Journal of Neurotrauma

DOI: 10.1089/neu.2022.0450

The Importance of Prospective Registries and Clinical Research Networks in the Evolution of Spinal Cord Injury Care

Authors and institutions

Margot Kelly-Hedrik[1], Muhammad M. Abd-El-Barr[2], Bizhan Aarabi[3], Armin Curt[4], Susan P. Howley[5], James S. Harrop[6] Steven Kirshblum[7], Christopher J. Neal[8], Vanessa Noonan[9], Christine Park[1], Beatrice Ugiliweneza[10], Charles Tator[11], Elizabeth G. Toups[12], Michael G. Fehling[11], Theresa Williamson[13], James D. Guest[14]

1. Duke University School of Medicine, Durham, NC, USA

2. Department of Neurosurgery, Duke University, Durham, NC, USA

3. University of Maryland School of Medicine, MD, USA

4. Spinal Cord Injury Center, Balgrist University Hospital, Zurich, Switzerland

5. Christopher & Dana Reeve Foundation, Short Hills, NJ, USA

6. Thomas Jefferson University Hospital, Philadelphia, PA, USA

7. Rutgers New Jersey Medical School, Newark, NJ; Kessler Institute for Rehabilitation, West Orange, NJ; Kessler Foundation, West Orange, NJ

8. Division of Neurosurgery, Walter Reed National Military Medical Center, Bethesda, MD, USA

9. Praxis Spinal Cord Institute, Vancouver, British Columbia, Canada

10. Kentucky Spinal Cord Injury Research Center, Louisville, KY, USA

11. Division of Neurosurgery and Spine Program, Department of Surgery, University of Toronto,

Toronto, Canada

12. Department of Neurosurgery, Houston Methodist Hospital, Houston, TX, USA

13. Department of Neurosurgery, Massachusetts General Hospital, Boston, MA, USA

14. Neurological Surgery and The Miami Project to Cure Paralysis, University of Miami, Miami,

USA

Running Title: Spinal cord injury registries

Keywords: Spinal Cord Injury, Registry, Digital Twin, Counterfactual, Personalized Medicine

Corresponding author: James Guest MD, Ph.D., FACS

University of Miami Miller School of medicine

jguest@med.miami.edu

ORCID-ID 0000-0003-0931-0286

Author Addresses

Margot Kelly-Hedrik

DUMC 2927

40 Duke Medicine Circle

Durham NC 27710

206-602-4545

margot.kellyhedrick@duke.edu

Muhammad M. Abd-El-Barr

200 Trent Drive DUMC 2480

Durham NC 27710

919-681-1948

m.abdelbarr@duke.edu

Bizhan Aarabi

22 South Greene Street, S12D

Baltimore, MD 21201

410-328-3162

baarabi@som.umaryland.edu

Armin Curt

<Zentrum für Paraplegie>

Forchstrasse 340

8008 Zürich, Schweiz

+41 44 386 3901

Armin.Curt@balgrist.ch

Susan P. Howley

15 Davenport Place

Morristown, New Jersey 07960

973-332-8303

showley4@gmail.com

James S. Harrop

909 Walnut Street, 3rd floor

Philadelphia, PA 1910

215-955-7959

James.harrop@jefferson.edu

Journal of Neurotrauma
The Importance of Prospective Registries and Clinical Research Networks in the Evolution of Spinal Cord Injury Care (DOI: 10.1089/neu.2022.0450)

Steven Kirshblum

1199 Pleasant Valley Way

West Orange, NJ 07052

973-972-2800

skirshblum@selectmedical.com

Christopher J. Neal

5010 Alta Vista Rd

Bethesda, MD

202-491-8991

chrisjneal@verizon.net

Vanessa Noonan

6400-818 West 10th Avenue

Vancouver, BC V5Z 1M9

t 604 827 2424

vnoonan@praxisinstitute.org

Christine Park

200 Trent Dr.

Durham, NC 27710

775-772-8063

christine.park@duke.ed

Journal of Neurotrauma
The Importance of Prospective Registries and Clinical Research Networks in the Evolution of Spinal Cord Injury Care (DOI: 10.1089/neu.2022.0450)

Beatrice Ugiliweneza

Beatrice Ugiliweneza

Kentucky Spinal Cord Injury Research Center

511 South Floyd St., Room 616

Louisville, KY 40202

502-852-8060

Charles Tator

399 Bathurst Street, Rm 4W-433

Toronto, Ontario M5T 2S8

416-603-5889

Charles.Tator@uhn.ca

Elizabeth G. Toups

82 N Wooded Brook Circle

The Woodlands, 77382

832-722-4055

elizabethtoups@outlook.com

Michael G. Fehling

399 Bathurst Street 4WW-449

Toronto, Ontario M5T-2S8

416-603-5072

Michael.Fehlings@uhn.ca

Journal of Neurotrauma
The Importance of Prospective Registries and Clinical Research Networks in the Evolution of Spinal Cord Injury Care (DOI: 10.1089/neu.2022.0450)

Theresa Williamson

55 Fruit Street, Wang 745

Boston, MA 02114

617-643-5687

TWILLIAMSON1@mgh.harvard.edu

James D. Guest

The Miami Project to Cure Paralysis

1095 NW 14th Terrace

Miami, FL. 33136

305-243-7144

jguest@med.miami.edu

Journal of Neurotrauma
The Importance of Prospective Registries and Clinical Research Networks in the Evolution of Spinal Cord Injury Care (DOI: 10.1089/neu.2022.0450)

Abstract: Only 100 years ago, traumatic spinal cord injury (SCI) was commonly lethal. Today, most people who sustain SCI survive with continual efforts to improve their quality of life and neurological outcomes. SCI epidemiology is changing as preventative interventions reduce injuries in younger individuals, and there is an increased incidence of incomplete injuries in aging populations. Early treatment has become more intensive with decompressive surgery and proactive interventions to improve spinal cord perfusion. Accurate data, including specialized outcome measures, are crucial to understanding the impact of epidemiological and treatment trends. Dedicated SCI clinical research and data networks and registries have been established in the United States, Canada, Europe, and several other countries. We review four registry networks, the North American Clinical Trials Network (NACTN) SCI Registry, the National Spinal Cord Injury Model Systems (SCIMS) Database, the Rick Hansen SCI Registry (RHSCIR), and the European Multi-Center Study about Spinal Cord Injury Study (EMSCI). We compare the registries' focuses, data platforms, advanced analytics use, and impacts. We also describe how registries' data can be combined with EHR or shared using federated analysis to protect registrants' identities. These registries have identified changes in epidemiology, recovery patterns, complication incidence, and the impact of practice changes like early decompression. They've also revealed latent disease-modifying factors, helped develop clinical trial stratification models, and served as matched control groups in clinical trials. Advancing SCI clinical science for personalized medicine requires advanced analytical techniques, including machine learning and includes counterfactual analysis, and the creation of digital twins. Registries and other data sources help drive innovation in SCI clinical science.

Word count: 250

Journal of Neurotrauma
The Importance of Prospective Registries and Clinical Research Networks in the Evolution of Spinal Cord Injury Care (DOI: 10.1089/neu.2022.0450)

Introduction

Spinal cord injury is an incurable condition affecting a person's entire life after injury onset. If one is injured at a young age, there is now a prospect of living 50 years or more with SCI. Before World War II, most people who sustained traumatic spinal cord injuries had limited survival. Advances in rehabilitation care pioneered at centers such as Stoke Mandeville in the United Kingdom[1] and the Spinal Cord Injury Model Systems program[2] in the United States (US) increased the post-SCI lifespan. The role of surgical decompression of the injured spinal cord, now widely practiced, remained controversial until the 21st century[3]. Advances in stabilization at the injury scene, resuscitation, and earlier operative management have improved acute survival and neurological outcomes[4]. Efforts were taken to unify care across the acute injury to rehabilitation phases. As a result of improved survival, there was a need to accurately track patients' recovery and further understand the challenges experienced during the chronic phase of SCI. Some countries such as Taiwan[5], Scotland[6], Sweden[7], and other Nordic countries have established national health care and patient registries that can identify all persons with SCI in their country, contributing significantly to our understanding of living with SCI over time[8]. Aside from longitudinal studies, Switzerland has applied a census-like strategy to capture a cross-sectional snapshot of the entire adult population with SCI in the SwiSCI Cohort Study[9]. National registries are more challenging in larger countries, such as the United States, that lack a universal health care system.

Although a complete national SCI registry does not exist in the United States, several large data analytic registries have been developed since 1970[2], providing significant samples for analyzing trends in aggregated data. Optimally, such registries are prospective and follow patients longitudinally, so the data is entered based on pre-defined protocols. Such uniform data can be used to improve clinical care directly (e.g., by changing practice guidelines), inform those planning clinical trials to increase their effectiveness and efficiency, measure healthcare results, and monitor epidemiological trends. Further, registries may provide a platform to recruit people with SCI for clinical studies. Guidance for creating and operating registries in the United States has been published by the Agency for Healthcare Research and Quality[10].

Journal of Neurotrauma
The Importance of Prospective Registries and Clinical Research Networks in the Evolution of Spinal Cord Injury Care (DOI: 10.1089/neu.2022.0450)

SCI registry datasets optimally track individuals from the moment of injury through their lifespan, although that is often not feasible. Here, we review four SCI registries (US, Canadian, and European) associated with clinical trial networks, their contributions to the field of SCI care, and their limitations. We then discuss advanced applications in the use of SCI datasets.

Review of SCI Registries

The traumatic SCI datasets are the US National SCIMS Database and NACTN SCI Registry, the Canadian RHSCIR, and the European EMSCI Study [11]. Each of these registries has contributed to improving the care of patients living with SCI and has specific strengths and limitations.

The SCI Model Systems

The SCI Model Systems was founded in 1970 to create a network of rehabilitation centers across the U.S. providing care for patients with SCI[2]. The lack of existing care programs linking acute and rehabilitative care was specifically viewed as suboptimal. SCIMS was conceptually influenced by the successes in the UK at Stoke Mandeville[12] and the Royal Perth Hospital in Australia[13]. Thus, the program aimed to develop a comprehensive care system linking acute and rehabilitative care[14] and to stimulate research on the long-term outcomes of SCI as described in the Federal Register[15]. To achieve this second aim, the program founded the National Spinal Cord Injury Model Systems (SCIMS) Database in 1975 to aggregate prospectively acquired data across the network's sites[16]. The funding for the SCI Model Systems was initially under the Rehabilitation Services Administration (RSA), then the National Institute of Handicapped Research (NIHR), and later, the National Institute on Disability, Independent Living, and Rehabilitation Research (NIDILRR). The SCIMS also provides competitive funding to the current member centers for independent and collaborative research studies supported by NIDILRR. The collected data continually updates the database hosted at the National Spinal Cord Injury Statistical Center (NSCISC) at the University of Alabama at Birmingham. The goals of the database are to explore the demographics of patients with SCI, track outcomes, identify trends across time, and facilitate research.

Journal of Neurotrauma
The Importance of Prospective Registries and Clinical Research Networks in the Evolution of Spinal Cord Injury Care (DOI: 10.1089/neu.2022.0450)

The database includes data from 29 centers representing over 35,000 patients as of March 2021. The SCIMS captures data from ~6% to 13% of new traumatic SCIs[17]. Data collected includes demographic information of participants and injury characteristics (e.g., cause of injury, neurological level). Outcomes included are impairment (neurological scores), functional (independence of daily living, caregiving needs), medical (hospitalization, physical health outcomes, complications), psychological (satisfaction with life), employment (employment status, income), and survival (mortality, cause of death).

