NACTN: The North American Clinical Trials Network “RISCIS and Beyond”

J Guest MD, PhD, FAANS

Professor of Neurological Surgery

University of Miami


Dr. Robert Grossman
Jan. 24, 1933 – Oct. 7, 2021

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NACTN is:

- An acute SCI clinical trial network
- An academic “think tank” that fosters transparency and academic rigor
- A longitudinal Registry
- A non-governmental, non-industry independent entity

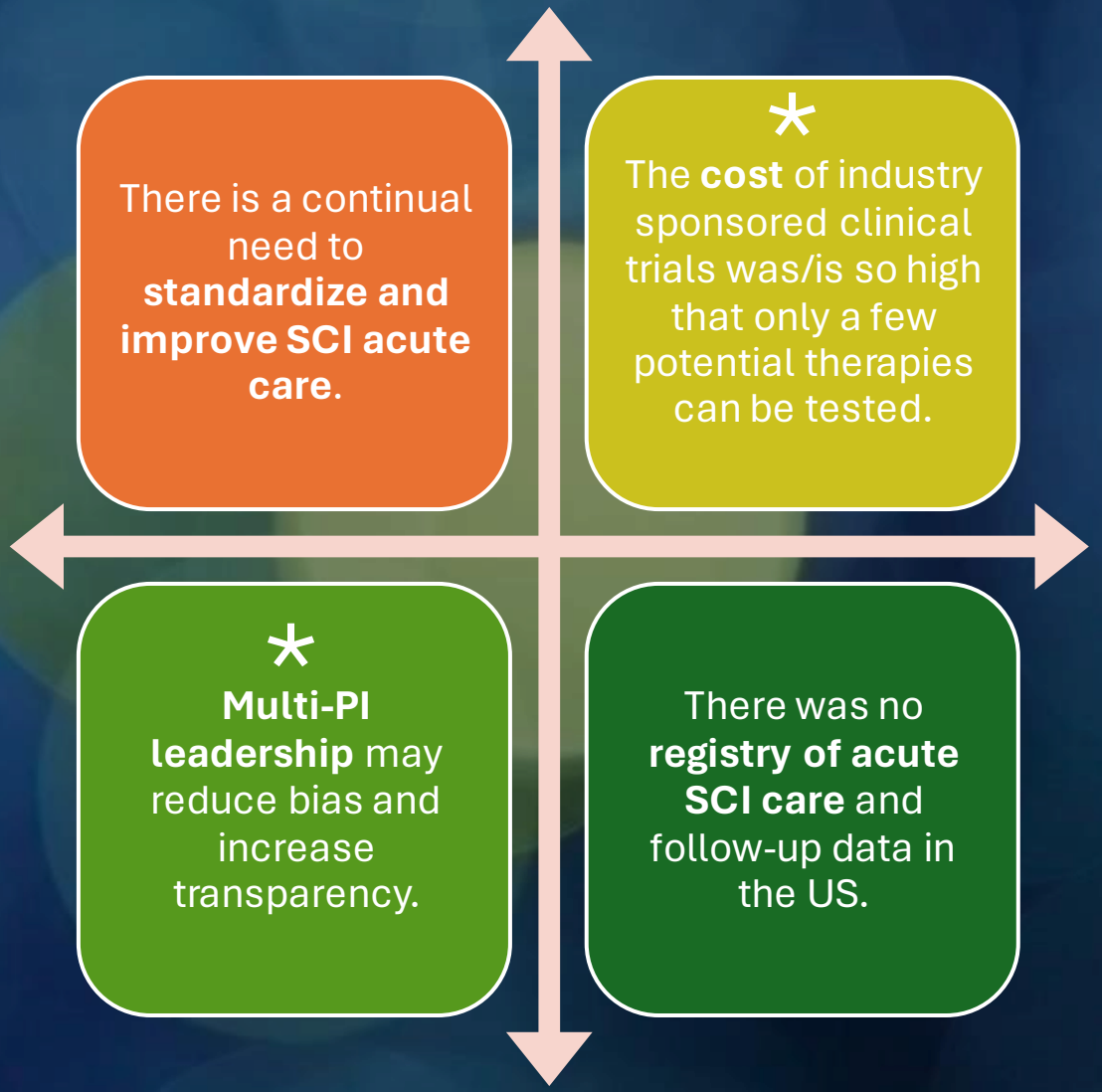
History and Structure

NACTN

The Network was formed to address the need for high quality North American clinical trial centers that could provide a platform for investigator-initiated studies.

Its Registry is designed to provide high quality longitudinal data from the moment of injury to 1-year after SCI.

Why was NACTN created?



Contributing Clinical Centers

- **University of Toronto**, Toronto Western Hospital
  Toronto, ON
  Michael G. Fehlings, MD, PhD
  Charles H. Tator, MD, PhD
- **Thomas Jefferson University**
  Philadelphia, PA
  James S. Harrop, MD
- **University of Maryland**
  Baltimore, MD
  Bizhan Aarabi, MD
- **University of Miami**
  Miami, FL
  James D. Guest, MD, PhD
- **University of Louisville**
  Louisville, KY
  Maxwell Boakye, MD
  Susan J. Harkema, PhD
- **Walter Reed National Military Medical** Center (WRNMMC)
  Bethesda, MD
  Christopher J. Neal, MD
- **University of Virginia**
  Charlottesville, VA
  Christopher I. Shaffrey, MD
- **Duke University**
  Durham, NC
  Muhammad Abd-El-Barr MD PhD
- **University of Texas Health Science Center**
  Houston, TX
  Karl Schmitt, MD
- **Louisiana State University Health Science Center**
  New Orleans, LA
  Jason Wilson, MD, MS
- **Brooke Army Medical Center** (BAMC)
  San Antonio, TX
  Sven Hochheimer, MD

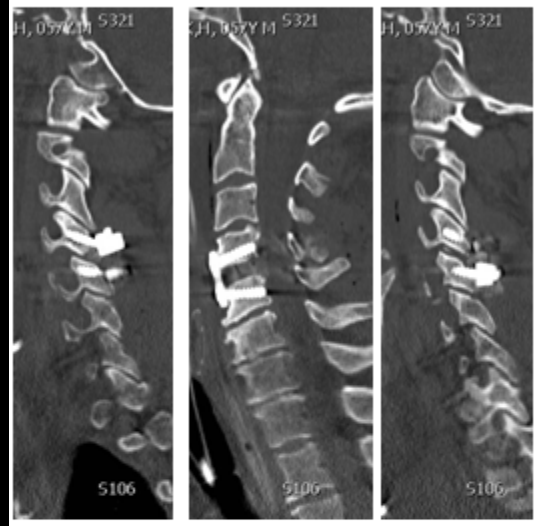
MVC at 12:45 pm 2/16/11, 57 white American male patient

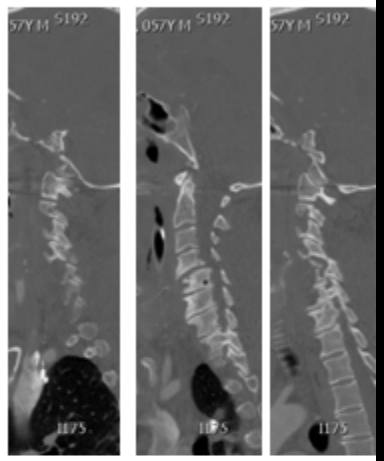
TRU transfer at 14:20 2/16/11 and NUS visit at 14:40: AMS:0, AIS:A DRE: No sensation no push.

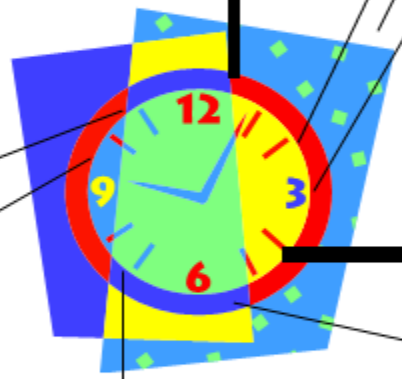
Consent signed at 14:45 2/16/11

Baseline blood studies 14:50

CT scan at 15:12 2/16/11



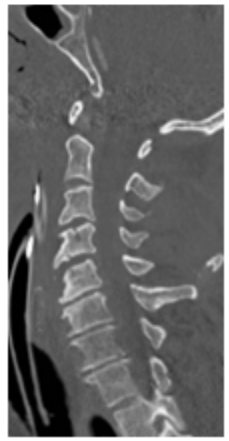




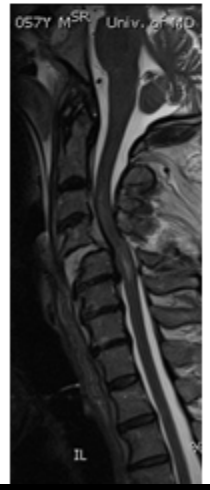
Riluzole in at 16:25

Internal fixation 09:31-14:15 2/17/11

Traction: Start at 19:30 reduced at 19:45 40: Lbs



MRI at 17:55

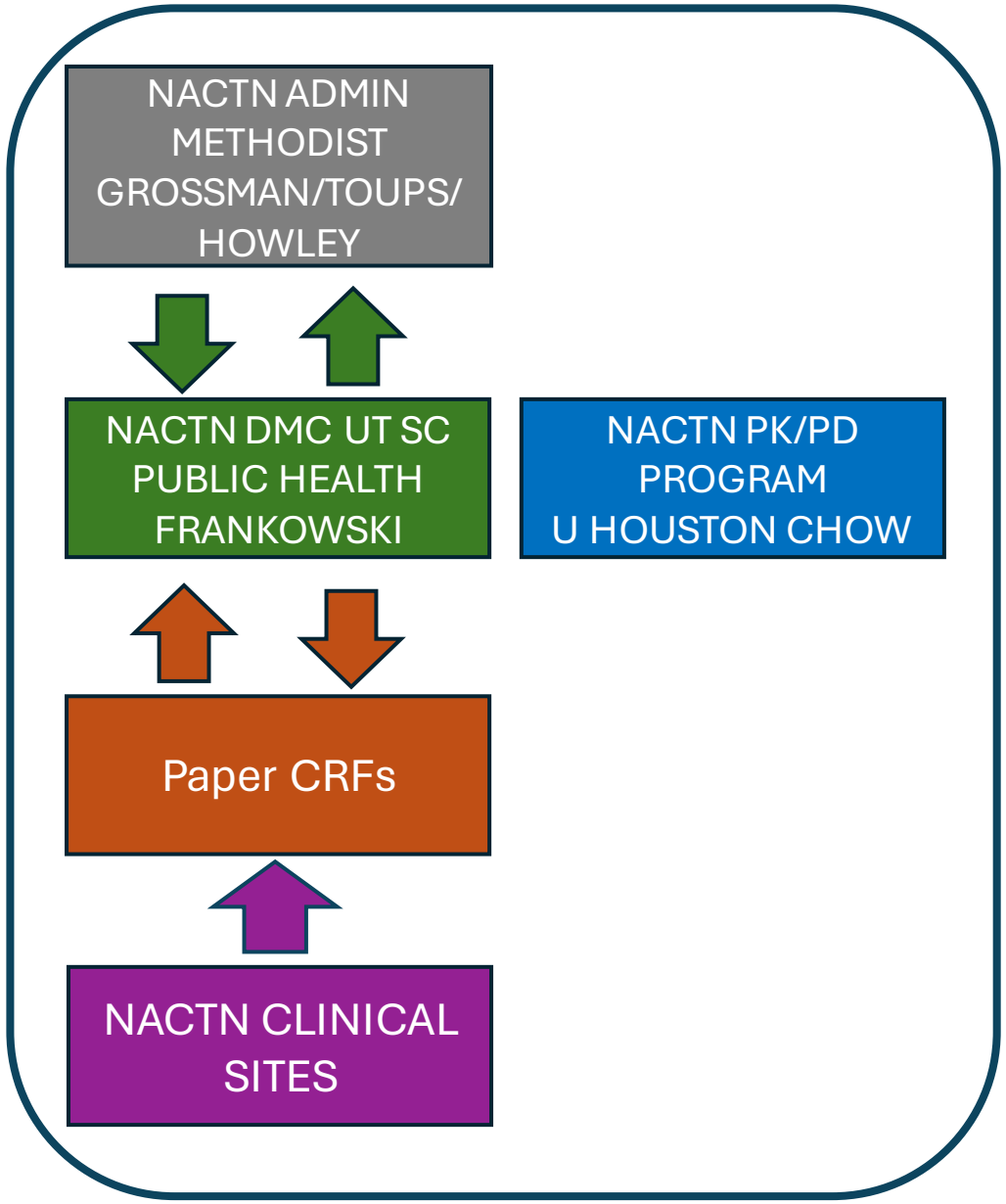


Dr. Bizhan Arabi
Univ of Maryland.

