Research Article

Systematic reviews in spinal cord injury: A step-by-step guide for rehabilitation science learners and clinicians

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Background: The COVID-19 pandemic has created opportunity for multiple rehabilitation science learners and clinicians to critically evaluate and synthesize published research in the field of spinal cord injury (SCI) rehabilitation.

Objective: To provide a step-by-step guide for rehabilitation science learners and clinicians outlining how to conduct rigorous systematic reviews in the field of SCI.

Results: Steps for conducting a systematic review (SR) include: (1) formation of the SR team consisting of interprofessional experts; (2) formulation of the research question(s) with patient/population/problem, Intervention, Comparison, and Outcome (PICO) specification; (3) determination of inclusion and exclusion criteria; (4) development of SR protocol and registration; (5) development of the search strategies (database specific); (6) screening of titles and abstracts (level 1 screening), and full-texts (level 2 screening); (7) quality assessment of the included studies; (8) data extraction; (9) summary of findings and discussion; and, (10) dissemination of results.

Conclusions: The enclosed ten steps for conducting SRs in SCI rehabilitation research have the potential to significantly improve the quality of evidence synthesis and the associated inferences. The importance of assembling team with diverse expertise is emphasized to assure a quality product with the potential to influence practice and inform the content of clinical practice recommendations.

Keywords: Methodology, Guide, Systematic review, Rehabilitation: Spinal cord injury

Introduction

The COVID-19 pandemic has resulted in the interruption in medical student and rehabilitation science student's training and widespread disruption of applied clinical research activities.[1] Conversely, working remotely in a safe environment has provided an excellent opportunity for trainees to conduct systematic reviews (SRs) and synthesizing the currently available evidence to advance the field of spinal cord injury (SCI) rehabilitation.

Clinical care and related research in the field of SCI rehabilitation has evolved in recent decades, changing the perspective of disability from "confinement to a wheelchair and a lifetime of medical comorbidity" to interventions that translate to "high hope for regeneration and functional restoration" among individuals with complex motor, sensory and autonomic impairments.[2] However, despite these advances in care, there have been a limited number of clinical trials in the field and few interventions with phase I through IV

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clinical trials,[3] Clinical trials in SCI rehabilitation have the following limitations: (i) they are relatively less prevalent; (ii) have small sample sizes due to the specificity of the eligibility criteria, (iii) low participation rates during the subacute period after injury; and (iv) high attrition rates.[4] An effort to address knowledge gaps and low rates of recruitment is the SCITrialsFinder (https://scitrialsfinder.net/) a website containing curated versions of clinical trial information in lay language for patients, their families and providers. Given the current state of the literature and the challenges of conducting clinical trials, SRs may provide a higher sample size by collecting the available evidence and reducing the variance of the effect size.[5]

In the hierarchy of scientific evidence (see Figure 1), SR and meta-analysis (MA; a statistical analysis quantitatively combining the findings from the SR) are considered the most robust and highest quality of evidence.[6–9] Therefore, the SCI community cannot rely on clinical trials alone to advance care.

An SR aims to answer a specific question (i.e. research, clinical care, or quality improvement)[10] and integrates the available evidence (i.e. studies which have similar objectives but may have similar or conflicting findings).[11] The main objectives of SRs are to: (i) systematically search, gather, and synthesize the scientific evidence (e.g. randomized controlled trials (RCTs), cohort studies, case–control studies, or cross-sectional studies); (ii) filter the available evidence to address a specific problem or issue; and (iii) answer a predefined research question using explicit search methods and critical appraisal techniques.[10] Granting agencies may require an SR to ensure there is justification for further research.

Conducting an SR in SCI research requires precise, systematic steps to ensure that the findings are comprehensive, reliable, and reproducible. The rigid methodology in conducting SRs limits bias and leads to improved precision of the conclusions. This paper outlines a step-by-step methodology to conduct SRs in the field of SCI rehabilitation. In Figure 2, we propose a ten step guide specifying the procedures for conducting an SR. We also present the results of a systematic literature search in SCI that targets the Spinal Cord Independence Measure (SCIM)[12] outcome as an example for readers.

The 10 steps to conduct a systematic review in SCI rehabilitation research

Step 1: Assemble the SR team

Individuals participating in SCI rehabilitation often have complex conditions and multimorbidity, in addition to their spinal cord related impairments that requires an interprofessional collaboration to provide appropriate care. Therefore, a collaborative effort (i.e. among individuals with expertise relevant to the problem of interest) is needed to conduct the most precise SR. The SR team's goal is to identify and refine a pertinent question that will influence SCI rehabilitation practice and help synthesize the products and discussion of the SR and its practice implications. The steps to conducting an SR should be outlined for all team members (as described in Steps 2–10) and the roles of individual team members identified before conduct of the review.