As the longest-standing and largest US SCI database, SCIMS has tracked outcomes for several decades after the injury, from which trends in SCI have been documented (e.g., demographics, mechanism of injury) since the 1970s[17-22]. Early in its evolution, the incidence of complications in specialized and non-specialized units was assessed, finding fewer severe complications, such as pressure sores, in specialized units[13]. The database has also contributed to understanding a broad range of medical and psychosocial outcomes following SCI. These have been highlighted in several specific publications dedicated to outcomes from the SCIMS, including in a textbook[23], special issues in the Archives of Physical Medicine and Rehabilitation in 1999, 2004, 2011, 2016, and 2021, and other publications[24]. Topics include neurological recovery [25,26], rehabilitation outcomes[18], and parameters including the impact of body weight[27,28] and other factors impacting recovery, including depression and access to mental health care[29,30] Medicare and Medicaid coverage changes[31], socioeconomic stress[32], discharge disposition[33], health literacy, and racial disparities as it relates to SCI care[34]. The SCIMS collaborative network has also been used to examine the treatment of comorbid conditions, including randomized controlled trials for depression[35,36] and hyperlipidemia in people with tetraplegia[37]. The Model Systems Knowledge Translation Center generates significant amounts of evidence-based KT from research conducted by SCIMS centers that have contributed to our understanding of SCI[38] and also provided important educational resources.

The National SCIMS Database website has two publicly available tools. The first query is the leading cause of SCI among different demographic groups for a given time frame. The second is a life expectancy calculator for people more than one-year post-SCI who have

not regained all sensory and motor functions. SCIMS also provides resources for knowledge translation.

Although SCIMS was conceived to address the care fragmentation characterized by a separation of acute care and rehabilitation centers in the United States[14], this has continued to be an issue limiting care coordination in the United States[14]. With its initial assessment occurring at rehabilitation admission, SCIMS has limited detailed prospective data regarding the acute management of SCI. That data can be bolstered from administrative sources or from the National Trauma Data Bank[39].

The North American Clinical Trials Network

The North American Clinical Trials Network (NACTN) was established by Dr. Robert Grossman in 2004 in cooperation with the Christopher & Dana Reeve Foundation. It aimed to facilitate the translation of neuroprotective and regenerative therapies in the face of known organizational, regulatory, and financial barriers[40]. Multiple stakeholders contributed to its structure and registry design, including experts in acute SCI care, statistics, pharmaceuticals, and rehabilitationists with outcome measure expertise. Governance standards were created, as well as a methodology to share data. NACTN is an active consortium of tertiary medical centers with neurosurgical units in the United States and Canada, as well as dedicated clinical coordinating, data management, and pharmacological centers[41]. Fifteen sites have contributed registry data. Walter Reed National Military Medical Center and Brooke Army Medical Center have participated in NACTN. The Telemedicine and Advanced Technology Research Center and the United States Army Medical Research Acquisitions Activity have provided important financial support.

The goals of NACTN include developing clinical trials and performing research into the early management and outcome of acute SCI as defined through the registry methodology. The current prospective registry of 1,017 patients supports these goals. Each entry captures a patient's demographics, injury characteristics, treatment, complications, discharge disposition, and neurological and functional outcomes up to one-year post-SCI. Events related to transfer from other centers, triage, and surgical timing are captured in

detail. This clinical data is used to assess longitudinal epidemiological changes in injury and recovery pertinent to NACTN's patient population, define best practices for acute SCI, develop new analytics methods[42], and provide matched control datasets for clinical trials.

NACTN has contributed to our knowledge of the acute phase of SCI, documenting events and interventions immediately after SCI and during hospitalization. Several NACTN accomplishments were reported in the Journal of Neurosurgery special issue in 2012[35]. In separate articles in the present Journal of Neurotrauma issue, we have described NACTN's more recent activities, some of which we will highlight here. One of the first major NACTN reports systematically detailed the type and rates of complications during acute SCI[31]. Subsequent data analyses investigated the effect of hospital-acquired illnesses, including pneumonia, on neurological recovery. Pneumonia was determined to be a disease-modifying factor linked to less neurological recovery at six months[43], a finding consistent with other prospective studies[44]. In a NACTN study, patient and injury characteristics associated with developing pneumonia were determined [45]. Notably, the development of pneumonia, wound infection, and sepsis was not associated with using steroids, a controversial topic reported in other studies[46].

One central mission of NACTN is "to carry out clinical trials of the comparative effectiveness of new therapies for SCI." NACTN thus formed a Therapeutic Selection Committee (TSC) to compare and select promising therapeutics for clinical trials to undertake this aim. The TSC aims to conduct an impartial and objective evaluation of prospective therapeutics, including drug repurposing candidates, through evidence evaluation and an iterative Delphi process[47]. Riluzole, a sodium-channel blocker approved for Amyotrophic Lateral Sclerosis (ALS) and with potential neuroprotective effects in acute SCI, was chosen as the first treatment for study in NACTN [48]. This off-patent, orally delivered drug offered several practical advantages, including lower costs and more straightforward regulatory issues. NACTN centers participated in a prospective, single-arm, open-label multicenter study of Riluzole used within 12 hours post-injury that indicated the possibility of improvement in motor scores in the treatment group. To strengthen the trial design, participants from the NACTN SCI Registry were closely matched to enrolled subjects as a control group[48]. The phase I study reported that oral Riluzole was safe with a

Journal of Neurotrauma
The Importance of Prospective Registries and Clinical Research Networks in the Evolution of Spinal Cord Injury Care (DOI: 10.1089/neu.2022.0450)

promising efficacy signal[49]. Important pharmacological findings established perturbations of drug distribution in the initial weeks after SCI and were incorporated into the subsequent pivotal study[50]. Regarding knowledge translation, NACTN has also significantly influenced the adoption of early spinal cord decompression[51].

Institutional memory and experience are critical to the success of health institutions through improved decision-making. NACTN principal investigators include those with decades of experience who actively mentor new network members. The participation of NACTN study coordinators in both the registry and institutional SCI clinical trials creates valuable skill sets that can be applied to new studies.

The European Multicenter Study about Spinal Cord Injury Database

The European Multicenter Study about Spinal Cord Injury Database [11] is a prospective, longitudinal cohort study founded in 2001 that includes 23 neurorehabilitation centers across Europe. The goal of EMSCI is to document the natural history of SCI and to examine investigator-driven research questions[52]. Participating centers send their data to a central data storage at the University of Zurich, where it is queried and cleared. The registry data includes a standardized set of neurological, physical, and functional (e.g., 6-minute walk test, Spinal Cord Independence Measure (SCIM)) evaluations at the time of injury and 4, 12, 24, and 48 weeks later. Assessments of pain, hand function, urology outcomes, and neurophysiological assessments are also collected. EMSCI provides annual training workshops for physicians and clinicians to improve data quality, and EMSCI has been ISO 9001:2015 certified since August 2010. As of October 2020, over 5,000 patients were included in the study. EMSCI is supported by the International Foundation for Research in Paraplegia (initial founding partner), Wings for Life, and the Deutsche Stiftung Querschnittlähmung. EMSCI does not prospectively collect detailed acute care information in its registry.

The EMSCI investigators have contributed to advances in our understanding of neurorehabilitation–including optimizing physical therapy, predicting and quantifying motor recovery, and retrospective studies examining the influence of commonly used drugs such as gabapentinoids on neurological recovery[11,53]. The analysis of EMSCI data has

Journal of Neurotrauma
The Importance of Prospective Registries and Clinical Research Networks in the Evolution of Spinal Cord Injury Care (DOI: 10.1089/neu.2022.0450)

been used to create algorithms to predict walking without assistance one year after injury based on baseline characteristics[54], to test walking recovery assisted by the Lokomat robot[55], and to develop stratification tools improving recovery prediction[56]. EMSCI has published several recommendations regarding the conduct of clinical SCI trials[57]. In addition, EMSCI serves as a clinical trial network to test the anti-Nogo antibody therapeutic[58,59] and to introduce and validate new outcome measures such as Graded Redefined Assessment of Strength, Sensibility, and Prehension (GRASSP)[60] and the Spinal Cord Ability Ruler (SCAR)[61].

EMSCI offers a free, web-based calculator for the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI), the international standard developed by the American Spinal Injury Association and the International Spinal Cord Society[62] (https://ais.emsci.org/).

The Canadian Rick Hansen SCI Registry

The Canadian Rick Hansen SCI Registry is a prospective, observational registry of traumatic SCI in Canada[63]. It has collected data from over 30 acute and rehab facilities with over 10,600 participants since its inception in 2004. Eligible patients are approached for consent. Data collected follows the patient's journey and include socio-demographics, medical history, injury details (e.g., cause of SCI), diagnosis, and neurology variables (i.e., ISNCSCI). The registry also includes the treatment and recovery course of the patient: admission and discharge details, procedures (e.g., surgery, intraoperative adverse events), interventions, and outcomes (e.g., SCIM, quality of life, respiratory function, pain, complications). A community follow-up is conducted on consenting participants at 1, 2, 5, and 10 years after discharge with the goal of continuing to follow patients until the time of death[63]. For participants who are missed or do not want to complete the questionnaires, a minimal data set is collected on all eligible patients at the sites using medical chart abstraction and administrative linkages.

The data from the registry has been used to explore many clinical and research questions in both longitudinal and cross-sectional studies and to identify potential research participants from within the database. RHSCIR investigators examined predictors

Journal of Neurotrauma
The Importance of Prospective Registries and Clinical Research Networks in the Evolution of Spinal Cord Injury Care (DOI: 10.1089/neu.2022.0450)

of functional independence, mental health, and life satisfaction[64], predictors of severe spasticity[65], and neurological outcomes[66]following SCI. Given observed heterogeneity in outcomes, a decision tree for initial stratification of patients into groups for clinical research, including the AO spine fracture classification, was developed using the registry[67]. Data from the registry has also been used to look at outcomes of subpopulations, including patients with traumatic cauda equina syndrome[68], the elderly[69], and comparing those who live in a rural area versus an urban area[70] given Canada's vast rural regions. A retrospective analysis of data from the RHSCIR network indicated a benefit in motor score recovery associated with early surgery (<24h)[71]. After surveying the opinion of Canadian surgeons regarding who should receive early spinal decompression surgery and actual performance data from the registry, a disparity was observed, mainly accounted for by administrative factors such as triage and transfer delays from outside hospitals [72,73]. This registry has contributed to identifying knowledge gaps and assessed the logistical feasibility of recruiting participants to therapeutics clinical trials[74]. RHSCIR sites have also been part of clinical studies such as the Canadian Multicentre CSF Monitoring and Biomarker (CAMPER)[75] (ClinicalTrials.gov Identifier: NCT01279811) Study and, more recently, the Canadian-American Spinal Cord Perfusion Pressure Monitoring and Biomarker (CASPER) Study (ClinicalTrials.gov Identifier: NCT03911492). Using the registry as a framework, the Access to Care Timing Model seeks to identify significant gaps in SCI care and delivery in Canada[76].

