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## Protocol for a living systematic review for the management of concussion in adults

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Protocol for a living systematic review for the management of concussion in adults

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Abstract

Introduction: Concussion/mild traumatic brain injury (mTBI) often presents initially with disabling symptoms that resolve, but for an unfortunate minority some of these symptoms may become prolonged. Although research into diagnosis and interventions for concussion is increasing, study quality overall remains low. A living systematic review that is updated as evidence becomes available is the ideal research activity to inform a living guideline targeting clinicians and patients. The purpose of this paper is to present the protocol of an ongoing living systematic review for the management of adult concussion that will inform living guidelines building off the Guideline for Concussion/Mild Traumatic Brain Injury and Persistent Symptoms: 3rd Edition.1

Methods and Analysis: The preferred reporting items for systematic review and meta-analysis-protocol (PRISMA-P) guidelines2 were followed in the reporting of this systematic review protocol. We are including English peer-reviewed observational studies, trials, qualitative studies, systematic reviews, and clinical practice guidelines related to diagnosis/assessment or treatment of adult concussion. Future searches will be conducted at minimum every six months using the following databases: MEDLINE, EMBASE, Cochrane, PsycInfo, and CINAHL. The data are managed in the Covidence website. Screening, data extraction, and risk of bias assessments are being done through multiple raters working independently. Multiple validated tools are being used to assess risk of bias, and the tool applied matches the document or study design (e.g., Downs and Black scale for health care interventions3). Many concussion experts in various clinical disciplines from across North America have volunteered to examine the evidence in order to make recommendations for the living guidelines.
Ethics and Dissemination: This protocol has been submitted for review to PROSPERO. No ethical approval is necessary because primary data are not collected. The results will be disseminated through peer-reviewed publications and on the living guidelines website once built.

Strengths and Limitations of this Study

- Frequent searches will ensure the accompanying adult concussion living guidelines are up to date.
- There is a large multidisciplinary concussion expert team who have volunteered to interpret the evidence.
- The review focuses only on adults while excluding the pediatric population.
Introduction

Concussion/mTBI describes an acute neurophysiological event related to a mechanical energy applied to the head, neck or body (with transmitting forces to the brain), such as from sudden acceleration, deceleration, rotational forces, or repetitive subconcussive hits. All concussions are considered to be a mTBI; however, mTBI can differ from concussion when there is evidence of brain injury on conventional neuroimaging or there is persistent neurologic deficit. Concussion can cause significant morbidity, with many persons who have sustained a concussion suffering from prolonged symptoms for years post-injury. Concussion is also among the most common neurological conditions with an estimated annual incidence of 503/100,000 in the United States based on emergency department data, and even higher estimates of up to 1,153/100,000 if community-based concussions are taken into account. Therefore, effective diagnosis/assessment and treatment is critical.

Systematic reviews provide the best evidence available, and there are many that focus on concussion management (e.g.,). However, systematic review currency and accuracy is challenged by the increasing rate of research output. People might consider conducting a traditional systematic review update, but these updates tend to be inefficient because a new team often needs to be assembled for each update meaning the “institutional memory” of the original team is lost. Living systematic reviews may be an effective solution. A living systematic review is defined as: “a systematic review that is continually updated, incorporating relevant new evidence as it becomes available” (p. 24). In addition to pushing the limits of currency and accuracy, living systematic reviews provide an a priori commitment to a frequency of review giving predictability to end users such as clinicians. Applying a living systematic review process to concussion diagnosis/assessment and treatment is appropriate given that research output in this
particular field is increasing every year\textsuperscript{16} and certainty in much of the existing evidence is low,\textsuperscript{1} making frequent updates necessary.

A living systematic review is the ideal research activity to inform living guidelines. Guidelines are normally developed to support clinicians and their patients in making choices to optimize outcomes.\textsuperscript{17} Living guidelines are: “an optimization of the guideline development process to allow updating of individual recommendations as soon as relevant new evidence becomes available”\textsuperscript{18} (p. 47). There have been a few guidelines published on adult concussion (e.g., \textsuperscript{1,19,20}). However, no group or organization has developed living guidelines to address all aspects of diagnosis/assessment and treatment of concussion in adults. The purpose of this paper is to present the protocol of an ongoing living systematic review for the management of adult concussion that will inform living guidelines building off the Guideline for Concussion/Mild Traumatic Brain Injury and Persistent Symptoms: 3rd Edition.\textsuperscript{1}

**Methods and Analysis**

The PRISMA-P guidelines\textsuperscript{2} were followed in the reporting of this systematic review protocol.

**Eligibility Criteria**

The inclusion criteria are: studies related to concussion diagnosis/assessment or treatment; at least 50\% of sample has concussion (i.e., a Glasgow Coma Scale score of 13-15)\textsuperscript{21} in cases where one group is analyzed; at least 50\% of the sample is 18 years of age or older; and the sample is human. Peer-reviewed observational studies (cross-sectional, cohort, case-control), clinical trials, qualitative studies, systematic reviews, and clinical practice guidelines are included. Documents are limited to English language and publication from May 2017 because
that covers literature that did not inform the Guideline for Concussion/Mild Traumatic Brain
Injury and Persistent Symptoms: 3rd Edition.¹

The exclusion criteria are: studies that focus on moderate or severe TBI (i.e., a Glasgow
Coma Scale score of less than 13); more than 50% of sample has moderate or severe TBI in
cases where one group is analyzed; more than 50% of sample is under 18 years of age; and the
sample is not human. Case reports/n of 1 studies, non-systematic reviews, conference
abstracts/presentations, theses, non-peer-reviewed articles (e.g., newspaper articles), letters or
commentaries, addendums/erratum, and book chapters are excluded. Documents not available
in English, published before May 2017, or originating from grey literature are also not included.

Information Sources

The search strategy (see next section) was originally created in April 2020 for the
MEDLINE database in collaboration with a librarian at a research-intensive hospital. The
strategy was then peer-reviewed by another librarian at a separate hospital according to the
PRESS guideline.²² The PRESS guideline is a checklist of topics that information specialists
should consider when evaluating an electronic search strategy. The strategy was approved with
minor revisions. EMBASE, Cochrane, PsycInfo, and CINAHL databases are also being searched
using the strategy.

Search Strategy

An initial search was completed at the beginning of April 2020 covering May 2017 to the
end of March 2020. That search yielded 19,745 results. The search was updated to cover recent
literature published April 2020 to the end of March 2021. The new search yielded 5,071 results,
meaning the total number of search results was 24,816. The full search strategy for the initial
MEDLINE search has been reported in Supplementary Material 1 as an example. The next
search will cover literature published from May 2021 to the end of February 2022 (search to be conducted on March 1, 2022). After this next search, consistent with living systematic review recommendations, the search is planned to repeat every six months at minimum to capture recent literature.

**Data Management**

The search results are being imported into the Covidence systematic review website. This website automatically removes duplicates, and provides the opportunity for screening, data extraction, and risk of bias assessments with multiple raters.

**Selection Process**

After duplicates from the initial searches were removed by Covidence, 16,086 documents remained (11,916 from the initial search and 4,170 from the updated search). At the title and abstract screening phase, raters select “yes,” “no,” or “maybe.” A rating of “maybe” is selected when there is not enough information to choose “yes.” However, a “maybe” rating does allow the document to move to the full-text screening phase.

