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ORIGINAL ARTICLE

History and Accomplishments of the North American Clinical Trials Network for Spinal Cord Injury, 2004–2022

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Abstract

This is a historical account of the origin and accomplishments of the North American Clinical Trials Network (NACTN) for traumatic spinal cord injury (SCI), which was established in 2004 by Christopher Reeve and Robert Grossman. Christopher Reeve was an actor who became quadriplegic and started the Christopher & Dana Reeve Foundation (CDRF), and Robert Grossman was a neurosurgeon experienced in neurotrauma and a university professor in Houston. NACTN has member investigators at university and military centers in North America and has contributed greatly to the improvement of care, primarily acute care, of patients sustaining traumatic SCI. Its accomplishments are a clinical registry database of >1000 acute SCI patients documenting the care pathways, including complications. NACTN has assessed the effectiveness of treatment, including pharmacotherapy and the role and timing of surgery, and has also identified barriers to early surgery. The principal focus has been on improving neurological recovery. NACTN has trained many SCI practitioners and has collaborated with other SCI networks and organizations internationally to promote the care of SCI patients.

Keywords: decompression; pharmacotherapy; spinal cord injury; surgery

Introduction

This report chronicles the history and accomplishments of the North American Clinical Trials Network (NACTN) for the study of acute spinal cord injury (SCI), from its inception in 2004 to the present. This history of NACTN starts with its scientific foundation based on the discoveries of the pathophysiology and treatment of SCI, followed by a description of NACTN's accomplishments during the two phases of its existence. The first phase was from its beginning in 2004 until 2012, when the NACTN investigators produced a comprehensive compendium of its activities in the first 8 years, encompassing 23 articles published in a focus issue of the *Journal of Neurosurgery: Spine*.[1] NACTN's second phase was from 2012 to 2022, chronicled in the articles in this special issue of the *Journal of Neurotrauma.* In the present article, the authors present an overall historical account of NACTN and its accomplishments from 2004 to 2022.

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Background to the Establishment of NACTN in 2004

Clinical trials in acute SCI have confronted a diverse number of challenges for several reasons[2]: (1) there are varying severity of injuries in terms of neurological deficits and associated injuries, (2) patients with acute SCI often have life-threatening injuries or associated morbidities, (3) SCI occurs in a wide variety of injury locations often causing delays in retrieval and treatment, (4) there is often a narrow therapeutic time window in which some treatments can be effective, and (5) there are limitations concerning the recruitment of patients of varying ages, and specific levels or severity of injury. Despite these challenges, it is acknowledged that preserving viable spinal cord tissue – neuroprotection – can improve neurological outcomes.[3] There are significant logistical hurdles for acute SCI treatment trials, generally requiring recruitment of several hundred patients.[2] It has become the norm to enlist multiple SCI centers to support enrollment needs. These problems were apparent to Grossman and other SCI clinical researchers, clinicians, and basic scientists in the SCI field. His solution in 2003 was to create a clinical trial SCI network of collaborating clinician-researchers, scientists, clinical coordinators, administrators, and funders. It is interesting to note that the necessity to work together continues to be recognized in SCI to undertake large, often investigator-initiated, clinical trials.[4,5] Networks with experience offer levels of potential standardization of study protocols that are highly desirable and substantially exceed what would happen if each new treatment trial had to recreate a new multi-center structure. It is important to recall the context in which NACTN was initiated, because it was after the three National Acute Spinal Cord Injury Studies (NASCIS) of methylprednisolone for neuroprotection[6–8] and after the large GM1 ganglioside neuroprotection trial.[9,10] Indeed, the latter continues to be the largest randomized prospective controlled trial (RPCT) in acute SCI, conducted in 28 participating centers and 760 patients. Both the third NASCIS and the GM1 ganglioside trials were conducted in the United States and Canada. They were industry-supported NASCIS by the Upjohn, Company in the United States for drug supply and by the National Institutes of Health (NIH) for other costs, and the GM1 ganglioside trial was supported by the Fidia Pharmaceutical Corporation of Italy. These trials contributed significantly to knowledge about acute SCI and trial design, resulting in the realization that there was a need for an ongoing, robust SCI-focused network to conduct further trials designed to test other pharmaceutical or non-pharmaceutical treatments to enhance neuroprotection and regeneration after SCI. The steroid and GM1 ganglioside trials showed that with these medications in acute SCI, the therapeutic effect sizes were modest in terms of patient recovery and that additional outcome measures were needed, such as reliable biofluid and imaging biomarkers, which are continuing unmet goals. Also, these trials were massive undertakings in terms of the financial burden, leading to considerable continuing efforts to utilize alternative statistical measures and trial designs to overcome the limitations of massive patient enrollment and too many participating centers, as well as the major costs involved.[11] In addition, alternative outcome methods have also been developed for SCI trials.[12] In summary, preceding NACTN's creation, there was a major expansion of knowledge of acute SCI gained through clinical trials. Still, there were also major problems with SCI trials, many of which have continued to affect the field.

