A Novel Approach to Assess the Multidimensional Nature of Functional Recovery in Spinal Cord Injury Trials

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Disclosures.

No relevant disclosures.

Summary

I. Challenges in SCI Trials
   - Clinical Priorities of SCI patients

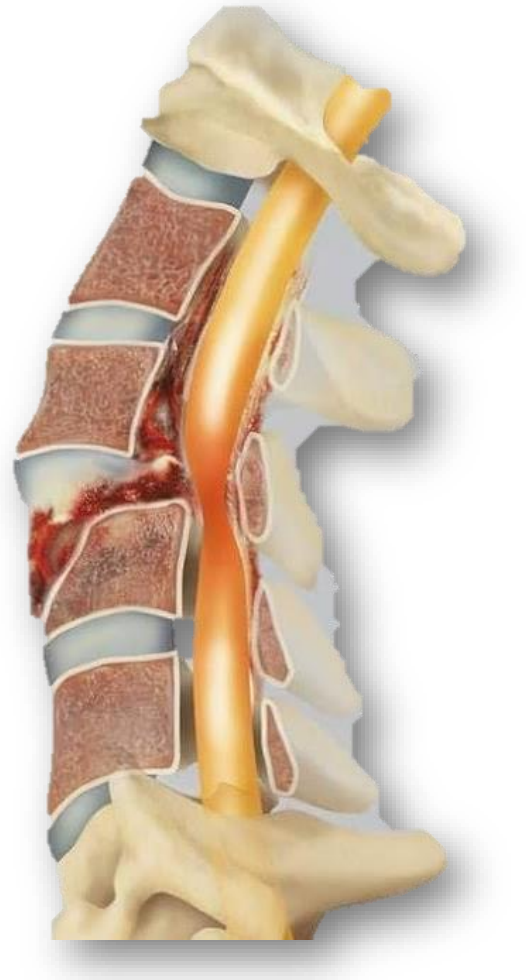
II. WHO ICF Framework

III. The Global Statistical Analysis
   - GST Application in DCM

IV. GST Application in SCI

V. Conclusion

Challenges in Spine Clinical Trial



Patient recruitment	Loss to follow-up	Heterogeneity of cases
Complex pathophysiology	Cost consideration	What is a positive effect?
Regulatory issues	Implementation issues	Shifting patient demographics

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Challenges in Clinical Trials

Heneghan et al. Trials (2017) 18:122
DOI 10.1186/s13063-017-1870-2

Trials

COMMENTARY Open Access

Why clinical trial outcomes fail to translate into benefits for patients

Carl Heneghan, Ben Goldacre and Kamal R. Mahtani

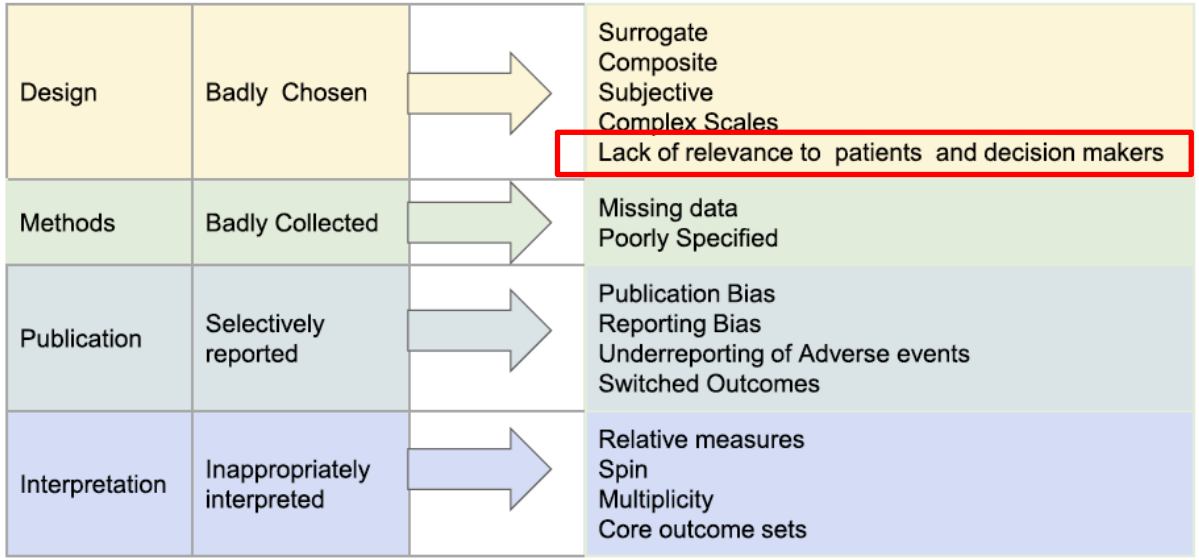

Fig. 1 Why clinical trial outcomes fail to translate into benefits for patients

Patient Priorities after SCI

CIHR IRSC Canadian Institutes of Health Research / Instituts de recherche en santé du Canada
Submitted by CIHR
Déposé par les IRSC

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The health and life priorities of individuals with spinal cord injury: A systematic review

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Abstract

Determining the priorities of individuals with spinal cord injury (SCI) can assist in aligning research priorities which ultimately improve these individuals' quality of life. This systematic review examined studies that directly surveyed people with SCI to ascertain their health priorities and life domains of importance. Twenty-four studies (combined sample of 5262) that met the inclusion criteria were identified using electronic databases (Medline, EMBASE, CINAHL, PsycINFO). The questionnaire methods and domains of importance were reviewed and described. While the questionnaires varied across the studies, a consistent set of priorities emerged. Functional recovery priorities were identified for the following areas: motor function (including arm/hand function for individuals with tetraplegia and mobility for individuals with paraplegia), bowel, bladder and sexual function. In addition, health, as well as relationships emerged as important life domains. The information from this study, which identified the priorities and domains of importance by individuals with SCI, may be useful for informing healthcare and research agenda-setting activities.

Keywords

SCI; consumer priorities; quality of life; well-being

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AUTHOR DISCLOSURE STATEMENT
The authors report no disclosures. No competing financial interests exist for any of the authors.

