## PEER REVIEW HISTORY



## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | The course and prognostic factors of cognitive status after central nervous system trauma: A systematic review protocol |
| **AUTHORS** | Mollayeva , Tatyana; Pacheco, Nicole; D'Souza, Andrea; Colantonio, Angela |

## VERSION 1 - REVIEW

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| **REVIEWER** | Marius Rehn<br>Norwegian Air Ambulance Foundation, Norway |
| **REVIEW RETURNED** | 05-May-2017 |

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| **GENERAL COMMENTS** | Thank you for the opportunity to comment on manuscript: "The course and prognostic factors of cognitive status after central nervous system trauma: A systematic review protocol".<br>This protocol outlines a plan to systematically review literature that assess cognition in patients with CNS trauma on at least two separate time points post-injury. The study aims to identify, appraise the methodological quality, extract data from included articles and perform meta-analysis, when applicable. The protocol is well-written and describes in detail the strategy to achieve these aims in a satisfactory way. The study is of particular clinical relevance, both from a primary and secondary prevention perspective. Further, it should also be of high relevance for health policy decision makers as long term consequences of CNS injury remain a major public health challenge. The study is registered in PROSPERO and there are no reported conflicts of interest. The language is reader-friendly and of high quality (as judged by a non-native English speaker)<br>I have only a few minor comments:<br>-Would it be of relevance to also include covariates such as history of illegal drug abuse, mental co-morbidity, pre-injury mental health status when available.<br>-Would SCI be limited to traumatic injuries or will other types of injuries (e.g. iatrogenic spinal haematomas, etc) be included?<br>-I understand that you have decided not to include grey literature. Could you please mention this active decision and provide a (short) rationale?<br>-Will you use Covidence software platform in the screening process? Personally, I have very good experiences with this low-cost and efficient review tool. |

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| **REVIEWER** | Julie Luker<br>University of South Australia<br>Australia |
| **REVIEW RETURNED** | 18-May-2017 |

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| **GENERAL COMMENTS** | I congratulate the authors for undertaking this important review and for their carefully constructed protocol. The overall methodology is sound and aligns well to the PRISMA guidelines. My comments are regarding minor amendments that would improve the readability of the protocol paper. In my opinion there are some sections that will benefit from rewriting to improve clarity, improve grammar and punctuation, and reduce confusion and repetition.<br>1. Cognitive deficits commonly result from the initial TBI, with some recovery occurring in the early months post-TBI. I understand that this is a different phenomenon to the one your SR addresses (cognitive decline in later life for people with previous TBI) however I think your protocol should address how your review will deal with early fluctuations in cognition.<br>2. There is inconsistent tense used currently. Some sentences throughout the manuscript refer to the past tense as if the work has already occurred (e.g. P3 L27, P16 L3), while other sections are written in future tense. Please rewrite in consistent tense or explain which work has already occurred.<br>3. From the supplemental files I note that your database searches have already run. The inclusion of CINAHL may have found additional studies.<br>4. The in-text citations jump from number 4 to 6. Reference 5 seems to be missing.<br>5. Alzheimer's disease (AD) is mentioned frequently in association with the cognitive decline of interest. As AD causes only 60-70% of dementia, there should be some explanation of why the SR will focus on AD, and how you will determine if the participants had AD or other forms of dementia. Alternatively the broader term 'dementia' may be preferable to AD.<br>6. There are some overly long sentences that are somewhat confusing, and would benefit from rewriting e.g P6 starting L48; P8 L8.<br>7. The unusual punctuation of using a double dash ( - -) instead of colons or semi-colons could be addressed.<br>8. The statement on P8 L8 (regarding womens' traditional inequalities resulting in scarce data) needs to be referenced if it is fact. If it is the authors' hypothesis then this should be made clear.<br>9. The definition of cognition currently appears in the middle on study inclusion criteria, and is then cross referenced with * symbols in various places within the text. You could consider stating you definition in the Introduction; you shouldn't need to use *<br>10. The sentence P10 L43 'We do not set limitations on settings in which the research took place' fits better under the criteria of 'Types of studies' than under 'Participants and assessment'<br>11. P11 L26. DSM-V needs the full wording first time. It also needs a reference.<br>12. P12 L53 do you mean that you will remove 'all papers/studies' rather than 'all citations'?<br>13. P13 L8 Update the role of the Cochrane team prior to publication<br>14. Please mention that a PRISMA flow chart will be used to report the study selection process.<br>15. P23 L25. Replace 'their design' with 'study design'. Currently the subject of this phrase refers to the data collection forms.<br>16. P15 L16. A two-step process is mentioned however only step (1) |