The steroid and GM1 ganglioside major multi-center acute SCI clinical trials referred to stimulated extensive planning and discussion among neurosurgeons and associated clinical trial experts about the need for additional organizational strategies to make gains in the SCI field. For example, there were significant efforts by Steeves, Fawcett, and colleagues. They formed the International Campaign for Cures of Spinal Cord Injury Paralysis (ICCP), which was very influential in improving SCI trials before and during the formative stages of NACTN.[13–15] Thus, there was a considerable effort by several investigators and organizations toward simplifying the design of SCI trials. Indeed, Grossman and several other future members of NACTN participated in the work of the ICCP.

Another important historical event that shaped NACTN was the emerging evidence from a multitude of clinical and experimental acute SCI studies that strict attention must be given to the timeliness of treatment. To accomplish expeditious treatment would require a new system of care to provide early removal of persisting cord compression, which was recognized as a frequent pathophysiological issue in most cases of major SCI. During the twentieth century, the pioneering experiments of Allen[16,17] and Tarlov[18] in dogs gave rise to the concept of early surgical decompression as a necessary treatment component to improve the poor prognosis for recovery after major SCI. Several experimental studies followed in small animal models showed that severely damaged and compressed spinal cord tissue experiences a profound loss of blood supply, and that post-traumatic infarction could be prevented by expeditious decompression of the spinal cord.[19–22] These findings became the basis for the clinical trials conducted in the late 1990s by the Surgical Treatment of Acute Spinal Cord Injury Studies (STASCIS) organized by the Joint Section of Neurotrauma of the American Association of Neurological Surgeons and the Congress of Neurological Surgeons.[23–27] The culminating STASCIS multi-center study, coordinated through the efforts of the Spine Trauma Study Group, showed that early surgery to treat persisting

spinal cord compression, which was present in most cases of acute severe SCI, could be performed expeditiously and safely.[27,28]

Creation of the NACTN for Spinal Cord Injury in 2004

NACTN was created in 2004 when Robert Grossman, head of Neurosurgery at Baylor University in Houston, presented his concept of a clinical trials network to the Christopher Reeve Paralysis Foundation Board in the United States. Grossman had a plan to improve the quantity and quality of RPCT in acute SCI. He envisioned creating an extensive network of highly specialized university-affiliated SCI centers with neurosurgical expertise and multi-disciplinary teams to provide timely expert diagnosis and critical care management of acute SCI with a focus on early and safe surgical management. The aim was to bring together clinicians and clinical researchers who had a significant interest in furthering research in SCI through clinical trials of new therapies. The primary goal was to advance the translation of novel basic science discoveries from the laboratory to clinical trials in patients with acute SCI. NACTN aimed to develop clinical trials in SCI capable of validating new treatments by generating strong evidence of safety and effectiveness. Grossman recruited neurosurgeons with experience in neuroprotection and early surgical decompression clinical trials who had been appointed to academic hospitals containing multi-disciplinary teams of healthcare professionals with expertise and interest in caring for acute SCI patients. Therefore, NACTN centers had neurosurgeons who were experienced in trauma and working as members of multi-disciplinary teams of SCI specialists in academic centers. Indeed, they were eager to participate in multi-center therapeutic trials in acute SCI, which provided multi-disciplinary care, including surgical decompression that was available ''24 hours a day, 7 days a week.''

Another important goal of the NACTN network was establishing a registry to document the natural course of recovery from acute traumatic SCI. NACTN was based on the premise that SCI required the commitment of a multi-disciplinary, experienced staff to ensure that patients would receive state-of-the-art care as the standard for the medical and surgical treatment of all aspects of acute SCI. Along with this came the commitment to documentation of crucial stages of care and accurate recording of neurological status using the American Spinal Injury Association (ASIA) standards. The stages include retrieval at the trauma scene, rapid transfer to a multidisciplinary unit containing an intensive care unit, and a subsequent rehabilitation program. The NACTN Registry of Acute SCI was further based on the principle of complete data management and documentation of patient assessment, care, and response to treatment in a standardized, pre-determined way applied to all SCI patients admitted to the participating centers. This registry was intentionally designed to establish contemporaneous comparison groups for SCI clinical trials and to facilitate clinical trial research through expert analysis and publication of the collected data.

