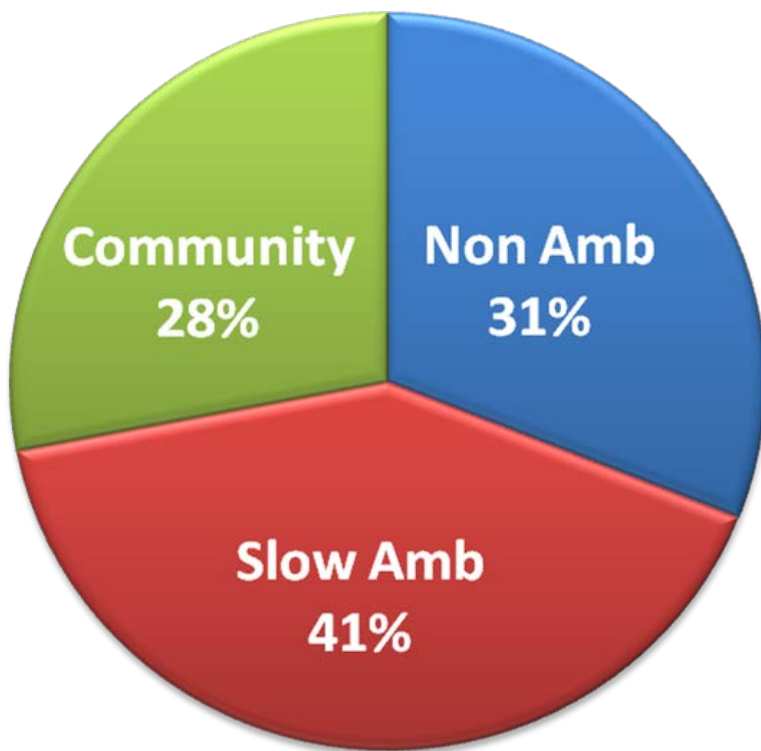
Buehner, J; Forrest, G; Schmidt-Read, M; White, S; Tansey, K; Basso, DM;

Highlights:

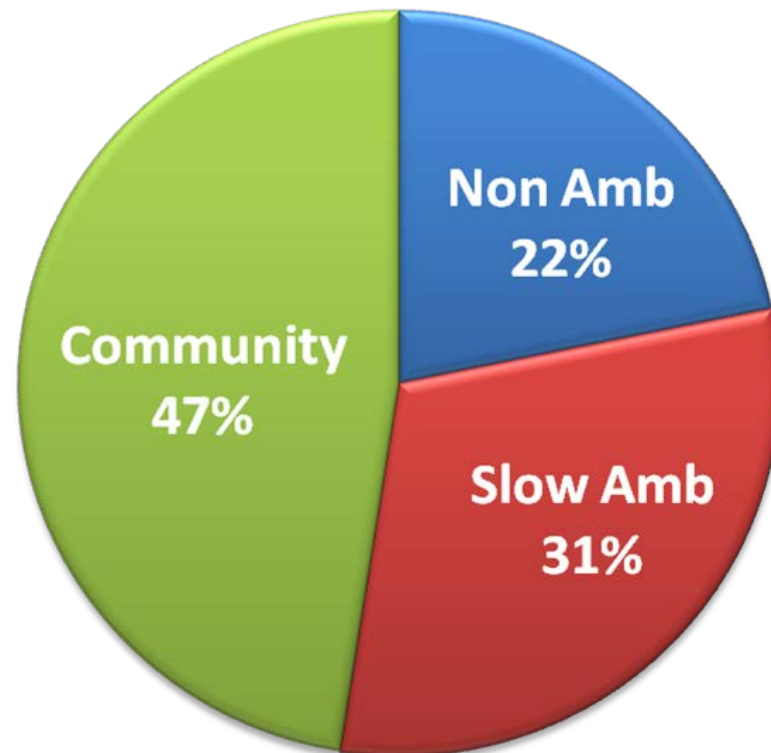
- The effects of Locomotor Training on:
 - 1) The International Standards for Neurological Classification of Spinal Cord Injury exam;
 - 2) locomotion (gait speed, distance);
 - 3) balance; and
 - 4) functional gait speed stratifications (slow and fast) after chronic incomplete SCI