For this first phase of screening, a test set of 100 references was exported from Covidence into an Excel file. All raters independently provided a vote for each document as a calibration training exercise. All votes were compiled on the spreadsheet and discussions were held to determine a consensus vote (as required) for each study. The actual screening was then started in Covidence in dual-screen mode (i.e., two votes were needed per document), until approximately 1,200 documents were completed. There was less than a 10% conflict rate, and any conflicts were resolved through discussion with the final decision being made by a senior researcher. Since the team has demonstrated satisfactory inter-rater reliability, only one vote is
now needed from raters to decide whether documents should move to the full-text screening phase.

Regarding full-text screening, a test set of documents (n = 50) was first exported as a training exercise for the raters (conflict rate was less than 20%), followed by group discussion. Each document requires two independent votes of “yes” to be included in data extraction. In the case of conflicts, the project leader (a physician with many years of clinical experience in the concussion field) or a third rater not involved in the conflict makes the final decision. Finally, each document has been given labels to reflect important themes in the research. Most documents have received at least one label that match the twelve sections appearing in the Guideline for Concussion/Mild Traumatic Brain Injury and Persistent Symptoms: 3rd Edition.¹ For example, a common label has been “diagnosis/assessment of concussion/mTBI,” which is the first section title of the current Guideline. Other labels such as “biomarkers” reflect other themes that may be added to the original twelve sections if the experts deem it appropriate.

**Data Collection Process**

A standardized data extraction form was created by the investigators in Covidence to ensure relevant data are collected (see next section for Data Items). The raters completed extraction together for several articles per main study design or document type (e.g., intervention, observational, systematic review, qualitative research, clinical practice guideline) in order to enhance inter-rater reliability. Two raters extract data from each included document independently. A third rater completes “consensus” for each article. In Covidence, the consensus rater has the ability to view the original two extractions simultaneously and can then select the best response or can write their own based on the information provided by the raters.

**Data Items**
The data extraction form has the following sections: document ID (assigned by Covidence); authors; year of publication; title of paper; country in which study was conducted; aim(s) of study related to assessment or treatment; study design; specific design information (e.g., group information, intervention treatment, measurement time points, etc.); relevant outcome measure information; study definition of concussion; number of participants for each group; gender frequencies and percentages for each group; average age and standard deviation for each group; and findings related to assessment or treatment.

Outcomes and Prioritization

Due to the breadth of the present review, no specific outcomes are sought. Any outcomes that contribute to understanding of diagnosis/assessment and treatment of adult concussion is considered relevant.

Risk of Bias in Individual Studies

Risk of bias assessment is currently being conducted at the study or document level (not outcome level). Inter-rater reliability optimization and the rating and consensus procedures are the same as those in data extraction. However, the consensus process only allows the third rater to select a final response due to the nature of the form.

A variety of validated tools have been included in the review. Each tool pertains to the study design or document type. The following tools were included with very minor modifications: Downs and Black scale for health care interventions;\textsuperscript{3} the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for observational studies;\textsuperscript{24} Critical Appraisal Skills Programme (CASP) for qualitative studies;\textsuperscript{25} A MeaSurement Tool to Assess Systematic Reviews (AMSTAR 2) for systematic reviews;\textsuperscript{26} and Appraisal of Guidelines for REsearch and Evaluation (AGREE II) for clinical practice guidelines.\textsuperscript{27}
scoring is as follows: Downs and Black (/28); STROBE (/23); CASP (/9); AMSTAR 2 (/20); AGREE II (23 items each scored on a scale ranging from 1 [strongly disagree] to 7 [strongly agree]). The tools are provided in Supplementary Material 2.

**Data Synthesis**

In order for the findings to be translated to recommendations in the living guidelines, over 35 concussion and traumatic brain injury experts from across North America have thus far volunteered to interpret the evidence. Currently, twelve groups covering the sections appearing in the Guideline for Concussion/Mild Traumatic Brain Injury and Persistent Symptoms: 3rd Edition have been created. A minimum of 5 experts have been assigned to domain areas that match their expertise. This number was deemed by consensus to be necessary to reduce bias in decision-making and to encourage discussion. Each expert is also required to declare any conflicts of interest.

The experts deal only with documents related to their domain area. The summarized information from the data extraction form (including risk of bias assessments and full-text copies of each document) is provided to the expert panels. The experts also receive documents/assessments of documents informing the 3rd edition recommendations for that domain area, related guidelines since 2010 (with AGREE II ratings), and a list of relevant evidence for each individual recommendation within a domain area. Ratings for the overall quality of evidence and the strength of recommendation pertaining to only relevant evidence for each recommendation is based on the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach (see Confidence in Cumulative Evidence section below for more details). Finally, there are voting options to keep, modify, or delete recommendations based on the new relevant evidence. Space to write a revised recommendation and to propose
new recommendations is also provided. Several weeks later, the expert panel meets virtually 1-2 times with a group moderator through a video call to make decisions. Afterwards, results of the meeting(s) are circulated to the entire expert team for feedback. Based on this feedback, the project team makes the necessary revisions. Finally, a round of voting (and feedback) will occur with the entire expert team. See Supplementary Material 3 for the full guideline domain update algorithm.

**Meta-bias(es)**

There are no planned assessments of meta-bias(es) (e.g., publication bias, selective reporting within studies) due to the nature of this review.

**Confidence in Cumulative Evidence**

The GRADE approach is being used to rate the overall quality of relevant evidence informing each recommendation. This approach initially labels randomized controlled trial evidence as high quality and observational study evidence as low quality. Ratings are lowered if there is risk of bias, inconsistency in results, indirectness (i.e., studies not examining interventions, patients, and outcomes of interest), imprecision (e.g., large confidence intervals), and publication bias. Ratings can be elevated if there are large effect sizes, evidence of a dose response gradient, and if all possible confounding would reduce a demonstrated effect or would suggest a spurious effect if no effect was observed. The quality of evidence is rated as very low, low, moderate, or high.28 We have made an amendment in cases where there is a mix of randomized controlled trials and observational studies informing a recommendation. In these cases, if at least 50% of the studies are randomized controlled trials, the grading will begin at high quality. Also, we have made the decision that in cases where a recommendation is based on expert opinion only, the quality of evidence will be “very low” because it is based on anecdotal
clinician observation. Each recommendation is also rated as being strong or weak based on a cost/benefit analysis. There are four specific factors that determine the strength of recommendation: magnitude of the difference between desirable and undesirable effects, quality of evidence, the values and preferences of patients, and the resources that need to be expended.

**Patient and Public Involvement**

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

**Discussion**

Concussion can lead to health issues acutely and in some cases may result in prolonged symptoms.4-6 There is continued need for up to date guidelines to assist clinicians in managing persons with concussion and prolonged symptoms where the complex presentation of symptoms can often be challenging for the primary care provider to manage. In addition to this, research output in this field is also increasing every year16 where study quality is typically low,1 making a living systematic review of diagnosis/assessment and treatment of adult concussion necessary.