It is important to note that before 2004, there was no network of committed academic hospitals and committed multi-disciplinary staff capable of delivering acute SCI care, including the provision of early surgery for all admitted SCI patients. This profound contribution was created by the efforts of Christopher Reeve and Robert Grossman. Susan Howley was the chief research administrative officer at the Reeve Foundation at the time of its creation, and she has been a critical reason for NACTN's success and continuation. The Christopher Reeve Foundation's initial funding of $500,000 in 2003 set the wheels in motion. Tragically, Christopher Reeve died in 2004, and his wife Dana died in 2006. In 2007, the foundation's name was changed to the Christopher & Dana Reeve Foundation (CDRF).

First Phase of NACTN from 2004 to 2012

The lead principal investigator (PI) of NACTN, Robert Grossman, had been an investigator in the first NASCIS[9] study and in studies of traumatic brain injury (TBI).[29] Of relevance to NACTN's goals is the fact that he had previously participated in the formation of the National Traumatic Coma Databank that initiated data collection in 1979[30] and in the analysis of therapeutic failures in TBI trials.[31] He also participated in other registries.[32] During the formation of NACTN, he moved to The Methodist Hospital in Houston, which became NACTN's headquarters. At Methodist, NACTN's affairs and communication with participating hospitals and investigators were expertly managed by Grossman's assistant and chief NACTN clinical administrator/project manager, Elizabeth Toups. The highlights of NACTN's first phase are listed in Box 1.

The prospective NACTN registry was developed in parallel to the clinical trial network; its data set provided close matching with early phase open-label trial enrolled patients as a form of control group to shorten development timelines. The registry collected data from the time of injury through hospitalization, rehabilitation, and long-term follow-up. Registry protocols were uniform across the participating centers, and registry data were checked monthly at the source participating center and collected on case report forms that were scanned using Teleform optical character recognition software, initially at the NACTN Data Management Center at the University of Texas School of Public Health at Houston under the guidance of Ralph Frankowski.

Box 1. History of the North American Clinical Trials Network (NACTN)

1991–2003

A. Pre-clinical research discoveries that underly the initiation of NACTN

- The complex pathophysiology of spinal cord injury (SCI) with multiple mechanisms, including post-traumatic ischemia, glutamate neurotoxicity, inflammation, edema, and hemorrhage, becomes known. Several therapeutic strategies show promise for neuroprotection or neuroregeneration.
- Mounting evidence of the importance of surgical decompression of persisting spinal cord compression is based on large and small animal experiments indicating that early decompression improves neurological recovery.

B. Clinical research discoveries that underly the initiation of NACTN

- Several partially or completely company-sponsored trials of SCI treatment, including steroids and GM1-ganglioside, showed the importance and difficulties of clinical trials in SCI.
- There was mounting evidence of improved neurological recovery after early surgery, including Surgical Treatment of Acute Spinal Cord Injury Studies (STASCIS).
- Early surgery requires a system of SCI care involving early triage to hospitals with skilled multi-disciplinary teams of clinicians and extensive diagnostic and therapeutic capability.
- There was more knowledge of adverse event mitigation plus available techniques for counteracting previous risk factors of early surgery such as post-decompression instability, and pulmonary and genitourinary infections.

2003

Search for funding of the new network and recruitment begins for NACTN principal investigators (PIs) and hospitals capable of acute multidisciplinary care of SCI

- Robert Grossman met Christopher Reeve in 2003 and received the agreement of the Christopher Reeve Paralysis Foundation to help develop NACTN with sufficient funding per center.
- There is initial recruitment of five university hospitals with one or more neurosurgeons as PIs and clinical coordinators at each center: Baylor College of Medicine, Houston; Rehabilitation Institute of Chicago; University of Texas Health Science Center at Houston; University of Toronto; and the University of Virginia, Charlottesville. The Biostatistics and Data Management Center was at Houston's University of Texas School of Public Health.

2004

NACTN begins, and participating centers admit first SCI patients to registry

- Coordinating Center at Houston Methodist Hospital (Dr. Robert Grossman)
- Data Management Center at the University of Texas at Houston, School of Public Health (Dr. Ralph Frankowski)

2007–2021

The United States Department of Defense (DOD), through its United States Army Medical Research Acquisition Activity Telemedicine and Advanced Technology Research Center (TATRC), funded the bulk of NACTN's budget from mid-2007 to December 2021, amounting to almost $18,000,000.