Step 2: Formulation of the research question

The purpose of a SR in rehabilitation science is to answer a clear and focused clinical question. Therefore, a well-formulated question of clinical importance is crucial to guide many aspects of the SR process, including determining inclusion and exclusion criteria, search strategy, extracting data, and presenting findings.[13] The individual responsible for conducting an SR should formulate a specific and clearly articulated research question at the beginning of the process.

The PICO mnemonic model[14,15] consisting of patient/population or problem (P), intervention (I), comparison (C), and outcomes (O), is a useful tool for defining exact, focused clinical questions and developing an SR protocol. Other PICO variations are PICOS and PICOT, where "S" implies study design (e.g. RCT or diagnostic study) and "T" implies time frame of the studies (e.g. one day, seven days, one month, or six months). The Cochrane Collaboration offers suggestions on the type of PICO model to choose.[13] Table 1 describes further details of the PICO model.

Step 3: Determination of the inclusion and exclusion criteria

Conduct of a SR requires that the investigators define clear inclusion and exclusion criteria for deciding which studies in the literature will be included. The decisions about inclusion and exclusion criteria should relate directly to the defined research question. Many factors can be applied as inclusion or exclusion criteria such as study design, language, participants, publication types, and a starting date based on the research question. For example, deciding only to include case series with at least 5 patients, including articles published in English, French and Spanish, or deciding only to include clinical trials with a common control intervention or only women with non-traumatic

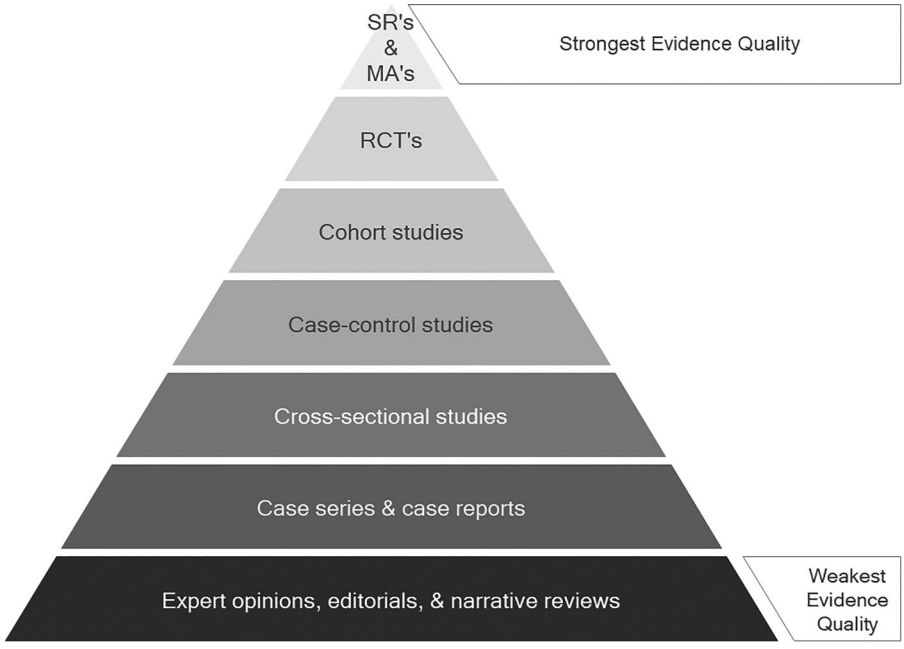

Figure 1 Hierarchy of research evidence. SR: systematic review; MA: meta-analysis; RCT: randomized controlled trials. Source: Adapted from Evans.[40]

SCI, to name a few. This process of specifying the inclusion and exclusion criteria are essential in a rigorous SR as it reduces bias in study selection. Furthermore, the rationale for including or excluding studies should be recorded for future summarization in the PRISMA chart. At least two members of the assembled SR team members should implement the inclusion/exclusion criteria review.[16] Each reviewer should keep a log file of the studies reviewed and incorporate the reasons for each study's inclusion or exclusion. If the study does not include sufficient details for the SR team to confidently include or exclude an article, the SR team may consider contacting the study authors.