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| | in made clear. Make step (2) clear.<br>17. The use of the heading 'measurements: description and properties..' is helpful. I suggest you use another heading for the section starting at the top of P17 where you are addressing the synthesis for your first 3 objectives (from P9).<br>18. P18 In the final pages there is a lot of repetition of information provided in the Introduction e.g. regarding measures used for cognition. I prefer the way it is written in this later section but it only needs to appear once.<br><br>I wish the authors ever success with this work and I look forward to reading the final review. |

**VERSION 1 – AUTHOR RESPONSE**

Reviewer: 1
Marius Rehn
Norwegian Air Ambulance Foundation, Norway
Please state any competing interests or state 'None declared': None declared
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Please leave your comments for the authors below

Thank you for the opportunity to comment on manuscript: "The course and prognostic factors of cognitive status after central nervous system trauma: A systematic review protocol".

This protocol outlines a plan to systematically review literature that assess cognition in patients with CNS trauma on at least two separate time points post-injury. The study aims to identify, appraise the methodological quality, extract data from included articles and perform meta-analysis, when applicable. The protocol is well-written and describes in detail the strategy to achieve these aims in a satisfactory way. The study is of particular clinical relevance, both from a primary and secondary prevention perspective. Further, it should also be of high relevance for health policy decision makers as long term consequences of CNS injury remain a major public health challenge. The study is registered in PROSPERO and there are no reported conflicts of interest. The language is reader-friendly and of high quality (as judged by a non-native English speaker)

Response: We thank the reviewer for taking the time to review the protocol and his positive feedback.

I have only a few minor comments:
-Would it be of relevance to also include covariates such as history of illegal drug abuse, mental co-morbidity, pre-injury mental health status when available.

Response: We considered the confounding effect of medications, both prescribed and over- the-counter/illicit use, as well as comorbidity/multimorbidity, pre-morbid and developed with time, and therefore will analyze the data in light of these factors. However, based on our previous works with the population of interest, studies inconsistently provided this relevant information.

We have added the following paragraph to the manuscript (to address the comment of the second reviewer) and a sentence to the limitations section of the protocol:

To address our research objective regarding the effect of CNS trauma on cognitive status, we will evaluate the literature regarding putative negative effects in light of other factors known to affect cognition; age and sex will be considered as a minimum required set of confounders associated with

cognition at each time point. Since timelines for establishing causal links between CNS trauma and development of cognitive decline are currently not established, we will not set any restrictions on periods between baseline assessment and subsequent follow-up assessment, and will use criteria such as the following in our report: temporal relation, lack of alternative causes, outcome response to alleviation or exacerbation of cognitive deficits over time. Confounding factors (such as sociodemographic characteristics, severity of injury, and comorbidities) that may affect the generalizability of the study and interpretation of results will be explored and clearly described. In addition, we will report on the possible effects of individual study quality indicators (for example, the follow-up period and instrument used to measure the outcome).

(4) potential confounders, such as medication effect, comorbidity load, and illicit substance use may not be adequately explored given lack of consistent reporting and effect consideration in TBI research; nonetheless, whenever possible, such effects will be explored;

-Would SCI be limited to traumatic injuries or will other types of injuries (e.g. iatrogenic spinal haematomas, etc) be included?

Response: Spinal cord injuries will be limited to that of traumatic origin (i.e., our primary focus is trauma to the central nervous system). We have clarified this in the protocol.

Studies of SCI of only traumatic origin will be considered.

-I understand that you have decided not to include grey literature. Could you please mention this active decision and provide a (short) rationale?

Response:

We thank the reviewer for raising the issue of grey literature. We are aware that the methodological standards for systematic reviews recommend extensive searching to address the potential for publication bias and to produce accurate and valid estimates of effect; this has also been reflected in the recent Cochrane guidelines. The rationale for excluding grey literature, clinical trial registries and other sources of unpublished information in our study was based on two reasons, one of which was the significant number of abstracts identified within our search databases even after removal of duplicates, i.e. more than 22,000 – these searches are by far the most comprehensive of all done on any topic in TBI or SCI populations combined; in comparison, the number of identified works in the initial screen generally does not exceed 5,000 abstracts. In addition, a recent systematic review on the topic has provided empiric evidence on the limited value of searching for and including grey literature (i.e., studies published in languages other than English, unpublished studies and dissertations). Inclusion of these study types may have an impact in situations where there are few relevant studies, or where there are questionable vested interests in the published literature, which is not a concern with regards to our research question.
Reference: Hartling L, Featherstone R, Nuspl M, Shave K, Dryden DM, Vandermeer B. Grey literature in systematic reviews: a cross-sectional study of the contribution of non-English reports, unpublished studies and dissertations to the results of meta-analyses in child-relevant reviews. Reference: BMC Med Res Methodol. 2017 Apr 19;17(1):64
We have added the following paragraph to the limitations section:

(5) additional limitations relate to the exclusion of grey literature, non- English language articles, and unpublished manuscripts and their potentially relevant results; the decision was based on the extensive number of studies identified within the databases searched, as well as limited empiric

evidence about the potential impact of selective searching and inclusion of these works on the results of systematic reviews.