Although this review has many strengths, it is not without limitations. First, only papers published in the English language are being included so other potentially valuable documents could be missed. Also, regarding demographics, the review focuses only on adults and on concussion while excluding the pediatric population. The guidelines could potentially be more comprehensive if pediatrics were included but it is not feasible given our infrastructure which is primarily adult expert focussed and there are now available parallel pediatric concussion living guidelines30 using similar rigorous approaches which have formal ties to these guidelines.
This continuous review process will greatly benefit clinicians and patients by informing living guidelines that will lead to timely guideline recommendations that over time will have increasing certainty as the evidence improves.

**Ethics and Dissemination:** No ethical approval is necessary because primary data are not collected. The review results will be published in peer-reviewed journals in addition to being on the guidelines website in order to enhance dissemination and implementation.

**Authors’ Contributions:** AL and SM were involved in conceptual development, writing, and editing. MTB, DC, LKF, CK, JL, MN, and DV were involved in conceptual development and editing.

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**Competing Interests Statement:** None declared.
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Initial MEDLINE Search Strategy

1. exp Brain Concussion/
2. Post-Concussion Syndrome/
3. (concuss* or postconcuss*).tw,kw.
4. commotio cerebri.tw,kw.
5. ((post commotion or post head injury) adj2 syndrome*).tw.
6. ((mild or minor or minimal) adj3 (traumatic brain or tbi)).tw.
7. ((tbi or traumatic brain injur*) adj3 symptom*).tw.
8. mtbi.tw,kw. or mild traumatic brain injur*.kw. or minor traumatic brain injur*.kw. or minimal traumatic brain injur*.kw.
9. (brain injur* and rehabilitat*).ti. or Brain Injuries/rh or "Brain Injuries, Traumatic"/rh
10. Craniocerebral Trauma/co
11. exp Brain Injuries/ or Craniocerebral Trauma/ or Head Injuries, Closed/
12. ((following or after or post or persistent or unresolved or delayed or prolong*) adj4 (brain or skull or head or injur*).tw. not (((severe or moderate) adj2 (head or brain or traumatic or tbi)) not (mild or minor)).ti.
13. (following or after or post or persistent or unresolved or delayed or prolong*).tw. and (headache/ or exp headache disorders/)
14. 11 and (12 or 13)
15. or/1-10,14
16. brain injuries/ or brain injuries, traumatic/ or Craniocerebral Trauma/ or Head Injuries, Closed/
17. Post-Traumatic Headache/
18. exp Sleep Wake Disorders/
19. exp Mental Disorders/
20. dizziness/ or vision disorders/
21. Fatigue/
22. Return to Work/ or Return to Sport/
23. Memory Disorders/ or amnesia/
24. cognition disorders/ or cognitive dysfunction/
25. or/17-24
26. 16 and 25
27. (brain injur* adj3 (headache* or cognitive disorder* or sleep disorder* or memory or amnesia or insomnia or mental disorder* or dizziness or vision disorder* or fatigue or "return to work" or "Return to Sport" or psychiatric symptom* or ptsd or post traumatic stress or depression or sleep problem* or cognitive dysfunction)).tw.
28. 26 or 27
29. 15 or 28
30. exp animals/ not humans/
31. (exp child/ or exp infant/) not exp adult/
32. ((child* or infant* or pediatric* or paediatric*) not adult*).ti.
33. or/30-32
34. 29 not 33
35. limit 34 to english language
36. (201706* or 201707* or 201708* or 201709* or 20171* or 2018* or 2019* or 2020*).dt.
37. 35 and 36
Risk of Bias Assessment Tools

Section 1: Interventions (Downs & Black, 1998)

Supporting text
Enter supporting text about your judgement

1. Is the hypothesis/aim/objective of the study clearly described?

Yes (1)
No (0)

Supporting text
Enter supporting text about your judgement

2. Are the main outcomes to be measured clearly described in the Introduction or Methods section?
If the main outcomes are first mentioned in the Results section, the question should be answered no.

Yes (1)
No (0)

Supporting text
Enter supporting text about your judgement

3. Are the characteristics of the patients included in the study clearly described?
In cohort studies and trials, inclusion and/or exclusion criteria should be given. In case-control studies, a case-definition and the source for controls should be given.

Yes (1)
No (0)

Supporting text
Enter supporting text about your judgement

4. Are the interventions of interest clearly described?
Treating and placebo (where relevant) that are to be compared should be clearly described.

Yes (1)
No (0)

Supporting text
Enter supporting text about your judgement
5. Are the distributions of principal confounders in each group of subjects to be compared clearly described?
A list of principal confounders is provided.

|        |        |
|--------|--------|
| Yes    | (2)    |
| Partially | (1)   |
| No     | (0)    |

Supporting text
Enter supporting text about your judgement

6. Are the main findings of the study clearly described?
Simple outcome data (including denominators and numerators) should be reported for all major findings so that the reader can check the major analyses and conclusions. (This question does not cover statistical tests which are considered below.)

|        |        |
|--------|--------|
| Yes    | (1)    |
| No     | (0)    |

Supporting text
Enter supporting text about your judgement

7. Does the study provide estimates of the random variability in the data for the main outcomes?
In non normally distributed data the inter-quartile range of results should be reported. In normally distributed data the standard error, standard deviation or confidence intervals should be reported. If the distribution of the data is not described, it must be assumed that the estimates used were appropriate and the question should be answered yes.

|        |        |
|--------|--------|
| Yes    | (1)    |
| No     | (0)    |

Supporting text
Enter supporting text about your judgement

8. Have all important adverse events that may be a consequence of the intervention been reported?
This should be answered yes if the study demonstrates that there was a comprehensive attempt to measure adverse events. (A list of possible adverse events is provided.)

|        |        |
|--------|--------|
| Yes    | (1)    |
| No     | (0)    |

Supporting text
Enter supporting text about your judgement

9. Have the characteristics of patients lost to follow-up been described?
This should be answered yes where there were no losses to follow-up or where losses to follow-up were so small that findings would be unaffected by their inclusion. This should be answered no where a study does not report the number of patients lost to follow-up.

|        |        |
|--------|--------|
| Yes    | (1)    |
| No     | (0)    |

Supporting text
Enter supporting text about your judgement
10. Have actual probability values been reported (e.g., 0.035 rather than < 0.05) for the main outcomes except where the probability value is less than 0.001?

| Yes (1) | No (0) |

Supporting text

11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?

The study must identify the source population for patients and describe how the patients were selected. Patients would be representative if they comprised the entire source population, an unselected sample of consecutive patients, or a random sample. Random sampling is only feasible where a list of all members of the relevant population exists. Where a study does not report the proportion of the source population from which the patients are derived, the question should be answered as unable to determine.

| Yes (1) | No (0) | Unable to determine (0) |

Supporting text

12. Were those subjects who were prepared to participate representative of the entire population from which they were recruited?

The proportion of those asked who agreed should be stated. Validation that the sample was representative would include demonstrating that the distribution of the main confounding factors was the same in the study sample and the source population.

| Yes (1) | No (0) | Unable to determine (0) |

Supporting text

13. Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?