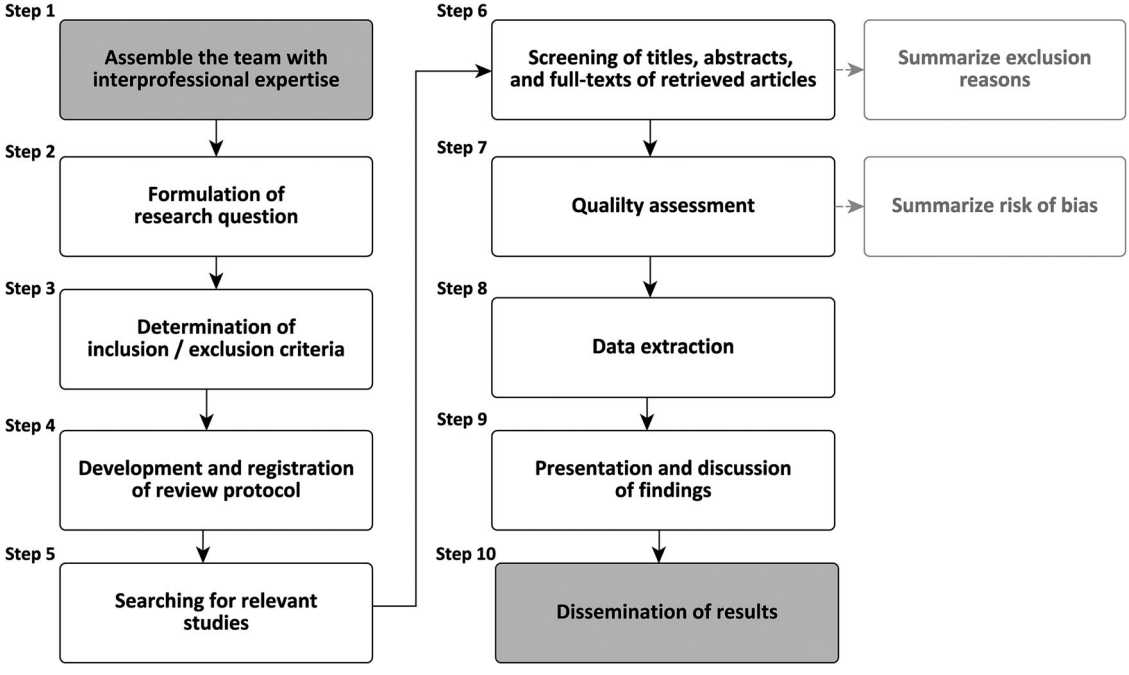

Figure 2 A step-by-step guide to conducting systematic reviews.

Table 1 An example process for formulation of the research question in SCI/D rehabilitation using the PICO mnemonic.

Component	Questions
Patient/Population or Problem (P)	• Patient: What type of individuals based on their SCI etiology or impairment level? *e.g. Individuals with American Spinal Injury Association (ASIA) impairment scale of Grade A and Grade B.* • Problem: What is the problem the researcher would like to address in SCI patients? *e.g. related to skincare, walking, wheeling, or urinary tract infection.*
Intervention (I)	• What is the specific intervention, strategy, diagnostic test? *e.g. specify the drug, food, surgical procedure, physical exercise, or rehabilitation tool/procedure.*
Comparison (C)	• What is the control/comparison/alternative to the intervention group? *e.g. placebo (a fake drug), no intervention, other intervention (strategy, diagnostic test, drug, food, surgical procedure, physical exercise, or rehabilitation tool/procedure).*
Outcome (O)	• What are the clinical outcomes/consequences of interest the researcher would like to investigate in SCI patients? *e.g. Spinal Cord Independence Measure (SCIM), 6-Minute Walking Test, pressure ulcer incidence.*

Source: Authors compiled.

Step 4: Registration of the review protocol

To prevent other researchers from duplicating the project, the SR team should register on PROSPERO, Cochrane Collaboration, or publish the SR protocol. This initial step will increase the review quality[17] and avoid academic conflicts. The first option is to register the SCI rehabilitation SR protocol on The International Prospective Register of SRs (PROSPERO: https://www.crd.york.ac.uk/prospero/). PROSPERO is an international database for the registration of review protocols in "health and social care, welfare, public health, education, crime, justice, and international development, where there is a health-related outcome" (https://www.crd.york.ac.uk/prospero/#aboutpage). Before registering a new SR protocol, the authors should check the Prospero database of registered protocols to ensure a similar investigation is not already underway. In the presence of any registered similar protocol, it is better not to duplicate the SR without any relevant scientific justification. The second option for registering an SR protocol is to register with a Cochrane Review Group [(CRG); https://www.cochrane.org/about-us/our-global-community/review-group-networks]. Currently, there are 52 CRGs that focus on a particular area of health. In the post-registration of the protocol, the CRG will provide support and advice to the authors throughout the review process. The third option is to submit an SR methods manuscript to a reputable journal in SCI rehabilitation that accepts methods papers.