More recently, the importance of non-traumatic spinal cord dysfunction (NTSCD) has been recognized. In 2020, RHSCIR rehabilitation facilities began collecting data on patients with NTSCD to better understand the epidemiology, patient journey, and care.

Canadian researchers developed an algorithm using Canadian Institutes of Health Research administrative health data to identify cases of NTSCD[77]. The use of an NTSCD algorithm is being explored to supplement NTSCD data in RHSCIR, given the difficulty of identifying eligible cases. This approach could inform the patient journey for diagnoses such as degenerative cervical myelopathy, a population that increasingly represents nearly half of SCI[78,79]. Advanced data analytics tools such as machine learning have been applied to the patient-level data to develop a more accurate algorithm to predict post-SCI

mortality[80]. In terms of tools and knowledge translation (KT), Praxis has developed an ISNCSCI Algorithm (similar to EMSCI), which is used to enhance the quality of ISNCSCI data in RHSCIR and is also used by other SCI registries (e.g., SCIMS). To enhance KT, sites receive reports (operational and clinical) twice yearly, calls are scheduled to review them, and an annual report is produced.

The value of SCI Networks and Registries

Together, these 4 North American and European registries have contributed significantly to research and clinical practice concerning the prognosis, management, and longer-term outcomes of patients with SCI. This has included identifying the evolving characteristics of the SCI patient, the ability of healthcare systems to treat these patients, and engaging researchers, clinicians, governments, healthcare companies, and society to achieve improved outcomes. Notably, the data has been important for prognostication in the clinical setting. Some prognostic factors may be unmodifiable, such as patient age or severity of the injury. Others are potentially actionable to improve the recovery trajectory[81], such as the timing of surgery[51], prevention of complications[43], timely and adequate rehabilitation, and social support.

In establishing recovery benchmarks, the registries have also helped to determine clinically meaningful clinical trial outcomes. For example, data compiled from NACTN, SCIMS, and EMSCI has been used to set benchmarks for outcomes six months after traumatic thoracic SCI as a comparison group for an early phase industry trial[82]. Data from SCIMS and EMSCI contributed to developing suggested outcome measures for phase II clinical trials for patients with AIS-A SCI[83]. As evidenced by these examples, there have been times when registry and industry teams have worked collaboratively to determine answers to clinical and research questions to improve SCI care. In their role as clinical networks, they have supplied critical and sustained infrastructure. As the amount and nature of data are constantly evolving in medicine, it is reasonable to reflect on how these registries and networks –or datasets – could evolve in parallel[84,85].

Journal of Neurotrauma
The Importance of Prospective Registries and Clinical Research Networks in the Evolution of Spinal Cord Injury Care (DOI: 10.1089/neu.2022.0450)

Other Registry Datasets

Our review is not intended to include all reported registries exhaustively. In 2011-12, the World Health Organization, in cooperation with the International Spinal Cord Society, published a detailed global survey of incidence, prevalence, and injury causes[86], and several other national and regional registries exist[87-90]. In China, a network initiated by Dr. Wise Young has supported therapeutics clinical trials[91]. Likewise, registry data is globally underrepresented in low- and middle-income countries, with inroads being made in the Middle East and Africa[92,93]. Several spinal surgery registries seek to inform the cost-effectiveness, safety, and efficacy of interventions[94]. The Transforming Research and Clinical Knowledge in Spinal Cord Injury (TRACK-SCI) Program at UCSF published data on 160 participants[85] and on the clinical implementation of an SCI blood pressure support protocol[95]. Several studies have utilized the American College of Surgeons Trauma Quality Improvement Program (TQIP) to assess performance questions and complication risk factors in acute SCI[96,97]. TQIP has defined SMART goals as performance measures, including being Specific, Measurable, Achievable, Relevant and realistic, and Timely.

Clinical Trials versus Registries as Data Sources

Data curation and real-time surveillance for inconsistencies are generally more limited in registries than in clinical trials employing professional contract research organizations (CROs). The Institute of Medicine published the workshop "Assuring Data Quality and Validity in Clinical Trials for Regulatory Decision Making"[98], and the US Agency for Healthcare Research and Quality has published a manual describing common sources of registry data error[99]. Ideally, procedures to ensure registry data quality are applied at the local enrollment site and centrally at the coordinating center and data repository[100].

The Sygen clinical study is an exemplary trial with significant contributions to the SCI field through extensive data-sharing[101,102]. However, it is important to understand the differences between who is enrolled in registries and clinical trials. Registries typically have fewer exclusion criteria, such as age and comorbid conditions, than clinical trials and are thus more representative of the injury spectrum. Trials enroll a restricted subset of the SCI population according to criteria optimized for the trial goals. Clinical trial participants in

the placebo and treatment groups may not be representative of patients not enrolled in trials if they have received special treatment. For example, in the Sygen trial, all patients received steroids, a care standard at that time, yet the data are often treated as if equivalent to a non-treated placebo group. In some instances, clinical trial data is not made accessible for sharing, limiting the study's impact, even if negative. This is an ethical problem because clinical trials utilize public resources and have a reporting responsibility to their enrolled participants[103]. Clinical trials funded by the National Institutes of Health are required by Federal statute to register and report their results using Clinicaltrials.gov. Since 2007, industry-sponsored studies regulated by the Food and Drug Administration also have mandated reporting requirements. Registry data could contribute to decisions by regulatory authorities if there is adequate data quality assurance, data protection, and well-defined consent regarding data uses [104]. As a clinical trial network, NACTN has conducted clinical trials with close CRO oversight and auditing[105], as well as enrolling in the registry, but participants are not double-enrolled. When both a clinical trial and registry are running in parallel, patients not meeting the criteria for trial inclusion may be enrolled in the registry, which may create a selection bias. The resources and expertise to achieve complete follow-up are usually greater when participants are enrolled in clinical trials. Further, the hypothesis of a clinical study is established a priori, while in registry studies hypotheses are often explored after data is collected. Thus the ability to draw causal inferences from registry data is may be more limited[106].

Registries and Care Standards

The datasets discussed herein derive from networks with a general consensus regarding optimal care practices, recognizing these may be in evolution and apply to different post-injury time frames. Within NACTN, compliance to optimal care practices is not systematically tracked as registries usually do not monitor individual institutions. However, it is possible in those networks tracking acute care to generally assess performance regarding benchmarks such as the timing of surgical decompression[51,71,107], blood pressure support[108], incidence of complications[96], time to tracheostomy[109], and triage and transport times to definitive care[110]. Registry data could contribute to decisions

by regulatory authorities if there is adequate data quality assurance, data protection, and well-defined consent regarding data uses [104].

Limitations of Registries

One factor to consider is that registries are voluntary, and agreement to participate and commit to follow-up may influence the inclusion of participants due to language, culture, and socioeconomic variables. Barriers to clinical trial participation have been described by the National Academies of Sciences[111]. Richard-Denis et al. studied for differences between patients who either agreed to enroll in the Rick Hansen SCI Registry or refused and found higher morbidity, older age, and less frequent medical follow-up in those who declined[112]. In the previously mentioned SwiSCI Cohort Study, those declining participation were more likely to have a non-traumatic injury and to be older[113]. The potential underrepresentation of minorities may also influence the generalizability of data from registries[114]. Demographic representativeness was assessed by comparing the National SCIMS Database to the Uniform Data System for Medical Rehabilitation (UDSMR), a dataset capturing a high proportion of all rehabilitation admissions in the US, and SCIMS demographics did not differ meaningfully from the larger population [115]. NACTN centers Registry participation is likely more difficult for those living rurally and those who receive care in non-academic centers. Generally, sophisticated US database studies have tended to be performed on data primarily drawn from regions associated with prominent academic centers[116]. Multinational registries such as EMSCI that span different nations and jurisdictions have complex challenges to balance representation and generalizability. However, the differences in administrative and clinical standards may provide insight into the potential impact of different medical systems and SCI care environments on clinical outcomes. Differences in demographics, health insurance, acute care policies, and rehabilitation standards may influence outcomes. As in other conditions, center effects may exist[117].

Looking to the Future: Registry Evolution and Advanced Data Methodologies

Digital information is vastly easier to share than paper-based records, although the risks of disclosing sensitive information require identity protection. It can also be

configured to facilitate data searching, retrievals, and analysis. Additional levels of organization and classification are required for data mining approaches.

Harmonized Datasets and Data Sharing

Predictive power is increased by larger numbers of observations[51]. Data aggregation requires interoperability, such as harmonized data dictionaries and data fields between differing sources. Ideally, data across registries would be readily comparable[118]. For example, international standards for the neurological exam have been crucial to allowing comparability between registries[119]. One effort to standardize reporting is the International Spinal Cord Injury Core Data Set[120] and the NINDS Common Data Element project[121]. These were developed to align with the International Classification of Function, Disability, and Health (ICF) with input from the International Spinal Cord Society and the American Spinal Injury Association.

Harmonization efforts have also included mapping the National SCIMS Database to the ICF[122]. Important outcome measures often undergo evolution, and being able to compare the prior data obtained using earlier measures is another important harmonization step. Crosswalks are algorithms that provide methodologies to match fields in separate datasets or outcome measures, such as allowing the Functional Independence Measure and SCIM to be aggregated for analysis[123].

Sharing data between registries in different countries has complex requirements, especially for personal data extracted from EGR systems. One methodology to protect patient data is federated analysis[124]. Federated analytics is a new decentralized paradigm to address data governance and privacy issues in which the computational analysis (code) is shared and then run at each site on encrypted data, with only the analysis results being shared[125]. This methodology prevents the reconstruction of individual data and has been tested for multi-site functional MRI machine learning [126].

The Future of Prospective SCI Registries: Will They Continue to be Needed?

As we are increasingly immersed in “real-time, real-world” personalized electronic health record (EHR) data, it is worth considering whether prospective registry datasets may eventually become obsolete due to less expensive alternative sources of similar data.

Journal of Neurotrauma
The Importance of Prospective Registries and Clinical Research Networks in the Evolution of Spinal Cord Injury Care (DOI: 10.1089/neu.2022.0450)

It is important to understand that prospective registries acquire structured data according to defined protocols using specifically trained skilled examiners. In contrast, EHR searching identifies narrative data that is generally not structured for research use. In addition, the data retrieval is filtered through the natural language processing methodology resulting in potential ambiguity. Registry data labels, such as the ISNCSCI, have explicit data definitions with verification of the accuracy and quality of data entry and rigorous follow-up documentation. Although the registries we discussed may not be conducted with the level of oversight characteristic of a major randomized clinical trial, the rigor exceeds EHR datasets and other sources that force classification to ICD-level coding based on a synthesis of EHR information by a coder, generally for the purpose of reimbursement[127]. Ideally, registry data is systematically checked for errors and discrepancies, and it is possible to ask a participating center to remediate an error by returning to the medical record if permissible. This form of correction may not be possible from de-identified EHR data. Another distinction is that at registry centers, the same trained experts acquire and enter the initial data and optimally conduct the follow-up testing according to specified protocols.

Real-world data sources are frequently gathered from a variety of practitioners and settings and lack such validation. EHR data may contain institutional idiosyncrasies, necessitating the use of orthogonal data sources to confirm a diagnosis[128]. High dimensionality[129], validity issues[130], data bias in algorithm development, ethical issues of consent, data ownership, and security, and medicolegal ramifications for treatment decisions all impact EHR data analysis[131]. Sources of bias that could confound SCI research based on EHR are the need for multiple EHR sources to capture SCI across the continuity of care and missing entries[130]. The vast quantity of EHR data may require machine learning to answer research and clinical questions, a highly popularized concept [132] but requiring critical scrutiny[133].