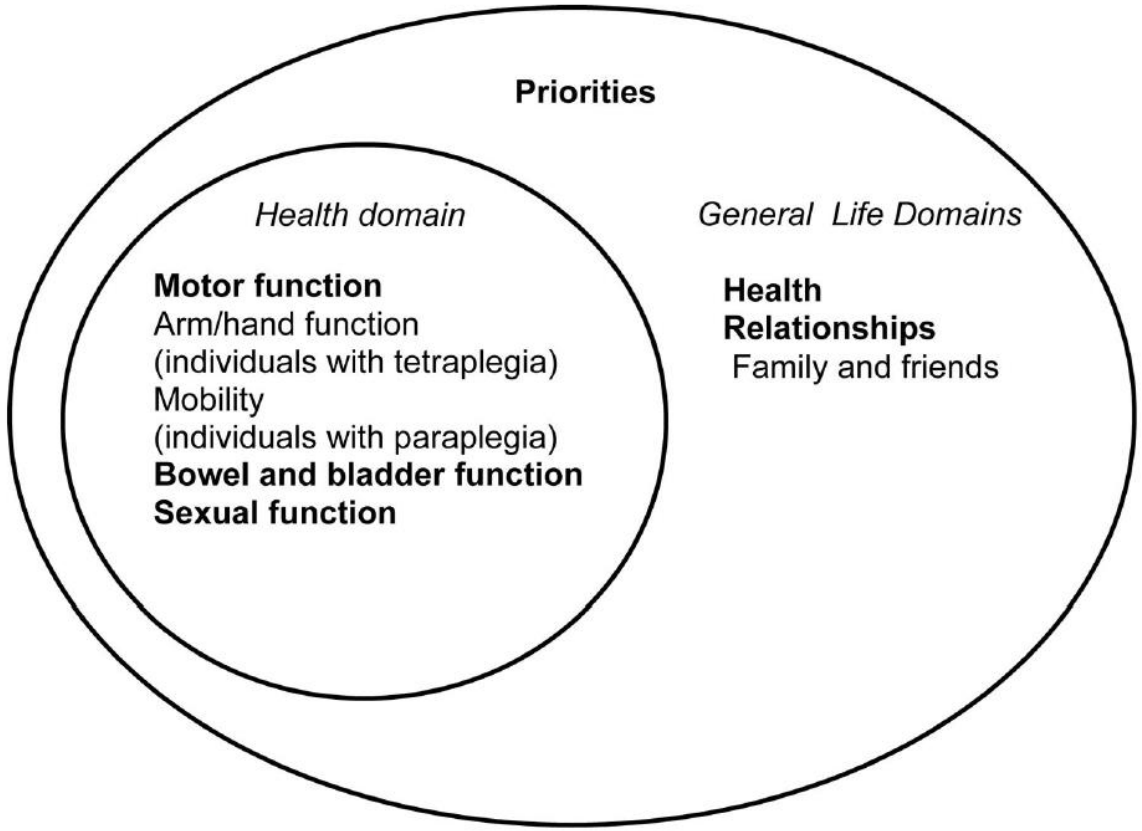


Figure 3.
Summary of review findings

J Neurotrauma. 2012 May 20; 29(8): 1548–1555

WHO Internation Classification of Functioning, Disability and Health (ICF)

WHO, 2001

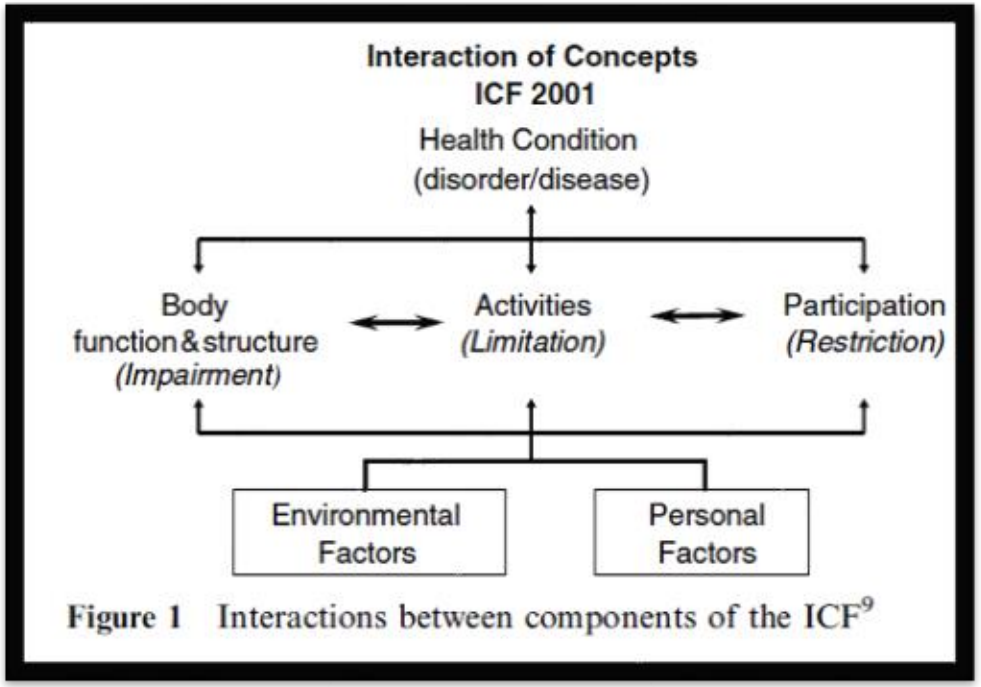
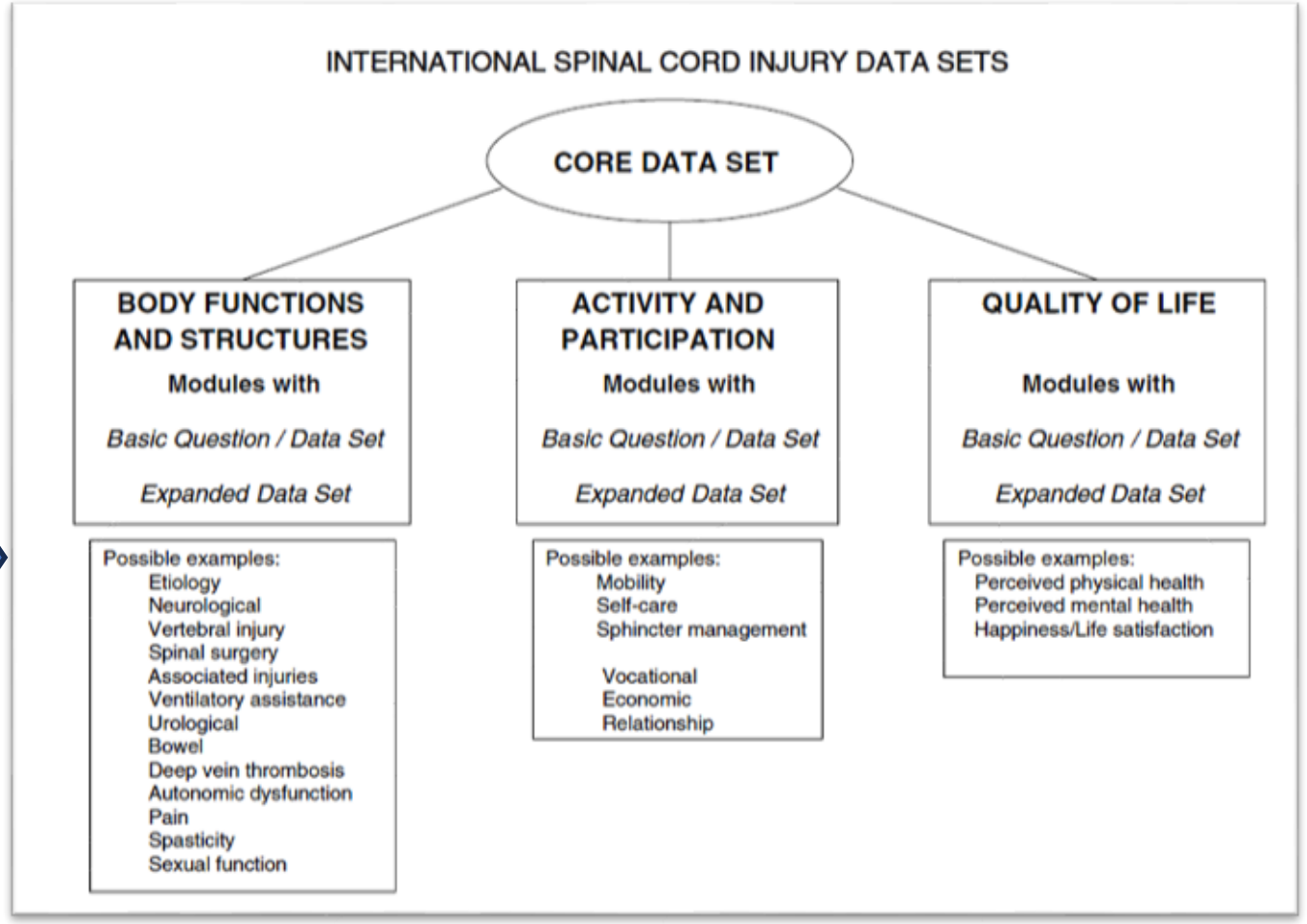
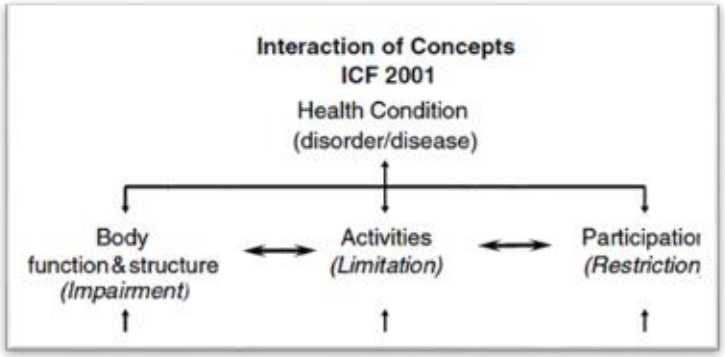