2009

NACTN establishes a treatment strategy selection committee

- This committee consists of 15 members from participating NACTN centers to guide the selection of agents for clinical trials. Committee members also included a basic scientist and a representative from National Institute of Neurological Disorders and Stroke (NINDS).
- Riluzole selected for clinical trial.

2011
Joint meeting of the NeuroRecovery Network (NRN) and NACTN and representatives of the Ontario Neurotrauma Foundation to discuss avenues for collaboration and streamlining the flow of information among the organizations was held.

2012
***NACTN reports progress from 2004–2012 in Special Edition of* Journal of Neurosurgery (Spine)**

- A total of 612 patients were admitted to the registry by 2012 from nine participating centers
- The Graded Redefined Assessment of Strength, Sensibility, and Prehension (GRASSP) tool was established as a useful clinical outcome measure for tracking upper limb recovery after SCI.
- There was in-depth analysis of complications experienced by 315 acute SCI patients in nine NACTN centers, including respiratory failure, pneumonia, and death.
- Riluzole phase I trial was completed by six NACTN centers enrolling 36 patients from 2010 to 2011.
- Two articles based on NACTN's Treatment Strategy Selection Committee defined the criteria for selecting pre-clinically tested agents for a clinical trial by NACTN.
- The pharmacokinetic analysis of riluzole in 36 SCI patients in NACTN's phase I riluzole trial showed altered pharmacokinetics with lower serum drug concentration than had been found in an amyotrophic lateral sclerosis (ALS) patient trial, demonstrating the importance of this type of analysis in SCI patients.

2013
NACTN moves the Data Management Center to the University of Louisville.

2014
Publication of riluzole results: NACTN's first pharmaco-therapy treatment trial was funded by DOD, a Phase 1 trial of 36 patients.

2015
NACTN joins with AO Spine North America (AOSNA) to begin phase II–III trial of riluzole funded by DOD and AOSPINE North America. The riluzole trial included a pharmacokinetics component funded by DOD and conducted by Diana Chow, College of Pharmacy, University of Houston.

2018
NACTN and the NRN hold a meeting to discuss joint programs. Three NACTN centers (located in Louisville, Houston, and Philadelphia) are also NRN centers.

2021
NACTN initiates the process of transferring its Clinical Coordinating Center to Thomas Jefferson University, Philadelphia.

2022
NACTN SCI Registry now includes 1019 patients, and the Christopher & Dana Reeve Foundation (CDRF) resumed its support of the Registry.

2022
NACTN Reports 2013–2022 progress in this Focus Issue of the *Journal of Neurotrauma.*

The accomplishments of this first phase are chronicled in 23 articles in the 2012 Focus Issue of the *Journal of Neurosurgery: Spine*, an academic collaboration between NACTN and AO Spine North America (AOSNA); readers are referred to the *Journal of Neurosurgery: Spine* for more details. Of particular interest is the article with Grossman as the lead author[1] in which six key aspects of NACTN's work during its first 8 years were featured.

Second Phase of NACTN from 2013 to 2022

The historical context of the second phase of NACTN was associated with the growth and development of

several other networks of SCI organizations, such as the Rick Hansen Spinal Cord Injury Registry (RHSCIR)[33] in Canada and the European Multicenter Study about Spinal Cord Injury (EMSCI).[12] These databases/networks also have multiple purposes. They have been valuable sources of information for NACTN investigators. In some instances, there have been collaborations among networks on data acquisition and clinical trials. It is noteworthy that the NACTN registry was created to be synergistic with the prospective multi-center STASCIS study and led to the use of combined NACTN-STASCIS data sets to address the role and timing of surgery, prediction of outcome, and assessment of complications.[34]

During this time, the riluzole phase II-III trial was completed in collaboration with AOSNA, which provided most of the funding. NACTN members had essential roles in this trial, Michael Fehlings as the PI, Grossman as co-PI, and Charles Tator as the Independent Medical Data Safety Monitor. Most of NACTN's clinical sites participated in the trial, the results of which will be published in 2023.

