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ORIGINAL ARTICLE

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

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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 (EMSCI). We compare the registries' focuses, data platforms, advanced analytics use, and impacts. We also describe how registries' data can be combined with electronic health records (EHRs) 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 such as 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, counter-

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factual analysis, and the creation of digital twins. Registries and other data sources help drive innovation in SCI clinical science.

Keywords: counterfactual; digital twin; personalized medicine; registry; spinal cord injury

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 SCIs 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 (SCIMS) Program[2] in the United States 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] and Scotland,[6] along with Sweden[7] and other Nordic countries have established national health care and patient registries that can identify all persons with SCI in the 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 Swiss Spinal Cord Injury (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 are entered based on predefined 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 health care 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 U.S. Agency for Healthcare Research and Quality.[10]

SCI registry data sets optimally track individuals from the moment of injury through their lifespan, although that is often not feasible. Here, we review four SCI registries (U.S., 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 data sets.

Review of SCI Registries

The traumatic SCI data sets are the U.S. National SCIMS Database and the North American Clinical Trials Network (NACTN) SCI Registry, the Canadian Rick Hansen SCI Registry (RHSCIR), and the European Multi-Center Study about Spinal Cord Injury (EMSCI).[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 SCIMS was founded in 1970 to create a network of rehabilitation centers across the United States providing care for patients with SCI.[2] The lack of existing care programs linking acute and rehabilitative care was specifically viewed as suboptimal. The SCIMS Program was conceptually influenced by the successes in the United Kingdom at Stoke Mandeville[12] and at 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 SCIMS Database in 1975 to aggregate prospectively acquired data across the network's sites.[16] The funding for the SCIMS 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 update 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.

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, the National SCIMS Database has tracked outcomes for several decades after injury, from which trends in SCI have been documented (e.g., demographics, mechanism of injury) since the 1970s.[17–22] Early in the evolution of the database, 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 the understanding of 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 in 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, such as 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 they 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 knowledge translation (KT) from research conducted by SCIMS centers that have contributed to our understanding of SCI[38] and also have provided important educational resources.

The National SCIMS Database has a publicly available life expectancy calculator for individuals with SCI that is linked to provisional life expectancy tables according to major demographic groupings. This comparison emphasizes the greatly reduced life span for those with SCI. The SCIMS also has resources for KT.

Although the 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, the 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 (NTDB).[39]

The North American Clinical Trials Network

The 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. The 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 the NACTN. The Telemedicine and Advanced Technology Research Center and the U.S. Army Medical Research Acquisitions Activity have provided important financial support.

The goals of the 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 1017 patients supports these goals. Each entry captures a patient's demographics, injury characteristics, treatment, complications, discharge disposition, and neurological and functional outcomes up to 1-year post-SCI. Events related to transfer from other centers, triage, and surgical timing are captured in detail. These clinical data are used to assess longitudinal epidemiological changes in injury and recovery pertinent to the NACTN's patient population, define best practices for acute SCI, develop new analytics methods,[42] and provide matched control data sets for clinical trials.

The 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 the 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 6 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 the NACTN is ''to carry out clinical trials of the comparative effectiveness of new therapies for SCI.'' the 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 the 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 multi-center study of riluzole used within 12 h 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 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 KT, the 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 Multi-Center Study About Spinal Cord Injury Database

The EMSCI Database[11] is a prospective, longitudinal cohort study founded in 2001 that includes 23 neurorehabilitation centers across Europe. The goal of the 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-min 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. The EMSCI provides annual training workshops for physicians and clinicians to improve data quality, and the EMSCI has been ISO 9001:2015 certified since August 2010. As of October 2020, over 5000 patients were included in the study. The EMSCI is supported by the International Foundation for Research in Paraplegia (initial founding partner), Wings for Life, and the Deutsche Stiftung Querschnittlähmung. The EMSCI does not prospectively collect detailed acute care information in its registry.

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 been used to create algorithms to predict walking without assistance 1 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] The EMSCI has published several recommendations regarding the conduct of clinical SCI trials.[57] In addition, the EMSCI serves as a clinical trial network to test the anti-Nogo-A 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]

The 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 (ASIA) and the International Spinal Cord Society.[62]

The Canadian Rick Hansen SCI Registry

The Canadian RHSCIR 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 follow the patient's journey and include sociodemographics, 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, intra-operative 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 have 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 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 have also been used to look at outcomes of subpopulations, including patients with traumatic cauda equina syndrome[68] and the elderly,[69] and for 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 (<24 h).[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 the 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 KT, Praxis has developed an ISNCSCI Algorithm (similar to the EMSCI), which is used to enhance the quality of ISNCSCI data in the RHSCIR and is also used by other SCI registries (e.g., the 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 four 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 health care systems to treat these patients, and engaging researchers, clinicians, governments, health care companies, and society to achieve improved outcomes. Notably, the data have 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 the NACTN, SCIMS, and EMSCI have been used to set benchmarks for outcomes 6 months after traumatic thoracic SCI as a comparison group for an early phase industry trial.[82] Data from the SCIMS and EMSCI contributed to developing suggested outcome measures for Phase II clinical trials for patients with ASIA Impairment Scale (AIS)-A designation 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 data sets—could evolve in parallel.[84,85]

Other Registry Data Sets

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 are

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 University of California, San Francisco 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 U.S. 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 are 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 U.S. 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, the NACTN has conducted clinical trials with close CRO oversight and auditing,[105] as well as enrollment 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*, whereas in registry studies hypotheses are often explored after data are collected. Thus the ability to draw causal inferences from registry data may be more limited.[106]

Registries and Care Standards

The data sets 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 the 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 and colleagues studied for differences between patients who either agreed to enroll in the RHSCIR or refused, and the investigators 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 with the Uniform Data System for Medical Rehabilitation (UDSMR), a data set capturing a high proportion of all rehabilitation admissions in the United States, and the 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 U.S. database studies have tended to be performed on data primarily drawn from regions associated with prominent academic centers.[116] Multinational registries such as the 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 Data Sets 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 National Institute of Neurological Disorders and Stroke (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 ASIA.