AWARD NUMBER: W81XWH-13-2-0040

TITLE: Clinical Trials Network / Building Infrastructure to Accelerate Transfer of Basic Research in Spinal Cord Injury (SCI) to Clinical Practice

PRINCIPAL INVESTIGATOR: Robert G. Grossman, MD

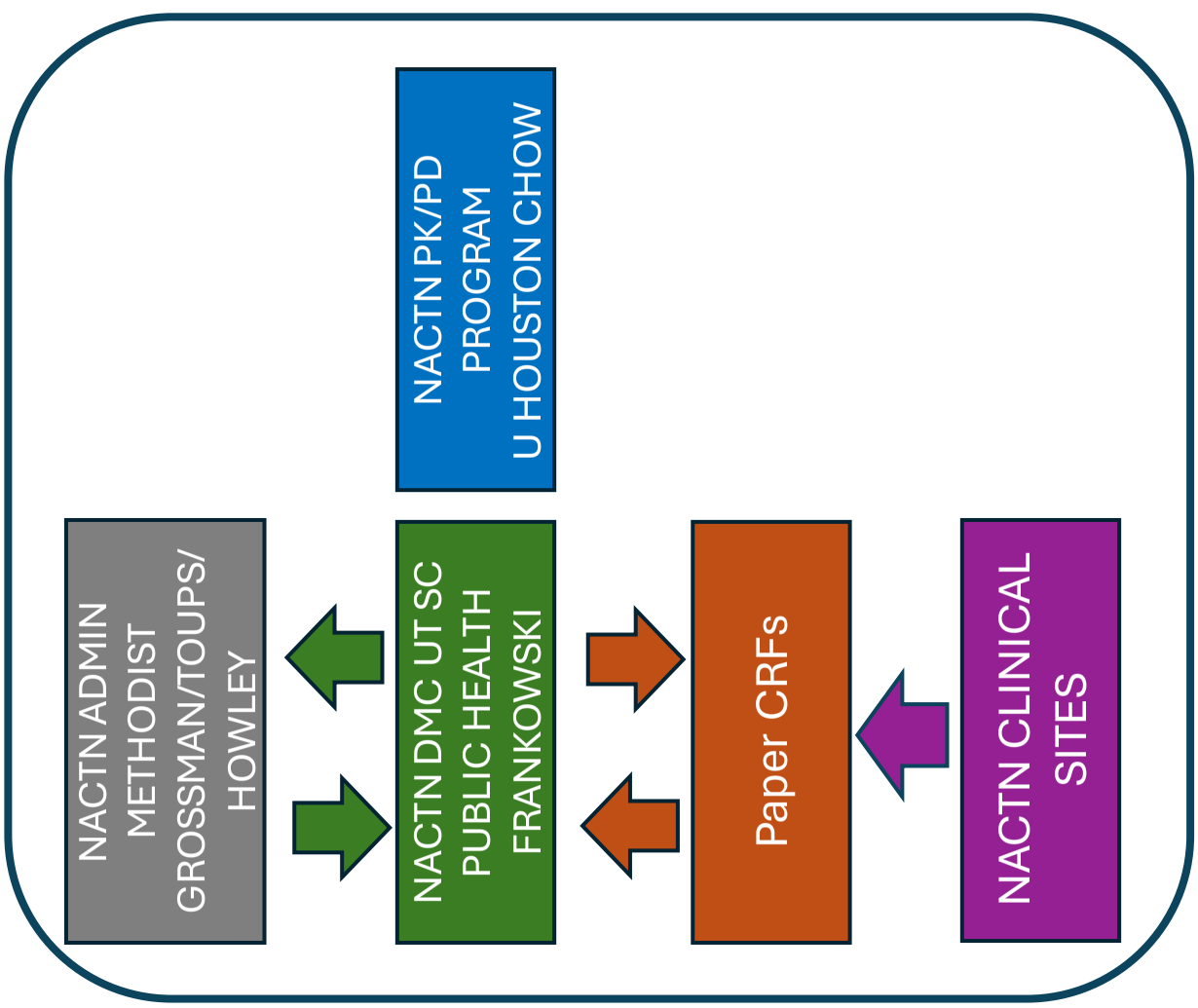


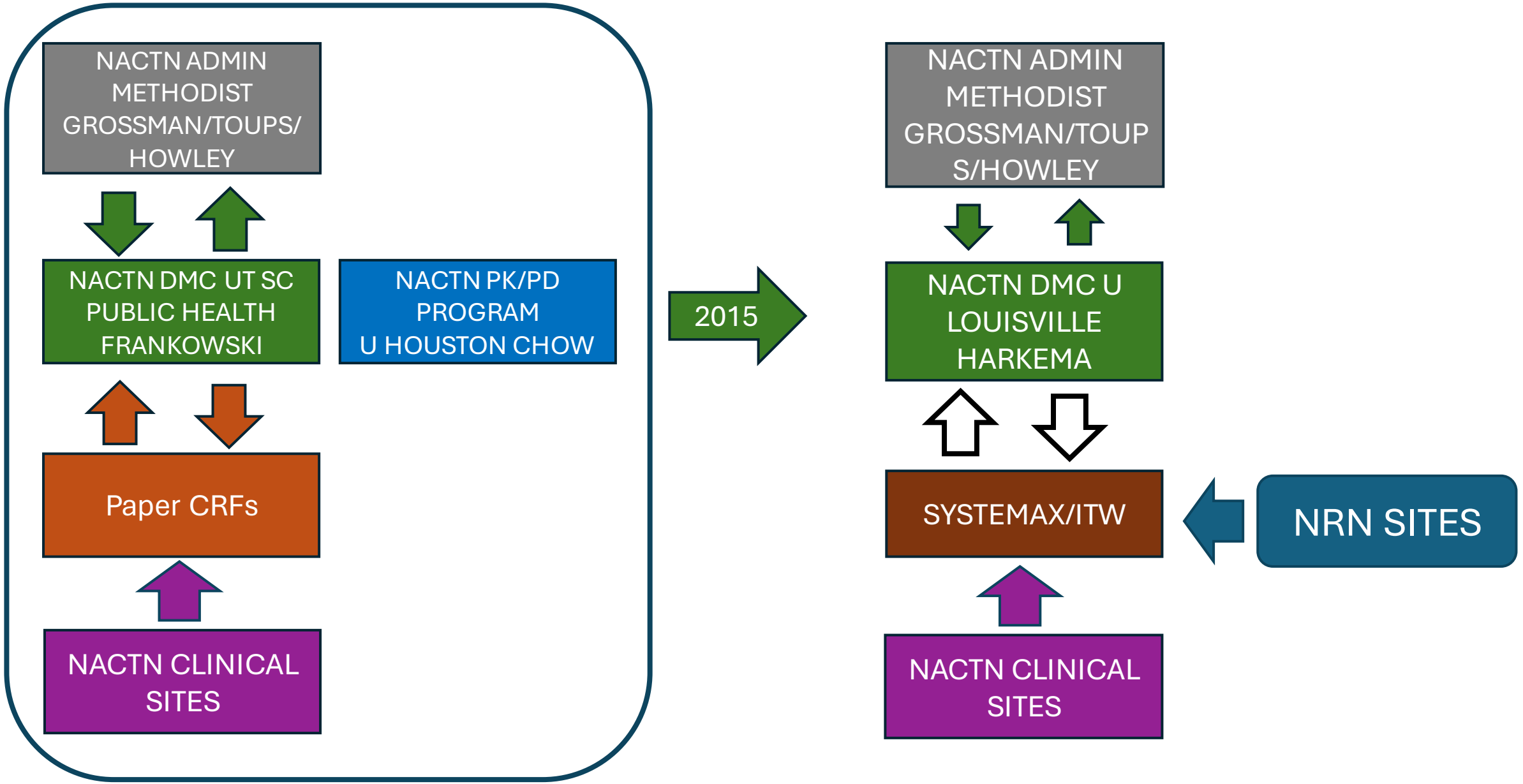
11 Centers

45 partially funded staff

J.Neurosurgery 2012 NACTN/AOSNA Focus Issue

RISICS PHASE 1 TRIAL

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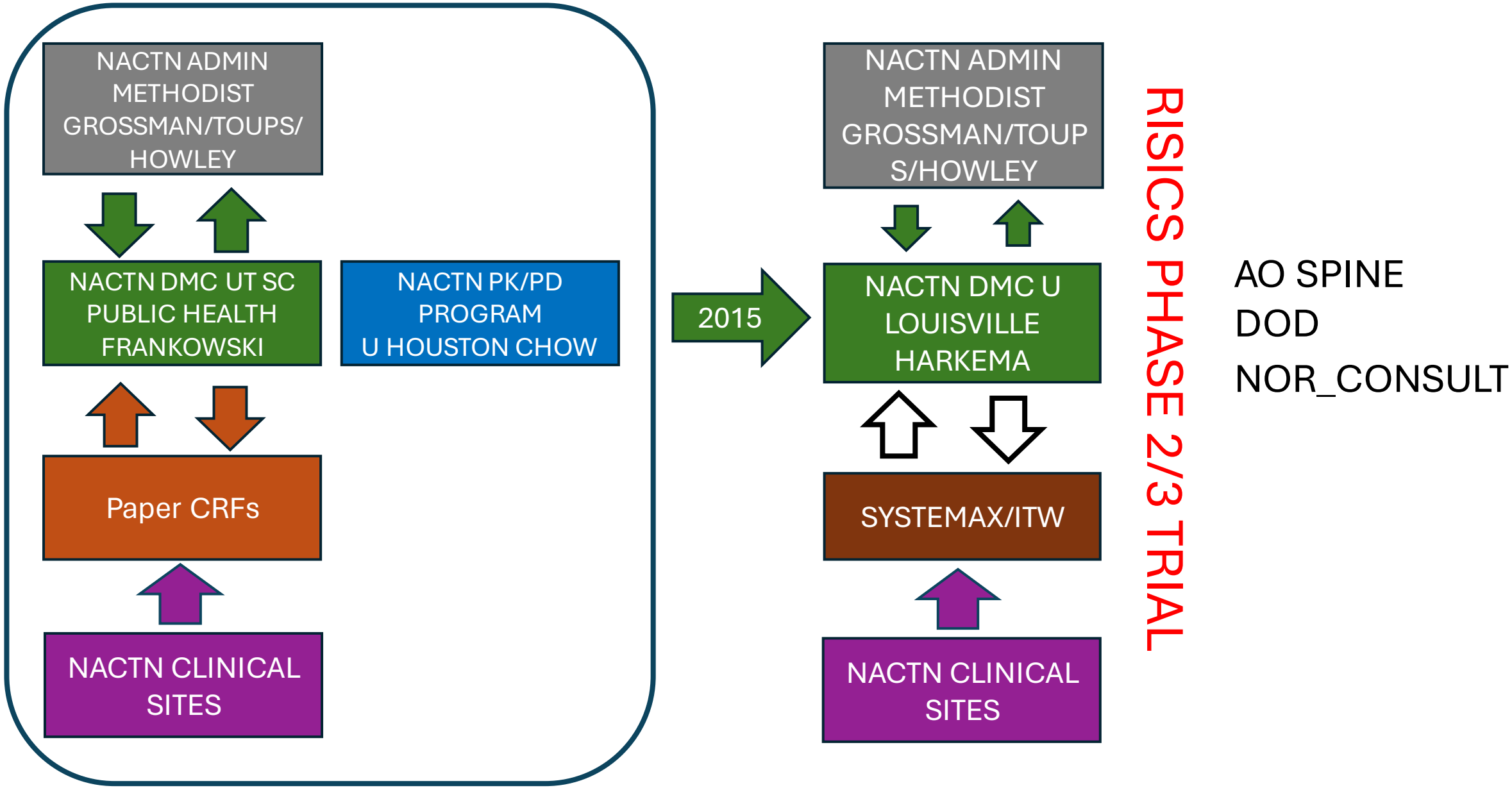
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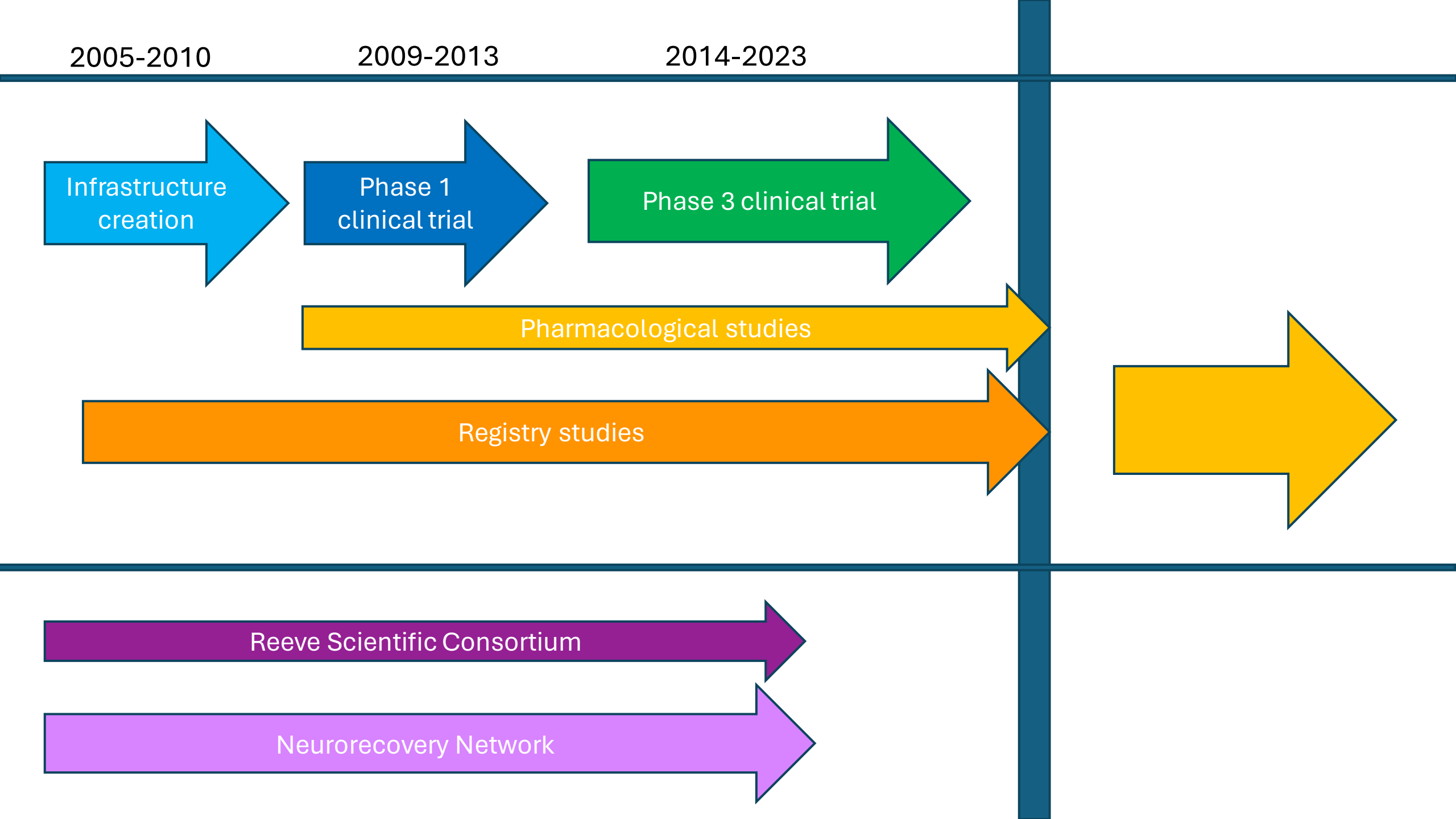
2005-2010
2009-2013
2014-2023
Infrastructure creation
Phase 1 clinical trial
Phase 3 clinical trial
Pharmacological studies
Registry studies
Reeve Scientific Consortium
Neurorecovery Network

Journal of Neurotrauma
40:1811–1816 (September 2023)

DOI: 10.1089/neu.2022.0402

Journal of Neurotrauma

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ORIGINAL ARTICLE

An Introduction to the North American Clinical Trials Network for Spinal Cord Injury Special Edition: Reflections on Accomplishments and a Look to the Future

Michael G. Fehlings,[1-3,*] Chris J. Neal,[4] Nader Hejrati,[1,2] James S. Harrop,[5] Elizabeth G. Toups,[6] and James D. Guest[7]

Focus Issue Reports

1) North American Clinical Trials Network for Spinal Cord Injury Registry: **Methodology and Analysis**
2) History and Accomplishments of the North American Clinical Trials Network for Spinal Cord Injury, 2004–2022
3) Importance of Prospective Registries and Clinical Research Networks in the Evolution of Spinal Cord Injury Care
4) Development of a Systems Medicine Approach to Spinal Cord Injury
5) **Safety and Efficacy of Riluzole in Acute Spinal Cord Injury Study: A Multi-Center, Randomized, Placebo-Controlled, Double-Blinded Trial**
6) **Riluzole in Spinal Cord Injury Study(RISCIS)–Pharmacokinetic (PK) Sub-Study: An Analysis of Pharmacokinetics, Pharmacodynamics, and Impact on Axonal Degradation of Riluzole in Patients With Traumatic Cervical Spinal Cord Injury Enrolled in the RISCIS Phase III Randomized Controlled Trial**
7) Variability in Early Surgery for Acute Cervical Spinal Cord Injury Patients: An Opportunity for Enhanced Care Delivery
8) Demographics, Mechanism of Injury, and Outcomes for Acute Upper and Lower Cervical Spinal Cord Injuries: An Analysis of 470 Patients in the Prospective, Multi-Center, North American Clinical Trials Network(NACTN) Registry