Advantages of EHR data include the ability to obtain a large amount of more recent information, given a decay in the relevance of clinical data over time[134,135]. Stanford University uses EHR data from within the institution to provide a data-driven clinical consultation tool that is similar to a retrospective observational study delivered in a timely,

patient-specific manner[136] with searches using ICD codes and unstructured EHR text[137]. The US Department of Veterans Affairs has a large population with chronic SCI and extensive searchable electronic health care records. This data may be especially important to study comorbidities[138]. Recently, the VA Informatics and Computing Infrastructure (VINCI) System used the Veteran's EHR to evaluate the application of a pressure injury risk tool for over 36,000 individuals. [139]. In 2018, EPIC introduced Cosmos, a platform for EHR research across numerous institutions, including 167 million patients, that allows for large-scale studies[140]. TheTriNetX network allows international studies using federated analytics in which propensity analysis and other comparisons can be executed[141]. These real-world datasets may be leveraged to understand secondary conditions in people with SCI.

In the United States, another alternative data source is the National Trauma Databank (NTDB), which has mandated reporting of trauma outcomes. It can be used to examine the impact of systems of care such as inter-hospital transfer between different levels of trauma centers[142]. Although registry data is generally de-identified, probabilistic algorithms are being tested to link the National SCIMS Database and NTDB to combine acute and longer-term data and understand the minimum data required to make this combination reliable, such as date of injury and zip codes[39]. Projects like this demonstrate how mandated reporting systems and EHR data can supplement SCI datasets. Integrating registries and EHR data could be a powerful tool for increasing data granularity. Adopting SCI-relevant common data elements may result in improved data harmonization and reliability.

Increased Clinical Trial Efficiency Using Registry Data

The aforementioned SCI datasets can be queried retrospectively for research studies investigating trends in the natural progression of SCI, given current standards of care. This is critical to document demographic changes that may not otherwise be captured and are highly relevant to planning acute and rehabilitative care. Increasingly, registries have been used to identify eligible research participants, and registry participants could potentially be used as a control group in a clinical trial[143], as was done with the NACTN phase I Riluzole study. Sensitivity analysis can be used to assess the comparability of the historical control and the treatment group[144]. Pocock first proposed a

method for determining differences between historical and clinical trial data[145]. These methods are suited to Bayesian methodologies in which dynamic borrowing is of interest for clinical trial design. This technique varies the weighting of the historical control by evaluating the heterogeneity between historical and emergent datasets as controlled by the degree of variance in a joint probability distribution[146].

There are several models for how a longitudinal database could be used to anchor prospective clinical trials. A master protocol is a study design that allows multiple studies to be run from a single protocol. These trial types arose from oncology and relied heavily on molecular or genetic markers. Master protocols used in oncologic studies include umbrella, basket, and platform trials[147]. In umbrella trials, multiple treatments for a single disease are based on subclassifications of that disease. Different therapies, for example, would be tested in colon cancer based on genetic markers of the tumors. Basket trials test a novel therapeutic on multiple diseases that share some common underlying factors. In this case, multiple tumors in different locations in the body may share a genetic marker (e.g., an oncogene); these would all receive the same therapy. Though there is emerging research regarding genetic factors and molecular markers associated with SCI, we are not yet at the point where this knowledge could be used for a basket or umbrella trial[148].

Platform trials, also known as multi-arm, multi-stage design trials, evaluate multiple interventions over time with a common control group. Platform trials rely less heavily on biological markers of disease and therefore are a more feasible goal for SCI research[148]. This allows interventions to be dropped and another started if efficacy is not demonstrated. Typically, these study designs have been used for oncology trials but may be adapted to other fields, such as neurology. Recently, an adaptive platform trial for ALS, the HEALEY study, has been initiated[149]. One possibility would be for an SCI database to serve as the "anchor" for a platform trial. Eligible patients enrolled in the registry could be identified and recruited to participate in an intervention (or interventions), while other patients in the registry could serve as a control group. Advantages of such an approach are cost and resource sharing, shared statistical planning, and faster testing of therapeutics[150,151]. Platform trials also encourage collaboration across stakeholders (e.g.,

Journal of Neurotrauma
The Importance of Prospective Registries and Clinical Research Networks in the Evolution of Spinal Cord Injury Care (DOI: 10.1089/neu.2022.0450)

industry, researchers, health care workers, patient advocacy groups) and institutions and – to some extent – necessitate the establishment of shared goals and values.

Use of Registry Data for Personalized Medicine: Machine Learning and Artificial Intelligence

New data technologies allow much larger datasets and more variables to be analyzed to create predictive methods and learn new correlations. Machine learning can be "supervised," in which the data categories are explicitly labeled, or "unsupervised," where the ML identifies clusters from the unlabeled data. Machine learning offers the prospect for improved predictions of recovery based on variables obtained in the acute phase of injury, including MRI signal change classifiers [152]. In a RHSCIR study, a combination of neural network and machine learning decision tree analysis generated a survival algorithm, the Spinal Cord Injury Risk Score, with superior mortality prediction compared to the commonly used Injury Severity Score. Notably, head, neck, and facial injuries had considerable weight, as did spinal column fractures with translation[80].

Recovery of walking has long been one outcome for which prognostic models have been refined[54]. DeVries et al. reassessed the prognostication of walking recovery using the RHSCIR data set. The accuracy of an unsupervised multivariable machine learning algorithm was compared to a previously validated algorithm that uses three variables[153]. Notably, in this analysis, an unsupervised machine learning approach did not improve upon the accurate prediction of walking recovery as defined with three previous variables previously[154]. This indicates that machine-learning approaches are not necessarily inherently superior to more conventional analyses.

Digital Twins

Generally, in clinical trial science, we think of treatments per their effect on similar groups but not on any given individual. As individual variables influencing neurological outcomes, such as genetic polymorphisms, are increasingly discovered[155], registries will need to expand the scope of the data collected, particularly data required for advanced individual modeling and analytics. The digital twin concept arose in aerospace engineering due to the inability to directly study space vehicles deployed long-term. The twin could be

used to predict the effects of variously modeled stresses. Digital twins are virtual patients created by mapping an actual patient after acute SCI to a cluster of other actual participants in a large data set containing known predictive variables. Ideally, the digital twin would be statistically indistinguishable from the real person in predicting disease outcomes. Many virtual twins of a patient may be generated and subjected to modeled perturbations and in silico simulations to predict the consequences of treatment[156]. The twin(s) share the baseline values of an actual patient, and moving forward in time, the digital twin could be further trained based on intermediate outcomes and events. Updating is likely critical because we increasingly understand that events like infections alter SCI recovery trajectory[157]. If valid, digital twins could reduce the need for placebo controls and be used to predict therapeutic effects. One method to create digital twins is to use the series of unique information and key measures in a registry from baseline enrollment through serial longitudinal assessments to generate probability distributions. Walsh and colleagues reported a methodology to predict clinical courses of patients with Multiple Sclerosis using a conditional probabilistic neural network in which each sequential variable measure is determined by the prior in a Markov chain[158]. Another model using a neural network accurately predicted the need for ventilator support in pneumonia patients[159].

Counterfactual Analysis

Counterfactual thinking asks the question, what would have happened if? This premise is inherent to the causal theory of randomization to test the consequences of treatment or control exposure on outcomes in clinical trials[160]. Real-world observational datasets as historical controls can be used to model predicted outcomes with changes in input variables such as a covariate[161]. This analysis has been used to reanalyze a large RCT data set from which mean group effects were determined to specify an individual outcome prediction based on logistic regression modeling using a set of binary and continuous variables [162]. Counterfactual analysis can also be used to model what changes would have occurred without an intervention, such as a prevention program. In the SwiSCI Cohort Study, counterfactual analysis was used to estimate the labor market participation for people with chronic SCI if dynamic and temporal factors were varied. Those found to be

important for returning to work were educational level, the severity of chronic pain, and functional independence[163].

Ethical Considerations for SCI Datasets

While data aggregation and sharing can increase analytical power, including collaborations across institutions and with industry, close attention to consent, ownership, and data security is needed. Participants must be consented so that the potential uses of their data are clear and securely stored and de-identified[164]. National and international bodies have developed recommendations to foster clinical trials and observational data sharing while reducing risks[165]. The potential for advanced artificial intelligence technology to be skewed by unbalanced demographic representation in datasets requires attentiveness to equitable enrollment[166].

Conclusions

Today, data comes in many forms that can be used to inform and advance SCI care. We have described four different SCI registries and other SCI data sources. In the US, NACTN and SCIMS primarily focus on acute injury and rehabilitative settings, respectively. EMSCI includes several European countries, while RHSCIR has cooperative interactions within Canada, facilitated by Canada's universal health insurance coverage. NACTN and EMSCI have provided platforms for acute therapeutics clinical trials[59,105], while RHSCIR has emphasized observational studies[108]. SCIMS has contributed significantly to our understanding of living with chronic SCI in the US. NACTN, EMSCI, and SCIMS have shared data with companies in support of their clinical trial designs[82]. Developing additional methods to share and compare data across registries should increase analytic power and validity. A larger global picture of data trends may inform SCI care measures in middle-income and developing countries.

Registry observational data systems require governance and administrative methods, data protection and analysis infrastructure, and methods to check data quality. Data analytics expertise and collaboration are essential to maximize data value and to detect previously unknown linkages between variables[167]. NACTN captures the highly dynamic acute injury phase and is useful for assessing parameters related to neurological

recovery and demographic changes in urban centers of North America. NACTN's Registry data, acquired over more than 15 years in the same contributing centers that have run neuroprotection studies, is an important foundation for emerging clinical trials. This stable continuous infrastructure is a critical asset for informing SCI medical and surgical care.

Transparency, Rigor, and Reproducibility

This review does not report primary data.

Funding

This material is based upon work supported by the US ARMY MEDICAL RESEARCH ACQUISITION ACTIVITY under Grant Nos.W81XWH-07-1-0361, W81XWH-10-2-0042, W81XWH-13-2-0040 and Contract No. W81XWH-16-C-0031, and the Christopher & Dana Reeve Foundation.

Author Disclosure Statement

No competing financial interests exist.

The views expressed in this manuscript are those of the authors and do not necessarily reflect the official policy of the Department of Defense of the U.S. Government.

Author Confirmation (CRediT format)

James D. Guest: Conceived of the review, writing- Original complete draft, resources.

Kelly-Hedrik, M: Wrote substantial portions of the manuscript drafts

Abdel-Barr, MM: Reviewed the manuscript and provided constructive feedback.

Aarabi, B: Reviewed the manuscript and provided constructive feedback.

Curt, A: Reviewed the manuscript and provided constructive feedback.

Fehlings, MG: Reviewed the manuscript and provided constructive feedback.

Howley, S: Reviewed the manuscript and provided constructive feedback.

Kirshblum, S: Reviewed the manuscript and provided constructive feedback.

Neal, C: Reviewed the manuscript and provided constructive feedback.

Noonan, V: Reviewed the manuscript and provided constructive feedback.

Park, C: Contributed to manuscript sections.

Tator, C: Reviewed the manuscript and provided constructive feedback.

Toups, E, Reviewed the manuscript and provided constructive feedback.