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 data sets 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 EHR 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 magnetic resonance imaging (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 data sets may eventually become obsolete due to less expensive alternative sources of similar data. 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 data sets and other sources that force classification to *International Classification of Diseases* (ICD)-level coding based on a synthesis of EHR information by a coder, generally for the purpose of reimbursement.[127] Ideally, registry data are 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 EHRs are the need to aggregate multiple potentially differing EHR sources between SCI centers and across the continuity of care and to deal

with missing data entries.[130] The vast quantity of EHR data may require machine learning to answer research and clinical questions, a highly popularized concept[132] but one that requires critical scrutiny.[133]

One advantage of EHR data is 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 U.S. Department of Veterans Affairs (VA) has a large population with chronic SCI and extensive searchable EHRs. These data may be especially important for study comorbidities.[138] Recently, the VA Informatics and Computing Infrastructure (VINCI) System used the VA's EHRs 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 data sets may be leveraged to understand secondary conditions in people with SCI.

In the United States, another alternative data source is the NTDB, which has mandated reporting of trauma outcomes. It can be used to examine the impact of systems of care such as interhospital transfer between different levels of trauma centers.[142] Although registry data are 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 data sets. 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 data sets 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 data sets 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 oncological 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. Although 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), whereas 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., 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 data sets and more variables to be analyzed to create predictive methods and

learn new correlations (Fig. 1). Machine learning can be ''supervised,'' in which the data categories are explicitly labeled, or ''unsupervised,'' where the machine learning 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 an 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 with 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 and colleagues[153] reassessed the prognostication of walking recovery using the RHSCIR data set. The accuracy of an unsupervised multi-variable machine learning algorithm was compared with 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 such as infections alter SCI recovery trajectory.[157]

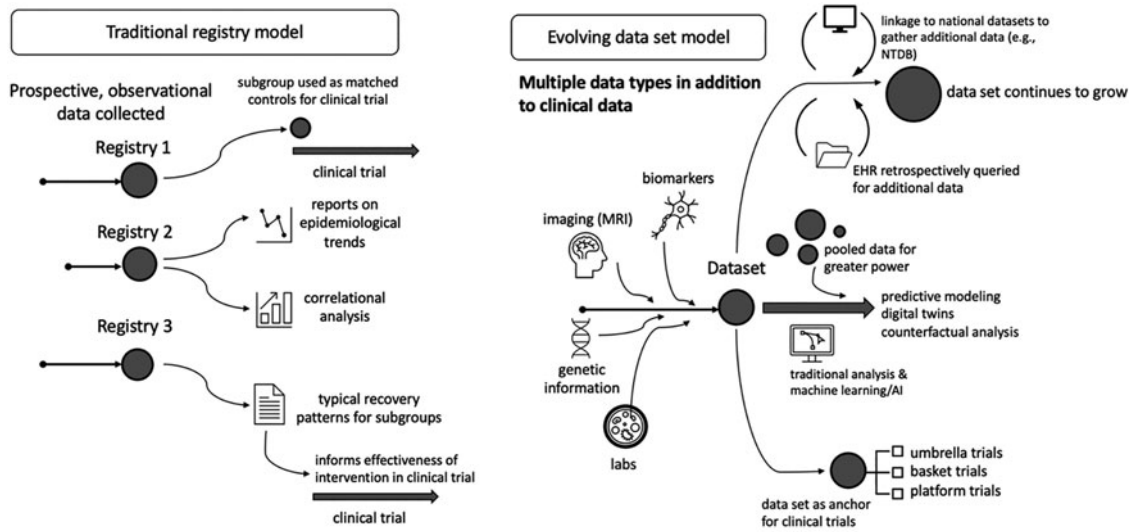

FIG. 1. Traditional and evolving data models. Registry data have been used to inform the natural history of recovery and epidemiological trends, provide matched controls, and evaluate hypotheses using suitable statistical models. In the evolving data set, further forms of data are incorporated, including biomarkers. The data set may be enriched by adding selected EHR information and linkage to other data sets to pool data for greater power, which may be used for predictive modeling. The data set may also serve as a control group anchor for sequences of clinical trials, thus preserving the added accruing power. AI, artificial intelligence; EHR, electronic health record; NTDB, National Trauma Data Bank; MRI, magnetic resonance imaging.

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 data sets 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 random controlled trial 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 Data Sets

Although 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 data sets requires attentiveness to equitable enrollment.[166]

Conclusions

Today, data come 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 United States, the NACTN and the SCIMS primarily focus on acute injury and rehabilitative settings, respectively. The EMSCI includes several European countries, whereas the RHSCIR has cooperative interactions within Canada, facilitated by Canada's universal health insurance coverage. The NACTN and the EMSCI have provided platforms for acute therapeutics clinical trials,[59,105] whereas the RHSCIR has emphasized observational studies.[108] The SCIMS has contributed significantly to our understanding of living with chronic SCI in the United States. The 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] The 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. The NACTN SCI 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 Summary

This article does not report primary data.

Data sharing

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

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Authors' Contributions

Guest, JD: 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.

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Author Disclosure Statement

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