For the question to be answered yes the study should demonstrate that the intervention was representative of that in use in the source population. The question should be answered no if, for example, the intervention was undertaken in a specialist centre unrepresentative of the hospitals most of the source population would attend.

| Yes (1) | No (0) | Unable to determine (0) |

Supporting text

14. Was an attempt made to blind study subjects to the intervention they have received?

For studies where the patients would have no way of knowing which intervention they received, this should be answered yes.

| Yes (1) | No (0) | Unable to determine (0) |

Supporting text
15. Was an attempt made to blind those measuring the main outcomes of the intervention?

| Yes (1) | No (0) | Unable to determine (0) |
|---------|--------|-------------------------|

Supporting text
Enter supporting text about your judgement

16. If any of the results of the study were based on “data dredging”, was this made clear?

Any analyses that had not been planned at the outset of the study should be clearly indicated. If no retrospective unplanned subgroup analyses were reported, then answer yes.

| Yes (1) | No (0) | Unable to determine (0) |
|---------|--------|-------------------------|

Supporting text
Enter supporting text about your judgement

17. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?

Where follow-up was the same for all study patients the answer should be yes. If different lengths of follow-up were adjusted for by, for example, survival analysis the answer should be yes. Studies where differences in follow-up are ignored should be answered no.

| Yes (1) | No (0) | Unable to determine (0) |
|---------|--------|-------------------------|

Supporting text
Enter supporting text about your judgement

18. Were the statistical tests used to assess the main outcomes appropriate?

The statistical techniques used must be appropriate to the data. For example nonparametric methods should be used for small sample sizes. Where little statistical analysis has been undertaken but where there is no evidence of bias, the question should be answered yes. If the distribution of the data (normal or not) is not described it must be assumed that the estimates used were appropriate and the question should be answered yes.

| Yes (1) | No (0) | Unable to determine (0) |
|---------|--------|-------------------------|

Supporting text
Enter supporting text about your judgement

19. Was compliance with the Intervention/s reliable?

Where there was non compliance with the allocated treatment or where there was contamination of one group, the question should be answered no. For studies where the effect of any misclassification was likely to bias any association to the null, the question should be answered yes.

| Yes (1) | No (0) | Unable to determine (0) |
|---------|--------|-------------------------|

Supporting text
Enter supporting text about your judgement
### 20. Were the main outcome measures used accurate (valid and reliable)?

For studies where the outcome measures are clearly described, the question should be answered yes. For studies which refer to other work or that demonstrates the outcome measures are accurate, the question should be answered as yes.

| Yes (1) | No (0) | Unable to determine (0) |

### 21. Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?

For example, patients for all comparison groups should be selected from the same hospital. The question should be answered unable to determine for cohort and case control studies where there is no information concerning the source of patients included in the study.

| Yes (1) | No (0) | Unable to determine (0) |

### 22. Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?

For a study which does not specify the time period over which patients were recruited, the question should be answered as unable to determine.

| Yes (1) | No (0) | Unable to determine (0) |

### 23. Were study subjects randomised to intervention groups?

Studies which state that subjects were randomised should be answered yes except where method of randomisation would not ensure random allocation. For example alternate allocation would score no because it is predictable.

| Yes (1) | No (0) | Unable to determine (0) |

### 24. Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?

All non-randomised studies should be answered no if assignment was concealed from patients but not from staff, it should be answered no.

| Yes (1) | No (0) | Unable to determine (0) |

### Supporting text

Enter supporting text about your judgement.
25. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?

This question should be answered no for trials if the main conclusions of the study were based on analyses of treatment rather than intention to treat, the distribution of known confounders in the different treatment groups was not described, or the distribution of known confounders differed between the treatment groups but was not taken into account in the analyses. In nonrandomised studies if the effect of the main confounders was not investigated or confounding was demonstrated but no adjustment was made in the final analyses the question should be answered as no.

| Yes (1) | No (0) | Unable to determine (0) |

Supporting text
Enter supporting text about your judgement

26. Were losses of patients to follow-up taken into account?

If the numbers of patients lost to follow-up are not reported, the question should be answered as unable to determine. If the proportion lost to follow-up was too small to affect the main findings, the question should be answered yes.

| Yes (1) | No (0) | Unable to determine (0) |

Supporting text
Enter supporting text about your judgement

27. Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?

| Yes (1) | No (0) |

Supporting text
Enter supporting text about your judgement

Section 2: Observational studies (STROBE; von Elm et al., 2007)

Supporting text
Enter supporting text about your judgement

1. Indicate the study’s design with a commonly used term in the title or the abstract.

| Yes (1) | No (0) |

Supporting text
Enter supporting text about your judgement

2. Provide in the abstract an informative and balanced summary of what was done and what was found.

| Yes (1) | No (0) |

Supporting text
Enter supporting text about your judgement
3. Explain the scientific background and rationale for the investigation being reported.

| | Yes (1) |
|---|---|
| | No (0) |

Supporting text

Enter supporting text about your judgement

4. State specific objectives, including any prespecified hypotheses.

| | Yes (1) |
|---|---|
| | No (0) |

Supporting text

Enter supporting text about your judgement

5. Present key elements of study design early in the paper.

| | Yes (1) |
|---|---|
| | No (0) |

Supporting text

Enter supporting text about your judgement

6. Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection.

| | Yes (1) |
|---|---|
| | No (0) |

Supporting text

Enter supporting text about your judgement

7. Cohort study—give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up. Case-control study—give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls. Cross-sectional study—give the eligibility criteria, and the sources and methods of selection of participants.

| | Yes (1) |
|---|---|
| | No (0) |

Supporting text

Enter supporting text about your judgement

8. Cohort study—for matched studies, give matching criteria and number of exposed and unexposed. Case-control study—for matched studies, give matching criteria and the number of controls per case.

| | Yes (1) |
|---|---|
| | No (0) |

Supporting text

Enter supporting text about your judgement
9. Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.

|   | Yes (1) | No (0) |
|---|---------|--------|

Supporting text
Enter supporting text about your judgement

10. For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group.

|   | Yes (1) | No (0) |
|---|---------|--------|

Supporting text
Enter supporting text about your judgement

11. Describe any efforts to address potential sources of bias.

|   | Yes (1) | No (0) |
|---|---------|--------|

Supporting text
Enter supporting text about your judgement

12. Explain how the study size was arrived at.

|   | Yes (1) | No (0) |
|---|---------|--------|

Supporting text
Enter supporting text about your judgement

13. Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why.

|   | Yes (1) | No (0) |
|---|---------|--------|

Supporting text
Enter supporting text about your judgement

14. Describe all statistical methods, including those used to control for confounding.

|   | Yes (1) | No (0) |
|---|---------|--------|

Supporting text
Enter supporting text about your judgement
15. Describe any methods used to examine subgroups and interactions.

|   | Yes (1) | No (0) | N/A (1) |
|---|---------|--------|---------|

Supporting text
Enter supporting text about your judgement

16. Explain how missing data were addressed.

|   | Yes (1) | No (0) |
|---|---------|--------|

Supporting text
Enter supporting text about your judgement

17. Cohort study—if applicable, explain how loss to follow-up was addressed. Case-control study—if applicable, explain how matching of cases and controls was addressed. Cross-sectional study—if applicable, describe analytical methods taking account of sampling strategy.

|   | Yes (1) | No (0) | N/A (1) |
|---|---------|--------|---------|

Supporting text
Enter supporting text about your judgement

18. Describe any sensitivity analyses.

|   | Yes (1) | No (0) | N/A (1) |
|---|---------|--------|---------|

Supporting text
Enter supporting text about your judgement

19. Report the numbers of individuals at each stage of the study—eg, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed.