9) Interhospital Transfer Delays Care for Spinal Cord Injury Patients: A Report from the North American Clinical Trials Network for Spinal Cord Injury
10) Trends in the Use of Corticosteroids in the Management of Acute Spinal Cord Injury in North American Clinical Trials Network Sites
11) Associations Between Diurnal Timing of Spinal Cord Injury and Its Etiology and Co-Morbidities
12) Bulbocavernosus Reflex Has No Prognostic Features During the Acute Evaluation of Spinal Cord Injuries'

The purpose of the NACTN SCI Registry is threefold:

Establish	Establish the **natural course of recovery** following a spinal cord injury using standardized and validated acute-care and follow-up data.
Facilitate	Facilitate **scholarly research** and publications.
Serve	Serve as a **comparison group** in spinal cord clinical trials and help establish clinical protocols.

The Registry data

- Demographics
- Medical history
- Initial clinical status
- Type of neurological and bony injury
- Surgical therapy and critical care
- Adverse events
- Magnetic resonance imaging (MRI)
- Outcomes: ISNCSCI, SCIM

Complications during spinal cord injury care worsen neurological recovery

Define incidence- Clinical pathways to mitigate

315 patients, 856 complications, 2.71 per patient, 78% <14d.

Incidence and severity of acute complications after spinal cord injury

Robert G. Grossman, M.D.,[1] Ralph F. Frankowski, Ph.D.,[2] Keith D. Burau, Ph.D.,[2] Elizabeth G. Toups, M.S., R.N.,[1] John W. Crommett, M.D.,[3] Michele M. Johnson, M.D.,[3] Michael G. Fehlings, M.D., Ph.D.,[4] Charles H. Tator, M.D., Ph.D.,[4] Christopher I. Shaffrey, M.D.,[5] Susan J. Harkema, Ph.D.,[6] Jonathan E. Hodes, M.D.,[6] Bizhan Aarabi, M.D.,[7] Michael K. Rosner, M.D.,[8] James D. Guest, M.D., Ph.D.,[9] and James S. Harrop, M.D.[10]

[1]Department of Neurosurgery, The Methodist Hospital; [2]Division of Biostatistics, University of Texas School of Public Health; [3]Department of Neurosurgery, University of Texas Health Science Center, Houston, Texas; [5]Department of Neurological Surgery, University of Virginia Health System, Charlottesville, Virginia; [6]Department of Neurosurgery, University of Louisville, Kentucky; [7]Department of Neurosurgery, University of Maryland, Baltimore; [8]Department of Neurosurgery, Walter Reed National Military Medical Center, Bethesda, Maryland; [9]Department of Neurosurgery, University of Miami, Florida; [10]Department of