In the second phase, there was a concerted effort to improve the data collection instruments, such as the clinical examination, and to employ other statistical measures to reduce the number of patients required for trials and the associated costs.[35] Indeed, the efforts of many clinical trial specialists in SCI, and trials experts from other fields have made important contributions in showing that adaptive designs can help trials networks such as NACTN control the enormous costs of human SCI trials.[36] It was also a time for collaboration between NACTN and other SCI research networks to achieve sufficient case numbers to detect the value of therapeutic procedures such as surgical decompression. For example, combining data sets can facilitate the evaluation of treatment, especially concerning early surgical decompression and associated complications.[34] Numerous NACTN collaborations during the second phase are detailed in several articles in this special issue of the *Journal of Neurotrauma.*

A dominant activity in the second phase was the detailed analysis of the early surgical treatment of acute SCI, described previously as one of the main reasons for the creation of NACTN. Several articles in this special issue show the effectiveness and safety of NACTN's early surgery program to relieve persisting spinal cord compression. Indeed, this may rank as one of NACTN's most significant contributions, as will be indicated subsequently.

Summary of NACTN's Accomplishments from 2004 to 2022 (Box 2)

Leadership and organization of NACTN

NACTN was designed to be led by individual PIs supported by clinical coordinators in each participating center, with the coordinating center at Houston Methodist Hospital in Houston, Texas, under the supervision of Grossman and Toups. An NACTN governance manual was created. A series of investigator meetings were held during which skilled experts trained the clinical coordinators and PIs on the protocols, case report forms, Functional Independence Measure, Spinal Cord Independence Measure, Walking Index for Spinal Cord Injury (WISCI), and the key neurological examination, the International Standards for Neurological Classification in Spinal Cord Injury (ISNCSCI). It had been recognized that the ISNCSCI was especially critical to accurately stratifying acute clinical trial enrollment between those with complete ASIA Impairment grade (AIS) A injuries and those with incomplete (AIS B–D) injuries. The training was conducted in the CDRF's NeuroRecovery Network (NRN) centers by outcome measure experts such as Mary Schmitt Read (Magee Rehabilitation Hospital), and Susan Harkema (University of Louisville), a NACTN PI and the lead NRN investigator.

Table 1 lists the current and former NACTN participating centers and the PIs in each center.

History of funding of NACTN

As has been indicated, the initial funding of NACTN was from the CDRF, which also provided crucial administrative support to NACTN. NACTN has also been supported by a sequence of grants from the United States Department of Defense (DOD) from 2007 to 2021. For the Riluzole in Acute Spinal Cord Injury Study (RISCIS), the phase II–III study, substantial funding was also obtained from AOSNA. This international organization facilitated extending the trial to other countries, including Australia.

Training of the next generation of acute SCI investigators and treatment staff

NACTN institutions and PIs have trained a generation of expert surgeons and clinical coordinators to apply the knowledge gained from the numerous innovations in SCI diagnosis and treatment of acute SCI, such as the use of magnetic resonance imaging and pharmacological restoration of mean arterial pressure, respectively. Clinical trainees and coordinators have also been taught the importance of thorough documentation and have learned innovative data analysis, including evolving statistical methods such as mixed models. There was extensive staff training when a new SCI outcome measure was introduced in NACTN centers. This was the Graded Redefined Assessment of Strength, Sensibility, and Prehension (GRASSP)[37] and related toolbox for evaluating upper extremity sensation, motor function, and prehension.

Box 2. Accomplishments of the North American Clinical Trials Network (NACTN), 2004–2022