Step 5: Searching for relevant studies

To ensure that the broadest scope of research is identified, it is imperative to conduct a comprehensive search of the literature and compile all available, relevant, published, and unpublished scientific research on the topic of interest. It is recommended to solicit collaboration from an Information Specialist (e.g. Medical Librarian) to assist with an in-depth search of the required studies (see Appendix 1). A well-constructed search strategy must be developed and then executed in those databases (e.g. PubMed or Medline, Embase, and The Cochrane Central Register of Controlled Trials (CENTRAL)). Dependent upon the topic, grey literature sources should also be considered for inclusion (e.g. Open Grey).[18] Many libraries have available resources to assist with the conduct of systematic searches. For instance, refer to the University of Toronto's Gerstein Science Information Centre website (https://guides.library.utoronto.ca/). Further details regarding four of the major electronic databases for identifying SCI rehabilitation research are presented in Table 2.

Typically, for medical or health-related topics, the Ovid Medline® search strategy will be designed first (see Table 3) and refined through an iterative process with the review team. This search strategy will form the foundation for searching in other databases. Any search limitations, such as specific year of publication, the published manuscript's language, type of studies included (e.g. RCTs) may be utilized, but need to be justified in the text when publishing the results. Often, potential limits are not consistent across databases (i.e. variance in age ranges), and instead of including them in the search strategy, these limits should be stated in the inclusion/exclusion criteria and applied during the screening process.

Once the search strategies for each database are developed and finalized, they should be executed on the same date and exported to a bibliographic citation software. This process allows the authors to stipulate a consistent and finite date range when reporting their written materials methodology. If the period from that search date to when the authors are ready to submit their completed paper exceeds 12 months, it is

Table 2 Major electronic databases suitable for systematic review search.

Database	Ovid MEDLINE®	CINAHL®	APA PsycINFO®	Embase®
Scope	Clinical and medical topics	Nursing and allied health professionals	Linkages of social and behavioral sciences with other fields	Clinical and medical topics, but particularly strong in pharmacology and psychiatry
Years	1946 to present	1937 to present	1597 to present, with comprehensive coverage from the 1880s	1974 to present (Embase classic from 1947 to present)
Structure	Very strong and widely recognized controlled thesaurus of Medline Subject Headings (MeSH) for good relevancy of results; advanced filters	Easy-to-use interface with basic and advanced search features; follows MeSH structure,	Well-structured controlled thesaurus of psychological indexed terms, filters	Well-structured controlled thesaurus (Emtree) for good relevancy of results; advanced filters
Indexing	Access to ePub Ahead of Print; access to in-process and non-indexed articles; includes citations from PubMed;	A comprehensive scope (over 50 nursing specialties); speech and language pathology, nutrition, physical therapy	Peer-reviewed articles, dissertations, books, grants/ funding resources, methodologies, clinical/ empirical case reports/studies	Coverage of Biomedical indexes, journals, conference abstracts

Source: Authors compiled.

Table 3 A systematic search strategy example in Ovid MEDLINE® for spinal cord injury and Spinal Cord Independence Measure.

#	Code
	[Population: Spinal Cord Injuries]
1	exp Spinal Cord Injuries/
2	((spine or spinal) adj3 (fracture* or wound* or trauma* or injur* or damag*)).tw,kw.
3	SCI.tw,kw.
4	(spinal cord adj3 (contusion* or laceration* or transection* or ischemi* or syndrome)).tw,kw.
5	(paraplegi* or quadriplegi* or tetraplegi*).mp.
6	exp Paraplegia/
7	exp Quadriplegia/
8	exp Spinal Cord/
9	exp Spinal Cord Ischemia/
10	central cord injury syndrome.tw,kw.
11	(myelopath* adj3 (traumatic or post-traumatic or ischemi*)).tw,kw.
12	exp Cervical Vertebrae/in [Injuries]
	[Intervention: Early decompression]
13	exp Decompression/ or exp Decompression, Surgical/
14	exp central cord syndrome/
15	((early or surgical) adj2 decompress*).ab,ti,tw,kw.
	[Outcomes: Spinal Cord Independence Measure]
16	exp Disability Evaluation/
17	"Activities of Daily Living"/
18	Outcome Assessment, Health Care/
19	(Spinal Cord Independence Measure or SCIM).tw,kw.
20	(function* or disabil* or outcom*) adj3 (assess* or measur* or diagnos* or chang* or recover* or measure* or study or studies).tw,kw.
21	(activit* adj3 (daily living)).tw,kw.
	[Combining results]
22	or/ 1–12
23	or/ 13–15
24	or/ 16–21
25	22 and 23
26	25 and 24

Source: Authors compiled.
Note: The comparison (C) will be individuals without early or surgical decompression.

advisable to re-run the search strategies for that intervening period to determine if any new, relevant materials have become available should be included in the paper. An example of a systematic search strategy in SCI research is presented in Table 3.