Figure 1 Interactions between components of the ICF[9]



Spinal Cord. 2009 August ; 47(8): 582–591. doi:10.1038/sc.2009.18.

WHO Internation Classification of Functioning, Disability and Health (ICF)



Old Terminology	New Terminology	Definition
Impairment	Body function/structure	-Physiological functions of body systems including psychological. Structures are anatomical parts or regions of their bodies and their components. Impairments are problems in body function or structure.
Disability	Activity	-The execution of a task by an individual. Limitations in activity are defined as difficulties an individual might experience in completing a given activity.
Handicap	Participation	-Involvement of an individual in a life situation. Restrictions to participation describe difficulties experienced by the individual in a life situation or role.

http://www.ebrsr.com

Application of ICF Framework in SCI

Table 2 Outcome measurement tools as they relate to ICF domains and potential independent variables that could influence the accuracy of the measurement and/or the appropriate interpretation of data derived from clinical therapies targeted to the CNS

International Classification of Functioning, disability and health (ICF) as ICF relates to CNS-targeted therapies for spinal cord injury

Level or domain	*Body structure and function*	*Activity*	*Participation*
What change in outcome is measured?	Improvement (or impairment), that is, Neurological or physiological	Functional capacity (or limitation)	Quality of life (or restriction)
Outcome tools (examples)	ISNCSCI scores, electrophysiology	SCIM, 10 m walk	CHART, SF-36
What factors influence outcomes within each domain?[a]	CNS integrity Neural circuits (sensory/motor)	CNS integrity Neural circuits Adaptive behaviours[a] Rehabilitation[a] Psychology/motivation[a]	CNS integrity Neural circuits Adaptive behaviours[a] Rehabilitation[a] Psychology/motivation[a] Community/family Support[a] Finances[a] Work/school[a]

Abbreviations: CHART, craig handicap and reporting technique; CNS, central nervous system; ISNCSCI, international standards for neurological classification of spinal cord injury; SF-36, short form 36; SCIM, spinal cord injury measure.
Increasing number of independent variables.
[a]Potential independent variable.

Spinal Cord **53**, 84–91 (2015). https://doi.org/10.1038/sc.2014.232

Outcome measures evolution in clinical trial

Spinal Cord (2010) 48, 674–684

www.nature.com/sc

REVIEW

Outcome measures: evolution in clinical trials of neurological/functional recovery in spinal cord injury

JF Ditunno

Thomas Jefferson University Hospital, Philadelphia, PA, USA

Finally, the linkage of body function, capacity and performance should be known before entering a phase 3 trial, especially if all measures are to be included in the primary outcome measure. It is possible to consider the use of multiple primary end points or a global statistical test.[65] These issues need to be examined on a regular basis and we must encourage and applaud the combined efforts by ASIA/ISCOS and SCOPE to update outcome measures for use in clinical trials.