Pre Training



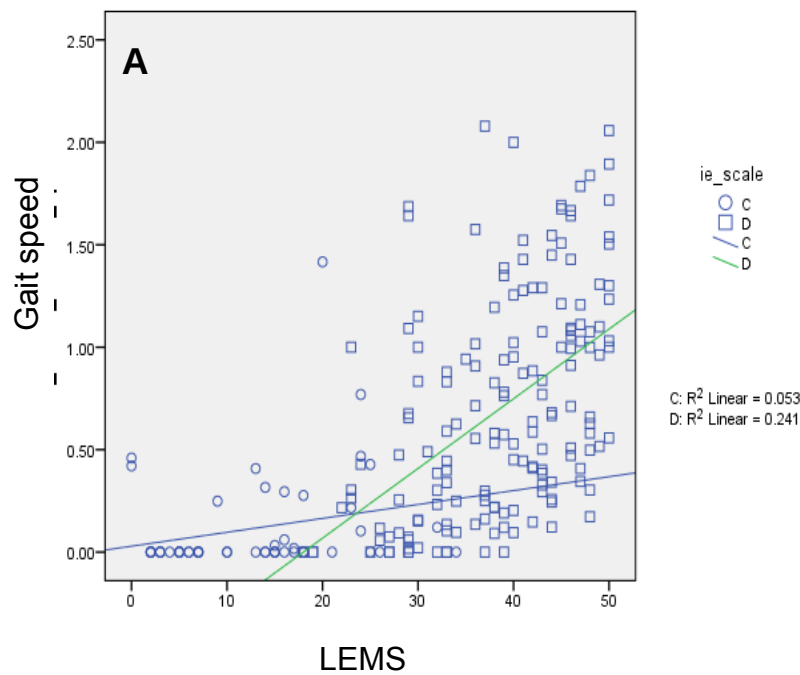
Post Training



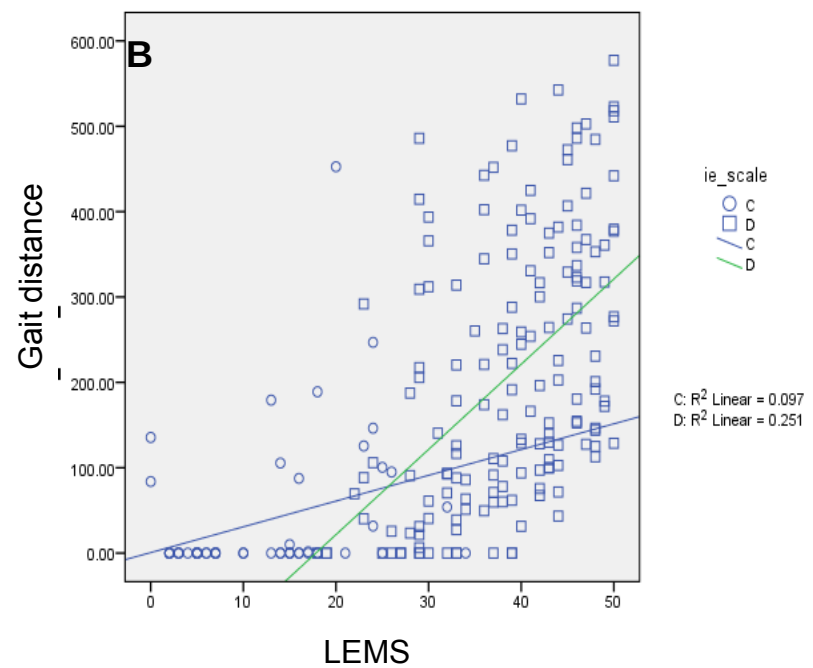
Functional stratifications based on van Hedel (1) cut-offs of Non-ambulatory, slow in-home ambulators (>0 to <0.44 m/s) and community ambulators (≥ 0.44 m/s) before and after manual Locomotor Training. Of the overall sample, 70% improved in gait speed with almost half the sample walking at community speeds after Locomotor Training. Twenty-two percent of the sample remained nonambulatory after training.

Overall LEMS at enrollment does not correlate with final outcomes in gait speed or endurance following LT regardless of severity of injury (AIS C and D)

10MWT



6MWT



Lower extremity motor score (LEMS) at enrollment compared to maximum 10 Meter Walk gait speed (A), maximum 6 Minute Walk gait distance (B) at DC.