Therapeutics Selection Committee

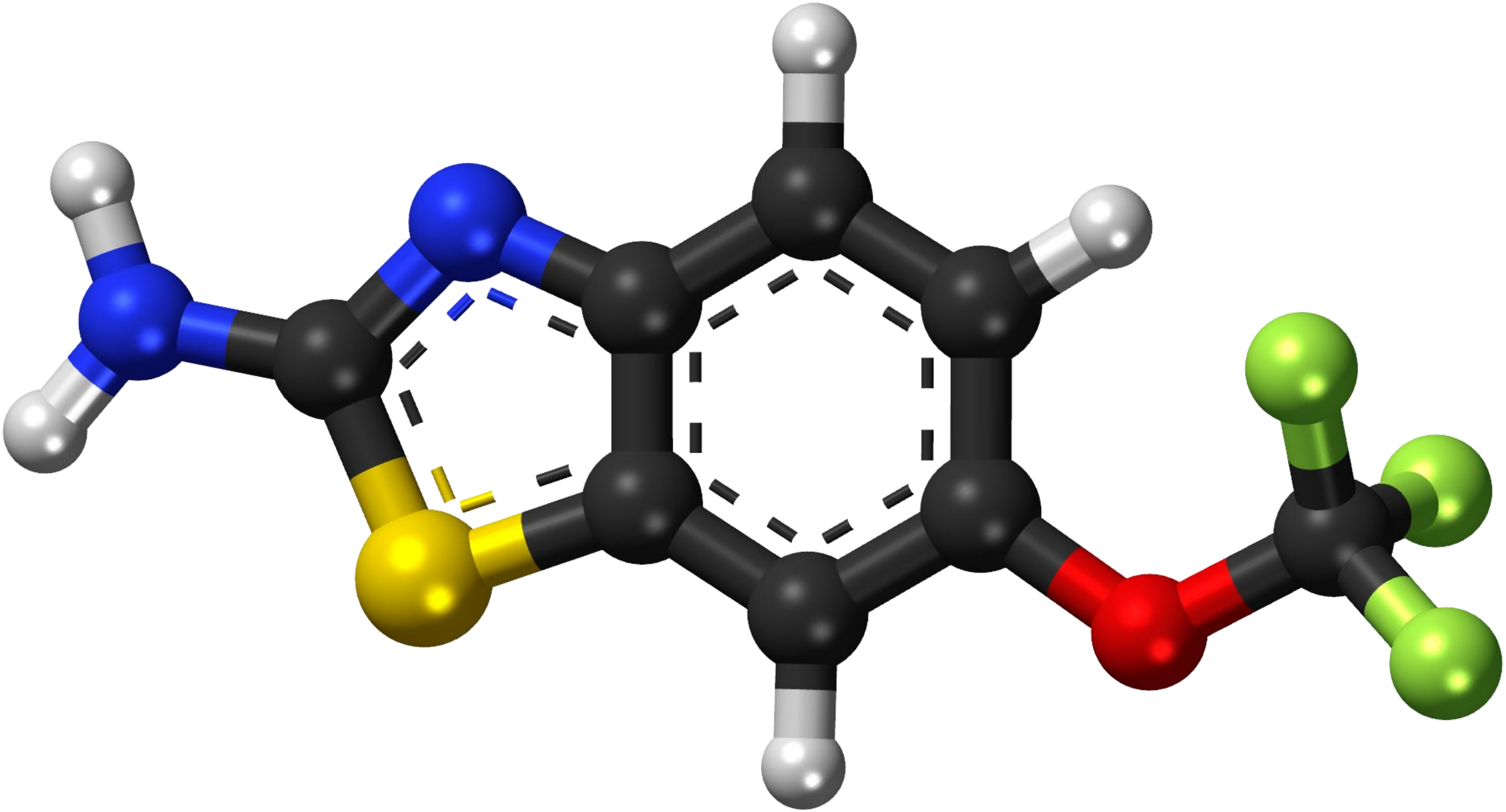
Optimization of the decision-making process for the selection of therapeutics to undergo clinical testing for spinal cord injury in the North American Clinical Trials Network

J Neurosurg Spine (Suppl) 17:94–101, 2012

James Guest, M.D., Ph.D.,[1] James S. Harrop, M.D.,[2] Bizhan Aarabi, M.D.,[3]
Robert G. Grossman, M.D.,[4] James W. Fawcett, M.D., Ph.D.,[5]
Michael G. Fehlings, M.D., Ph.D.,[6] and Charles H. Tator, M.D., Ph.D.[6]

TABLE 1: Decision matrix*

Preclinical Variable	Wt	%	Wt × %	Clinical Variable	Wt	%	Wt × %	NACTN Variable	Wt	%	Wt × %
relevant outcome assessments that provide persuasive evidence of safety & efficacy	0.21			relevance to SCI	0.26			fit w/ NACTN priorities & principles	0.30		
relevant animal SCI model(s)	0.18			quality of the research design, such as randomization, controls, blinding, study power, & outcome measures employed	0.23			suitability for multicenter study at NACTN centers	0.21		
clinically feasible delivery method	0.16			degree of invasiveness & risk	0.18			cost & possible funding for clinical testing	0.19		
readiness for clinical translation	0.14			extent & quality of follow-up data, especially safety data	0.16			timing of availability for clinical testing	0.11		
optimization of dose, duration of therapy, & therapeutic window	0.12			standardization of therapeutic & procedures	0.10			proposed duration of the study	0.10		
relevant timing of intervention	0.10			regulatory status	0.07			requirement for specialized rehabilitation	0.09		
independent replication	0.09										



Cochrane Library

Cochrane Database of Systematic Reviews

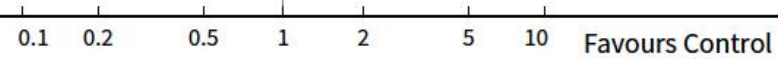
Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND) (Review)

Miller RG, Mitchell JD, Moore DH

Miller RG, Mitchell JD, Moore DH.
Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND).
Cochrane Database of Systematic Reviews 2012, Issue 3. Art. No.: CD001447.
DOI: 10.1002/14651858.CD001447.pub3.

Analysis 1.1. Comparison 1 Riluzole 100 mg versus placebo, Outcome 1 Per cent mortality at 12 months.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Per cent mortality at 12 mos					
Bensimon 1994	20/77	33/78		18.7%	0.61[0.39,0.97]
Lacomblez 1996	62/235	90/241		50.68%	0.71[0.54,0.92]
Bensimon 2002	52/82	55/86		30.62%	0.99[0.79,1.25]
Subtotal (95% CI)	**394**	**405**		**100%**	**0.78[0.65,0.92]**
Total events: 134 (Treatment), 178 (Control)					
Heterogeneity: Tau^2=0; Chi^2=5.89, df=2(P=0.05); I^2=66.02%					
Test for overall effect: Z=2.91(P=0)					
Total (95% CI)	**394**	**405**		**100%**	**0.78[0.65,0.92]**
Total events: 134 (Treatment), 178 (Control)					
Heterogeneity: Tau^2=0; Chi^2=5.89, df=2(P=0.05); I^2=66.02%					
Test for overall effect: Z=2.91(P=0)					



J Neurosurg Spine (Suppl) 17:151

Riluzole for the treatment of acute traumatic spinal cord injury: rationale for and design of the NACTN Phase I clinical trial

Michael G. Fehlings, M.D., Ph.D.,[1] Jefferson R. Wilson, M.D.,[1]
Ralph F. Frankowski, Ph.D.,[2] Elizabeth G. Toups, M.Sc.,[3] Bizhan Aarabi, M.D.,[4]
James S. Harrop, M.D.,[5] Christopher I. Shaffrey, M.D.,[6] Susan J. Harkema, Ph.D.[7]
James D. Guest, M.D., Ph.D.,[8] Charles H. Tator, M.D., Ph.D.,[1] Keith D. Burau,[3]
Michele W. Johnson, M.D.,[9] and Robert G. Grossman, M.D.[3]

JOURNAL OF NEUROTRAUMA 31:239–255 (February 1, 2014)

DOI: 10.1089/neu.2013.2969

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

Robert G. Grossman,[1,*] Michael G. Fehlings,[2,*] Ralph F. Frankowski,[3] Keith D. Burau,[3] Diana S.L. Chow,[4] Charles Tator,[2] Angela Teng,[4] Elizabeth G. Toups,[1] James S. Harrop,[5] Bizhan Aarabi,[6] Christopher I. Shaffrey,[7] Michele M. Johnson,[8] Susan J. Harkema,[9] Maxwell Boakye,[9] James D. Guest,[10] and Jefferson R. Wilson[2]

Network performance

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

Time window	*Minimum (h)*	*25th percentile (h)*	*Median/mean (h) (SD)*	*75th 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.

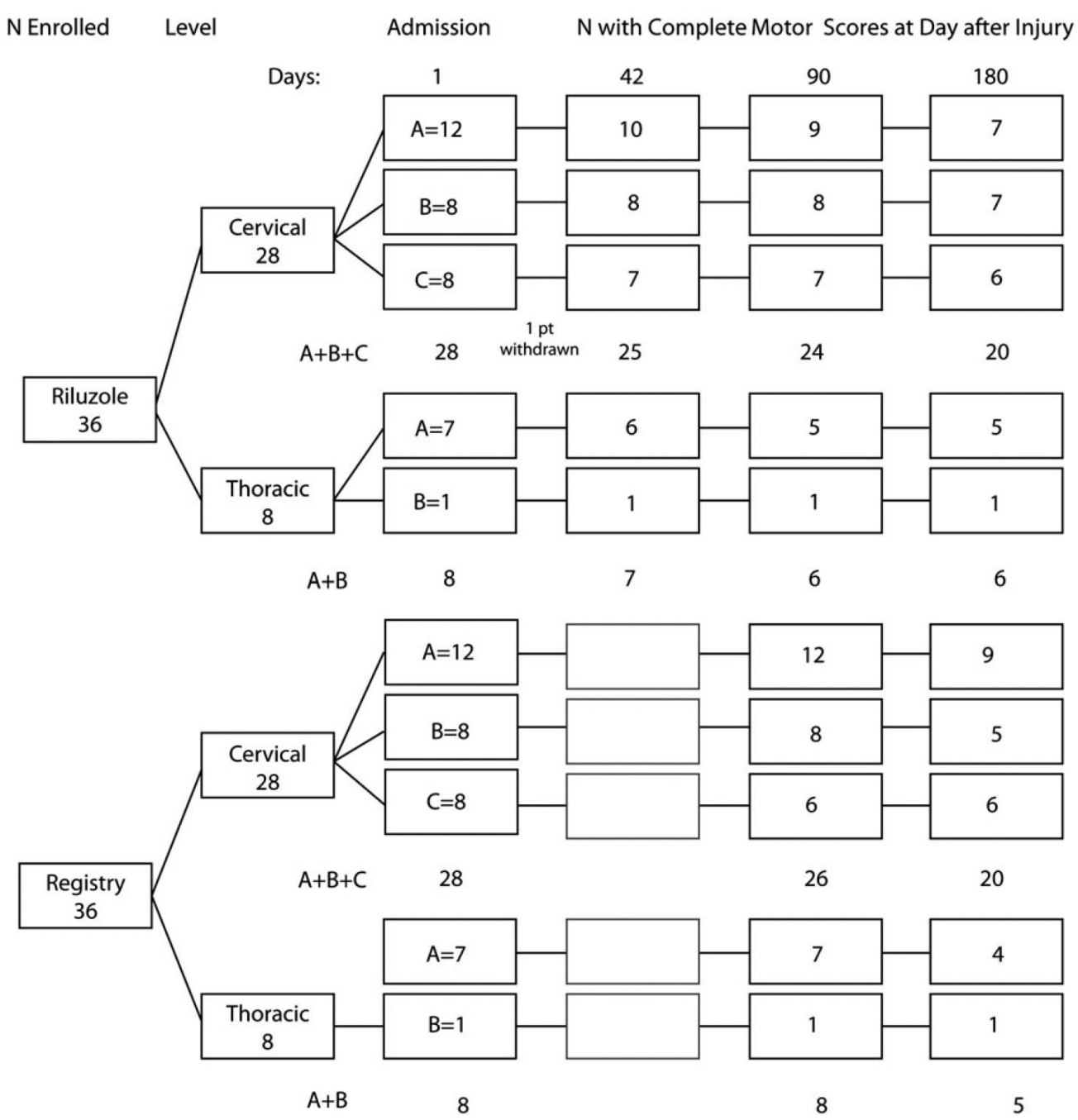


FIG. 1. Patient flow diagram of numbers of riluzole and registry patients available with complete motor scores on admission and at 42, 90, and 180 days.