-Will you use Covidence software platform in the screening process? Personally, I have very good experiences with this low-cost and efficient review tool.

Response: We thank you for the suggestion, and will explore the Covidence software platform as a tool in the screening process in future research.

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Reviewer: 2
Julie Luker
University of South Australia, Australia
Please state any competing interests or state 'None declared': none declared

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Please leave your comments for the authors below

I congratulate the authors for undertaking this important review and for their carefully constructed protocol. The overall methodology is sound and aligns well to the PRISMA guidelines. My comments are regarding minor amendments that would improve the readability of the protocol paper. In my opinion there are some sections that will benefit from rewriting to improve clarity, improve grammar and punctuation, and reduce confusion and repetition.

Response: Thank you for your feedback. We have made changes to the structure of the manuscript to the best of our ability, refining the flow of information we believe to have high potential value to the readership's comprehension.

1. Cognitive deficits commonly result from the initial TBI, with some recovery occurring in the early months post-TBI. I understand that this is a different phenomenon to the one your SR addresses (cognitive decline in later life for people with previous TBI) however I think your protocol should address how your review will deal with early fluctuations in cognition.

Response: We did not set restrictions on the effect of time in this review. Therefore, both short and long-term effects will be explored. The early and potentially late fluctuations in cognition will be assessed by grouping results of studies that reported improvement, or decline, or stability and assessed cognitive function at similar points of time (we refer the reviewer to the methodology section for specifics).

2. There is inconsistent tense used currently. Some sentences throughout the manuscript refer to the past tense as if the work has already occurred (e.g. P3 L27, P16 L3), while other sections are written in future tense. Please rewrite in consistent tense or explain which work has already occurred.

Response: At this time we have completed the first screening, developed a strategy for prognostication analyses, data synthesis, and fully defined criteria of assessment of study quality. We have also initiated review of psychometric properties (evaluative, i.e., construct validity and test-retest reliability) of the most commonly used tools to assess cognition in patients with CNS trauma. The tense used throughout the manuscript has been revised, and has been kept consistent to represent the status of each step.

3. From the supplemental files I note that your database searches have already run. The inclusion of CINAHL may have found additional studies.

Response: The Cochrane handbook recommends searching a minimum of 3 databases: Medline, Embase, and CENTRAL (section 6.2.1.1). A recent publication on the topic has established that: “In total, 99% of articles included in each SR were found in two databases, with the majority being found in PubMed/MEDLINE, Embase, or Cochrane. SRs that found articles in three or more databases screened an additional 923 records in order to find one additional included article, plus an additional 2410 records from databases that did not return any additional included articles, adding an average of 756 hours of work to each SR” (Reference: Posey,R., Walker, J., Crowell,K. Knowing When to Stop: Final Results vs. Work Involved in Systematic Review Database Searching. Medical Library Association. Annual Meeting (2016: Toronto, Ont.) https://cdr.lib.unc.edu/record/uuid:d15efa48-8491-48d7-a77f-1e8ee4daca8e).

To ensure a comprehensive search, we have searched all the recommended databases, and added Scopus (covering allied health and nursing literature), PsycINFO (covering behavioral and social science research), and supplemental PubMed. When considering which additional databases to include, we followed the recommendation of inclusion of ONE “specialized” database. We selected PsycINFO, for its mental health focus, rather than CINAHL where any potential unique content would be predominantly related to specialty nursing and allied health fields. To solidify the search strategy comprehensiveness in light of the reviewer’s comment, the supplemental search methodologies, such as hand searching and cited reference searching will be applied. This strategy has been described in the methodology section of the manuscript.

We have added citations and the following sentence to the manuscript:
We refer the reader to the Cochrane handbook and other published sources for justification of the selected databases.

4. The in-text citations jump from number 4 to 6. Reference 5 seems to be missing.

Response: We thank the reviewer for pointing out the error. This has been fixed.

5. Alzheimer’s disease (AD) is mentioned frequently in association with the cognitive decline of interest. As AD causes only 60-70% of dementia, there should be some explanation of why the SR will focus on AD, and how you will determine if the participants had AD or other forms of dementia. Alternatively the broader term ‘dementia’ may be preferable to AD.