1. Developed a multi-center network of acute care hospitals with full capability for management of acute spinal cord injury (SCI), including surgery and intensive care units (ICU) and the ability to enroll a sufficient number of patients with SCI for phase I, II, and III studies**;** established governance policies and procedures and avenues of communication among centers.
2. Developed a data management center (DMC) and a database at the University of Texas under Ralph Frankowski on the natural history of recovery after SCI, from the time of injury through the multiple stages of repair, and established a prior control group for evaluating the efficacy of new therapies.
3. Created a registry of acute SCI based on a comprehensive database of the mechanism of SCI and the severity of medical and surgical complications that occur during acute and subacute treatment, to be used as a prior control group for evaluating the safety of new therapies. The number of acute SCI patients in the registry in 2022 was 1019.
4. Fostered the development of the Graded Redefined Assessment of Strength, Sensibility, and Prehension (GRASSP) as a new sensitive, quantitative measure of upper limb performance after SCI.
5. Created an efficient mechanism to develop clinical trial designs and write the protocols for clinical trials of a new therapy for SCI.
6. Developed a pharmacological center with the ability to perform pharmacokinetic and pharmacodynamic studies of therapeutic drugs for SCI under the direction of Diana Chow at the University of Houston, and showed significant differences between SCI and amyotrophic lateral sclerosis (ALS) patients in riluzole pharmacokinetics.
7. Created a treatment selection committee in 2009 composed of NACTN principal investigators (PIs) to select promising therapies for consideration for phase I, II or III clinical trials. This committee selected riluzole for a phase I study and then for a phase II–III study and created a critical process for evaluating strategies that had been found promising in pre-clinical studies. The process was described in the 2012 article entitled, ''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.'' [38]
8. NACTN centers performed the riluzole phase I trial, ''Safety and pharmacokinetics of riluzole in patients with acute traumatic spinal cord injury'' in 36 patients; results were reported in 2014 in the *Journal of Neurotrauma*.[40]
9. NACTN helped launch the phase II–III Multi-Center, Placebo-Controlled, Double-Blinded, Trial of Efficacy and Safety of Riluzole in Acute Spinal Cord Injury Study, with AO Spine North America (AOSNA), which included the participation of NACTN's clinical centers. DOD provided support for their participation and for the RISCIS pharmacokinetics substudy, also reported in this Focus Issue.
10. Early surgical management of acute cervical SCI of those patients who presented within 24 h from injury was accomplished in more than 73% of patients admitted to NACTN centers since 2004. Thus, the NACTN goal of early surgery for patients requiring urgent surgical decompression has been accomplished for many patients, and the reasons for any delay have been analyzed. See the report in this Focus Issue by Neal et al., ''Variability in Early Surgery for Acute Cervical Spinal Cord Injury Patients: An Opportunity for Enhanced Care Delivery.''
11. Interhospital transfer was specifically found to be a cause of delayed admission and delayed surgical treatment based on the study included in this Focus Issue by Kelly-Hedrick, M. et al entitled ''Interhospital Transfer Delays Care for Spinal Cord Injury Patients: A Report from the North American Clinical Trials Network for Spinal Cord Injury.''
12. The most comprehensive analysis to date of the complications of acute SCI, including operative complications, was provided. ''Incidence and severity of acute complications after spinal cord injury, including operative complications.'' The report was published in the 2012 Special Focus Issue of the *Journal of Neurosurgery: Spine*.
13. NACTN has convened or attended as an invitee several joint educational meetings to find common ground for collaboration on clinical SCI trials with several drug companies and with other clinical consortia in North America and Europe, including Novartis, AOSpine, European Clinical Trials Network (EUCTN), and the European Multicentre Study about Spinal Cord Injury.[49]
14. Since its inception, NACTN has been an international consortium that has benefited patients in Canada and the United States in its studies and treatment and has enlarged its funding capability.

15. NACTN has included both civilian and military centers and thus has participated in the management of a wide variety of SCI patients, which has enriched its experience of, relevance to, and knowledge of the management of all types of acute SCI.
16. NACTN participating centers have trained a large number of clinician-scientists, trialists, science students at all levels, and multi-disciplinary SCI specialists, including physicians in many specialties and non-physician healthcare professionals who comprise the care team involved in making the patient's recovery as extensive as possible, as well as making the clinical research team as vigilant and accurate as possible in the evaluation of neurological function and the detection and recording of adverse events and complications.

Recruitment of sufficient numbers of patients and consistent management for SCI trials

As noted, SCI trials require the recruitment of sufficient patients to provide conclusive results. When the combination of small effect sizes and patient variability are modeled in research designs, a substantial number of patients is needed to provide adequate study power. Successful recruitment was accomplished through NACTN's multi-center design and collaboration with AOSNA. Further, the effects of variables such as age, concomitant injuries, and pre-existing medical events were assessed. Overall, within NACTN, there has been strong consensus and uniformity regarding applying management guidelines for the timing of surgical decompression, management of blood pressure, pulmonary care, measures to reduce disease-modifying infections, and timely transfer to high-quality rehabilitation.

Selection process for therapeutic agents and the decision for a phase 1 trial of riluzole

NACTN operates through a consensus decision-making process among committed PIs and their hospitals. In 2009 NACTN created the Therapeutic Selection Committee (TSC) with the aim of selecting agents for acute SCI treatment trials in humans. The first committee chair was Charles Tator, followed by James Guest in

Table 1. North American Clinical Trials Network (NACTN): Current and Former Centers