TABLE 13. CERVICAL INJURIES: RILUZOLE AND REGISTRY PATIENTS

Riluzole

Admission		*90 days*				
Grade	*N = 27*	*A* N (%)	*B* N (%)	*C* N (%)	*D* N (%)	*E* N (%)
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)

Registry

Admission		*90 days*				
Grade	*N = 26*	*A* N (%)	*B* N (%)	*C* N (%)	*D* N (%)	*E* N (%)
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.

50%
87%
86%

25%
50%
50%

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

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

J Neurosurg Spine (Suppl) 17:129–140, 2012

Pharmacology of riluzole in acute spinal cord injury

Diana S. L. Chow, Ph.D.,[1] Yang Teng, B.S.,[1] Elizabeth G. Toups, M.S.,[2] Bizhan Aarabi, M.D.,[3] James S. Harrop, M.D.,[4] Christopher I. Shaffrey, M.D.,[5] Michele M. Johnson, M.D.,[6] Maxwell Boakye, M.D.,[7] Ralph F. Frankowski, Ph.D.,[8] Michael G. Fehlings, M.D., Ph.D.,[9] and Robert G. Grossman, M.D.[2]

[1]Department of Pharmacological and Pharmaceutical Sciences, University of Houston; [2]Department of Neurosurgery, The Methodist Hospital, Houston; [6]Department of Neurosurgery, University of Texas, Health Science Center, Houston; [8]Division of Biostatistics, University of Texas School of Public Health, Houston, Texas; [3]Department of Neurosurgery, University of Maryland, Baltimore, Maryland; [4]Department of Neurosurgery, Thomas Jefferson University, Philadelphia, Pennsylvania; [5]Department of Neurosurgery, University of Virginia Health System, Charlottesville, Virginia; [7]Department of Neurosurgery, University of Louisville, Kentucky; and [9]Division of Neurosurgery, Toronto Western Hospital, University of Toronto, Ontario, Canada

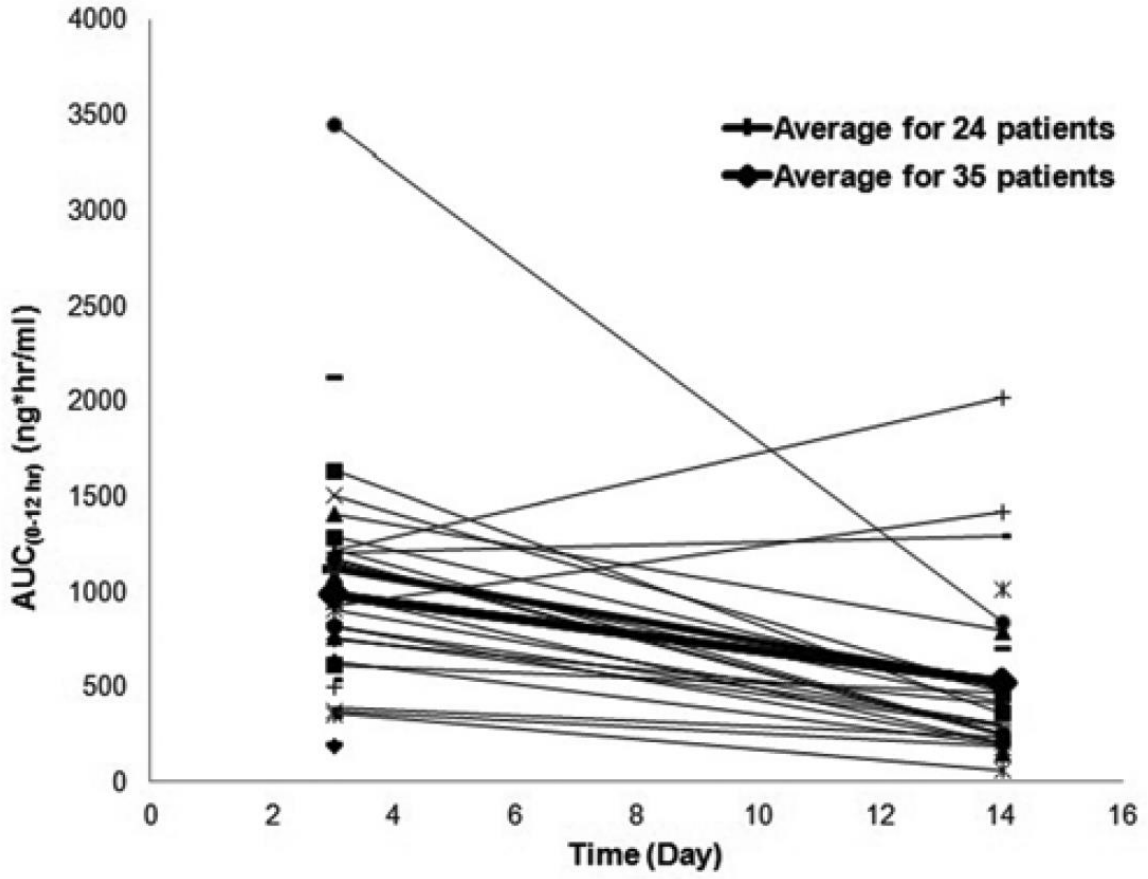


FIG. 4. Spaghetti plots of AUC_{0-12} on Day 3 and Day 14. C_{max} and C_{min} exhibited the same trend as AUC_{0-12} from Day 3 to Day 14 on the same dose basis. Twenty-four patients had both Day 3 and Day 14 data available. Symbols without lines connecting Days 3 and 14 have values only for Day 3 or Day 14.

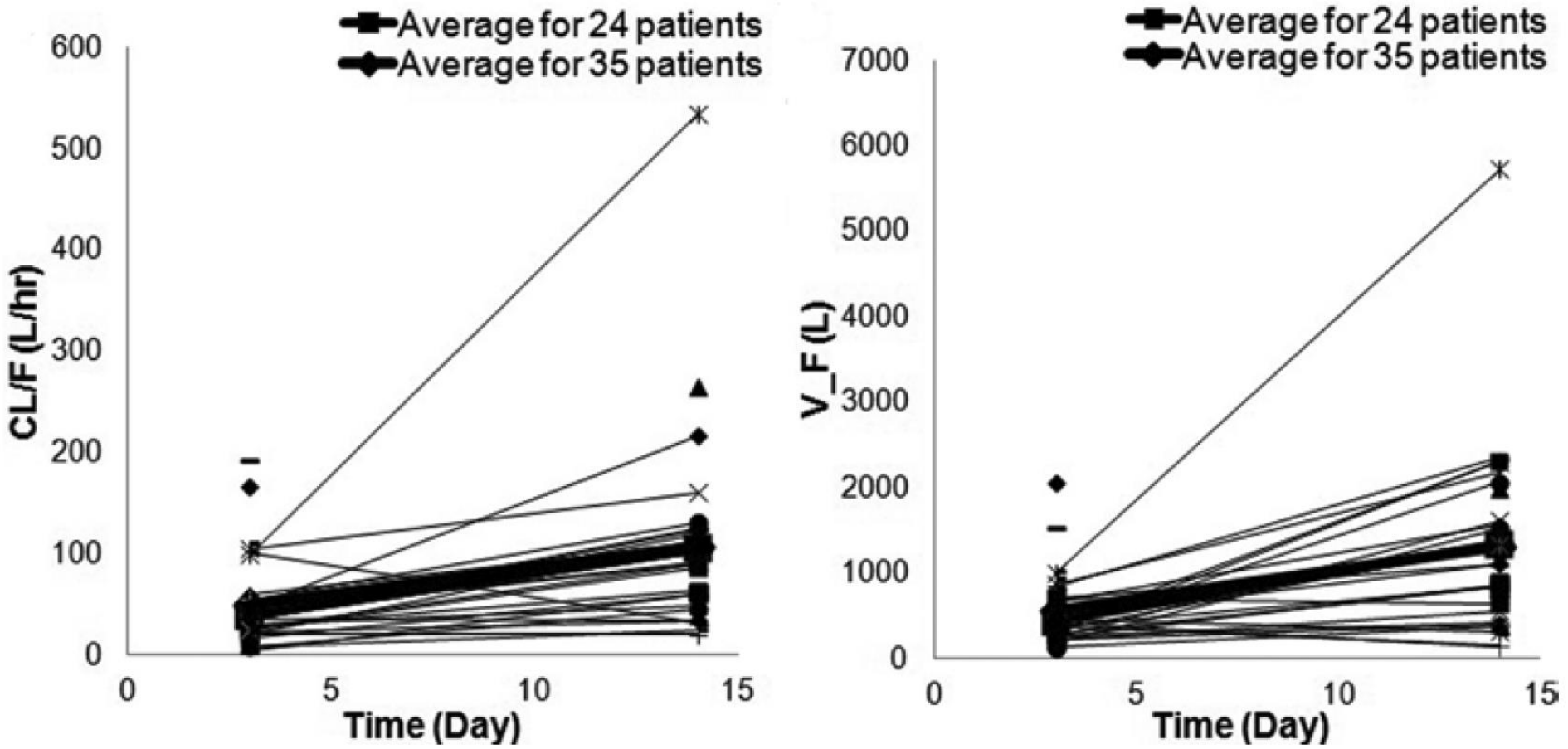


FIG. 5. Spaghetti plots of clearance (CL/F) **(left)** and volume of distribution (V_F) **(right)** on Day 3 and Day 14. Twenty-four patients had both Day 3 and Day 14 data available. Symbols without lines connecting Days 3 and 14 have values only for Day 3 or Day 14.