|   | Yes (1) | No (0) |
|---|---------|--------|

Supporting text
Enter supporting text about your judgement

20. Give characteristics of study participants (eg, demographic, clinical, social) and information on exposures and potential confounders.

|   | Yes (1) | No (0) |
|---|---------|--------|

Supporting text
Enter supporting text about your judgement
21. Indicate the number of participants with missing data for each variable of interest.

|   | Yes (1) | No (0) |
|---|---------|--------|

Supporting text

Enter supporting text about your judgement

22. Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included.

|   | Yes (1) | No (0) |
|---|---------|--------|

Supporting text

Enter supporting text about your judgement

23. Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based.

|   | Yes (1) | No (0) |
|---|---------|--------|

Supporting text

Enter supporting text about your judgement

Section 3: Qualitative studies (CASP; 2018)

Supporting text

Enter supporting text about your judgement

1. Was there a clear statement of the aims of the research?

|   | Yes (1) | No (0) |
|---|---------|--------|

Supporting text

Enter supporting text about your judgement

2. Is a qualitative methodology appropriate?

HINT: Consider
- if the research seeks to interpret or illuminate the actions and/or subjective experiences of research participants
- is qualitative research the right methodology for addressing the research goal

|   | Yes (1) | No (0) |
|---|---------|--------|

Supporting text

Enter supporting text about your judgement
3. Was the research design appropriate to address the aims of the research?

HINT: Consider
- if the researcher has justified the research design (e.g. have they discussed how they decided which method to use)

| Yes (1) | No (0) |
|---------|--------|

Supporting text
Enter supporting text about your judgement

4. Was the recruitment strategy appropriate to the aims of the research?

HINT: Consider
- if the researcher has explained how the participants were selected
- if they explained why the participants they selected were the most appropriate to provide access to the type of knowledge sought by the study
- if there are any discussions around recruitment (e.g. why some people chose not to take part)

| Yes (1) | No (0) |
|---------|--------|

Supporting text
Enter supporting text about your judgement

5. Was the data collected in a way that addressed the research issue?

HINT: Consider
- if the setting for the data collection was justified
- if it is clear how data were collected (e.g. focus group, semi-structured interview etc.)
- if the researcher has justified the methods chosen
- if the researcher has made the methods explicit (e.g. for interview method, is there an indication of how interviews are conducted, or did they use a topic guide)
- if methods were modified during the study. If so, has the researcher explained how and why
- if the form of data is clear (e.g. tape recordings, video material, notes etc.)
- if the researcher has discussed saturation of data

| Yes (1) | No (0) |
|---------|--------|

Supporting text
Enter supporting text about your judgement

6. Has the relationship between researcher and participants been adequately considered?

HINT: Consider
- if the researcher critically examined their own role, potential bias and influence during (a) formulation of the research questions (b) data collection, including sample recruitment and choice of location
- how the researcher responded to events during the study and whether they considered the implications of any changes in the research design

| Yes (1) | No (0) |
|---------|--------|

Supporting text
Enter supporting text about your judgement
7. Have ethical issues been taken into consideration?
HINT: Consider
- if there are sufficient details of how the research was explained to participants for the reader to assess whether ethical standards were maintained
- if the researcher has discussed issues raised by the study (e.g. issues around informed consent or confidentiality or how they have handled the effects of the study on the participants during and after the study)
- if approval has been sought from the ethics committee

| Yes (1) | No (0) |
|---------|--------|

Supporting text
Enter supporting text about your judgement

8. Was the data analysis sufficiently rigorous?
HINT: Consider
- if there is an in-depth description of the analysis process
- if thematic analysis is used; if so, is it clear how the categories/themes were derived from the data
- whether the researcher explains how the data presented were selected from the original sample to demonstrate the analysis process
- if sufficient data are presented to support the findings
- to what extent contradictory data are taken into account
- whether the researcher critically examined their own role, potential bias and influence during analysis and selection of data for presentation

| Yes (1) | No (0) |
|---------|--------|

Supporting text
Enter supporting text about your judgement

9. Is there a clear statement of findings?
HINT: Consider whether
- if the findings are explicit
- if there is adequate discussion of the evidence both for and against the researcher’s arguments
- if the researcher has discussed the credibility of their findings (e.g. triangulation, respondent validation, more than one analyst)
- if the findings are discussed in relation to the original research question

| Yes (1) | No (0) |
|---------|--------|

Supporting text
Enter supporting text about your judgement

Section 4: Systematic reviews (AMSTAR 2; Shea et al., 2017)

Supporting text
Enter supporting text about your judgement

1. Did the research questions and inclusion criteria for the review include the components of PICO?
For Yes:
- Population
- Intervention
- Comparator group
- Outcome

| Yes (1) | No (0) |
|---------|--------|

Supporting text
Enter supporting text about your judgement
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?

For Partial Yes:
The authors state that they had a written protocol or guide that included ALL the following:
- review question(s)
- a search strategy
- inclusion/exclusion criteria
- a risk of bias assessment

For Yes:
As for partial yes, plus the protocol should be registered and should also have specified:
- a meta-analysis/synthesis plan, if appropriate, and
- a plan for investigating causes of heterogeneity
- justification for any deviations from the protocol

| Yes (2) |
|---------|
| Partial Yes (1) |
| No (0) |

Supporting text
Enter supporting text about your judgement

3. Did the review authors explain their selection of the study designs for inclusion in the review?

For Yes, the review should satisfy ONE of the following:
- Explanation for including only RCTs
- OR Explanation for including only NRRI
- OR Explanation for including both RCTs and NRRI

| Yes (1) |
|---------|
| No (0) |

Supporting text
Enter supporting text about your judgement

4. Did the review authors use a comprehensive literature search strategy?

For Partial Yes (all the following):
- searched at least 2 databases (relevant to research question)
- provided key word and/or search strategy
- justified publication restrictions (eg, language)

For Yes, should also have (all the following):
- searched the reference lists/bibliographies of included studies
- searched trial/study registries
- included/consulted content experts in the field
- where relevant, searched for grey literature
- conducted search within 24 months of completion of the review

| Yes (2) |
|---------|
| Partial Yes (1) |
| No (0) |

Supporting text
Enter supporting text about your judgement
5. Did the review authors perform study selection in duplicate?
For Yes, either ONE of the following:
- at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include
- OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 per cent), with the remainder selected by one reviewer

| Yes (1) | No (0) |

Supporting text
Enter supporting text about your judgement

6. Did the review authors perform data extraction in duplicate?
For Yes, either ONE of the following:
- at least two reviewers achieved consensus on which data to extract from included studies
- OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 per cent), with the remainder extracted by one reviewer

| Yes (1) | No (0) |

Supporting text
Enter supporting text about your judgement

7. Did the review authors provide a list of excluded studies and justify the exclusions?
For Partial Yes:
- provided a list of all potentially relevant studies that were read in full text form but excluded from the review
- Justified the exclusion from the review of each potentially relevant study

| Yes (2) | Partial Yes (1) | No (0) |

Supporting text
Enter supporting text about your judgement

8. Did the review authors describe the included studies in adequate detail?
For Partial Yes (ALL the following):
- described populations
- described interventions
- described comparators
- described outcomes
- described research designs
For Yes, should also have ALL the following:
- described population in detail
- described intervention and comparator in detail (including doses where relevant)
- described study’s setting
- timeframe for follow-up

| Yes (2) | Partial Yes (1) | No (0) |

Supporting text
Enter supporting text about your judgement
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review (RCTs only)?