Relationship between ASIA exam and functional outcomes in the NeuroRecovery Network locomotor training program

Buehner, J; Forrest, G; Schmidt-Read, M; White, S; Tansey, K; Basso, DM;

Highlights:

- LT significantly increased conversion between functional gait speed categories (slow → fast speed).
 - Equal proportions of AIS C and Ds converting.
 - Upper extremity muscle strength which increased by 8% without an intervention directed to the arms.
 - Overall LEMS at enrollment does not correlate with final outcomes in gait speed or endurance following LT regardless of severity of injury (AIS C and D).
-
- If the overall LEMS is not related to gait performance, maybe we need to look at the proportion of muscle groups with good vs poor strength. we examined the number of lower extremity muscle groups within AIS C and D groups for each gait speed classification Data showed non-ambulatory AIS D subjects that become walkers after Locomotor Training have 60-80% of lower extremity muscles with good strength (4 or 5).



Research Papers: Focused on Outcome Measures.

Ambulation and balance outcomes measure different aspects of recovery in individuals with chronic incomplete spinal cord injury

Forrest GF, Lorenz DJ, Hutchinson KA, VanHiel L, Basso DM, Datta S, Sisto SA, Harkema SJ.

Assessment of functional improvement without compensation reduces variability of outcome measures after human SCI

Behrman, AB; Ardolino, E; VanHiel LR; Kern, M; Atkinson, D ; Lorenz, DJ; Harkema SJ;

The ABLE Scale: The Development and Psychometric Properties of an Outcome Measure for the Spinal Cord Injury Population.

Ardolino E , Hutchinson K PintoZipp G, Clark MA , Datta S, Harkema SJ. *Physical Therapy* [2012].





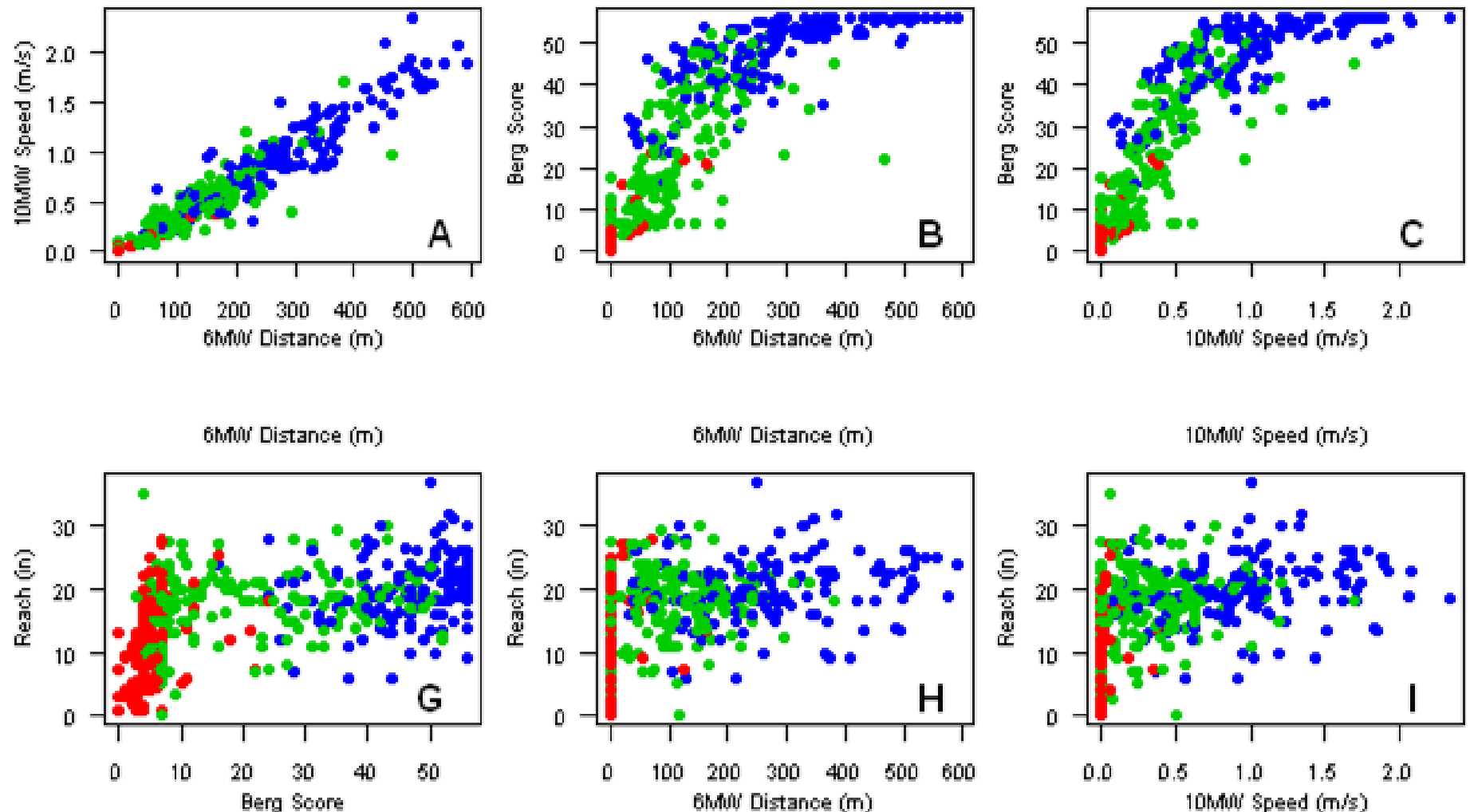
Ambulation and balance outcomes measure different aspects of recovery in individuals with chronic incomplete spinal cord injury