Spinal Cord (2015), 1–8

www.nature.com/sc

ORIGINAL ARTICLE

Rationale, design and critical end points for the Riluzole in Acute Spinal Cord Injury Study (RISCIS): a randomized, double-blinded, placebo-controlled parallel multi-center trial

MG Fehlings[1], H Nakashima[1,2], N Nagoshi[1,3], DSL Chow[4], RG Grossman[5] and B Kopjar[6]

Journal of Neurotrauma
40:1878–1888 (September 2023)
Mary Ann Liebert, Inc.
DOI: 10.1089/neu.2023.0163

Journal of Neurotrauma

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ORIGINAL ARTICLE

Safety and Efficacy of Riluzole in Acute Spinal Cord Injury Study (RISCIS): A Multi-Center, Randomized, Placebo-Controlled, Double-Blinded Trial

Michael G. Fehlings,[1,2,*] Ali Moghaddamjou,[1] James S. Harrop,[3] Ralph Stanford,[4] Jonathon Ball,[5] Bizhan Aarabi,[6] Brian J. C. Freeman,[7] Paul M. Arnold,[8] James D. Guest,[9] Shekar N. Kurpad,[10] James M. Schuster,[11] Ahmad Nassr,[12] Karl M. Schmitt,[13] Jefferson R. Wilson,[1] Darrel S. Brodke,[14] Faiz U. Ahmad,[15] Albert Yee,[1] Wilson Z. Ray,[16] Nathaniel P. Brooks,[17] Jason Wilson,[18] Diana S-L Chow,[19] Elizabeth G. Toups,[20] and Branko Kopjar[21]

55% enrollment

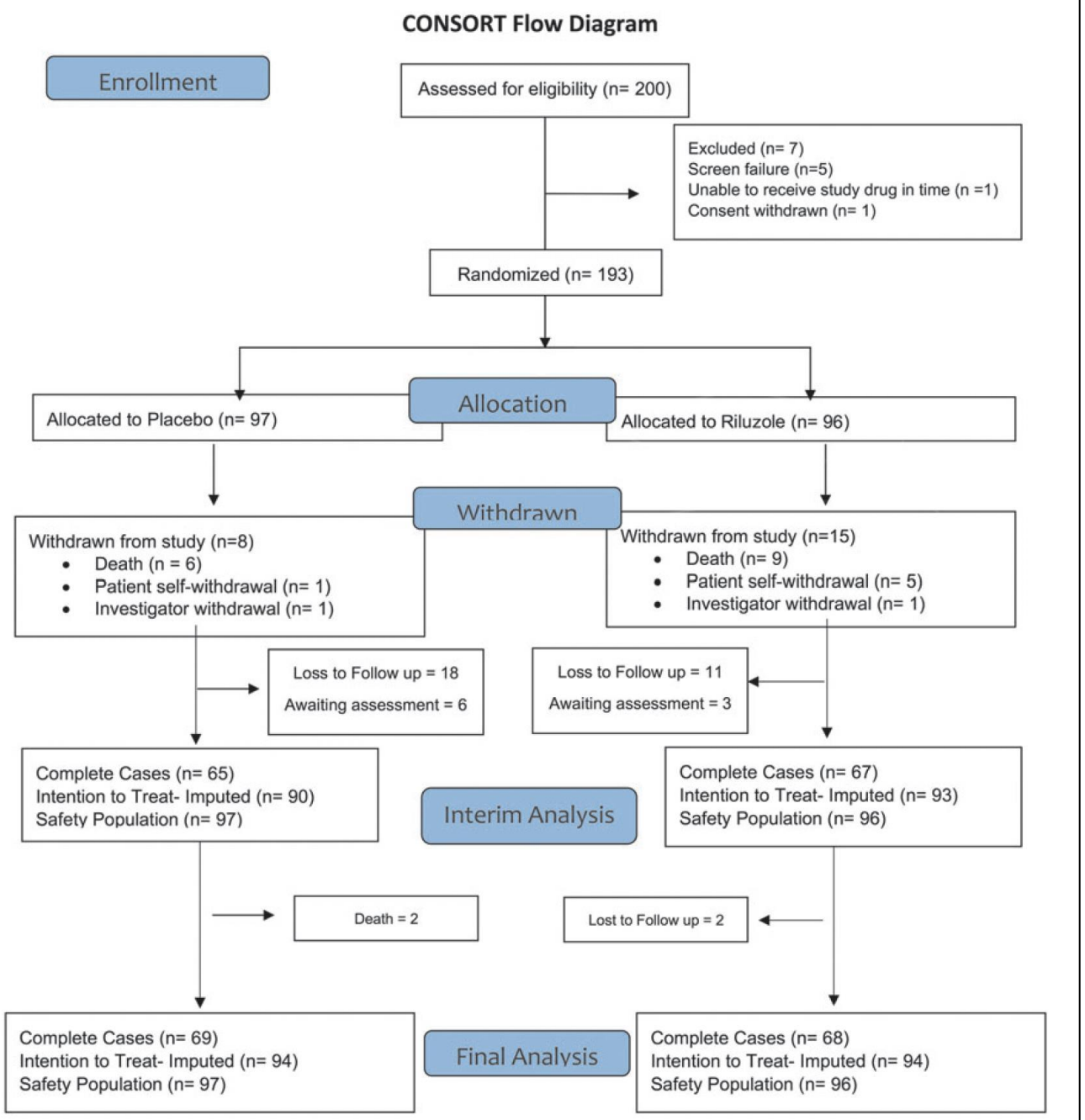
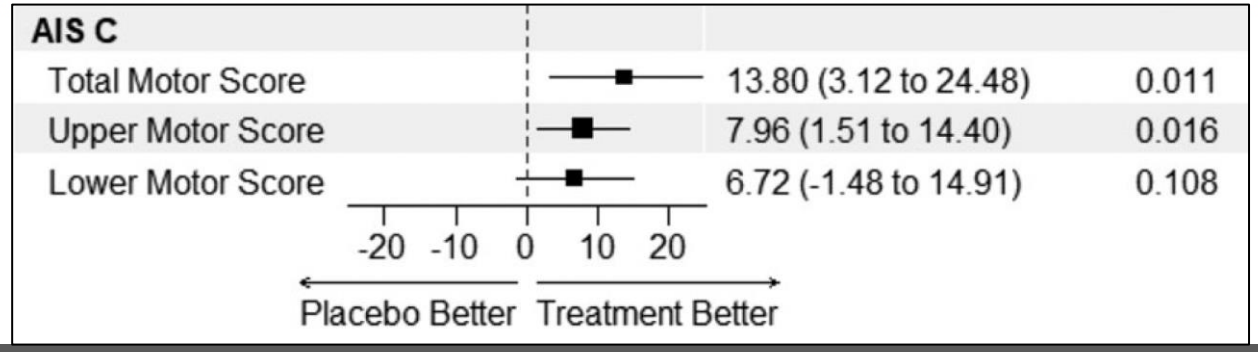


FIG. 1. Consolidated Standards of Reporting Trials (CONSORT) flow diagram of the Riluzole in Spinal Cord Injury Study (RISCIS) at the 180-day follow-up visit.

AIS Grade, *n* (%)		
* A	49 (51.58)	52 (53.61)
B	19 (20.00)	19 (19.59)
C	26 (27.37)	26 (26.80)
D	0	1 (1.05%)
Neurological Level of Injury, *n* (%)		
C3	0	2 (2.06)
* C4	47 (48.96)	57 (58.76)
C5	29 (30.21)	20 (20.62)
C6	13 (13.54)	9 (9.28)
C7	5 (5.21)	5 (5.15)
C8	0	1 (1.03)
T2	0	1 (1.03)

Table 2. Mean, Number of Patients, and Difference in Means by Treatment Group for Motor Scores Gained at 180-Days

	Placebo		*Riluzole*			
	Mean	*n*	Mean	*n*	Difference (95% CI)	*p* Value
Complete Cases (*n*: 137)						
* Primary Outcome: Change in Upper Extremity Motor Scores at 180 days	14.65	66	16.42	65	1.76 (-2.54-6.06)	0.2093
Change in Lower Extremity Motor Scores at 180 days	16.10	68	17.55	65	1.45 (-4.80-7.70)	0.3235
Change in Total Motor Scores at 180 days	31.11	66	34.00	65	2.86 (-6.79-12.52)	0.2792
Intention to Treat- Imputed data (N: 188)						
Primary Outcome: Change in Upper Extremity Motor Scores at 180 days	14.35	94	15.59	94	1.24 (-1.90-4.38)	0.2190
Change in Lower Extremity Motor Scores at 180 days	16.54	94	15.99	94	0.02 (-4.7-4.77)	0.4962
Change in Total Motor Scores at 180 days	29.83	90	31.25	93	1.42 (-5.78-8.62)	0.3490



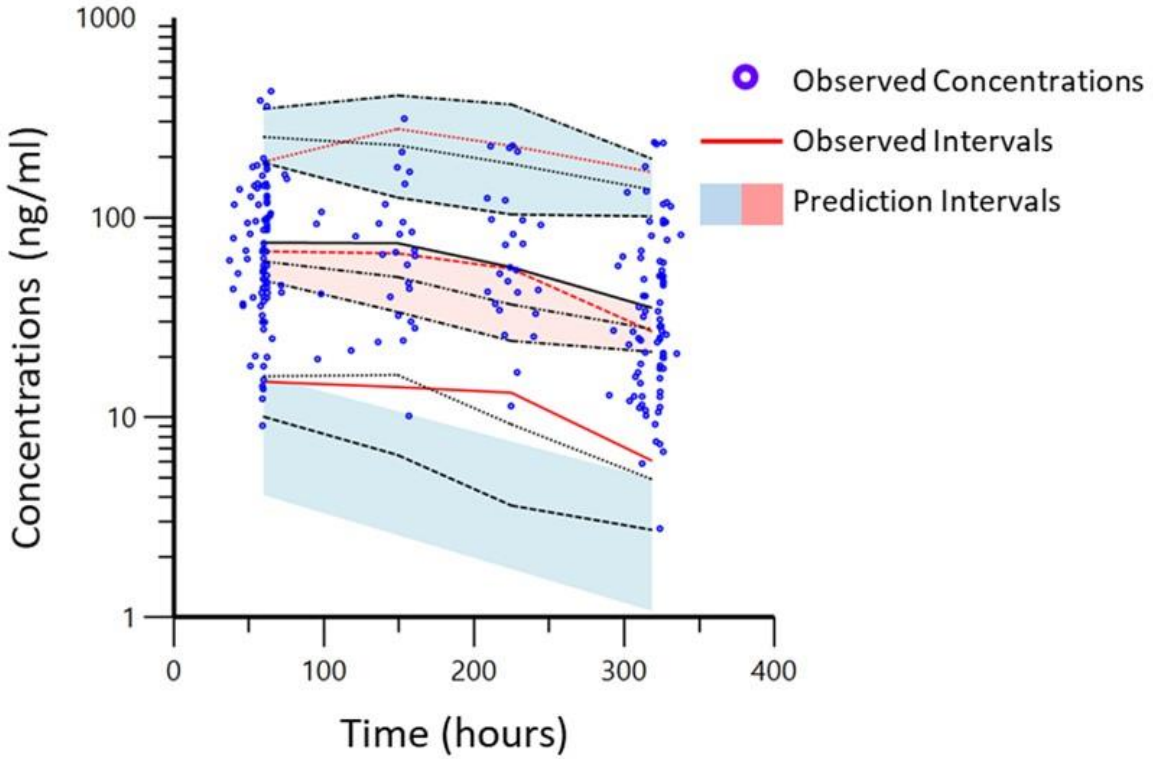
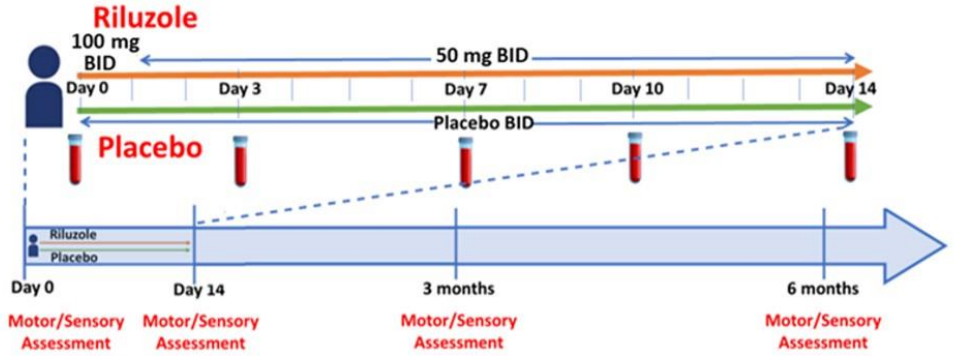


Figure 4. Visual predictive check of riluzole population pharmacokinetic model. Individual observations are presented by the blue dots. The 5th, 50th, and 95th percentiles of observed data are presented by the red lines. The 5th, 50th, and 95th percentiles of predicted data are presented by the black lines.