Response: We appreciate the reviewer’s comment, and below elaborate on the terms utilized in this review.

This systematic review concerns sustained and/or degrading cognitive function post-injury, as well as cognitive complaints of uncertain clinical significance (i.e., mild cognitive impairments (MCI) with questionable deficits on quantitative tests) starting early after the injury. While at present there is sparse data on how many persons with CNS trauma will eventually progress to definite Alzheimer’s disease (AD), some TBI patients with MCI have shown, on autopsy, findings of histopathological AD. The animal literature also revealed evidence of features of AD arising shortly after TBI. These results suggest that in patients with CNS trauma MCI detected very early post-injury may represent the initial clinical presentation of AD. As part of this review, we will pay close attention to patients with MCI at baseline early after the injury (particularly to mild injury severity cases) but who has progressed rapidly into cognitive deficits within first few years post-injury, with uniform progression of cognitive impairments in several domains (i.e., memory, speech) and impaired activities of daily living, at risk of having a high probability of AD. Further, the term dementia refers to a syndrome of brain dysfunction that is progressive, and has many possible causes; we intend to study CNS trauma as a risk for

cognitive decline, with an open view to the natural course of cognitive status (improvement, decline, or relative stability) with time. Consequently, any sustained decline in cognitive status longitudinally is more reasonable in the discussion of risk of AD rather than dementia.

6. There are some overly long sentences that are somewhat confusing, and would benefit from rewriting e.g P6 starting L48; P8 L8.

Response: We have made changes to the structure of overly long sentences.

7. The unusual punctuation of using a double dash ( - -) instead of colons or semi-colons could be addressed.

Response: This has been fixed.

8. The statement on P8 L8 (regarding womens' traditional inequalities resulting in scarce data) needs to be referenced if it is fact. If it is the authors' hypothesis then this should be made clear.

Response: References have been provided.

9. The definition of cognition currently appears in the middle on study inclusion criteria, and is then cross referenced with * symbols in various places within the text. You could consider stating you definition in the Introduction; you shouldn't need to use *

Response: This has been fixed.

10. The sentence P10 L43 'We do not set limitations on settings in which the research took place' fits better under the criteria of 'Types of studies' than under 'Participants and assessment'

Response: The sentence has moved to the Types of studies section.

11. P11 L26. DSM-V needs the full wording first time. It also needs a reference.

Response: DSM-V has been defined.

12. P12 L53 do you mean that you will remove 'all papers/studies' rather than 'all citations'?

Response: This meant to be" citations" as at this stage (first screen) full articles were not accessed.

13. P13 L8 Update the role of the Cochrane team prior to publication.

Response: The role has been described in the acknowledgement section.

14. Please mention that a PRISMA flow chart will be used to report the study selection process.

Response: We have specified in our abstract and the manuscript that the systematic review will be conducted and reported in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A flow chart is part of the PRISMA guidelines requirement.

15. P23 L25. Replace 'their design' with 'study design'. Currently the subject of this phrase refers to

the data collection forms.
Response: This has been done.

16. P15 L16. A two-step process is mentioned however only step (1) in made clear. Make step (2) clear.

Response: This has been done.

17. The use of the heading ‘measurements: description and properties..’ is helpful. I suggest you use another heading for the section starting at the top of P17 where you are addressing the synthesis for your first 3 objectives (from P9).

Response: This has been done.

18. P18 In the final pages there is a lot of repetition of information provided in the Introduction e.g. regarding measures used for cognition. I prefer the way it is written in this later section but it only needs to appear once.

Response: The writing of the final pages has been refined. We have removed repetitive statements to the best of our abilities, retaining the information we believe to have high potential value to the readership.
I wish the authors ever success with this work and I look forward to reading the final review.

**VERSION 2 – REVIEW**

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| **REVIEWER** | Marius Rehn<br>Norwegian Air Ambulance Foundation, Norway |
| **REVIEW RETURNED** | 01-Jul-2017 |

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| **GENERAL COMMENTS** | I thank for the opportunity to comment again on manuscript: “The course and prognostic factors of cognitive status after central nervous system trauma: A systematic review protocol”. The authors have addressed reviewers concerns successfully. I find the protocol suitable for publication. I look forward to see the results of this relevant review. |

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| **REVIEWER** | Dr Julie Luker<br>University of South Australia |
| **REVIEW RETURNED** | 06-Jul-2017 |

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| **GENERAL COMMENTS** | I thank the authors for carefully addressing the comments for both reviewers. This is a very good protocol and I wish the authors every success in taking this important review through to publication |