Ugiliweneza, B: reviewed the manuscript and provided constructive feedback.

Williamson, T: Wrote portions of the manuscript draft.

Acknowledgments: NACTN has been supported by the US Department of Defense and the Christopher & Dana Reeve Foundation.

Disclaimer

The views expressed in this manuscript are those of the author(s) and do not necessarily reflect the official policy of the Department of Defense of the U.S. Government.

Funding Statement: This material is based upon work supported by the US ARMY MEDICAL RESEARCH ACQUISITION ACTIVITY under Grant Nos.W81XWH-07-1-0361, W81XWH-10-2-0042, W81XWH-13-2-0040, and Contract No. W81XWH-16-C-0031, and the Christopher & Dana Reeve Foundation.

Data Sharing. NACTN data may be shared upon appropriate request and internal review.

References

1. Silver JR. A history of Stoke Mandeville Hospital and the National Spinal Injuries Centre. J R Coll Physicians Edinb 2019;49(4):328-335, doi:10.4997/JRCPE.2019.417

2. Stover SL, DeVivo MJ, Go BK. History, implementation, and current status of the National Spinal Cord Injury Database. Arch Phys Med Rehabil 1999;80(11):1365-71, doi:10.1016/s0003-9993(99)90246-0

3. Donovan WH. Operative and nonoperative management of spinal cord injury. A review. Paraplegia 1994;32(6):375-88, doi:10.1038/sc.1994.64

4. Fehlings MG, Vaccaro A, Wilson JR, et al. Early versus delayed decompression for traumatic cervical spinal cord injury: results of the Surgical Timing in Acute Spinal Cord Injury Study (STASCIS). PLoS One 2012;7(2):e32037, doi:10.1371/journal.pone.0032037

5. Chen LF, Chang HK, Chen YC, et al. Five-year medical expenses of central cord syndrome: analysis using a national cohort. J Neurosurg Sci 2020;64(2):147-153, doi:10.23736/S0390-5616.16.03897-2

6. McCaughey EJ, Purcell M, McLean AN, et al. Changing demographics of spinal cord injury over a 20-year period: a longitudinal population-based study in Scotland. Spinal Cord 2016;54(4):270-6, doi:10.1038/sc.2015.167

7. Levi R, Hultling C, Seiger A. The Stockholm Spinal Cord Injury Study: 2. Associations between clinical patient characteristics and post-acute medical problems. Paraplegia 1995;33(10):585-94, doi:10.1038/sc.1995.125

8. Moschovou M, Antepohl W, Halvorsen A, et al. Temporal changes in demographic and injury characteristics of traumatic spinal cord injuries in Nordic countries - a systematic review with meta-analysis. Spinal Cord 2022, doi:10.1038/s41393-022-00772-3

9. Post MW, Brinkhof MW, von Elm E, et al. Design of the Swiss Spinal Cord Injury Cohort Study. Am J Phys Med Rehabil 2011;90(11 Suppl 2):S5-16, doi:10.1097/PHM.0b013e318230fd41

10. Gliklich RE, Dreyer NA, Leavy MB. Registries for Evaluating Patient Outcomes: A User's Guide. Agency for Healthcare Research Research and Quality (US): 2014.

11. Warner FM, Cragg JJ, Jutzeler CR, et al. Early Administration of Gabapentinoids Improves Motor Recovery after Human Spinal Cord Injury. Cell Rep 2017;18(7):1614-1618, doi:10.1016/j.celrep.2017.01.048

12. Guttmann L. I. Organisation of spinal units. History of the National Spinal Injuries Centre, Stoke Mandeville Hospital, Aylesbury. Paraplegia 1967;5(3):115-26, doi:10.1038/sc.1967.14

13. Donovan WH, Carter RE, Bedbrook GM, et al. Incidence of medical complications in spinal cord injury: patients in specialised, compared with non-specialised centres. Paraplegia 1984;22(5):282-90, doi:10.1038/sc.1984.46

14. Donovan WH, Clifton G, Carter RE. Developing a system of comprehensive care for the spinal cord injured patient in Houston, Texas, U.S.A. Paraplegia 1982;20(3):174-9, doi:10.1038/sc.1982.32

15. Administration RS. Federal Register. 1979.

16. DeVivo MJ, Go BK, Jackson AB. Overview of the national spinal cord injury statistical center database. J Spinal Cord Med 2002;25(4):335-8, doi:10.1080/10790268.2002.11753637

17. Chen Y, DeVivo MJ, Richards JS, et al. Spinal Cord Injury Model Systems: Review of Program and National Database From 1970 to 2015. Arch Phys Med Rehabil 2016;97(10):1797-804, doi:10.1016/j.apmr.2016.02.027

18. Chen Y, Deutsch A, DeVivo MJ, et al. Current research outcomes from the spinal cord injury model systems. Arch Phys Med Rehabil 2011;92(3):329-31, doi:10.1016/j.apmr.2010.12.011

19. Go BK DM, Richards JS. . The epidemiology of spinal cord injury. In: Spinal cord injury: clinical outcomes from the model systems. (Stover SL DJ, Whiteneck GC. ed.) Aspen: Gaithersburg; 1995; pp. 21-25.

20. Jackson AB, Dijkers M, Devivo MJ, et al. A demographic profile of new traumatic spinal cord injuries: change and stability over 30 years. Arch Phys Med Rehabil 2004;85(11):1740-8, doi:10.1016/j.apmr.2004.04.035

21. Nobunaga AI, Go BK, Karunas RB. Recent demographic and injury trends in people served by the Model Spinal Cord Injury Care Systems. Arch Phys Med Rehabil 1999;80(11):1372-82, doi:10.1016/s0003-9993(99)90247-2

22. Chen Y, Wen H, Baidwan NK, et al. Demographic and Health Profiles of People Living With Traumatic Spinal Cord Injury in the United States During 2015-2019: Findings from the Spinal Cord Injury Model Systems Database. Arch Phys Med Rehabil 2022;103(4):622-633, doi:10.1016/j.apmr.2021.11.001

23. Stover SL DJ, Whiteneck GG. . Spinal cord injury: clinical outcomes from the model systems. . Aspen Pub, 1st edition: 1995.

24. Boninger ML, Field-Fote EC, Kirshblum SC, et al. Research progress from the SCI Model Systems (SCIMS): An interactive discussion on future directions. J Spinal Cord Med 2018;41(2):216-222, doi:10.1080/10790268.2017.1314879

25. Marino RJ, Burns S, Graves DE, et al. Upper- and lower-extremity motor recovery after traumatic cervical spinal cord injury: an update from the national spinal cord injury database. Arch Phys Med Rehabil 2011;92(3):369-75, doi:10.1016/j.apmr.2010.09.027

26. Kirshblum S, Botticello A, Benedetto J, et al. Characterizing Natural Recovery of People With Initial Motor Complete Tetraplegia. Arch Phys Med Rehabil 2022;103(4):649-656, doi:10.1016/j.apmr.2021.09.018

27. Chen Y, Cao Y, Allen V, et al. Weight matters: physical and psychosocial well being of persons with spinal cord injury in relation to body mass index. Arch Phys Med Rehabil 2011;92(3):391-8, doi:10.1016/j.apmr.2010.06.030

28. Stenson KW, Deutsch A, Heinemann AW, et al. Obesity and inpatient rehabilitation outcomes for patients with a traumatic spinal cord injury. Arch Phys Med Rehabil 2011;92(3):384-90, doi:10.1016/j.apmr.2010.07.235

29. Fann JR, Bombardier CH, Richards JS, et al. Depression after spinal cord injury: comorbidities, mental health service use, and adequacy of treatment. Arch Phys Med Rehabil 2011;92(3):352-60, doi:10.1016/j.apmr.2010.05.016

30. Hoffman JM, Bombardier CH, Graves DE, et al. A longitudinal study of depression from 1 to 5 years after spinal cord injury. Arch Phys Med Rehabil 2011;92(3):411-8, doi:10.1016/j.apmr.2010.10.036

31. Qu H, Shewchuk RM, Chen Y, et al. Impact of Medicare prospective payment system on acute rehabilitation outcomes of patients with spinal cord injury. Arch Phys Med Rehabil 2011;92(3):346-51, doi:10.1016/j.apmr.2010.07.236

32. Botticello AL, Chen Y, Cao Y, et al. Do communities matter after rehabilitation? The effect of socioeconomic and urban stratification on well-being after spinal cord injury. Arch Phys Med Rehabil 2011;92(3):464-71, doi:10.1016/j.apmr.2010.08.028

33. DeVivo MJ. Discharge disposition from model spinal cord injury care system rehabilitation programs. Arch Phys Med Rehabil 1999;80(7):785-90, doi:10.1016/s0003-9993(99)90228-9

34. Myaskovsky L, Burkitt KH, Lichy AM, et al. The association of race, cultural factors, and health-related quality of life in persons with spinal cord injury. Arch Phys Med Rehabil 2011;92(3):441-8, doi:10.1016/j.apmr.2010.10.007

35. Fann JR, Bombardier CH, Richards JS, et al. Venlafaxine extended-release for depression following spinal cord injury: a randomized clinical trial. JAMA Psychiatry 2015;72(3):247-58, doi:10.1001/jamapsychiatry.2014.2482

36. Bombardier CH, Fann JR, Wilson CS, et al. A randomized controlled trial of venlafaxine XR for major depressive disorder after spinal cord injury: Methods and lessons learned. J Spinal Cord Med 2014;37(3):247-63, doi:10.1179/2045772313Y.0000000138

37. Nash MS, Lewis JE, Dyson-Hudson TA, et al. Safety, tolerance, and efficacy of extended-release niacin monotherapy for treating dyslipidemia risks in persons with chronic tetraplegia: a randomized multicenter controlled trial. Arch Phys Med Rehabil 2011;92(3):399-410, doi:10.1016/j.apmr.2010.06.029

38. Monden KR, Coker J, Charlifue S, et al. Long-Term Follow-Up of Patients With Ventilator-Dependent High Tetraplegia Managed With Diaphragmatic Pacing Systems. Arch Phys Med Rehabil 2022;103(4):773-778, doi:10.1016/j.apmr.2021.03.005

39. Chen Y, Wen H, Griffin R, et al. Linking Individual Data From the Spinal Cord Injury Model Systems Center and Local Trauma Registry: Development and Validation of Probabilistic Matching Algorithm. Top Spinal Cord Inj Rehabil 2020;26(4):221-231, doi:10.46292/sci20-00015

40. Grossman R, Toups E, Frankowski R, et al. NACTN: building a clinical trials network for spinal cord injury. Thieme: 2012.