Current centers	*Principal investigators*	*Locations*
Duke University Medical Center	Christopher I. Shaffrey, MD Muhammad Abd-El-Barr, MD, PhD	Durham, NC
Medical College of Wisconsin	Shekar N. Kurpad, MD, PhD	Milwaukee, WI
Thomas Jefferson University *Coordinating Center*	James S. Harrop, MD	Philadelphia, PA
University of Houston *Pharmacology Center*	Diana S-L Chow, PhD	Houston, TX
University of Louisville *Data Management Center*	Susan J. Harkema, PhD	Louisville, KY
University of Maryland	Bizhan Aarabi, MD	Baltimore, MD
University of Miami	James D. Guest, MD, PhD	Miami, FL
University of Toronto	Michael G. Fehlings, MD, PhD Charles H. Tator, MD, PhD	Toronto, Ontario, Canada
University of Virginia	Chun-Po Yen, MD	Charlottesville, VA
Walter Reed National Military Medical Center	Chris J. Neal, MD	Bethesda, MD
Former centers	***Principal investigators***	***Locations***
Brooke Army Medical Center	Ryan P. Morton, MD	Fort Sam Houston, TX
Houston Methodist Hospital *Coordinating Center*	Robert G. Grossman, MD	Houston, TX
Louisiana State University Health Sciences Center	Jason D. Wilson	New Orleans, LA
Rehabilitation Institute Research Corporation (RIC)	David Chen, MD	Chicago, IL
University of Louisville	Maxwell Boakye, MD	Louisville, KY
University of Texas, School of Public Health *Data Management Center*	Ralph F. Frankowski, PhD	Houston, TX
University of Texas Health Science Center	Karl M. Schmitt, MD	Houston, TX
Vanderbilt University Medical Center	Hamid M. Shah, MD	Nashville, TN

2017. The first description of the committee's methodology was published in 2012.[38] In considering possible therapeutics to be studied by NACTN as investigator-initiated studies, it was recognized that use of off-patent drugs approved for other indications conferred advantages for obtaining an academic sponsor.

Further, such therapeutics were unlikely to be tested in SCI by industry when the intellectual property was no longer available. For these reasons, the drug riluzole was selected for a phase I trial as proposed by Fehlings, an NACTN investigator, who had used the drug in experimental SCI and found that it improved recovery.[39] Advantages attributed to riluzole included that it was inexpensive and that there was extensive safety information from widespread use in amyotrophic lateral sclerosis (ALS). In addition, its mechanisms of action of N-Nitrosodimethylamin (NMDA) and sodium channel antagonism are known to be significant secondary injury effects of acute SCI. The United States Food and Drug Administration agreed that riluzole could be tested without filing an investigational new drug application (IND), provided that ALS recommended doses were used. Thus, a phase I trial was designed to utilize the resources of NACTN, including its registry, as a proof-of-concept study of the therapeutic effect and safety of riluzole in patients with acute SCI. The recovery profiles of the patients and the drug's safety were compared with profiles of matched patients in the NACTN SCI Registry. The NACTN trial leaders recognized that pharmacokinetic testing would be essential for an orally delivered drug in acute SCI. Therefore, a collaboration was created with Diana Chow at the University of Houston, College of Pharmacy. The lead statistician for the phase I trial was Ralph Frankowski, who had extensive experience in prior clinical trials.

Results of the phase I-IIa trial, safety, and pharmacokinetics of riluzole in patients with acute traumatic SCI

The results in 36 patients who received riluzole and whose outcomes were compared with 36 NACTN registry control patients were reported in 2014.[40] This trial accomplished several goals: determining the (1) feasibility of administering riluzole orally in SCI patients and that there were no serious adverse events related to the drug; (2) the value of pharmacokinetic analysis of therapeutic agents in SCI patients who showed different riluzole pharmacokinetics than ALS patients; and (3) the possibility of comparing the drug treatment group with an NACTN registry group of patients who did not receive the drug but were managed during the same period in the same group of NACTN centers. The phase I study was completely enrolled within 1.5 years. Some elevated liver enzymes were detected, but overall toxicity was minimal. Based on the knowledge of the phase 1 trial, the NACTN Treatment Selection Committee proposed a larger phase II–III trial of this agent in acute SCI. The larger trial was designed by Fehlings[41] and required more substantial funding. It was ultimately funded and managed by AOSNA, with Fehlings as PI. DOD support enabled several NACTN centers to participate in the trial and conduct a substudy of the pharmacology and pharmacodynamics of riluzole.

Key publications from the first phase of the NACTN SCI Network: 2004–2012

A significant milestone for NACTN was the publication of the Focus Issue Supplement of *Journal of Neurosurgery: Spine* in 2012 in collaboration with AOSNA containing 23 articles relating to NACTN's progress from its inception in 2004 to 2012. The reader of this article is referred to this excellent compendium of NACTN articles, one of which was on the incidence of complications during the acute care of spinal cord injury.[42] This article emphasized the type and incidence of specific complications and their major effects on SCI patients by physiological systems. Indeed, subsequent studies found that infectious complications such as pneumonia correlated with reduced neurological recovery.[43] This has led to infection being described as a disease-modifying event.