For Partial Yes, must have assessed RoB from:
- unconfounded allocation, and
- lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all cause mortality).
For Yes, must also have assessed RoB from:
- allocation sequence that was not truly random, and
- selection of the reported result from among multiple measurements or analyses of a specified outcome

| No. | Condition                                              |
|-----|--------------------------------------------------------|
| 1   | Yes (2)                                                |
| 2   | Partial Yes (1)                                        |
| 3   | No (0)                                                 |

10. Did the review authors report on the sources of funding for the studies included in the review?

For Yes
- Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information but it was not reported by study authors also qualifies

| No. | Condition                                              |
|-----|--------------------------------------------------------|
| 1   | Yes (1)                                                |
| 2   | No (0)                                                 |

Supporting text
Enter supporting text about your judgement

11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?

For RCTs
- The authors justified combining the data in a meta-analysis
- AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present
- AND investigated the causes of any heterogeneity

For NRSI
For Yes:
- The authors justified combining the data in a meta-analysis
- AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available
- AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review

For other studies
For Yes:
- Use appropriate criteria from above points.

| No. | Condition                                              |
|-----|--------------------------------------------------------|
| 1   | Yes (1)                                                |
| 2   | No (0)                                                 |
| 3   | No meta-analysis (1)                                   |
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?

For Yes:
- Included only low risk of bias RCTs
- OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect

| Yes (1) | No (0) | No meta-analysis (1) |

Supporting text
Enter supporting text about your judgement

13. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?

For Yes:
- There was no significant heterogeneity in the results
- OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review

| Yes (1) | No (0) |

Supporting text
Enter supporting text about your judgement

14. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?

For Yes:
- Performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias

| Yes (1) | No (0) | No meta-analysis (1) |

Supporting text
Enter supporting text about your judgement

15. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

For Yes:
- The authors reported no competing interests OR
- The authors described their funding sources and how they managed potential conflicts of interest

| Yes (1) | No (0) |

Supporting text
Enter supporting text about your judgement

Section 5: Guidelines (AGREE II; 2017)
A score of 1 should be given when there is no information that is relevant to the AGREE II item, if the concept is very poorly reported, or if the authors state explicitly that criteria were not met.

A score of 7 should be given if the quality of reporting is exceptional and where the full criteria and considerations articulated in the User’s Manual have been met.

Supporting text
Enter supporting text about your judgement
*Supporting text boxes were present on the actual form but have been omitted from the following items to save space. Also, the scale has been omitted from items 2-23 for the same reason.

1. The overall objective(s) of the guideline is (are) specifically described.

   Item content includes the following CRITERIA:
   • health intent(s) (i.e., prevention, screening, diagnosis, treatment, etc.)
   • expected benefit or outcome
   • target(s) (e.g., patient population, society)

   Additional CONSIDERATIONS:
   • Is the item well written? Are the descriptions clear and concise?
   • Is the item content easy to find in the guideline?

| 1 (Strongly Disagree) |
|-----------------------|
| 2                     |
| 3                     |
| 4                     |
| 5                     |
| 6                     |

7 (Strongly Agree)

2. The health question(s) covered by the guideline is (are) specifically described.

   Item content includes the following CRITERIA:
   • target population
   • intervention(s) or exposure(s)
   • companions (if appropriate)
   • outcome(s)
   • health care setting or context

   Additional CONSIDERATIONS:
   • Is the item well written? Are the descriptions clear and concise?
   • Is the item content easy to find in the guideline?
   • Is there enough information provided in the question(s) for anyone to initiate the development of a guideline on this topic or to understand the patients/populations and contexts profiled in the guideline?

3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.

   How to Rate:
   Item content includes the following CRITERIA:
   • target population, gender and age
   • clinical condition (if relevant)
   • severity/stage of disease (if relevant)
   • comorbidities (if relevant)
   • excluded populations (if relevant)

   Additional CONSIDERATIONS:
   • Is the item well written? Are the descriptions clear and concise?
   • Is the item content easy to find in the guideline?
   • Is the population information specific enough so that the correct and eligible individuals would receive the action recommended in the guideline?

4. The guideline development group includes individuals from all relevant professional groups.

   This item refers to the professionals who were involved at some stage of the development process. This may include members of the steering group, the research team involved in selecting and reviewing the evidence and individuals involved in formulating the final recommendations. This item excludes individuals who have externally reviewed the guideline (see item 13).
   This item excludes target population representation (see item 5). Information about the composition, discipline, and relevant expertise of the guideline development group should be provided.

5. The views and preferences of the target population (patients, public, etc.) have been sought.

   Item content includes the following CRITERIA:
   • statement of type of strategy used to capture patients’/public’s views and preferences (e.g., participation in the guideline development group, literature review of values and preferences)
   • methods by which preferences and views were sought (e.g., evidence from literature, surveys, focus groups)
   • outcomes/information gathered on patient/public information
   • description of how the information gathered was used to inform the guideline development process and/or formation of the recommendations

   Additional CONSIDERATIONS:
   • Is the item well written? Are the descriptions clear and concise?
   • Is the item content easy to find in the guideline?
6. The target users of the guideline are clearly defined.
   - clear description of intended guideline audience (e.g. specialists, family physicians, patients, clinical or institutional leaders/administrators)
   - description of how the guideline may be used by its target audience (e.g., to inform clinical decisions, to inform policy, to inform standards of care)
   Additional considerations:
   - Is the item well written? Are the descriptions clear and concise?
   - Is the item content easy to find in the guideline?
   - Are the target users appropriate for the scope of the guideline?

7. Systematic methods were used to search for evidence.
   Details of the strategy used to search for evidence should be provided including search terms used, sources consulted, and dates of the literature covered. Sources may include electronic databases (e.g., MEDLINE, EMBASE, CINAHL), databases of systematic reviews (e.g., the Cochrane Library, DARE), handsearching journals, reviewing conference proceedings, and other guidelines (e.g., the US National Guideline Clearinghouse, the German Guidelines Clearinghouse). The search strategy should be as comprehensive as possible and executed in a manner free from potential biases and sufficiently detailed to be replicated.

8. The criteria for selecting the evidence are clearly described.
   Criteria for including/excluding evidence identified by the search should be provided. These criteria should be explicitly described and reasons for including and excluding evidence should be clearly stated. For example, guideline authors may decide to only include evidence from randomized clinical trials and to exclude articles not written in English.

9. The strengths and limitations of the body of evidence are clearly described.
   Statements highlighting the strengths and limitations of the evidence should be provided. This ought to include explicit descriptions - using informal or formal tools/methods - to assess and describe the risk of bias for individual studies and/or for specific outcomes and/or explicit commentary of the body of evidence aggregated across all studies. This may be presented in different ways, for example: using tables commenting on different quality domains, the application of a formal instrument or strategy (e.g., Jadad scale, GRADE method); or descriptions in the text.

10. The methods for Formulating the recommendations are clearly described.
   A description of the methods used to formulate the recommendations and how final decisions were arrived at should be provided. For example, methods may include a voting system, informal consensus, and formal consensus techniques (e.g., Delphi, G lucer techniques). Areas of disagreement and methods of resolving them should be specified.