Forrest, GF; Lorenz DJ; Hutchinson KA; VanHiel L; Basso DM; Datta S; Sisto SA; Harkema SJ.

Highlights:

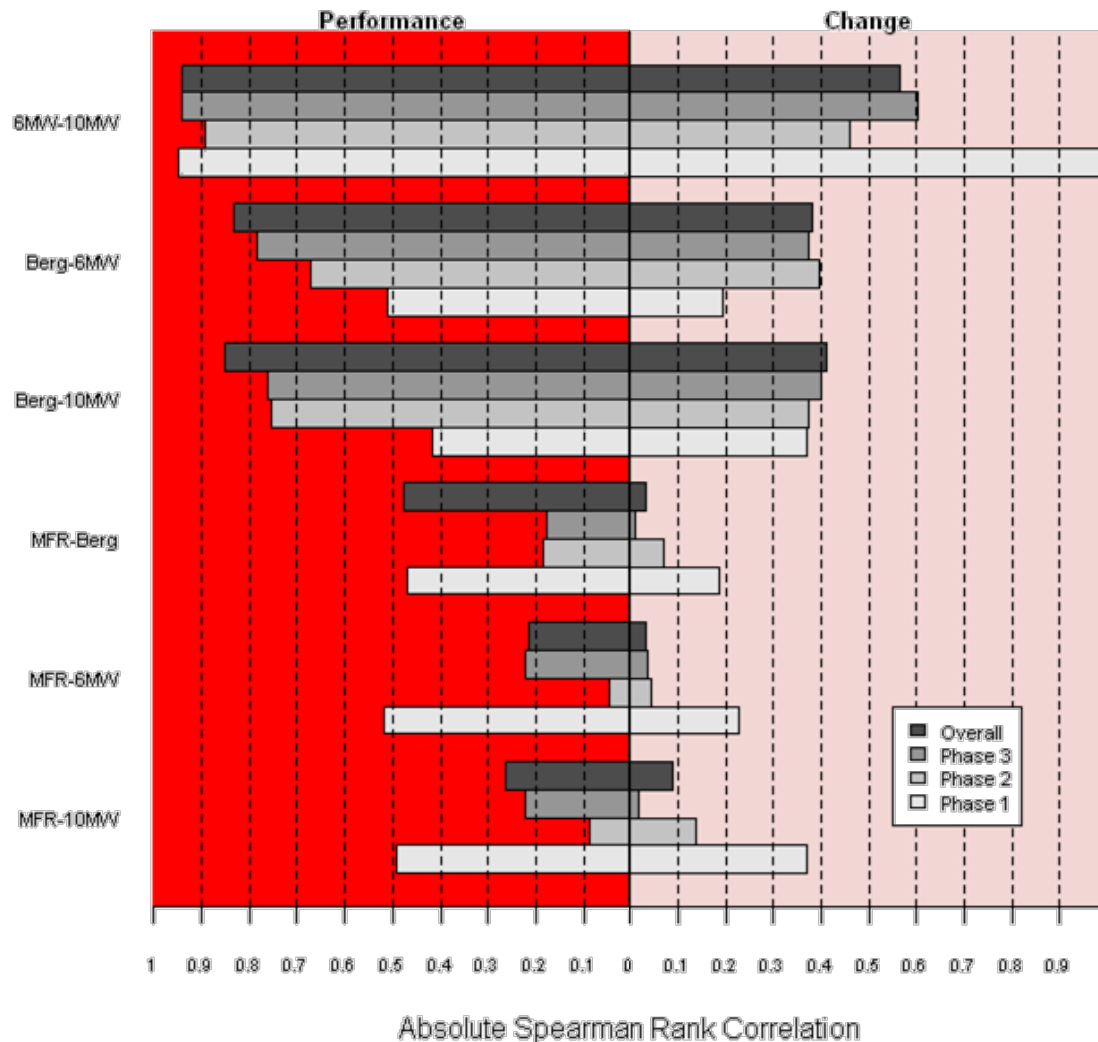
- Evaluation of relationships among ambulation and balance outcome performance measures over time after incomplete spinal cord injury (SCI) with Locomotor Training to facilitate the selection of effective and sensitive rehabilitation outcomes. Measure include walking (6MWT, 10MWT) and balance (BERG, MFR) measures and Neuromuscular Recovery Scale (NRS).
- Evaluation of relationship among **evaluation-to-evaluation (or recovery) changes.**