41. Grossman RG, Toups EG, Frankowski RF, et al. North American Clinical Trials Network for the Treatment of Spinal Cord Injury: goals and progress. J Neurosurg Spine 2012;17(1 Suppl):6-10, doi:10.3171/2012.4.AOSPINE1294

42. Wilson JR, Grossman RG, Frankowski RF, et al. A clinical prediction model for long-term functional outcome after traumatic spinal cord injury based on acute clinical and imaging factors. J Neurotrauma 2012;29(13):2263-71, doi:10.1089/neu.2012.2417

43. Jaja BNR, Jiang F, Badhiwala JH, et al. Association of Pneumonia, Wound Infection, and Sepsis with Clinical Outcomes after Acute Traumatic Spinal Cord Injury. J Neurotrauma 2019;36(21):3044-3050, doi:10.1089/neu.2018.6245

44. Kopp MA, Watzlawick R, Martus P, et al. Long-term functional outcome in patients with acquired infections after acute spinal cord injury. Neurology 2017;88(9):892-900, doi:10.1212/WNL.0000000000003652

45. Aarabi B, Harrop JS, Tator CH, et al. Predictors of pulmonary complications in blunt traumatic spinal cord injury. J Neurosurg Spine 2012;17(1 Suppl):38-45, doi:10.3171/2012.4.AOSPINE1295

46. Sultan I, Lamba N, Liew A, et al. The safety and efficacy of steroid treatment for acute spinal cord injury: A Systematic Review and meta-analysis. Heliyon 2020;6(2):e03414, doi:10.1016/j.heliyon.2020.e03414

47. Guest J, Harrop JS, Aarabi B, et al. 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 2012;17(1 Suppl):94-101, doi:10.3171/2012.5.AOSPINE1289

48. Fehlings MG, Wilson JR, Frankowski RF, et al. Riluzole for the treatment of acute traumatic spinal cord injury: rationale for and design of the NACTN Phase I clinical trial. J Neurosurg Spine 2012;17(1 Suppl):151-6, doi:10.3171/2012.4.AOSPINE1259

49. Grossman RG, Fehlings MG, Frankowski RF, et al. A prospective, multicenter, phase I matched-comparison group trial of safety, pharmacokinetics, and preliminary efficacy of riluzole in patients with traumatic spinal cord injury. J Neurotrauma 2014;31(3):239-55, doi:10.1089/neu.2013.2969

50. Chow DS, Teng Y, Toups EG, et al. Pharmacology of riluzole in acute spinal cord injury. J Neurosurg Spine 2012;17(1 Suppl):129-40, doi:10.3171/2012.5.Aospine12112

51. Badhiwala JH, Wilson JR, Witiw CD, et al. The influence of timing of surgical decompression for acute spinal cord injury: a pooled analysis of individual patient data. Lancet Neurol 2021;20(2):117-126, doi:10.1016/S1474-4422(20)30406-3

52. van Middendorp JJ, Hosman AJ, Pouw MH, et al. Is determination between complete and incomplete traumatic spinal cord injury clinically relevant? Validation of the ASIA sacral sparing criteria in a prospective cohort of 432 patients. Spinal Cord 2009;47(11):809-16, doi:10.1038/sc.2009.44

53. Cragg JJ, Jutzeler CR, Grassner L, et al. Beneficial "Pharmaceutical Pleiotropy" of Gabapentinoids in Spinal Cord Injury: A Case for Refining Standard-of-Care. Neurorehabil Neural Repair 2020;34(8):686-689, doi:10.1177/1545968320931516

54. van Middendorp JJ, Hosman AJ, Donders AR, et al. A clinical prediction rule for ambulation outcomes after traumatic spinal cord injury: a longitudinal cohort study. Lancet 2011;377(9770):1004-10, doi:10.1016/S0140-6736(10)62276-3

55. Wirz M, Mach O, Maier D, et al. Effectiveness of Automated Locomotor Training in Patients with Acute Incomplete Spinal Cord Injury: A Randomized, Controlled, Multicenter Trial. J Neurotrauma 2017;34(10):1891-1896, doi:10.1089/neu.2016.4643

56. Tanadini LG, Steeves JD, Hothorn T, et al. Identifying Homogeneous Subgroups in Neurological Disorders: Unbiased Recursive Partitioning in Cervical Complete Spinal Cord Injury. Neurorehabil Neural Repair 2014;28(6):507-15, doi:10.1177/1545968313520413

57. Blight AR, Hsieh J, Curt A, et al. The challenge of recruitment for neurotherapeutic clinical trials in spinal cord injury. Spinal Cord 2019;57(5):348-359, doi:10.1038/s41393-019-0276-2

58. Zorner B, Schwab ME. Anti-Nogo on the go: from animal models to a clinical trial. Ann N Y Acad Sci 2010;1198 Suppl 1(E22-34, doi:10.1111/j.1749-6632.2010.05566.x

59. Kucher K, Johns D, Maier D, et al. First-in-Man Intrathecal Application of Neurite Growth-Promoting Anti-Nogo-A Antibodies in Acute Spinal Cord Injury. Neurorehabil Neural Repair 2018;32(6-7):578-589, doi:10.1177/1545968318776371

60. Velstra IM, Curt A, Frotzler A, et al. Changes in Strength, Sensation, and Prehension in Acute Cervical Spinal Cord Injury: European Multicenter Responsiveness Study of the GRASSP. Neurorehabil Neural Repair 2015;29(8):755-66, doi:10.1177/1545968314565466

61. Reed R, Mehra M, Kirshblum S, et al. Spinal cord ability ruler: an interval scale to measure volitional performance after spinal cord injury. Spinal Cord 2017;55(8):730-738, doi:10.1038/sc.2017.1

62. Schuld C, Wiese J, Hug A, et al. Computer implementation of the international standards for neurological classification of spinal cord injury for consistent and efficient derivation of its subscores including handling of data from not testable segments. J Neurotrauma 2012;29(3):453-61, doi:10.1089/neu.2011.2085

63. Noonan VK, Kwon BK, Soril L, et al. The Rick Hansen Spinal Cord Injury Registry (RHSCIR): a national patient-registry. Spinal Cord 2012;50(1):22-7, doi:10.1038/sc.2011.109

64. Rivers CS, Fallah N, Noonan VK, et al. Health Conditions: Effect on Function, Health-Related Quality of Life, and Life Satisfaction After Traumatic Spinal Cord Injury. A Prospective Observational Registry Cohort Study. Arch Phys Med Rehabil 2018;99(3):443-451, doi:10.1016/j.apmr.2017.06.012

65. Mills PB, Holtz KA, Szefer E, et al. Early predictors of developing problematic spasticity following traumatic spinal cord injury: A prospective cohort study. J Spinal Cord Med 2020;43(3):315-330, doi:10.1080/10790268.2018.1527082

66. Paquet J, Rivers CS, Kurban D, et al. The impact of spine stability on cervical spinal cord injury with respect to demographics, management, and outcome: a prospective cohort from a national spinal cord injury registry. Spine J 2018;18(1):88-98, doi:10.1016/j.spinee.2017.06.032

67. Tee JW, Rivers CS, Fallah N, et al. Decision tree analysis to better control treatment effects in spinal cord injury clinical research. J Neurosurg Spine 2019;1-9, doi:10.3171/2019.3.SPINE18993

68. Attabib N, Kurban D, Cheng CL, et al. Factors Associated with Recovery in Motor Strength, Walking Ability, and Bowel and Bladder Function after Traumatic Cauda Equina Injury. J Neurotrauma 2021;38(3):322-329, doi:10.1089/neu.2020.7303

69. Inglis T, Banaszek D, Rivers CS, et al. In-Hospital Mortality for the Elderly with Acute Traumatic Spinal Cord Injury. J Neurotrauma 2020;37(21):2332-2342, doi:10.1089/neu.2019.6912

70. Glennie RA, Batke J, Fallah N, et al. Rural and Urban Living in Persons with Spinal Cord Injury and Comparing Environmental Barriers, Their Health, and Quality-of-Life Outcomes. J Neurotrauma 2017;34(20):2877-2882, doi:10.1089/neu.2016.4931

71. Dvorak MF, Noonan VK, Fallah N, et al. The influence of time from injury to surgery on motor recovery and length of hospital stay in acute traumatic spinal cord injury: an observational Canadian cohort study. J Neurotrauma 2015;32(9):645-54, doi:10.1089/neu.2014.3632

72. Glennie RA, Bailey CS, Tsai EC, et al. An analysis of ideal and actual time to surgery after traumatic spinal cord injury in Canada. Spinal Cord 2017;55(6):618-623, doi:10.1038/sc.2016.177

73. Cheng CL, Noonan VK, Shurgold J, et al. Geomapping of Traumatic Spinal Cord Injury in Canada and Factors Related to Triage Pattern. J Neurotrauma 2017;34(20):2856-2866, doi:10.1089/neu.2016.4929

74. Thibault-Halman G, Rivers CS, Bailey CS, et al. Predicting Recruitment Feasibility for Acute Spinal Cord Injury Clinical Trials in Canada Using National Registry Data. J Neurotrauma 2017;34(3):599-606, doi:10.1089/neu.2016.4568

75. Squair JW, Bélanger LM, Tsang A, et al. Spinal cord perfusion pressure predicts neurologic recovery in acute spinal cord injury. Neurology 2017;89(16):1660-1667, doi:10.1212/wnl.0000000000004519

76. Dvorak MF, Cheng CL, Fallah N, et al. Spinal Cord Injury Clinical Registries: Improving Care across the SCI Care Continuum by Identifying Knowledge Gaps. J Neurotrauma 2017;34(20):2924-2933, doi:10.1089/neu.2016.4937

77. Jaglal SB, Voth J, Guilcher SJT, et al. Creation of an Algorithm to Identify Non-traumatic Spinal Cord Dysfunction Patients in Canada Using Administrative Health Data. Top Spinal Cord Inj Rehabil 2017;23(4):324-332, doi:10.1310/sci2304-324

78. Milligan J, Ryan K, Fehlings M, et al. Degenerative cervical myelopathy: Diagnosis and management in primary care. Can Fam Physician 2019;65(9):619-624

79. Zipser CM, Margetis K, Pedro KM, et al. Increasing awareness of degenerative cervical myelopathy: a preventative cause of non-traumatic spinal cord injury. Spinal Cord 2021;59(11):1216-1218, doi:10.1038/s41393-021-00711-8

80. Fallah N, Noonan VK, Waheed Z, et al. Development of a machine learning algorithm for predicting in-hospital and 1-year mortality after traumatic spinal cord injury. Spine J 2022;22(2):329-336, doi:10.1016/j.spinee.2021.08.003

81. Jaja BNR, Badhiwala J, Guest J, et al. Trajectory-Based Classification of Recovery in Sensorimotor Complete Traumatic Cervical Spinal Cord Injury. Neurology 2021, doi:10.1212/WNL.0000000000012028

82. Aimetti AA, Kirshblum S, Curt A, et al. Natural history of neurological improvement following complete (AIS A) thoracic spinal cord injury across three registries to guide acute clinical trial design and interpretation. Spinal Cord 2019;57(9):753-762, doi:10.1038/s41393-019-0299-8

83. Steeves JD, Lammertse DP, Kramer JL, et al. Outcome Measures for Acute/Subacute Cervical Sensorimotor Complete (AIS-A) Spinal Cord Injury During a Phase 2 Clinical Trial. Top Spinal Cord Inj Rehabil 2012;18(1):1-14, doi:10.1310/sci1801-1

84. Chhabra HS, Sachdeva G, Kovindha A, et al. International Spinal Cord Society (ISCoS) database: Asian Spinal Cord Network (ASCoN) Pilot Project [IDAPP]. Spinal Cord Ser Cases 2018;4(45, doi:10.1038/s41394-018-0076-5

85. Tsolinas RE, Burke JF, DiGiorgio AM, et al. Transforming Research and Clinical Knowledge in Spinal Cord Injury (TRACK-SCI): an overview of initial enrollment and demographics. Neurosurg Focus 2020;48(5):E6, doi:10.3171/2020.2.FOCUS191030