11. The health benefits, side effects, and risks have been considered in formulating the recommendations.
   The guideline should consider health benefits, side effects, and risks when formulating the recommendations. For example, a guideline on the management of breast cancer may include a discussion on the overall effects on various final outcomes. These may include: survival, quality of life, adverse effects, and symptom management or a discussion comparing one treatment option to another. There should be evidence that these issues have been addressed.

12. There is an explicit link between the recommendations and the supporting evidence.
   An explicit link between the recommendations and the evidence on which they are based should be included in the guideline. The guideline user should be able to identify the components of the body of evidence relevant to each recommendation.

13. The guideline has been externally reviewed by experts prior to its publication.
   A guideline should be reviewed externally before it is published. Reviewers should not have been involved in the guideline development group. Reviewers should include experts in the clinical area as well as some methodological experts. Target population (patients, public) representatives may also be included. A description of the methodology used to conduct the external review should be presented, which may include a list of the reviewers and their affiliation.

14. A procedure for updating the guideline is provided.
   Guidelines need to reflect current research. A clear statement about the procedure for updating the guideline should be provided. For example, a timescale has been given or a standing panel is established who receives regularly updated literature searches and makes changes as required.

15. The recommendations are specific and unambiguous.
   A recommendation should provide a concrete and precise description of which option is appropriate in which situation and in what population group, as informed by the body of evidence.
   - An example of a specific recommendation is: Antibiotics should be prescribed in children two years or older with a diagnosis of acute otitis media if the pain lasts longer than three days or if the pain increases after the consultation despite adequate treatment with painkillers; in these cases, amoxicillin should be given for 7 days (supplied with a dosage scheme).
   - An example of a vague recommendation is: Antibiotics are indicated for cases with an abnormal or complicated course.

   It is important to note that in some instances, evidence is not always clear cut and there may be uncertainty about the best care option(s). In this case, the uncertainty should be stated in the guideline.

16. The different options for management of the condition or health issue are clearly presented.
   A guideline that targets the management of a disease should consider the different possible options for screening, prevention, diagnosis or treatment of the condition it covers. These possible options should be clearly presented in the guideline. For example, a recommendation on the management of depression may contain the following treatment alternatives:
   a. Treatment with TCA
   b. Treatment with SSRIs
   c. Psychotherapy
   d. Combination of pharmacological and psychological therapy

17. Key recommendations are easily identifiable.
   Users should be able to find the most relevant recommendations easily. These recommendations answer the main question(s) that have been covered by the guideline and can be identified in different ways. For example, they can be summarized in a box, typed in bold, underlined or presented as flow charts or algorithms.
18. The guideline describes facilitators and barriers to its application.

There may be existing facilitators and barriers that will impact the application of guideline recommendations.

For example:
- A guideline on stroke may recommend that care should be coordinated through stroke units and stroke services. There may be a special funding mechanism in the region to enable the formation of stroke units.
- A guideline on diabetes in primary care may require that patients are seen and followed up in diabetic clinics. There may be an insufficient number of clinicians available in a region to enable clinics to be established.

19. The guideline provides advice and/or tools on how the recommendations can be put into practice.

For a guideline to be effective it needs to be disseminated and implemented with additional materials. For example, these may include: a summary document, a quick reference guide, educational tools, results from a pilot test, patient leaflets, or computer support. Any additional materials should be provided with the guideline.

20. The potential resource implications of applying the recommendations have been considered.

The recommendations may require additional resources in order to be applied. For example, there may be a need for more specialized staff, new equipment, and expensive drug treatment. These may have cost implications for health care budgets. There should be a discussion in the guideline of the potential impact of the recommendations on resources.

21. The guideline presents monitoring and/or auditing criteria.

Measuring the application of guideline recommendations can facilitate their ongoing use. This requires clearly defined criteria that are derived from the key recommendations in the guideline. The criteria may include process measures, behavioural measures, clinical or health outcome measures. Examples of monitoring and audit criteria are:
- The HbA1c should be < 8.0%.
- The level of diastolic blood pressure should be < 95 mmHg.
- 80% of the population aged 50 years should receive colorectal cancer screening rates using faecal occult blood tests.
- If complaints of acute otitis media last longer than three days, amoxicillin should be prescribed.

22. The views of the funding body have not influenced the content of the guideline.

Many guidelines are developed with external funding (e.g., government, professional associations, charity organizations, pharmaceutical companies). Support may be in the form of financial contribution for the complete development, or for parts of it (e.g., printing of the guidelines). There should be an explicit statement that the views or interests of the funding body have not influenced the final recommendations.

23. Competing interests of guideline development group members have been recorded and addressed.

There are circumstances when members of the development group may have competing interests. For example, this would apply to a member of the development group whose research on the topic covered by the guideline is also funded by a pharmaceutical company. There should be an explicit statement that all group members have declared whether they have any competing interests.

Item content includes the following CRITERIA:
- description of the types of competing interests considered
- methods by which potential competing interests were sought
- description of the competing interests
- description of how the competing interests influenced the guideline process and development of recommendations

Additional CONSIDERATIONS:
- is the item well written? Are the descriptions clear and concise?
- is the item content easy to find in the guideline?
- What measures were taken to minimize the influence of competing interests on guideline development or formulation of the recommendations?
Guideline Domain Update Algorithm

1. Panel meetings (3-4 weeks)
   - Keep, modify, or create recommendations. New recommendations are proposed.

2. Optional feedback by entire team (2 weeks)
   - Kept recommendations
   - Modified recommendations (minor changes)
   - Modified (major changes), deleted, or new recommendations

3. Revisions by project team (1 week)
   - Revisions based on comments
   - Revisions based on comments
   - Revisions based on comments

4. Feedback and vote by entire team (2 weeks)
   - Available for viewing/to be published
   - Available for viewing/to be published
   - Keep or delete (90% needed) suggestions for comments

5. Clean-up by project team (1 week)
   - Publish (60% approval)
   - Delete if non-important recommendation
   - Revisions back to step 4
## Protocol for a living systematic review for the management of concussion in adults

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Protocol for a living systematic review for the management of concussion in adults

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Abstract

Introduction: Concussion/mild traumatic brain injury (mTBI) often presents initially with disabling symptoms that resolve, but for an unfortunate minority some of these symptoms may become prolonged. Although research into diagnosis and interventions for concussion is increasing, study quality overall remains low. A living systematic review that is updated as evidence becomes available is the ideal research activity to inform a living guideline targeting clinicians and patients. The purpose of this paper is to present the protocol of an ongoing living systematic review for the management of adult concussion that will inform living guidelines building off the Guideline for Concussion/Mild Traumatic Brain Injury and Persistent Symptoms: 3rd Edition.1

Methods and Analysis: The preferred reporting items for systematic review and meta-analysis-protocol (PRISMA-P) guidelines2 were followed in the reporting of this systematic review protocol. We are including English peer-reviewed observational studies, trials, qualitative studies, systematic reviews, and clinical practice guidelines related to diagnosis/assessment or treatment of adult concussion. Future searches will be conducted at minimum every six months using the following databases: MEDLINE ALL, EMBASE, Cochrane, PsycInfo, and CINAHL. The data are managed in the Covidence website. Screening, data extraction, and risk of bias assessments are being done through multiple raters working independently. Multiple validated tools are being used to assess risk of bias, and the tool applied matches the document or study design (e.g., Downs and Black scale for health care interventions3). Many concussion experts in various clinical disciplines from across North America have volunteered to examine the evidence in order to make recommendations for the living guidelines.
Ethics and Dissemination: The PROSPERO registration number is: CRD42022301786. No ethical approval is necessary because primary data are not collected. The results will be disseminated through peer-reviewed publications and on the living guidelines website once built.