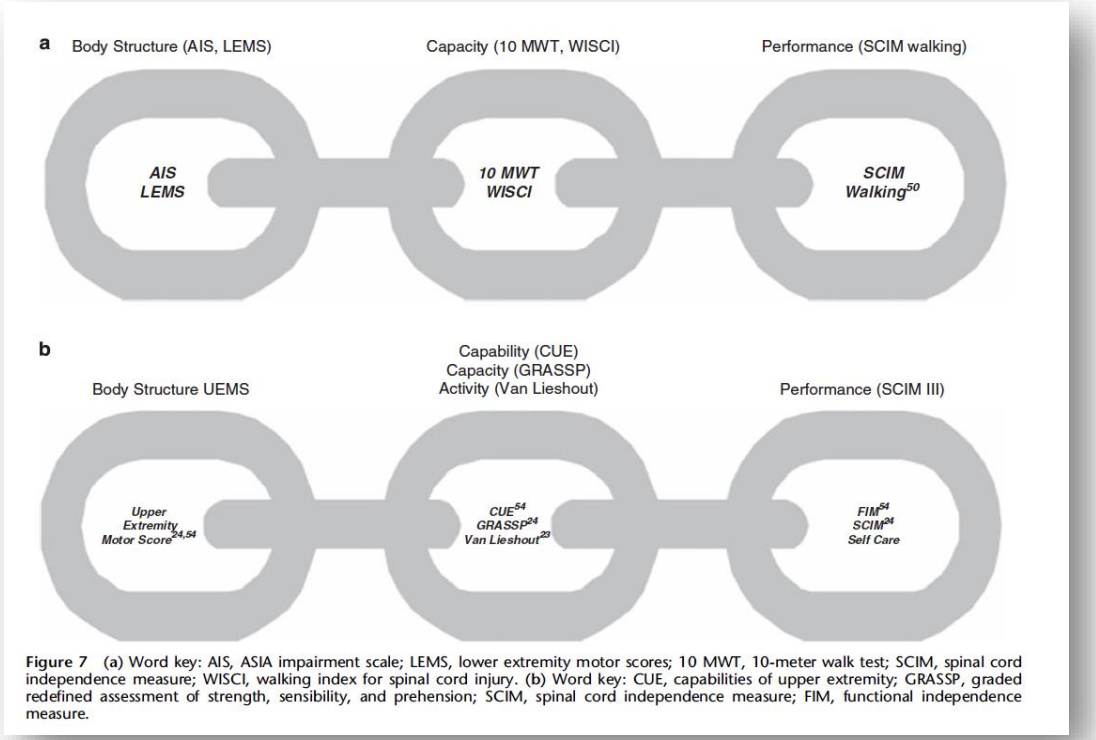


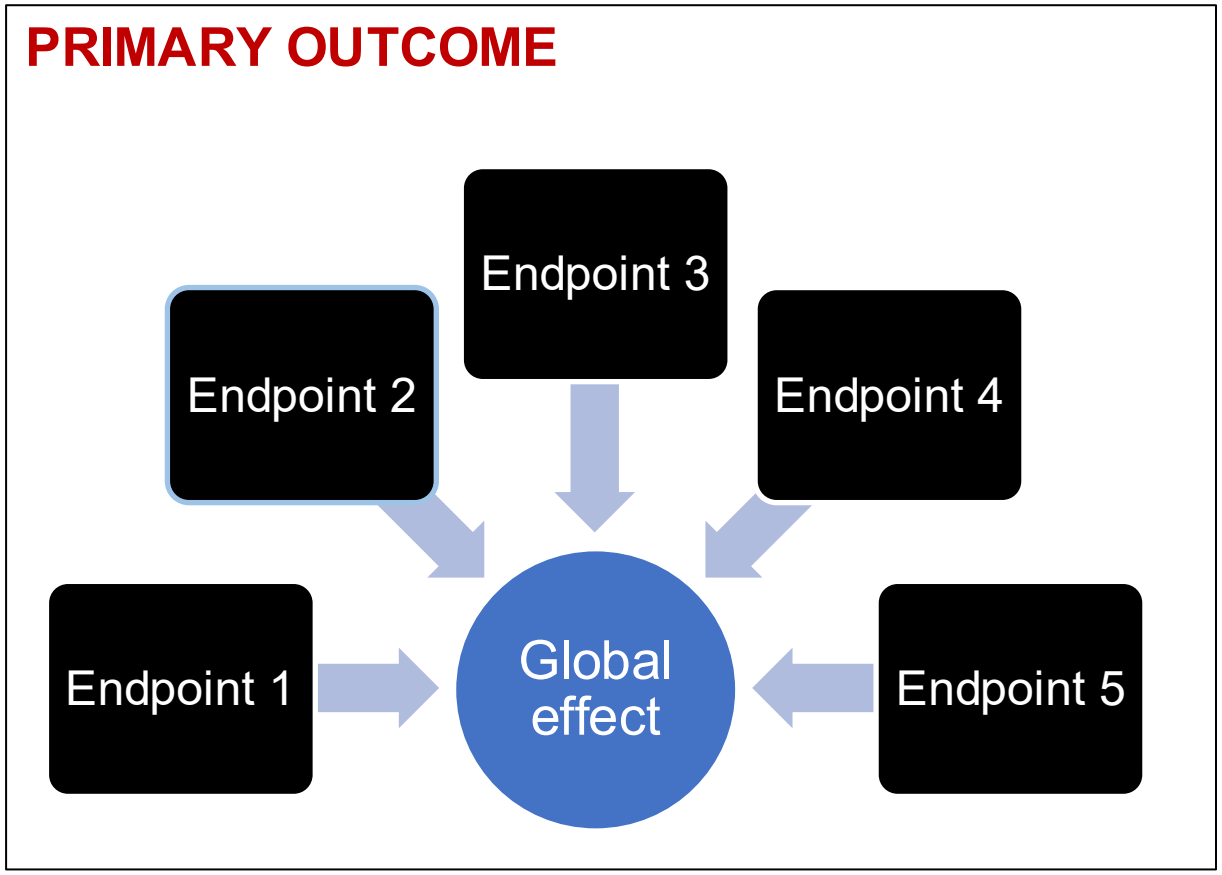
Figure 7 (a) Word key: AIS, ASIA impairment scale; LEMS, lower extremity motor scores; 10 MWT, 10-meter walk test; SCIM, spinal cord independence measure; WISCI, walking index for spinal cord injury. (b) Word key: CUE, capabilities of upper extremity; GRASSP, graded redefined assessment of strength, sensibility, and prehension; SCIM, spinal cord independence measure; FIM, functional independence measure.

Global Statistical Technique (GST)

Peter O' Brien
(Mayo Clinic)

Biometrics . 1979 Sep;35(3):549-56.

Biometrics 2005; 61:532-539

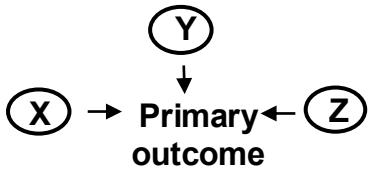


- Gives a global summary of treatment effect
- High statistical power when treatment shows benefit on majority of outcomes
- Penalizes conflicting results (e.g treatment shows both benefit and detrimental results)

Global statistical test is a validated approach.

	Method of outcome representation	Salient Features
Conventional method	Primary Outcome: X	✗ Not multidimensional
Composite outcome	Primary Outcome: X or Y or Z	✗ Difficult to use if outcomes are on different scales
Co-primary outcome	Primary Outcome: X and Y and Z	✗ Lack a global assessment of outcome

Global statistical approach (GST)

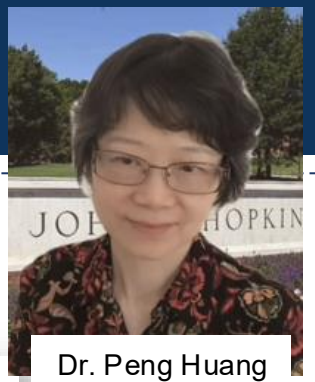


✓ **Multidimensional** → **H_0 : ranks in $treatment_A$ = ranks in $treatment_B$**

✓ **Gives a global summary of effect** → **Global Treatment Effect (GTE):**

GTE = 0 → no benefit
GTE > 0 → (+) beneficial effect
GTE < 0 → detrimental effect

Global statistical test is a validated approach



Dr. Peng Huang (Johns Hopkins University)

- NINDS-sponsored trial on creatine supplementation in Parkinson Disease
- Used a GST approach in primary endpoint
- *…" Given that PD is a multi-faceted disease, there is no single clinical measurement that reflects the full range of PD signs and symptomås*

Research

Original Investigation

Effect of Creatine Monohydrate on Clinical Progression in Patients With Parkinson Disease
A Randomized Clinical Trial

Writing Group for the NINDS Exploratory Trials in Parkinson Disease (NET-PD) Investigators

Supplemental content at jama.com

IMPORTANCE There are no treatments available to slow or prevent the progression of Parkinson disease, despite its global prevalence and significant health care burden. The National Institute of Neurological Disorders and Stroke Exploratory Trials in Parkinson Disease program was established to promote discovery of potential therapies.

OBJECTIVE To determine whether creatine monohydrate was more effective than placebo in slowing long-term clinical decline in participants with Parkinson disease.

DESIGN, SETTING, AND PATIENTS The Long-term Study 1, a multicenter, double-blind, parallel-group, placebo-controlled, 1:1 randomized efficacy trial. Participants were recruited from 45 investigative sites in the United States and Canada and included 1741 men and women with early (within 5 years of diagnosis) and treated (receiving dopaminergic therapy) Parkinson disease. Participants were enrolled from March 2007 to May 2010 and followed up until September 2013.

INTERVENTIONS Participants were randomized to placebo or creatine (10 g/d) monohydrate for a minimum of 5 years (maximum follow-up, 8 years).

MAIN OUTCOMES AND MEASURES The primary outcome measure was a difference in clinical decline from baseline to 5-year follow-up, compared between the 2 treatment groups using a global statistical test. Clinical status was defined by 5 outcome measures: Modified Rankin Scale, Symbol Digit Modalities Test, PDQ-39 Summary Index, Schwab and England Activities of Daily Living scale, and ambulatory capacity. All outcomes were coded such that higher scores indicated worse outcomes and were analyzed by a global statistical test. Higher summed ranks (range, 5-4775) indicate worse outcomes.