Data management tools, such as Covidence (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia, available at www.covidence.org), allows multiple reviewers to apply the inclusion and exclusion criteria to conduct first level (abstracts) and second level (full text) screening. It also allows the SR project team leader to oversee the reference filtering and selection process. This tool is beneficial when multiple members of the SR team are working remotely.

Step 6: Screening

Once the search is completed, the retrieved literature should be stored in a commercial reference manager such as EndNote (Clarivariate, PA, US) or Mendeley (Elsevier, London, UK). Following the storage of the selected articles, first-level screening should be done. For this step, a double-screening method (i.e. two independent reviewers conduct the screening) is preferred compared to the single-screening method (i.e. only one reviewer conducts the screening) as this will limit the number of missed studies.[19] Each reviewer should first screen the titles and abstracts against the inclusion and exclusion criteria. Then, the full-text of the studies that satisfied the inclusion criteria should be screened (i.e. level two screening), and any paper that meets the exclusion criteria should be removed. Agreement between team members in all steps of conducting SR,

including title, abstract, and full-text screening, should be recorded and the inter-rater reliability (IRR) calculated. Unfortunately, inadequate attention has been paid to reporting the IRR, especially when multiple reviewers work at different SR steps.[16] A third reviewer may resolve any disagreements for including or excluding the studies. The reasons for excluding the studies in this step should be summarized and reported in the PRISMA diagram. An automatic PRISMA diagram creator may be accessed at http://prisma.thetacollaborative.ca/.

Covidence is a user-friendly tool that is most appropriate for level 1 title and abstract screening and level 2 screening (full-text) (see Figure 3 as a screenshot of the level 1screening step in the Covidence tool).

Step 7: Quality assessment

The quality of the included studies should be evaluated and reported in the SR manuscript to inform the reader about the evidence's robustness. For this aim, various tools have been developed to assess the quality of evidence, including randomized and non-randomized trials. Members of the research team will need to select and apply a quality assessment tool to describe the risk of bias to infer the quality of the included articles. The most frequently used quality assessment tools are summarized in Table 4. The SR team will need to use different tools for assessing the risk of bias based on the designs of the studies included in the SR. A comprehensive list of the available tools can be accessed at https://www.nihlibrary.nih.gov/services/systematic-review-service/tools-resources and https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools.

Step 8: Data extraction

In this step, the SR team should aim to extract the relevant data from the full text of each selected study for inclusion to evaluate, compare, and synthesize the current and most updated evidence. Since a large amount of information is extracted in SRs, proper information management – a standardized data extraction spreadsheet – is crucial. This spreadsheet should be developed and tested by the SR team members before conducting the full data extraction. Upon reading the full-texts of the included articles, the reviewers should populate the spreadsheet. If the SR team intends to conduct a quantitative evidence synthesis (e.g. meta-analysis), the reviewers should computerize the data collection and analysis processes.[20] In addition to reference management, some SR management software can help track team progress, facilitate communication between members, enable data extraction, and perform meta-analyses; every tool is not suitable for every kind of synthesis or review. Therefore, the SR team should ensure that the right tool is selected.

To use RevMan Web, the researcher should be a confirmed Cochrane author, which indicates that the SR team member should have authored at least one published SR in the Cochrane Collaborative group or the CRG. RevMan 5 is the desktop version (https://training.cochrane.org/online-learning/core-software-cochrane-reviews/revman) of the software used for non-Cochrane reviews and offline usage. Other available tools for data extraction include Review Manager (RevMan; https://revman.cochrane.org/), Systematic Review Data Repository (https://srdr.ahrq.gov/), Distiller (https://www.evidencepartners.com/), and EPPI-Reviewer (https://eppi.ioe.ac.uk/cms/) and the aforementioned Covidence software (https://app.covidence.org/).