Scatter plots for Performance Evaluations: Ten Meter Test, 6 Minute Test, Berg, Modified Functional Reach.





Correlations



Ambulation and balance outcomes measure different aspects of recovery in individuals with chronic incomplete spinal cord injury

Forrest GF, Lorenz DJ, Hutchinson KA, VanHiel L, Basso DM, Datta S, Sisto SA, Harkema SJ.

Highlights:

- Results showed that walking and standing balance measures were strongly correlated ($r \geq .83$ for all correlations);
- Standing and sitting balance measures were not highly correlated ($r \leq .48$ for all correlations).
- Walking measures were weakly related to sitting balance.
- Correlations among **evaluation-to-evaluation** changes (change Correlations) not well correlated even for walking measures.
- May need more than one walking measure to properly reflect recovery

Results show walking and balance measures reflect different aspects of recovery and are highly influenced by functional status and the utilization of assistive devices. These factors should be carefully considered when assessing clinical progress and designing clinical trials for rehabilitation.



Assessment of functional improvement without compensation reduces variability of outcome measures after human SCI

*Behrman, AB; Ardolino, E; VanHiel LR; Kern, M; Atkinson, D ; Lorenz, DJ;
Harkema SJ;*

Highlights:

- The ability of Neuromuscular Recovery Scale to reduce the variability in outcome measures in persons with motor incomplete SCI participating in standardized Locomotor Training program.
- Outcome measures at **initial evaluation** and discharge for balance and walking measures and **NeuroRecovery Scale**.