RESULTS The trial was terminated early for futility based on results of a planned interim analysis of participants enrolled at least 5 years prior to the date of the analysis (n = 955). The median follow-up time was 4 years. Of the 955 participants, the mean of the summed ranks for placebo was 2360 (95% CI, 2249-2470) and for creatine was 2414 (95% CI, 2304-2524). The global statistical test yielded $t_{5865.8} = -0.75$ (2-sided $P = .45$). There were no detectable differences ($P < .01$ to partially adjust for multiple comparisons) in adverse and serious adverse events by body system.

CONCLUSIONS AND RELEVANCE Among patients with early and treated Parkinson disease, treatment with creatine monohydrate for at least 5 years, compared with placebo did not improve clinical outcomes. These findings do not support the use of creatine monohydrate in patients with Parkinson disease.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT00449865

Group Information: Members of the Writing Group for the NINDS Exploratory Trials in Parkinson Disease (NET-PD) Investigators are listed at the end of this article.

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Table 2. Components of the Global Statistical Test by Treatment Group for LS-1 Cohort 1; Change From Baseline to Year 5[a]

Components Included in the Computation of Global Outcome	Treatment Group, Mean (SD)		Difference, Mean (95% CI)[b]
	Placebo (n = 478)	Creatine (n = 477)	
Ambulatory capacity score	2.8 (5.0)	3.1 (5.5)	−0.3 (−1.0 to 0.4)
Modified Rankin[c]	2.1 (1.5)	2.2 (1.6)	−0.1 (−0.3 to 0.1)
PDQ-39 Summary Index	13 (23.2)	14.2 (23.5)	−1.2 (−4.2 to 1.7)
Schwab and England ADL[d]	14.8 (26.0)	16.8 (28.3)	−2.0 (−5.5 to 1.5)
Symbol Digit Modalities[d]	4.5 (16.8)	4.9 (17.7)	−0.4 (−2.7 to 1.8)

Features of GST

Advantages

1. Useful to test a treatment's *global benefit* across different outcomes and determine whether a treatment is preferred to use.

2. *High statistical power* when treatment shows benefit on majority of outcomes.

3. *Avoids misinterpretation* of data if some outcomes show improvement but at the price of serious decline in other key target outcomes.

Limitations

1. Lose power if the objective is to detect any type of treatment difference when both beneficial and detrimental effects are seen from different outcomes.

Application of GST in DCM

Original Investigation | Surgery

Riluzole for Degenerative Cervical Myelopathy

A Secondary Analysis of the CSM-PROTECT Trial

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Abstract

IMPORTANCE The modified Japanese Orthopaedic Association (mJOA) scale is the most common scale used to represent outcomes of degenerative cervical myelopathy (DCM); however, it lacks consideration for neck pain scores and neglects the multidimensional aspect of recovery after surgery.

OBJECTIVE To use a global statistical approach that incorporates assessments of multiple outcomes to reassess the efficacy of riluzole in patients undergoing spinal surgery for DCM.

DESIGN, SETTING, AND PARTICIPANTS This was a secondary analysis of prespecified secondary end points within the Efficacy of Riluzole in Surgical Treatment for Cervical Spondylotic Myelopathy (CSM-PROTECT) trial, a multicenter, double-blind, phase 3 randomized clinical trial conducted from January 2012 to May 2017. Adult surgical patients with DCM with moderate to severe myelopathy (mJOA scale score of 8-14) were randomized to receive either riluzole or placebo. The present study was conducted from July to December 2023.

INTERVENTION Riluzole (50 mg twice daily) or placebo for a total of 6 weeks, including 2 weeks prior to surgery and 4 weeks following surgery.

MAIN OUTCOMES AND MEASURES The primary outcome measure was a difference in clinical improvement from baseline to 1-year follow-up, assessed using a global statistical test (GST). The 36-Item Short Form Health Survey Physical Component Score (SF-36 PCS), arm and neck pain numeric rating scale (NRS) scores, American Spinal Injury Association (ASIA) motor score, and Nurick grade were combined into a single summary statistic known as the global treatment effect (GTE).

RESULTS Overall, 290 patients (riluzole group, 141; placebo group, 149; mean [SD] age, 59 [10.1] years; 161 [56%] male) were included. Riluzole showed a significantly higher probability of global improvement compared with placebo at 1-year follow-up (GTE, 0.08; 95% CI, 0.00-0.16; $P = .02$). A similar favorable global response was seen at 35 days and 6 months (GTE for both, 0.07; 95% CI, −0.01 to 0.15; $P = .04$), although the results were not statistically significant. Riluzole-treated patients had at least a 54% likelihood of achieving better outcomes at 1 year compared with the placebo group. The ASIA motor score and neck and arm pain NRS combination at 1 year provided the best-fit parsimonious model for detecting a benefit of riluzole (GTE, 0.11; 95% CI, 0.02-0.16; $P = .007$).

CONCLUSIONS AND RELEVANCE In this secondary analysis of the CSM-PROTECT trial using a global outcome technique, riluzole was associated with improved clinical outcomes in patients with

(continued)

Key Points

Question Can a composite outcome be used to represent the diverse aspects of functional recovery in patients with degenerative cervical myelopathy (DCM) to assess the potential efficacy of perioperative riluzole in optimizing recovery?

Findings In this secondary analysis of a randomized clinical trial including 290 surgical patients with DCM, use of a global statistical approach combining 5 distinct outcome scales revealed a superior global treatment effect with riluzole compared with placebo, with a statistically significant difference in clinical improvement at 1-year follow-up.

Meaning In this study, treatment with riluzole was associated with an improved composite outcome among patients with DCM managed surgically.

+ Invited Commentary

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

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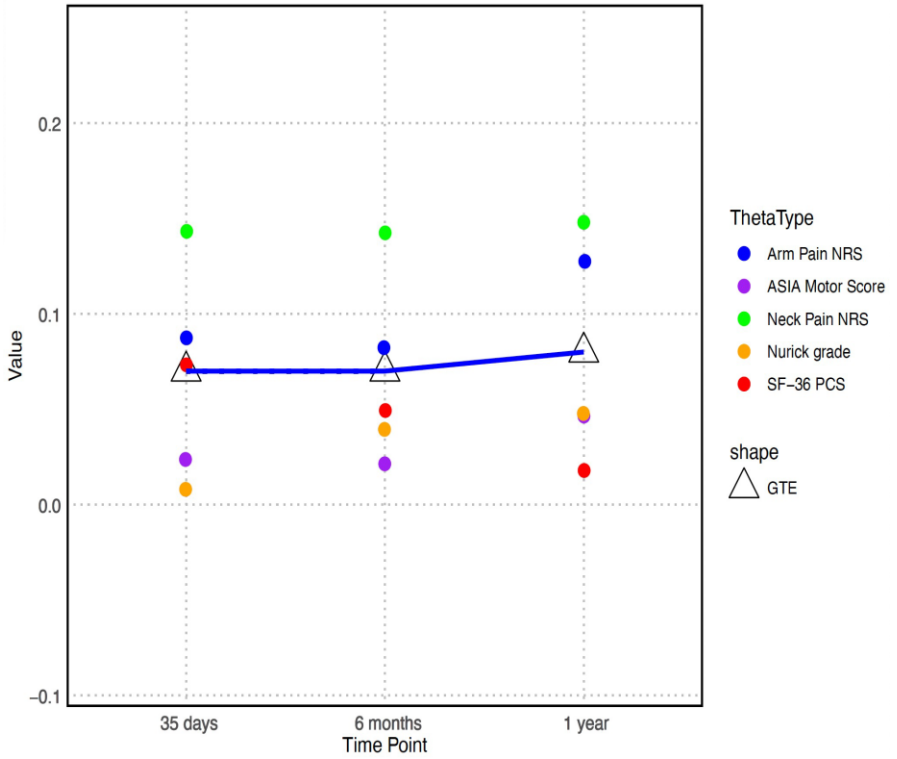
CSM-Protect Trial Analysis using GST