86. Cripps RA, Lee BB, Wing P, et al. A global map for traumatic spinal cord injury epidemiology: towards a living data repository for injury prevention. Spinal Cord 2011;49(4):493-501, doi:10.1038/sc.2010.146

87. Rupp R, Jersch P, Schuld C, et al. [Germany-wide, Web-based ParaReg Registry for Lifelong Monitoring of People with Spinal Cord Injury: Data Model, Ethico-legal Prerequisites and Technical Implementation]. Gesundheitswesen 2021;83(S 01):S18-S26, doi:10.1055/a-1538-6537

88. Azadmanjir Z, Mohtasham-Amiri Z, Ziabari SM, et al. Sustaining the National Spinal Cord Injury Registry of Iran (NSCIR-IR) in a Regional Center: Challenges and Solutions. Iran J Public Health 2020;49(4):736-743

89. Pattanakuhar S, Kammuang-Lue P, Kovindha A, et al. Is admission to an SCI specialized rehabilitation facility associated with better functional outcomes? Analysis of data from the Thai Spinal Cord Injury Registry. Spinal Cord 2019;57(8):684-691, doi:10.1038/s41393-019-0267-3

90. O'Connor P. Incidence and patterns of spinal cord injury in Australia. Accid Anal Prev 2002;34(4):405-15, doi:10.1016/s0001-4575(01)00036-7

91. Yang ML, Li JJ, So KF, et al. Efficacy and safety of lithium carbonate treatment of chronic spinal cord injuries: a double-blind, randomized, placebo-controlled clinical trial. Spinal Cord 2012;50(2):141-6, doi:10.1038/sc.2011.126

92. Elshahidi MH, Monir NY, Elzhery MA, et al. Epidemiological Characteristics of Traumatic Spinal Cord Injury (TSCI) in the Middle-East and North-Africa (MENA) Region: A Systematic Review and Meta-Analysis. Bull Emerg Trauma 2018;6(2):75-89, doi:10.29252/beat-060201

93. Zuckerman SL, Haghdel A, Lessing NL, et al. Cervical Spine Trauma in East Africa: Presentation, Treatment, and Mortality. Int J Spine Surg 2021;15(5):879-889, doi:10.14444/8113

94. McGirt MJ, Parker SL, Asher AL, et al. Role of prospective registries in defining the value and effectiveness of spine care. Spine (Phila Pa 1976) 2014;39(22 Suppl 1):S117-28, doi:10.1097/BRS.0000000000000552

95. Yue JK, Hemmerle DD, Winkler EA, et al. Clinical Implementation of Novel Spinal Cord Perfusion Pressure Protocol in Acute Traumatic Spinal Cord Injury at U.S. Level I Trauma Center: TRACK-SCI Study. World Neurosurg 2020;133(e391-e396, doi:10.1016/j.wneu.2019.09.044

96. Balas M, Guttman MP, Badhiwala JH, et al. Earlier Surgery Reduces Complications in Acute Traumatic Thoracolumbar Spinal Cord Injury: Analysis of a Multi-Center Cohort of 4108 Patients. J Neurotrauma 2022;39(3-4):277-284, doi:10.1089/neu.2020.7525

97. Li R, Grigorian A, Nahmias JT, et al. Development of a novel tool to predict pulmonary complications in trauma patients with and without chest injury. Am J Surg 2022;224(1 Pt A):64-68, doi:10.1016/j.amjsurg.2022.01.023

98. Assuring Data Quality and Validity in Clinical Trials for Regulatory Decision Making. In: Institute of Medicine (US) Roundtable on Research and Development of Drugs, Biologics, and Medical Devices. (JR D, VP N, J W. eds.) National Academies Press (US): Washington, DC; 1999.

99. Gliklich R DN, Leavy M. Registries for Evaluating Patient Outcomes: A User's Guide. Third edition. AHRQ Publication 2014;13(14)- EHC 111(

100. Arts DG, De Keizer NF, Scheffer GJ. Defining and improving data quality in medical registries: a literature review, case study, and generic framework. J Am Med Inform Assoc 2002;9(6):600-11, doi:10.1197/jamia.m1087

101. Geisler FH, Coleman WP, Grieco G, et al. The Sygen multicenter acute spinal cord injury study. Spine (Phila Pa 1976) 2001;26(24 Suppl):S87-98, doi:10.1097/00007632-200112151-00015

102. Geisler FH, Coleman WP, Grieco G, et al. Recruitment and early treatment in a multicenter study of acute spinal cord injury. Spine (Phila Pa 1976) 2001;26(24 Suppl):S58-67, doi:10.1097/00007632-200112151-00013

103. Hudson KL, Collins FS. Sharing and reporting the results of clinical trials. JAMA 2015;313(4):355-6, doi:10.1001/jama.2014.10716

104. McGettigan P, Alonso Olmo C, Plueschke K, et al. Patient Registries: An Underused Resource for Medicines Evaluation : Operational proposals for increasing the use of patient registries in regulatory assessments. Drug Saf 2019;42(11):1343-1351, doi:10.1007/s40264-019-00848-9

105. Fehlings MG, Nakashima H, Nagoshi N, et al. 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. Spinal Cord 2016;54(1):8-15, doi:10.1038/sc.2015.95

106. Rothman KJ, Greenland S. Causation and causal inference in epidemiology. Am J Public Health 2005;95 Suppl 1(S144-50, doi:10.2105/ajph.2004.059204

107. Balas M, Prommel P, Nguyen L, et al. Reality of Accomplishing Surgery within 24 Hours for Complete Cervical Spinal Cord Injury: Clinical Practices and Safety. J Neurotrauma 2021;38(21):3011-3019, doi:10.1089/neu.2021.0177

108. Squair JW, Belanger LM, Tsang A, et al. Spinal cord perfusion pressure predicts neurologic recovery in acute spinal cord injury. Neurology 2017;89(16):1660-1667, doi:10.1212/WNL.0000000000004519

109. Anand T, Hanna K, Kulvatunyou N, et al. Time to tracheostomy impacts overall outcomes in patients with cervical spinal cord injury. J Trauma Acute Care Surg 2020;89(2):358-364, doi:10.1097/TA.0000000000002758

110. Ahn H, Singh J, Nathens A, et al. Pre-hospital care management of a potential spinal cord injured patient: a systematic review of the literature and evidence-based guidelines. J Neurotrauma 2011;28(8):1341-61, doi:10.1089/neu.2009.1168

111. National Academies of Sciences E, Medicine. Improving Representation in Clinical Trials and Research: Building Research Equity for Women and Underrepresented Groups. The National Academies Press: Washington, DC; 2022.

112. Richard-Denis A, Gravel LF, Dionne A, et al. An evaluation of the representativeness of a national spinal cord injury registry: a population-based cohort study. Spinal Cord 2021;59(10):1072-1078, doi:10.1038/s41393-021-00622-8

113. Fekete C, Gurtner B, Kunz S, et al. Inception cohort of the Swiss Spinal Cord Injury Cohort Study (SwiSCI): Design, participant characteristics, response rates and non-response. J Rehabil Med 2021;53(2):jrm00159, doi:10.2340/16501977-2795

114. Brown DR, Topcu M. Willingness to participate in clinical treatment research among older African Americans and Whites. Gerontologist 2003;43(1):62-72, doi:10.1093/geront/43.1.62

115. Ketchum JM, Cuthbert JP, Deutsch A, et al. Representativeness of the Spinal Cord Injury Model Systems National Database. Spinal Cord 2018;56(2):126-132, doi:10.1038/s41393-017-0010-x

116. Kaushal A, Altman R, Langlotz C. Geographic Distribution of US Cohorts Used to Train Deep Learning Algorithms. JAMA 2020;324(12):1212-1213, doi:10.1001/jama.2020.12067

117. Dijkland SA, Jaja BNR, van der Jagt M, et al. Between-center and between-country differences in outcome after aneurysmal subarachnoid hemorrhage in the Subarachnoid Hemorrhage International Trialists (SAHIT) repository. J Neurosurg 2019;1-9, doi:10.3171/2019.5.JNS19483

118. Biering-Sorensen F, Noonan VK. Standardization of Data for Clinical Use and Research in Spinal Cord Injury. Brain Sci 2016;6(3), doi:10.3390/brainsci6030029

119. Rupp R, Biering-Sorensen F, Burns SP, et al. International Standards for Neurological Classification of Spinal Cord Injury: Revised 2019. Top Spinal Cord Inj Rehabil 27(2):1-22, doi:10.46292/sci2702-1

120. DeVivo MJ, Biering-Sorensen F, New P, et al. Standardization of data analysis and reporting of results from the International Spinal Cord Injury Core Data Set. Spinal Cord 2011;49(5):596-9, doi:10.1038/sc.2010.172

121. Biering-Sorensen F, Alai S, Anderson K, et al. Common data elements for spinal cord injury clinical research: a National Institute for Neurological Disorders and Stroke project. Spinal Cord 2015;53(4):265-77, doi:10.1038/sc.2014.246

122. Maritz R, Pongpipatpaiboon K, Melvin JL, et al. Content comparison of the Spinal Cord Injury Model System Database to the ICF Generic Sets and Core Sets for spinal cord injury. Spinal Cord 2019;57(12):1023-1030, doi:10.1038/s41393-019-0326-9

123. Jones LAT, Li CY, Weitzenkamp D, et al. Development and Validation of Crosswalks Between FIM(R) and SCIM III for Voluntary Musculoskeletal Movement Functions. Neurorehabil Neural Repair 2021;35(10):880-889, doi:10.1177/15459683211033854

124. Hallock H, Marshall SE, 't Hoen PAC, et al. Federated Networks for Distributed Analysis of Health Data. Frontiers in Public Health 2021;9(doi:10.3389/fpubh.2021.712569

125. Froelicher D, Troncoso-Pastoriza JR, Raisaro JL, et al. Truly privacy-preserving federated analytics for precision medicine with multiparty homomorphic encryption. Nature Communications 2021;12(1):5910, doi:10.1038/s41467-021-25972-y

126. Li X, Gu Y, Dvornek N, et al. Multi-site fMRI analysis using privacy-preserving federated learning and domain adaptation: ABIDE results. Medical Image Analysis 2020;65(101765, doi:https://doi.org/10.1016/j.media.2020.101765

127. O'Malley KJ, Cook KF, Price MD, et al. Measuring diagnoses: ICD code accuracy. Health Serv Res 2005;40(5 Pt 2):1620-39, doi:10.1111/j.1475-6773.2005.00444.x

128. Bastarache L, Brown JS, Cimino JJ, et al. Developing real-world evidence from real-world data: Transforming raw data into analytical datasets. Learn Health Syst 2022;6(1):e10293, doi:10.1002/lrh2.10293

129. Berisha V, Krantsevich C, Hahn PR, et al. Digital medicine and the curse of dimensionality. NPJ Digit Med 2021;4(1):153, doi:10.1038/s41746-021-00521-5

130. Gianfrancesco MA, Goldstein ND. A narrative review on the validity of electronic health record-based research in epidemiology. BMC Med Res Methodol 2021;21(1):234, doi:10.1186/s12874-021-01416-5

131. Char DS, Shah NH, Magnus D. Implementing Machine Learning in Health Care - Addressing Ethical Challenges. N Engl J Med 2018;378(11):981-983, doi:10.1056/NEJMp1714229