Step 9: Presentation and discussion of findings

Depending on the type of extracted data (i.e. quantitative or qualitative), the reviewers may compile the information in tabular, text, or graphical formats.[21] A 'Summary of Findings' (SOF) table is a great medium to compile the studies' critical information such as outcome(s), effect sizes, sample sizes, and quality of evidence.[22] The SR team should consider using the GRADEpro Guideline Development Tool (https://methods.cochrane.org/gradeing/gradepro-gdt) to create the SOF table (see Table 5). The SOF table should include a summary of each evidence body in a transparent, structured, and straightforward format.[22] When results are mathematically combined (e.g. meta-analysis), it is common for different trials to be depicted in a graphical format (e.g. forest plot or network diagram). The pooled results are often shown as a diamond at the bottom of the plot. A detailed discussion regarding the conduct of meta-analyses can be found elsewhere.[20]

The aforementioned visual representation of the data is necessary to summarize the findings in lay and straightforward language and discuss clinical practice implications. This later stage is critical to ensure the SR results are communicated in a manner that clinicians can use to guide quality care, advance research, or improve patient outcomes. A meeting with the SR team is recommended to discuss the results and their limitations and potential biases related to lay terms before disseminating the results to relevant stakeholders.

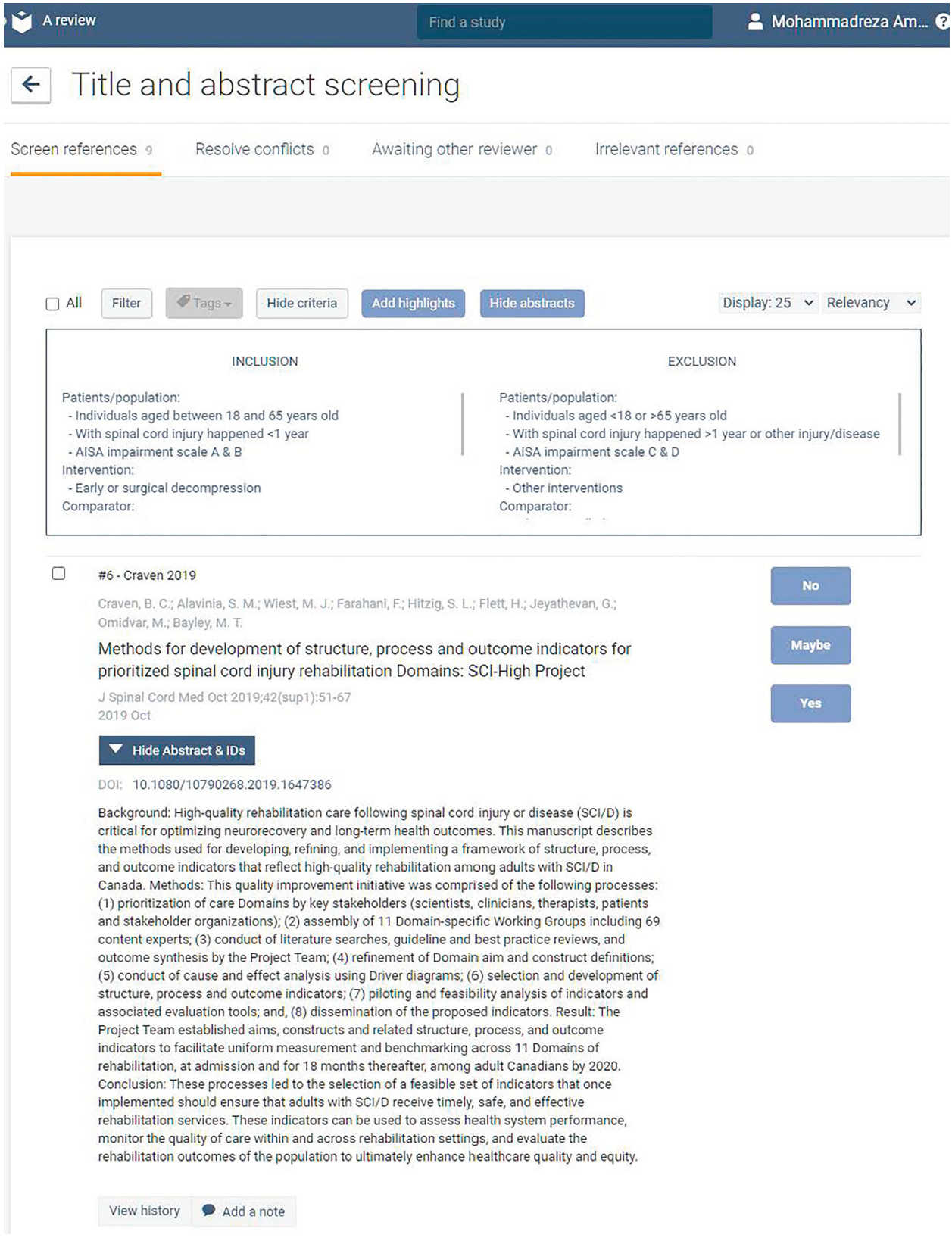

Figure 3 The level 1 screening step in Covidence.