JAMA Network Open

Table 2. Application of a global statistical approach in the estimation of GTE and in significance testing

	Global treatment effect computation						Hypothesis testing		
	Theta Values					GTE (SD)	Mean Rank-sum (placebo)	Mean Rank-sum (Riluzole)	p value
	SF-36 PCS	Neck Pain NRS	Arm Pain NRS	ASIA Motor Score	Nurick Grade				
Direction	+	-	-	+	-				
35 days	0.07	0.14	0.09	0.02	0.01	0.07 (0.04)	704.10	752.30	0.04
6 months	0.05	0.14	0.08	0.02	0.04	0.07 (0.04)	703.20	753.20	0.04
1 year	0.016	0.15	0.13	0.05	0.05	0.08 (0.04)	698.80	757.80	0.02

$$probablity\ of\ improvementin\ Riluzole = \frac{(1+0.08)}{2} = 54\%$$



International Campaign for Cures of Spinal Cord Injury Paralysis (ICCP) - 2007

Review

Guidelines for the conduct of clinical trials for spinal cord injury (SCI) as developed by the ICCP panel: clinical trial outcome measures

JD Steeves*[,1], D Lammertse[2], A Curt[1], JW Fawcett[3], MH Tuszynski[4], JF Ditunno[5], PH Ellaway[6], MG Fehlings[7], JD Guest[8], N Kleitman[9], PF Bartlett[10], AR Blight[11], V Dietz[12], BH Dobkin[13], R Grossman[14], D Short[15], M Nakamura[16], WP Coleman[17], M Gaviria[18] and A Privat[18]

An international panel reviewed the methodology for clinical trials of spinal cord injury (SCI), and provided recommendations for the valid conduct of future trials. This is the second of four papers. It examines clinical trial end points that have been used previously, reviews alternative outcome tools and identifie unmet needs for demonstrating the efficcy of an experimental intervention after SCI. The panel focused on outcome measures that are relevant to clinical trials of experimental cell-based and pharmaceutical drug treatments. Outcome measures are of three main classes: (1) those that provide an anatomical or neurological assessment for the connectivity of the spinal cord, (2) those that categorize a subject's functional ability to engage in activities of daily living, and (3) those that measure an individual's quality of life (QoL). The American Spinal Injury Association impairment scale forms the standard basis for measuring neurologic outcomes. Various electrophysiological measures and imaging tools are in development, which may provide more precise information on functional changes following treatment and/or the therapeutic action of experimental agents. When compared to appropriate controls, an improved functional outcome, in response to an experimental treatment, is the necessary goal of a clinical trial program. Several new functional outcome tools are being developed for measuring an individual's ability to engage in activities of daily living. Such clinical end points will need to be incorporated into Phase 2 and Phase 3 trials. QoL measures often do not correlate tightly with the above outcome tools, but may need to form part of Phase 3 trial measures.

Three Main Classes of Outcome Measures:

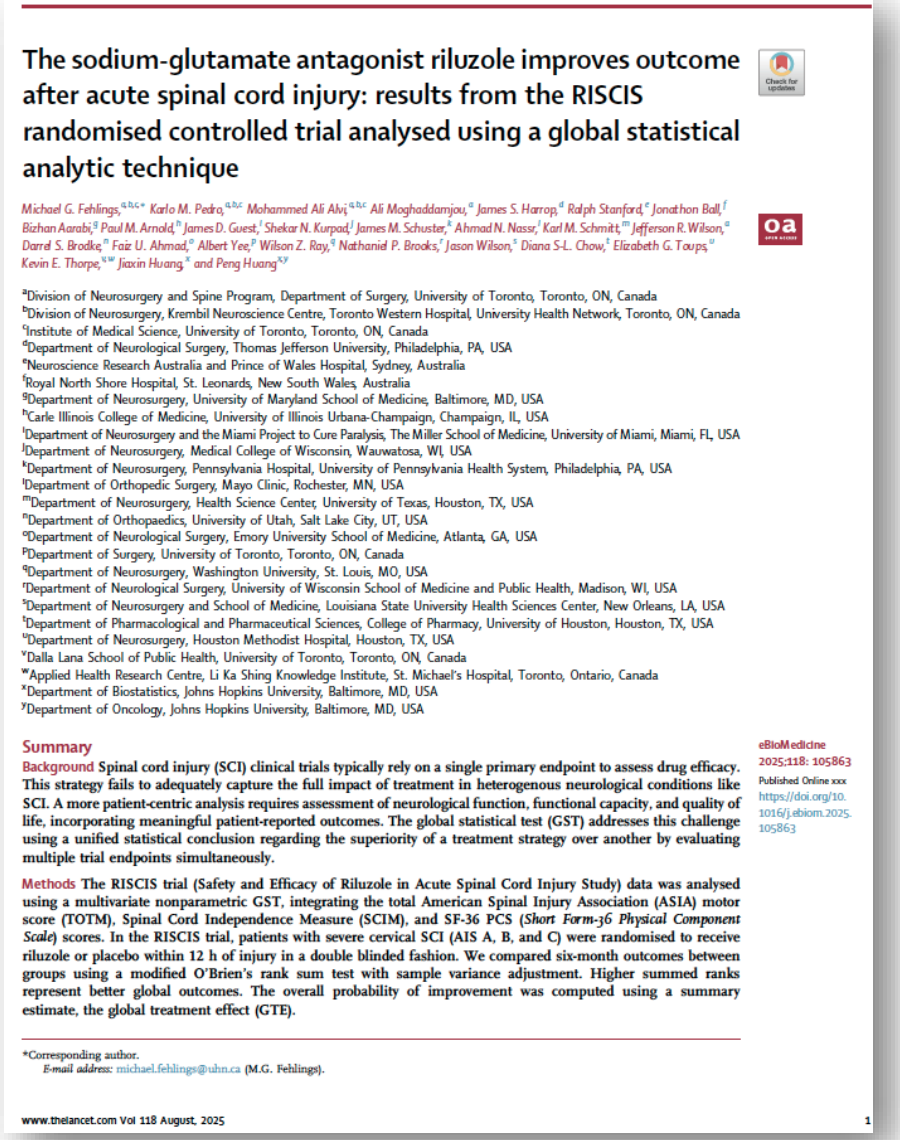
1. Measures that ***provide an anatomical or neurological assessment*** for the connectivity of the spinal cord
2. Measures that categorize a subject's ***functional ability*** to engage in activities of daily living
3. Measures that assess individual's ***quality of life***

" Improved functional outcomes,.., is the necessary goal of a clinical trial program.."

" QoL measures may need to form part of Phase 3 trial measures."