SC090246 Behrman (PI) 10/1/10-9/30/13

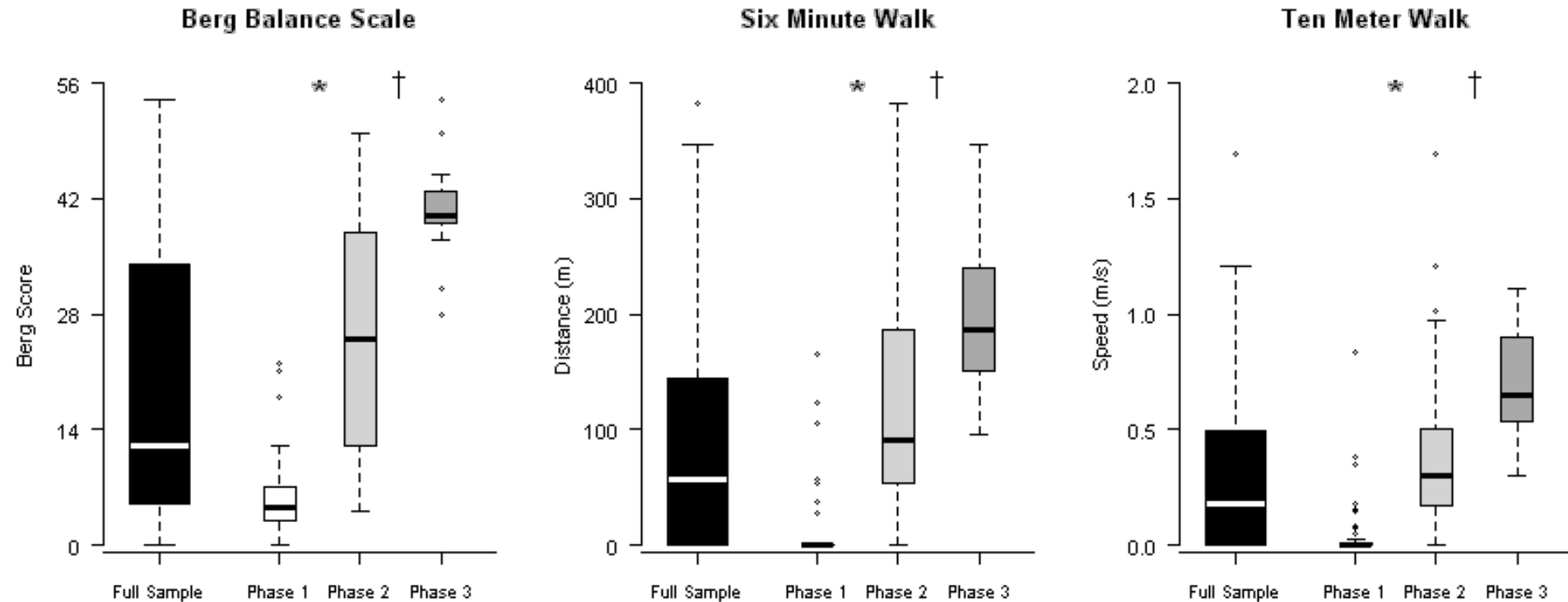
Department of Defense/NRN

A new measure of neurological and behavioral recovery after SCI

Behrman (PI) 10/1/10-9/30/12

Craig H Neilson Foundation

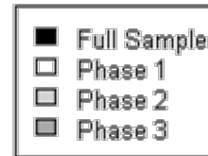
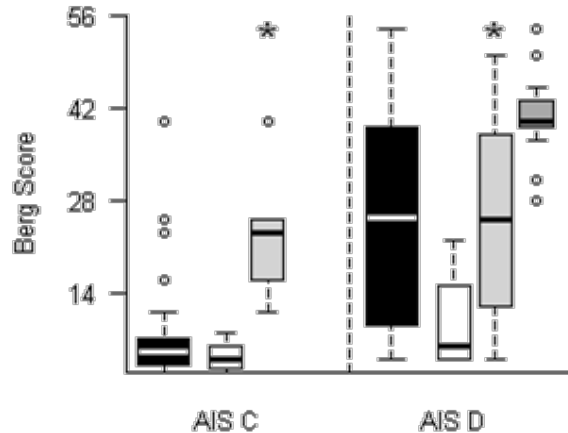




Boxplots of NRN enrollment measurements of the Berg Balance Scale (left panel), 6 Minute Walk (center), and 10 Meter Walk (right) at NRN enrollment for the full sample and by phase at enrollment.

- phases significantly differed on outcome measure, Kruskal-Wallis test, $p < .001$,
- † - variances significantly differed among phases, Fligner-Killeen test, $p < .001$)*