Nguyen A, Chow DS, Wu L, Teng YA, Sarkar M, Toups EG, Harrop JS, Schmitt KM, Johnson MM, Guest JD, Aarabi B, Shaffrey CI, Boakye M, Frankowski RF, Fehlings MG, Grossman RG. Longitudinal Impact of Acute Spinal Cord Injury on Clinical Pharmacokinetics of Riluzole, a Potential Neuroprotective Agent. J Clin Pharmacol. 2021 Sep;61(9):1232-1242. doi: 10.1002/jcph.1876. Epub 2021 Jul 9. PMID: 33908635; PMCID: PMC8457124.

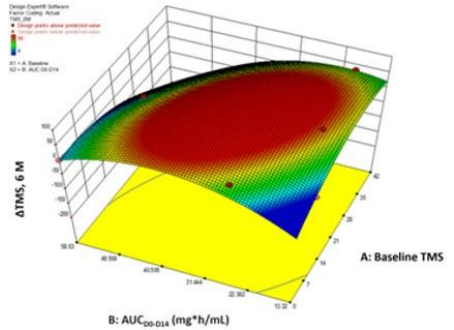
Model-informed, Pharmacokinetic-guided Riluzole Dosing for Individual Acute Spinal Cord Injured Patients

1 RISCIS Clinical Trial

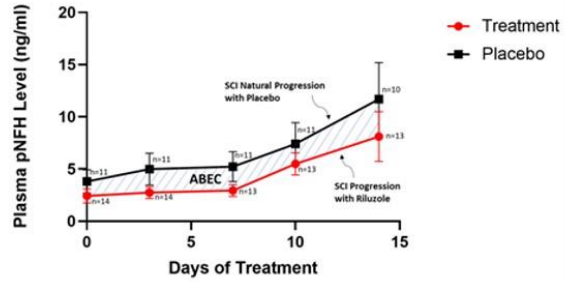


2 Characterizations of PK/PD and PD Models

3D PK/PD (CO) Model

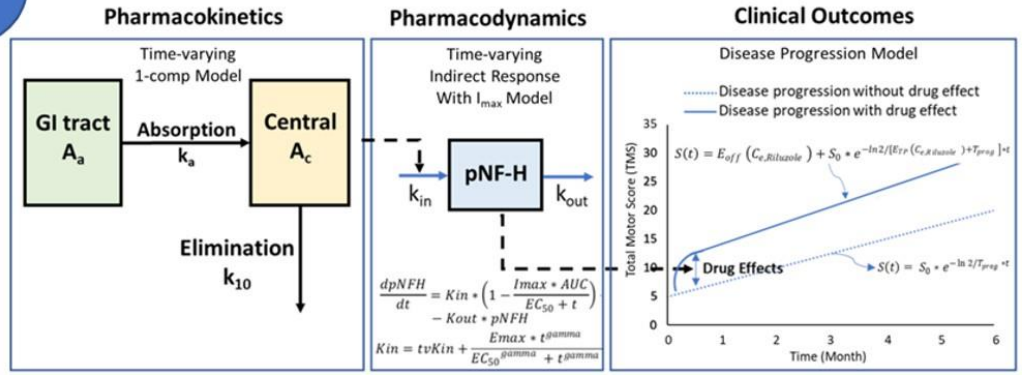


PD (pNF-H)/ABEC Model



$$ABEC = |pNFH_{nat} * t_r - AUEC_{0-t_r}|$$

3 PK/PD/CO Modeling

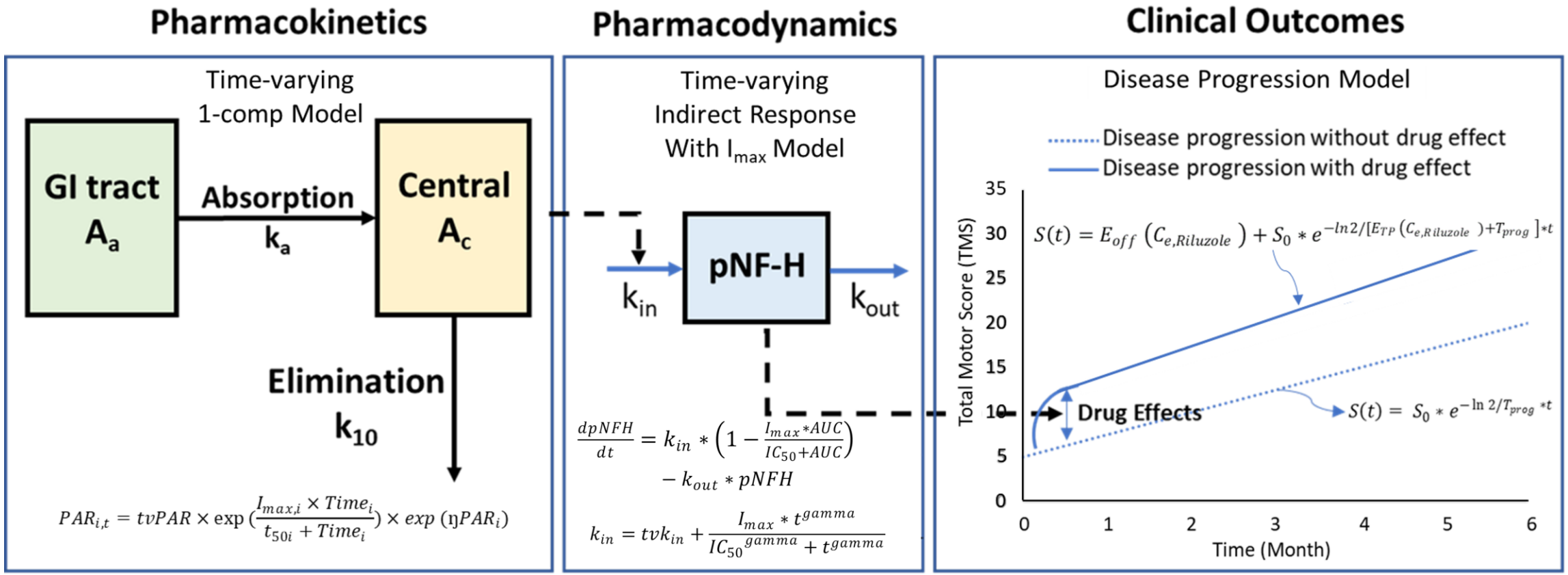


4 Optimal Dosing Regimen Design

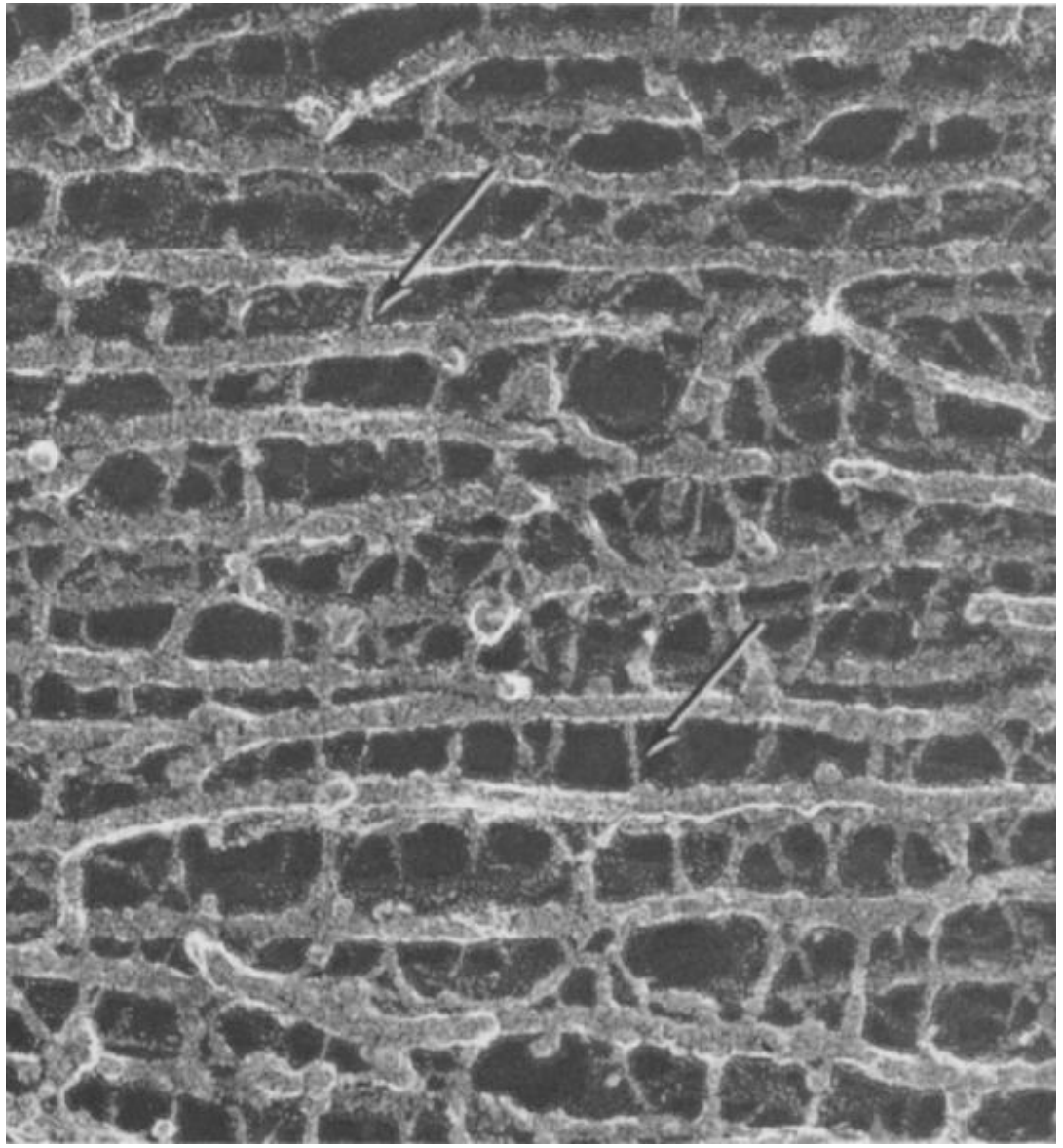
Rational PK-guided regimen
&
Individualized dosing

Summary: Understanding the natural recovery of SCI and the progressive PK/PD profile of riluzole can facilitate the development of optimal dosing regimens and future therapeutics.