Application of GST in SCI Research

EBioMedicine
Published by THE LANCET



The sodium-glutamate antagonist riluzole improves outcome after acute spinal cord injury: results from the RISCIS randomised controlled trial analysed using a global statistical analytic technique

Michael G. Fehlings,[a,b,c,*] Karlo M. Pedro,[a,b,c] Mohammed Ali Alvi,[a,b,c] Ali Moghaddamjou,[a] James S. Harrop,[d] Ralph Stanford,[e] Jonathon Ball,[f] Bizhan Aarabi,[g] Paul M. Arnold,[h] James D. Guest,[i] Shekar N. Kurpad,[j] James M. Schuster,[k] Ahmad N. Nassr,[l] Karl M. Schmitt,[m] Jefferson R. Wilson,[a] Darrel S. Brodke,[n] Faiz U. Ahmad,[o] Albert Yee,[p] Wilson Z. Ray,[q] Nathaniel P. Brooks,[r] Jason Wilson,[s] Diana S-L. Chow,[t] Elizabeth G. Toups,[u] Kevin E. Thorpe,[v,w] Jiaxin Huang,[x] and Peng Huang[x,y]

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Summary

Background Spinal cord injury (SCI) clinical trials typically rely on a single primary endpoint to assess drug efficacy. This strategy fails to adequately capture the full impact of treatment in heterogenous neurological conditions like SCI. A more patient-centric analysis requires assessment of neurological function, functional capacity, and quality of life, incorporating meaningful patient-reported outcomes. The global statistical test (GST) addresses this challenge using a unified statistical conclusion regarding the superiority of a treatment strategy over another by evaluating multiple trial endpoints simultaneously.

Methods The RISCIS trial (Safety and Efficacy of Riluzole in Acute Spinal Cord Injury Study) data was analysed using a multivariate nonparametric GST, integrating the total American Spinal Injury Association (ASIA) motor score (TOTM), Spinal Cord Independence Measure (SCIM), and SF-36 PCS (*Short Form-36 Physical Component Scale*) scores. In the RISCIS trial, patients with severe cervical SCI (AIS A, B, and C) were randomised to receive riluzole or placebo within 12 h of injury in a double blinded fashion. We compared six-month outcomes between groups using a modified O'Brien's rank sum test with sample variance adjustment. Higher summed ranks represent better global outcomes. The overall probability of improvement was computed using a summary estimate, the global treatment effect (GTE).

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RISCIS Trial Re-analysis using GST

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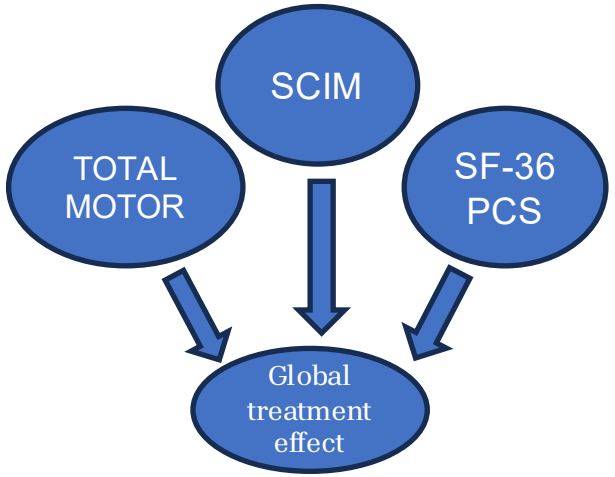

Riluzole is a drug option in severe SCI.

Table 2. Univariate testing vs GST analysis of outcomes (change from baseline to 6 months) between riluzole and placebo

	Outcome Scale	Student t-test		Wilcoxon rank sum test		GST		GTE
		t-statistics	p value	z-statistics	p value	t-statistics [a]	p value	
All Patients (n = 131)	SCIM	-1.85	0.97	-2.00	0.97	-	-	0.13
	TOTM	-0.59	0.72	-0.64	0.74	-	-	0.06
	SF-36 PCS	-0.75	0.77	-0.80	0.79	-	-	0.11
	All scales	-	-	-	-	1.76	0.04	0.10
AIS A (n = 65)	SCIM	-0.77	0.78	-1.11	0.87	-	-	0.29
	TOTM	0.64	0.26	-0.27	0.61	-	-	0.05
	SF-36 PCS	-0.99	0.33	-0.63	0.73	-	-	0.14
	All scales	-	-	-	-	2.11	0.02	0.16
AIS B (n = 27)	SCIM	-2.06	0.97	-2.13	0.98	-	-	0.24
	TOTM	-0.32	0.63	0	0.50	-	-	0.03
	SF-36 PCS	-0.00	0.99	-0.31	0.62	-	-	0.10
	All scales	-	-	-	-	0.70	0.26	0.10
AIS C (n = 38)	SCIM	-0.18	0.57	-0.43	0.66	-	-	-0.20
	TOTM	-0.73	0.76	-1.02	0.85	-	-	0.28
	SF-36 PCS	0.22	0.41	0.35	0.36	-	-	-0.03
	All scales	-	-	-	-	0.16	0.44	0.02

GST – global statistical test; GTE – global treatment effect; SCIM – Spinal Cord Independence Measure; SF-36 PCS – Short Form Health Survey Physical Component Score; TOTM – total motor score

[a] Using O'Brien's rank sum type test with variance adjustment for testing the general nonparametric Behrens-Fisher hypothesis

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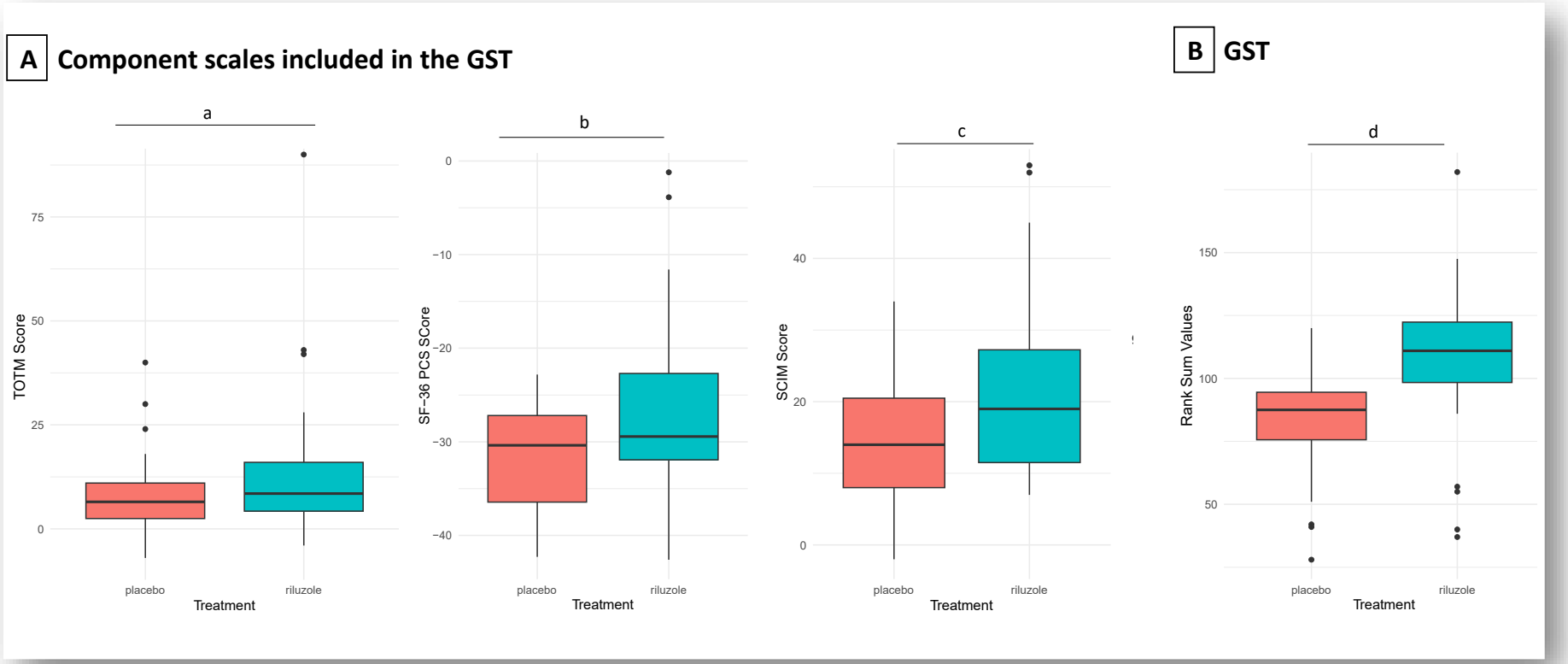
Figure 2. Boxplot of individual outcome scale (change from baseline to 6 months) compared between placebo and riluzole group in *AIS A* subgroup (n=65). (A.) Total Motor Score (TOTM), Short Form Physical Component Score (SF-36 PCS), and Spinal Cord Independence Measure (SCIM). (B) The boxplot representing the rank sum used for the GST analysis was added for comparative purpose. All p values were derived using t-test.