132. Obermeyer Z, Emanuel EJ. Predicting the Future - Big Data, Machine Learning, and Clinical Medicine. N Engl J Med 2016;375(13):1216-9, doi:10.1056/NEJMp1606181

133. Rajpurkar P, Chen E, Banerjee O, et al. AI in health and medicine. Nat Med 2022;28(1):31-38, doi:10.1038/s41591-021-01614-0

134. Chen JH, Alagappan M, Goldstein MK, et al. Decaying relevance of clinical data towards future decisions in data-driven inpatient clinical order sets. Int J Med Inform 2017;102(71-79, doi:10.1016/j.ijmedinf.2017.03.006

135. Chen JH, Asch SM. Machine Learning and Prediction in Medicine - Beyond the Peak of Inflated Expectations. N Engl J Med 2017;376(26):2507-2509, doi:10.1056/NEJMp1702071

136. Gombar S, Callahan A, Califf R, et al. It is time to learn from patients like mine. NPJ Digit Med 2019;2(16, doi:10.1038/s41746-019-0091-3

137. Schuler A, Callahan A, Jung K, et al. Performing an Informatics Consult: Methods and Challenges. J Am Coll Radiol 2018;15(3 Pt B):563-568, doi:10.1016/j.jacr.2017.12.023

138. Curtin CM, Suarez PA, Di Ponio LA, et al. Who are the women and men in Veterans Health Administration's current spinal cord injury population? J Rehabil Res Dev 2012;49(3):351-60, doi:10.1682/jrrd.2010.11.0220

139. Bogie KM, Roggenkamp SK, Zeng N, et al. Development of Predictive Informatics Tool Using Electronic Health Records to Inform Personalized Evidence-Based Pressure Injury Management for Veterans with Spinal Cord Injury. Mil Med 2021;186(Suppl 1):651-658, doi:10.1093/milmed/usaa469

140. Kim EG, Kaelber DC. Phenotypic prevalence of obesity and metabolic syndrome among an underdiagnosed and underscreened population of over 50 million children and adults. Front Genet 2022;13(961116, doi:10.3389/fgene.2022.961116

141. Topaloglu U, Palchuk MB. Using a Federated Network of Real-World Data to Optimize Clinical Trials Operations. JCO Clin Cancer Inform 2018;2(1-10, doi:10.1200/CCI.17.00067

142. Williamson T, Hodges S, Yang LZ, et al. Impact of US hospital center and interhospital transfer on spinal cord injury management: An analysis of the National Trauma Data Bank. J Trauma Acute Care Surg 2021;90(6):1067-1076, doi:10.1097/TA.0000000000003165

143. Ghadessi M, Tang R, Zhou J, et al. A roadmap to using historical controls in clinical trials - by Drug Information Association Adaptive Design Scientific Working Group (DIA-ADSWG). Orphanet J Rare Dis 2020;15(1):69, doi:10.1186/s13023-020-1332-x

144. Ghadessi M, Tang R, Zhou J, et al. A roadmap to using historical controls in clinical trials – by Drug Information Association Adaptive Design Scientific Working Group (DIA-ADSWG). Orphanet Journal of Rare Diseases 2020;15(1):69, doi:10.1186/s13023-020-1332-x

145. Pocock SJ. The combination of randomized and historical controls in clinical trials. J Chronic Dis 1976;29(3):175-88, doi:10.1016/0021-9681(76)90044-8

146. Kaplan D, Chen J, Yavuz S, et al. Bayesian Dynamic Borrowing of Historical Information with Applications to the Analysis of Large-Scale Assessments. Psychometrika 2022, doi:10.1007/s11336-022-09869-3

147. Barker AD, Sigman CC, Kelloff GJ, et al. I-SPY 2: an adaptive breast cancer trial design in the setting of neoadjuvant chemotherapy. Clin Pharmacol Ther 2009;86(1):97-100, doi:10.1038/clpt.2009.68

148. Mulcahey MJ, Jones LAT, Rockhold F, et al. Adaptive trial designs for spinal cord injury clinical trials directed to the central nervous system. Spinal Cord 2020;58(12):1235-1248, doi:10.1038/s41393-020-00547-8

149. Paganoni S, Berry JD, Quintana M, et al. Adaptive Platform Trials to Transform Amyotrophic Lateral Sclerosis Therapy Development. Ann Neurol 2022;91(2):165-175, doi:10.1002/ana.26285

150. Karanatsios B, Prang KH, Verbunt E, et al. Defining key design elements of registry-based randomised controlled trials: a scoping review. Trials 2020;21(1):552, doi:10.1186/s13063-020-04459-z

151. Mikita JS, Mitchel J, Gatto NM, et al. Determining the Suitability of Registries for Embedding Clinical Trials in the United States: A Project of the Clinical Trials Transformation Initiative. Ther Innov Regul Sci 2021;55(1):6-18, doi:10.1007/s43441-020-00185-5

152. Inoue T, Ichikawa D, Ueno T, et al. XGBoost, a Machine Learning Method, Predicts Neurological Recovery in Patients with Cervical Spinal Cord Injury. Neurotrauma Rep 2020;1(1):8-16, doi:10.1089/neur.2020.0009

153. DeVries Z, Hoda M, Rivers CS, et al. Development of an unsupervised machine learning algorithm for the prognostication of walking ability in spinal cord injury patients. Spine J 2020;20(2):213-224, doi:10.1016/j.spinee.2019.09.007

154. Hicks KE, Zhao Y, Fallah N, et al. A simplified clinical prediction rule for prognosticating independent walking after spinal cord injury: a prospective study from a Canadian multicenter spinal cord injury registry. Spine J 2017;17(10):1383-1392, doi:10.1016/j.spinee.2017.05.031

155. Jha A, Lammertse DP, Coll JR, et al. Apolipoprotein E epsilon4 allele and outcomes of traumatic spinal cord injury. J Spinal Cord Med 2008;31(2):171-6, doi:10.1080/10790268.2008.11760708

156. Bjornsson B, Borrebaeck C, Elander N, et al. Digital twins to personalize medicine. Genome Med 2019;12(1):4, doi:10.1186/s13073-019-0701-3

157. Elliott CS, Kopp MA, Stampas A, et al. The Effect of Early Infection on the Rate of Volitional Voiding after Spinal Cord Injury: A Potential Modifiable Risk Factor for Bladder Outcomes. J Urol 2022;207(1):137-143, doi:10.1097/JU.0000000000002122

158. Walsh JR SA, Pouliot Y, Li-Bland D, Loukianov A, Fisher GK. Generating digital twins with multiple sclerosis using probabilistic neural networks. arXiv 2020, doi:https://doi.org/10.48550/arXiv.2002.02779

159. Chakshu NK, Nithiarasu P. An AI based digital-twin for prioritising pneumonia patient treatment. Proc Inst Mech Eng H 2022;9544119221123431, doi:10.1177/09544119221123431

160. McGue M, Osler M, Christensen K. Causal Inference and Observational Research: The Utility of Twins. Perspectives on Psychological Science 2010;5(5):546-556, doi:10.1177/1745691610383511

161. Hernan MA, Robins JM. Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available. Am J Epidemiol 2016;183(8):758-64, doi:10.1093/aje/kwv254

162. Nguyen TL, Collins GS, Landais P, et al. Counterfactual clinical prediction models could help to infer individualized treatment effects in randomized controlled trials-An illustration with the International Stroke Trial. J Clin Epidemiol 2020;125(47-56, doi:10.1016/j.jclinepi.2020.05.022

163. Schwegler U, Fekete C, Finger M, et al. Labor market participation of individuals with spinal cord injury living in Switzerland: determinants of between-person differences and counterfactual evaluation of their instrumental value for policy. Spinal Cord 2021;59(4):429-440, doi:10.1038/s41393-020-00598-x

164. Fellows LK, Stark M, Berg A, et al. Patient registries in cognitive neuroscience research: advantages, challenges, and practical advice. J Cogn Neurosci 2008;20(6):1107-13, doi:10.1162/jocn.2008.20065

165. Committee on Strategies for Responsible Sharing of Clinical Trial D, Board on Health Sciences P, Institute of M. In: Sharing Clinical Trial Data: Maximizing Benefits, Minimizing Risk. National Academies Press (US)

166. Straw I. The automation of bias in medical Artificial Intelligence (AI): Decoding the past to create a better future. Artif Intell Med 2020;110(101965, doi:10.1016/j.artmed.2020.101965

167. Nielson JL, Paquette J, Liu AW, et al. Topological data analysis for discovery in preclinical spinal cord injury and traumatic brain injury. Nature Communications 2015;6(1):8581, doi:10.1038/ncomms9581

Figure Legends

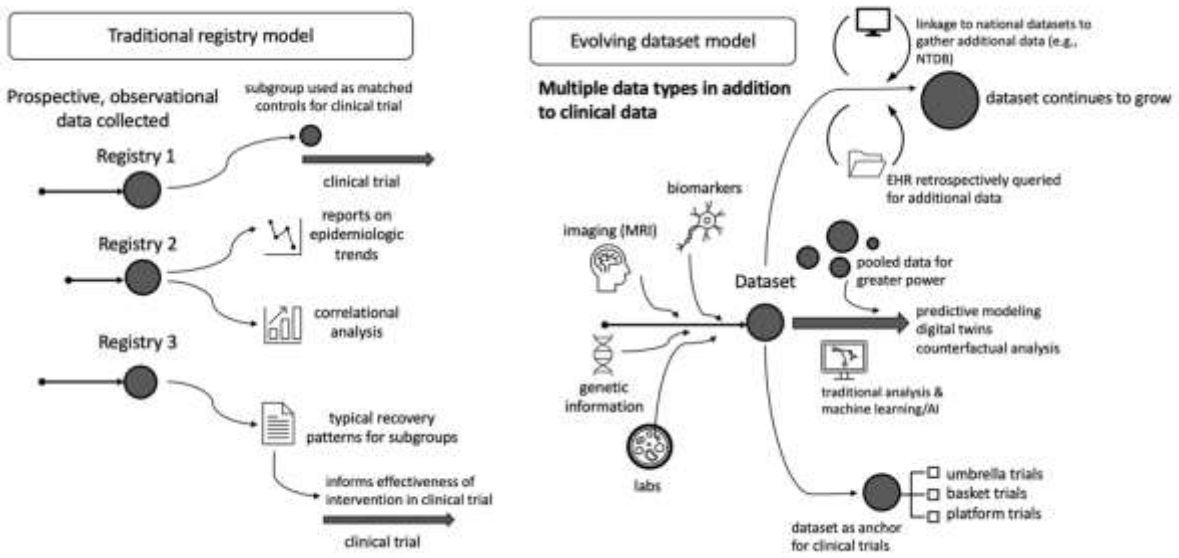

Figure 1. Traditional and evolving data models. Registry data has been used to inform the natural history of recovery and epidemiologic trends, provide matched controls, and evaluate hypotheses using suitable statistical models. In the evolving dataset, further forms of data are incorporated, including biomarkers. The dataset may be enriched by adding selected EHR information and linkage to other datasets to pool data for greater power which may be used for predictive modeling. The dataset may also serve as a control group anchor for sequences of clinical trials, thus preserving the added accruing power.

Journal of Neurotrauma
The Importance of Prospective Registries and Clinical Research Networks in the Evolution of Spinal Cord Injury Care (DOI: 10.1089/neu.2022.0450)