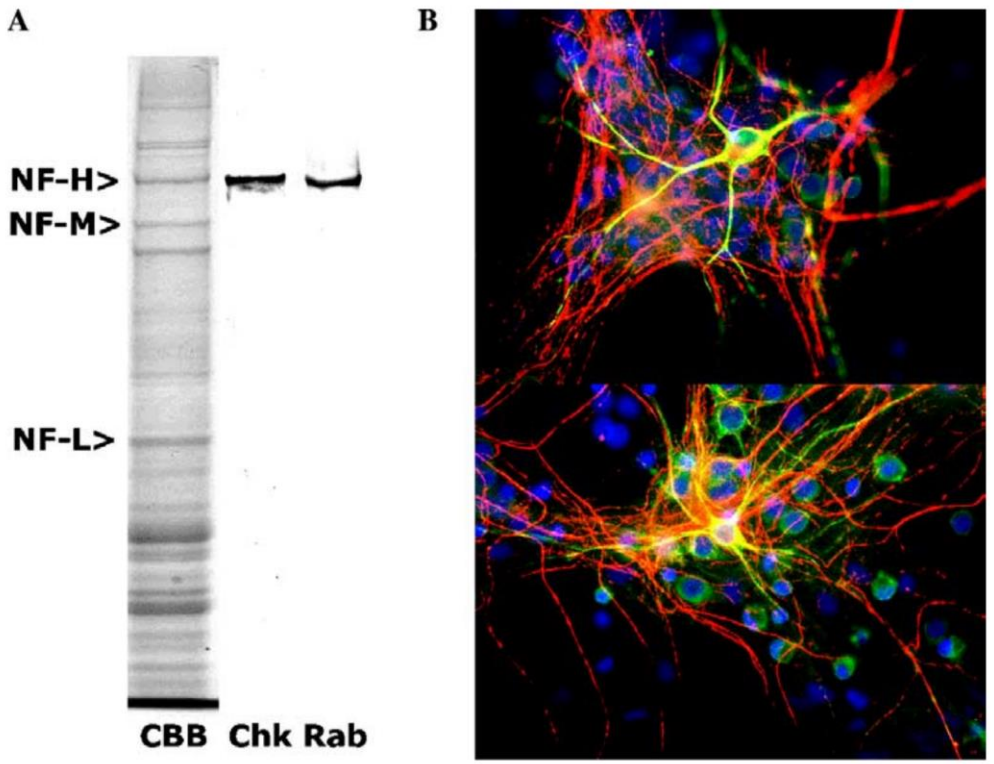
Proposed PK/PD/CO Model Scheme

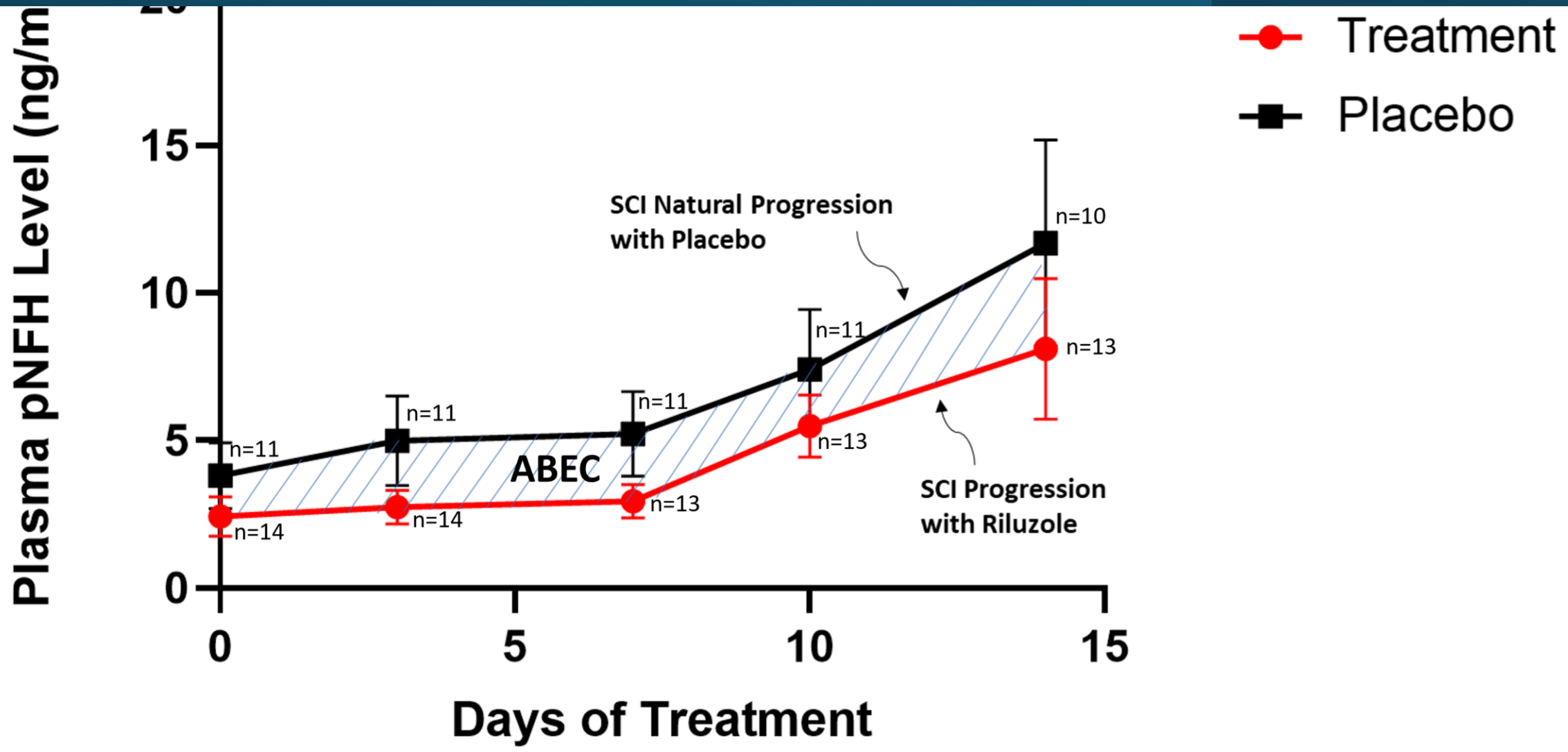


Chow DS, Nguyen A, Park J, Wu L, Toups EG, Harrop JS, Guest JD, Schmitt KM, Aarabi B, Fehlings MG, Boakye M, Grossman RG. Riluzole in Spinal Cord Injury Study (RISCIS)-Pharmacokinetic (PK) Sub-Study: An Analysis of Pharmacokinetics, Pharmacodynamics, and Impact on Axonal Degradation of Riluzole in Patients With Traumatic Cervical Spinal Cord Injury Enrolled in the RISCIS Phase III Randomized Controlled Trial. J Neurotrauma. 2023 Sep;40(17-18):1889-1906. doi: 10.1089/neu.2022.0499. PMID: 37130044.

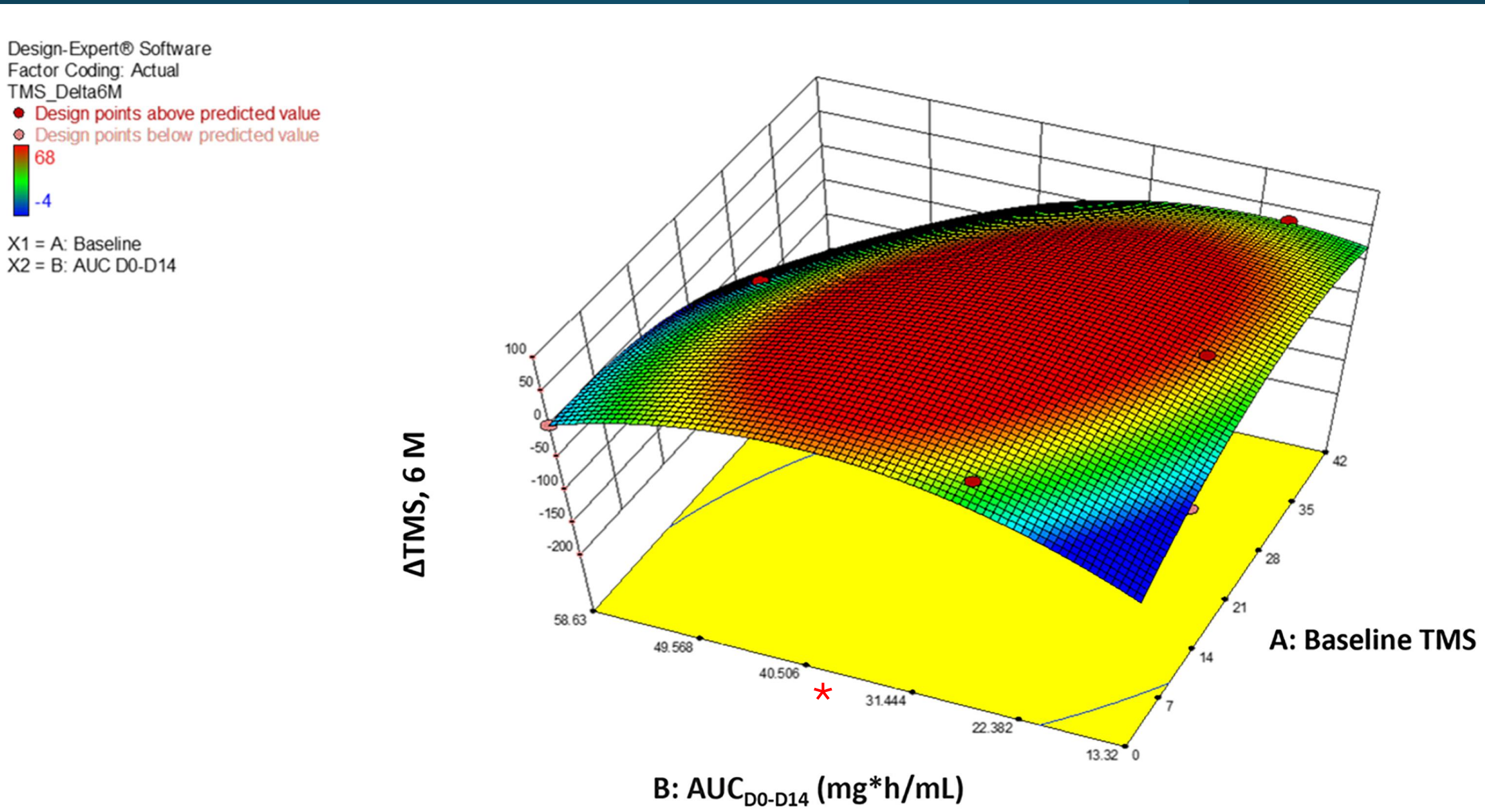


G. Shaw et al. / Biochemical and Biophysical Research Communications 336 (2005) 1268–1277





$$ABEC = \left| pNFH_{nat} * t_r - AUEC_{0-t_r} \right|$$


Design-Expert® Software
Factor Coding: Actual
TMS_Delta6M
Design points above predicted value
Design points below predicted value
68
-4
X1 = A: Baseline
X2 = B: AUC D0-D14
ΔTMS, 6 M
100
50
0
-50
-100
-150
-200
58.63
49.568
40.506
31.444
22.382
13.32
0
7
14
21
28
35
42
A: Baseline TMS
B: AUC D0-D14 (mg*h/mL)

Relevance

- **Research-** Longitudinal quality clinical data from trials and the Registry.

- **Clinicians/Clinical Care-** Platform for clinical trials and evolving clinical pathways- best practices.

- **People with SCI-** Best care to protect neurological recovery potential.

Spinal Cord Outcomes SCOPE Partnership Endeavor