Table 4 Overview of Quality Assessment Tools.

Tool	Usage	Items
Grading of Recommendations, Assessment, Development and Evaluations (GRADE)[34]	Clinical guideline and Randomized trials	Study design, risk of bias, inconsistency, indirectness, imprecision
Newcastle-Ottawa Scale[35]	Non-randomized studies (case-control and cohort studies)	Selection, comparability, exposure/outcome
Oxford Quality Rating Scale (Jadad Scale)[36]	Randomized trials	randomization, blinding, and the dropout rate
van Tulder scale[37]	Randomized trials	randomization, allocation concealment, baseline characteristics, blinding, co-intervention, compliance, dropout rate, end-point assessment time point, and analysis of intention-to-treat
Downs and Black[38]	Randomized and non-randomized trials	Study quality, external validity, study bias, confounding and selection bias, study power
Cochrane Collaboration's Risk of Bias Tool[39]	Randomized trials	sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, validity bias

Source: Authors compiled.

Step 10: Dissemination of results

If reviews are conducted through the Cochrane Collaboration, they will be published in the online Cochrane Database of Systematic Reviews which is a lengthy and detailed process. Therefore, it is also possible and encouraged to publish abbreviated versions of the SR in other relevant peer-reviewed journals. The aim of the preferred reporting items for systematic reviews and meta-analyses (PRISMA) is to help authors improve their SR and meta-analysis papers and show how to report and write an SR and meta-analysis article (see Appendix 2). The PRISMA's focus is on the SR of RCTs but can be useful for other research types. Although the PRISMA checklist may also be a valuable tool for critical appraisal of published SRs, it does not assess the quality of SRs.

Table 5 Methods to present the systematic review findings.

Name	Details
Systematic Reviews	
Summary of findings	Outcome(s) Effect size (the difference between intervention and control groups) Number of participants in the study (sample size) The certainty of the evidence (risk of bias) Other comments
Risk of Bias Table	Selection bias Performance bias Detection bias Attrition bias Reporting bias Other bias
Meta-Analysis	
Funnel Plot	Illustrates the precision of effect estimates
Forest Plot	Shows the overall effect estimates
Network Diagram	A network of interventions in network meta-analysis

Source: Authors compiled.

A PRISMA flow chart must be included in any SR report.[23] The pragmatic implications of the systematic review should be shared with stakeholders using a variety of integrated knowledge translation tools.

Conclusion

In this article, we present a step-by-step guide to conducting SRs in SCI rehabilitation and provide several directions and examples for learners and clinicians in conducting a robust SR. Also, we identify several tools and methodologies to assist the SR team in conducting a rigorous review and producing clear documentation, summarization, and reporting of their SR results.

Conducting SR's in the SCI rehabilitation research may have some limitations. On the one hand, the heterogeneity among included SCI studies is inevitable[21] due to heterogeneity of clinical characteristics of patients (e.g. etiology of injury or impairment; impairment – complete/incomplete, paraplegic or quadriplegic, clinical settings – acute, subacute or chronic; intervention utilized – unimodal or multi-modal), length of intervention, protocol followed – frequency and intensity of sessions, devices used, adherence, and time from injury.[4] On the other hand, the SR in SCI rehabilitation research demands a team of interprofessional experts in the field to interpret the summarized effect size and results from the included studies.[24] Strong interprofessional SR teams will recognize the diversity of research design and rigor of study conduct, interventions used and the impacts on outcomes among patients with specific demographic and

impairment characteristics.[21] However, it is important for the reader to understand that the quality of the systematic review is ultimately limited by the strength and relevance of the primary question and the quality and lack of bias in the available evidence.