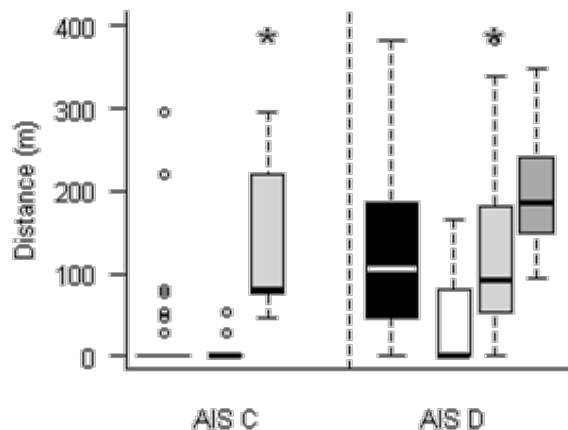
Berg Balance Scale



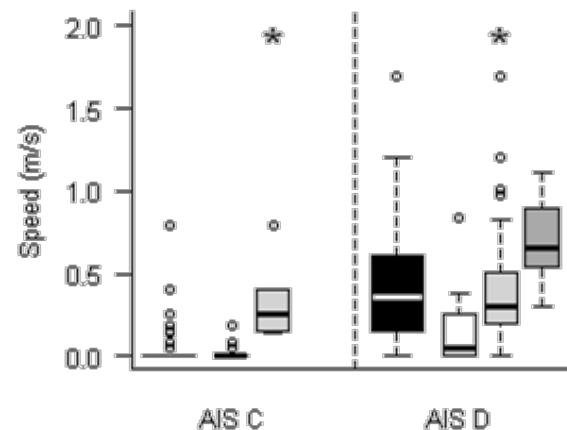
Boxplots of outcome measures at enrollment by AIS level and NRS classification at enrollment.

At enrollment, performance significantly* differed among the NRS-phase groups within groups of AIS C and AIS D, Kruskal-Wallis test, $p < .001$, all measures).

Six Minute Walk



Ten Meter Walk



Assessment of functional improvement without compensation reduces variability of outcome measures after human SCI

Behrman, AB; Ardolino, E; VanHiel LR; Kern, M; Atkinson, D ; Lorenz, DJ; Harkema SJ;

Highlights:

- The NRS differentiates individuals with AIS C and D classified injuries into distinct performance groups that are significantly different from one another

Clinical and Research Implications: Advantage for using NRS

- Clinically, a patient's recovery can be distinctly classified according to criteria for task performance without compensation - useful tool to assess progress
- With an increase in group homogeneity (compared to AIS D classification), the likelihood of detecting change in a population from an intervention is improved.





The ABLE Scale: The Development and Psychometric Properties of an Outcome Measure for the Spinal Cord Injury Population.

Ardolino E , Hutchinson K PintoZipp G, Clark MA , Datta S, Harkema SJ. *Physical Therapy* [2012].

Highlights:

To develop a scale capturing the wide spectrum of functional ability following spinal cord injury and to subsequently assess the initial psychometric properties using a Rasch analysis.

Item	Task	Item	Task
1	Sitting	8	Sit to stand
2	Seated Forward Reach	9	Standing
3a	Seated lateral reach (right)	10	Stand to sit
3b	Seated lateral reach (left)	11	Stand with eyes closed
4	Pick up object in sitting	12	Standing with feet together
5	Scooting forward in chair	13	External perturbations in standing
6	Transfers	14	Standing forward reach
7	Wheelchair perturbations	15	Pick up object from standing

Item	Task	Item	Task
16	Look over shoulder in standing	22	Walking with head turns
17	Turn 180 degrees	23	Walking with change in direction
18	Alternate step-ups	24	Stepping over object while walking
19	Tandem stance	25	Walking with object in 2 hands
20a	Standing on one leg (right)	26	Walking up/down stairs
20b	Standing on one leg (left)	27	Walking up/down incline
21	Walking over level surface	28	Walking perturbations



The ABLE Scale: The Development and Psychometric Properties of an Outcome Measure for the Spinal Cord Injury Population.

Ardolino E , Hutchinson K PintoZipp G, Clark MA , Datta S, Harkema SJ. *Physical Therapy* [2012].

Highlights:

- Initial development of an all-inclusive clinical instrument assessing balance in the SCI population was accomplished using the Delphi technique.
- Modifications of the ABLE scale based on the Rasch analysis yielded a 28-item scale with minimal floor or ceiling effects.
- Larger studies using the revised scale and factor analyses are necessary to establish unidimensionality and reduction of the total item number.

Unique Opportunities available through NRN and/or NACTN:

- ✓ Established infrastructure
- ✓ Network of multiple clinics that can provide standardized clinical or research protocols
- ✓ Standardized outcome measurement
- ✓ Continuum of care (acute through rehab through wellness)
- ✓ Centralized and secure database
- ✓ Intense data integrity process
- ✓ Established network reducing start up time for research clinical trials