Data sharing by the NACTN SCI Registry

NACTN has allowed sharing of data from the NACTN SCI Registry with other non-NACTN investigators. For example, NACTN provided data to enable another group to facilitate estimating the size of the control group in the planning of a neuroprotection clinical trial. NACTN registry data also served as a reference group for In Vivo Therapeutics for its INSPIRE study.[44] Registry data has also been used by other academic institutions and pharmaceutical companies to create comparison data sets for phase I clinical trials of new therapies. The data sharing mechanism used by NACTN requires completing a data dissemination request form submitted to the Data Management Center and approval by all NACTN PIs.

Interaction With Other SCI Networks and Investigators

The EMSCI[45] has accumulated an extensive registry of patients with SCI and supported clinical trials such as NISCI (NOGO Inhibition in Spinal Cord Injury). There is an ongoing collaboration with EMSCI. The Canadian Rick Hansen Institute has supported multi-center studies such as the minocycline study[46] and systematic reviews based on the RHSCIR cases, which overlaps with the Canadian sites participating in NACTN.[33] Wilson and coworkers[48] combined NACTN and STASCIS data for an outcome study of acute SCI based on clinical and imaging features. NACTN data have likely also contributed to systematic reviews of the timing of surgical decompression of SCI.[48]

Key publications from the second phase of NACTN SCI Network: 2013–2022

There have been many accomplishments during NACTN's second phase, which are described in detail in this Special Focus Issue of the *Journal of Neurotrauma*. Indeed, the design and completion of the riluzole phase III trial is a significant accomplishment for NACTN, because the groundwork for it and the decision to proceed with the extensive trial were made by NACTN investigators. Training a cadre of acute SCI investigators and trial coordinators is also a major accomplishment. Other significant contributions have been the interactions with many other SCI organizations in North America and Europe.

The generation of extensive data in NACTN centers about the demographics and management of the 1017 acute SCI patients treated in those centers represents a considerable contribution to the world's knowledge of how people sustain acute SCI, their clinical manifestations, and their management and outcomes. Perhaps the most lasting contribution will be a large number of findings about their initial course after injury in terms of triage to a treatment destination, either timely direct transfer to a fully qualified acute SCI center with the acute surgical capability for decompression of persisting spinal cord compression within 24 h of injury or being off-loaded to a lesser acuity center necessitating interhospital transfer and inability to undergo acute surgical decompression within 24 h. The article by Kelly-Hedrick et al. ''Effect of Interhospital Transfer Delays Care for Spinal Cord Injury Patients: A Report from the North American Clinical Trials Network for Spinal Cord Injury'' provides critical insights into the issue of early surgical management of SCI, documents the early events in humans, and provides strong evidence that mirrors the improved neurological recovery from expeditious decompression shown in many pre-clinical research studies.

Future Funding of NACTN's Registry and Clinical Trials Activities

There is a continuing need for future clinical trials in SCI to ensure that the leading basic science discoveries can be translated for the benefit of people with acute or chronic SCI. The funding of clinical trials is complex, and NACTN has engaged in several collaborative funding methods. It is anticipated that traditional sources of funding (such as through nonprofit organizations or federal agencies, the CDRF, and the DOD in the United States) will require augmentation by additional sources of income from organizations such as AOSPINE and commercial entities such as pharmaceutical and cell therapy companies. NACTN has benefited from its administrative team, which has performed many of the functions of a contract research organization. This efficient method should be attractive to companies with products to test clinically. NACTN will continue to carefully scrutinize its pathways for recruitment of cases, to perform of clinical care for acute SCI, and to carefully monitor compliance. NACTN will also seek to reduce the costs of its trials by using state-of-the-art adaptive trial designs[36] and by working in concert with the other SCI networks described in this article.

Authors' Contributions

Charles H. Tator was responsible for conceptualization, writing of the original complete draft, and resources; James D. Guest was responsible for conceptualization, resources, writing – review and editing, and supervision; Chris J. Neal was responsible for writing – review and editing; Susan P. Howley was responsible for writing – original draft, and resources; Elizabeth G. Toups was responsible for writing – review and editing, and project administration; James S. Harrop was responsible for conceptualization, resources, and writing – review and editing; Bizhan Aarabi was responsible for writing – review and editing; Christopher I. Shaffrey was responsible for writing – review and editing; and Michael G. Fehlings was responsible for conceptualization, resources, and writing – review and editing.

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