In addition to systematically reviewing the studies, other methods for evidence synthesis include: scoping reviews, rapid reviews, integrative review and realist reviews among other types.[25] These types of reviews address questions that go beyond the effectiveness of an intervention and are beyond the scope of this guide. For example, an integrative review is an approach that enables reviewers to combine diverse methodologies such as experimental and non-experimental, as well as qualitative and quantitative research, and has the potential to play a more significant role in evidence-based practice.[26,27]

Rehabilitation science and medical learners, rehabilitation clinicians and scientists may use the proposed steps for conducting SRs in SCI rehabilitation research, which can significantly improve the evidence synthesis quality. Practicing medicine in the field of SCI rehabilitation requires clinicians and learners to have broad-based knowledge and understanding of various diagnostic imaging, and interventional therapies, psychosocial, physical, medical or surgical treatments,[2] medical complications,[28] social participation,[29] outcomes (quality of life),[30] and indicators (post-injury employment).[31] A best practice to synthesize the most current evidence relatively quickly, compared to guideline development, is to conduct an SR on a relevant question in SCI rehabilitation.[32] The proliferating scientific evidence in SCI or disease requires parallel and ongoing synthesis of the most current research to inform clinical guidelines and healthcare policymaking.[33] We encourage ongoing rich evaluations of available literature by interprofessional SR teams in the field of SCI rehabilitation.

Disclaimer statements

Contributors MA and SMA contributed equally to the conceptualization of the guide, draft, review, and revisions; MO and MP developed the search strategy and citation management; BCC provided information about the interprofessional aspect of the guide and finalized the draft.

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Abbreviations

CENTRAL: The Cochrane Central Register of Controlled Trials; CRG: Cochrane review group; MA: meta-analysis; PICO: patient, intervention, control/comparison, outcome; PRISMA: preferred reporting items for systematic reviews and meta-analyses; QoL: quality of life; RCT: randomized controlled trials; SCI: spinal cord injury; SCIM: Spinal Cord Independence Measure; SOF: summary of findings; SR: systematic review.

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Appendices

Appendix 1. Additional information regarding the search strategy

Libraries/databases

Databases are subject-specific and index materials found in a specified group of journal titles covering that topic. The journals included will vary from database to database, and there will be similar and unique titles within each. A guide for each database, available as a link within the database, outlines the general topics and timeframes covered. Since few databases are freely available, the variety of databases available to researchers will depend on their institution's subscriptions. For medical topics, Medline and/or PubMed and Embase must be searched. Other recommended databases for SCI rehabilitation include Cochrane, PsycINFO, Emcare, and CINAHL (Cumulative Index to Nursing and Allied Health Literature). Dependent on the reviewer's institution's resources, other databases are available covering similar or more specific content that should be considered, such as Allied Health databases (e.g. PEDro or OTseeker). University libraries often have subject guides that list the best databases for the varied disciplines. The reviewer should check his/her local

university library for database suggestions to determine if the institution provides access to these resources.

Medical subject headings

All databases use controlled language, known generally as Subject Headings, to represent specific biomedical concepts. In Medline, these subject headings are referred to as MeSH terms. This will lead to more efficient and effective searching. MeSH terms will gather all information on that topic, regardless of variant spellings, changing trends in terminology or lay terms. MeSH terms can also be directed to include narrower subject headings (known as "exploding") or limited to materials where the topic is the "major focus" of the article rather than a minor aspect of the paper. For example, searching for the word cancer as a keyword could potentially exclude relevant results where papers have used alternate terms to represent the cancer being discussed. However, a search for the MeSH term "Neoplasms" would return all records discussing cancer, regardless of the name used, since an indexer had applied that subject heading to the record, which saves time and effort while improving precision (1). Subject headings and the tree structures vary for each database, requiring the development of a separate search strategy for each database.

Grey literature

Literature not indexed in traditional databases is called the "grey literature" and includes materials produced by individuals or governmental or non-governmental organizations outside of traditional academic or commercial publishing sources. Searching for grey literature is a time-consuming process that does not always yield satisfactory results to warrant the required time and effort. A better strategy is to complete the screening process, narrow the results down to those that will be included in the analyses, and then check the reference lists of those materials to determine if additional materials not found through the traditional database searches are noted there, i.e. institutional reports or government documents.

Appendix 2. Checklist of the preferred reporting items for systematic reviews and meta-analyses (PRISMA)

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g. Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g. PICOS, length of follow-up) and report characteristics (e.g. years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g. databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e. screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g. piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	

Continued

Section/topic	#	Checklist item	Reported on page #
Data items	11	List and define all variables for which data were sought (e.g. PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g. risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g. I^2) for each meta-analysis.	
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g. publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g. sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g. study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g. sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g. health care providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g. risk of bias), and at review level (e.g. incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g. supply of data); role of funders for the systematic review.	

From: Moher *et al.* (2)

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