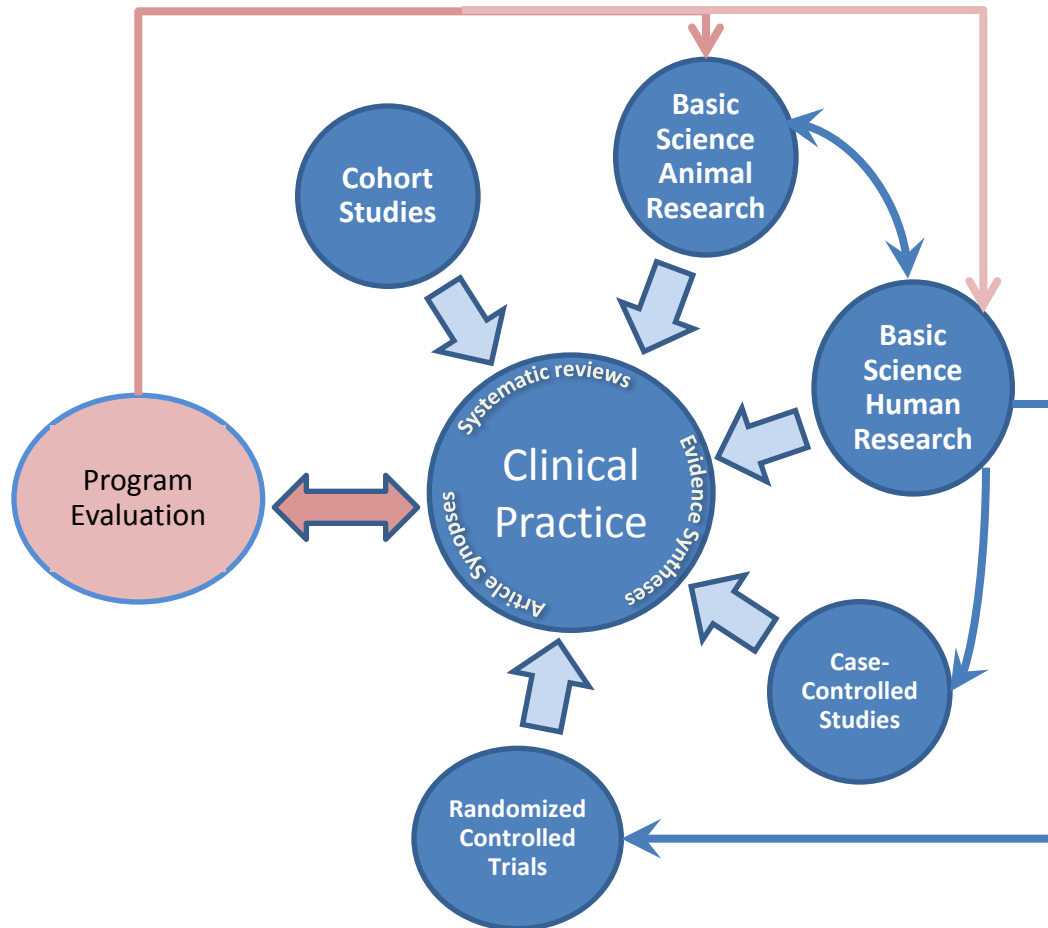


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Quarterly Report Format

1. Award No. W81XWH-10-1-0042
2. Report Date: August 6, 2013
3. Reporting period: April 19-July 18, 2013
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
Steve Coleman	Admin	10
Elizabeth Toups RN	Study Coordinator	40

9. Contract expenditures to date (as applicable):

COST ELEMENTS	THIS QUARTER	CUMULATIVE
Personnel	55,896	3,037,777
Fringe Benefits	15,930	865,768
Supplies		
Equipment		
Travel	84	521
Other Direct Costs	30,000	538,813
Subtotal	101,910	4,442,879
Indirect Costs		
Fee	10,192	439,433
Total	112,102	4,882,312

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 of each 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
Jenny De Jong, RN	Study Coordinator	60
Susan Harkema, PhD, Maxwell Boayke, MD	Co-PIs	15
Lori Clark	Study Coordinator	60
Bizhan Aarabi MD	PI	15
Christina Aldrich	Study Coordinator	60
James Guest, MD	PI	20
Christopher Gilbert	Study Coordinator	100
Marina Dididze MD	Scientific Trials Coordinator	25
James Harrop, MD	PI	20
John Furlong	Study Coordinator	100
Michael K. Rosner MD	PI	20
Vicki Miskovsky	Study Coordinator	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
Diana Chow	Co-PI	9.1
Yang Teng	Technician	50
Robert Marsh MAJ, MD	PI	20
Shalece Kofford	Study Coordinator	60
Aida Paredes, RN	Nurse Coordinator	60