[a]P= 0.26 by student t-test.

[b]P=0.84 by student t-test.

[c]P=0.78 by student t-test.

[d]P=0.02 by O'Brien modified t-test

Benefits of the GST Approach

COMPOSITE ENDPOINT

- Potential higher statistical power
- Difficult to construct a composite score if outcomes are in different scales
- Results are not straightforward to interpret (which outcome drives the result?)

PRIMARY OUTCOME: any of the

Endpoint 1

Endpoint 2

Endpoint 3

Endpoint 4

Endpoint 5

CO-PRIMARY ENDPOINT

- True multifactorial test
- Lower power compared to other tests
- Lack global assessment of treatment benefit

PRIMARY OUTCOME:

Endpoint 1 and

Endpoint 2 and

Endpoint 3 and

Endpoint 4 and

Endpoint 5 and

GST Analysis using Experimental Data

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Global test statistics for treatment effect of stroke and traumatic brain injury in rats with administration of bone marrow stromal cells

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Abstract

Because no single test measures disability in rats with middle cerebral artery occlusion/traumatic brain injury (MCAo/TBI), multiple tests are needed to assess the effect of bone marrow stromal cell (MSC) on functional recovery. Testing the treatment effect on each outcome at the 0.05 level without adjusting for multiple outcomes can increase type I error. Therefore, we applied the global test to evaluate a common MSC dose effect on multiple outcomes in two applications: (i) MCAo rats with the MSC dose of zero (BPS), 1 $\times$10^6 and 3 $\times$10^6, and (ii) TBI rats with the MSC dose of zero, 1 $\times$10^6, 2 $\times$10^6 and 4 $\times$10^6, administered intravenously at 1 day after injury. For the MCAo rats, 3 $\times$10^6 MSCs improved the 14 day functional recovery (P B 0.05) compared to the controls. TBI rats with the MSC dose 4 $\times$10^6 were improved significantly at 1 month compared to controls, rats with 1 $\times$10^6 or 2 $\times$10^6 MSCs (P B 0.05). The global test on multiple outcomes is more efficient than a single outcome when treatment effects are consistent. The less correlation among the outcomes, the more power and, therefore, the higher efficiency of the global test. We demonstrated that the global test for continuous outcomes could be implemented under careful statistical modeling and proper data transformation.

Keywords: Stroke; Traumatic brain injury; Rat; Data analysis; Global test

Table 2
MSC dose response on 14 days functional recovery

Treatment	Adhesive-Removal (s) mean ± S.D.	Rotarod (%) mean ± S.D.	mNSS (score) mean ± S.D.
Pre-treatment (baseline)			
Control ($n = 6$)	116.0 ± 8.0	43.3 ± 21.3	8.3 ± 1.5
1×10^6 MSCs ($n = 6$)	111.7 ± 13.3	35.9 ± 21.7	8.7 ± 2.3
3×10^6 MSCs ($n = 7$)	106.9 ± 23.8	49.1 ± 22.4	8.6 ± 2.8
Post-treatment (14 d)			
Control	86.3 ± 28.0	68.8 ± 16.1	7.3 ± 0.8
1×10^6 MSCs[a]	52.0 ± 22.2	65.6 ± 21.5	5.2 ± 3.1
3×10^6 MSCs[a,b]	33.6 ± 15.8	73.5 ± 18.3	4.6 ± 1.8

[a] Significant improvement on functional recovery compared to controls based on the global test.
[b] $P = 0.06$, marginal differences on functional recovery between MSC dose 1×10^6 and 3×10^6.

The global test on multiple outcomes is more efficient than a single outcome when treatment effects are consistent

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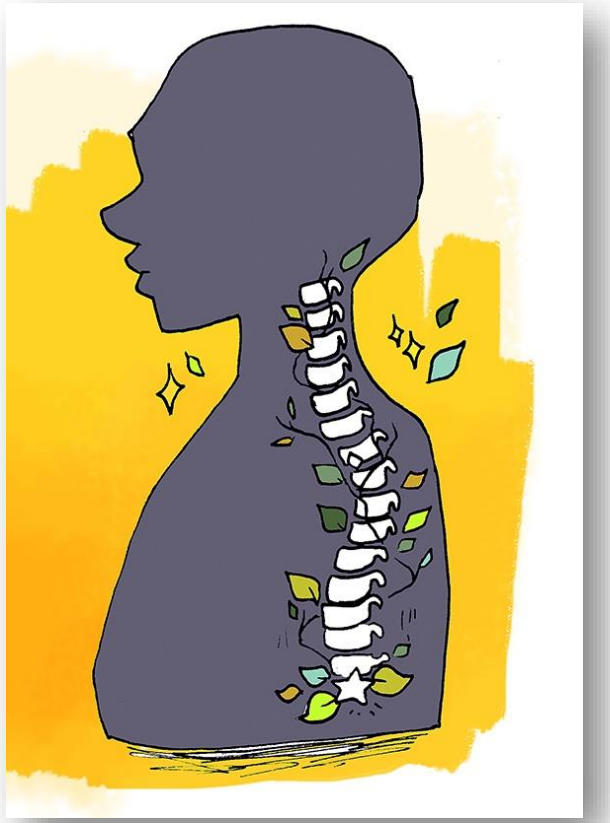
CONCLUSION

- Heterogeneity is inherent in the SCI population – *this is not a limitation*
- The use of *single outcome measure* have limitations in representing outcomes in SCI
- GST is a potential solution to *analyze trials with multiple endpoints*
- GST is a *non-parametric, adaptable, and truly multidimensional* solution for clinical trial analysis



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- Thank you very much!