Strengths and Limitations of this Study

- Frequent searches will ensure the accompanying adult concussion living guidelines are up to date.
- There is a large multidisciplinary concussion expert team who have volunteered to interpret the evidence.
- The review focuses only on adults while excluding the pediatric population which is a limitation.
- The review is limited to documents published in the English language.
- Perspectives of the expert team is geographically limited to North America and may not reflect the full global perspective.
Introduction

Concussion/mTBI describes an acute neurophysiological event related to a mechanical energy applied to the head, neck or body (with transmitting forces to the brain), such as from sudden acceleration, deceleration, rotational forces, or repetitive subconcussive hits.\(^1\) All concussions are considered to be a mTBI; however, mTBI can differ from concussion when there is evidence of brain injury on conventional neuroimaging or there is persistent neurologic deficit.\(^1\) Concussion can cause meaningful morbidity, with many persons who have sustained a concussion suffering from prolonged symptoms for years post-injury.\(^4-6\) Concussion is also among the most common neurological conditions with an estimated annual incidence of 503 per 100,000 in the United States based on emergency department data,\(^7\) and even higher estimates of up to 1,153 per 100,000 if community-based concussions are taken into account.\(^8\) Therefore, effective diagnosis/assessment and treatment is critical.

Systematic reviews provide the best evidence available, and there are many that focus on concussion management.\(^9-12\) However, systematic review currency and accuracy is challenged by the increasing rate of research output.\(^13\)\(^14\) People might consider conducting a traditional systematic review update, but these updates tend to be inefficient because a new team often needs to be assembled for each update meaning the “institutional memory” of the original team is lost.\(^15\) Living systematic reviews may be an effective solution. A living systematic review is defined as: “a systematic review that is continually updated, incorporating relevant new evidence as it becomes available”\(^15\) (p. 24). In addition to pushing the limits of currency and accuracy, living systematic reviews provide an \textit{a priori} commitment to a frequency of review giving predictability to end users such as clinicians.\(^15\) Applying a living systematic review process to concussion diagnosis/assessment and treatment is appropriate given that research output in this
particular field is increasing every year\textsuperscript{16} and certainty in much of the existing evidence is low,\textsuperscript{1} making frequent updates necessary.

A living systematic review is the ideal research activity to inform living guidelines. Guidelines are normally developed to support clinicians and their patients in making choices to optimize outcomes.\textsuperscript{17} Living guidelines are: “an optimization of the guideline development process to allow updating of individual recommendations as soon as relevant new evidence becomes available”\textsuperscript{18} (p. 47). There have been a few guidelines published on adult concussion (e.g., \textsuperscript{1,19,20}). However, no group or organization has developed living guidelines to address all aspects of diagnosis/assessment and treatment of concussion in adults. The purpose of this paper is to present the protocol of an ongoing living systematic review for the management of adult concussion (e.g., diagnosis, initial management, post-traumatic headache, return to activity) that will inform living guidelines building off the Guideline for Concussion/Mild Traumatic Brain Injury and Persistent Symptoms: 3rd Edition.\textsuperscript{1}

\textbf{Methods and Analysis}

The PRISMA-P guidelines\textsuperscript{2} (see Supplementary Material 1 for the completed checklist) were followed in the reporting of this systematic review protocol.

\textbf{Eligibility Criteria}

The inclusion criteria are: studies related to concussion diagnosis/assessment or treatment; at least 50\% of sample has concussion (e.g., a Glasgow Coma Scale score of 13-15,\textsuperscript{21} confirmation through a standardized concussion assessment tool, diagnosis by a physician or nurse practitioner) in cases where one group is analyzed; at least 50\% of the sample is 18 years of age or older; and the sample is human. Peer-reviewed observational studies (cross-sectional, cohort, case-control), clinical trials, qualitative studies, systematic reviews, and clinical practice
guidelines are included. Documents are limited to English language and publication from May 2017 because that covers literature that did not inform the Guideline for Concussion/Mild Traumatic Brain Injury and Persistent Symptoms: 3rd Edition.¹

The exclusion criteria are: studies that focus on moderate or severe TBI (i.e., a Glasgow Coma Scale score of less than 13); more than 50% of sample has moderate or severe TBI in cases where one group is analyzed; more than 50% of sample is under 18 years of age; and the sample is not human. Case reports/n of 1 studies, non-systematic reviews, conference abstracts/presentations, theses, non-peer-reviewed articles (e.g., newspaper articles), letters or commentaries, addendums/erratums, and book chapters are excluded. Documents not available in English, published before May 2017, or originating from grey literature are also not included.

Information Sources

The search strategy (see next section) was originally created in April 2020 for the MEDLINE ALL database in collaboration with a librarian at a research-intensive hospital. The strategy was then peer-reviewed by another librarian at a separate hospital according to the PRESS guideline.²² The PRESS guideline is a checklist of topics that information specialists should consider when evaluating an electronic search strategy. The strategy was approved with minor revisions. EMBASE, Cochrane, PsycInfo, and CINAHL databases are also being searched using the strategy.

Search Strategy

An initial search was completed at the beginning of April 2020 covering May 2017 to the end of March 2020. That search yielded 19,745 results. The search was updated to cover recent literature published April 2020 to the end of March 2021. The new search yielded 5,071 results, meaning the total number of search results was 24,816. The full search strategy for the initial
MEDLINE ALL search has been reported in Supplementary Material 2 as an example. The next search will cover literature published from April 2021 to the end of February 2022 (search to be conducted on March 1, 2022). After this next search, consistent with living systematic review recommendations, the search is planned to repeat every six months at minimum to capture recent literature.

**Data Management**

The search results are being imported into the Covidence systematic review website. This website automatically removes duplicates, and provides the opportunity for screening, data extraction, and risk of bias assessments with multiple raters.

**Selection Process**

After duplicates from the initial searches were removed by Covidence, 16,086 documents remained (11,916 from the initial search and 4,170 from the updated search). At the title and abstract screening phase, raters select “yes,” “no,” or “maybe.” A rating of “maybe” is selected when there is not enough information to choose “yes.” However, a “maybe” rating does allow the document to move to the full-text screening phase.

For this first phase of screening, a test set of 100 references was exported from Covidence into an Excel file. All raters independently provided a vote for each document as a calibration training exercise. All votes were compiled on the spreadsheet and discussions were held to determine a consensus vote (as required) for each study. The actual screening was then started in Covidence in dual-screen mode (i.e., two votes were needed per document), until approximately 1,200 documents were completed. There was less than a 10% conflict rate, and any conflicts were resolved through discussion with the final decision being made by a senior researcher. Since the team has demonstrated satisfactory inter-rater reliability, only one vote is
now needed from raters to decide whether documents should move to the full-text screening phase.

Regarding full-text screening, a test set of documents (n = 50) was first exported as a training exercise for the raters (conflict rate was less than 20%), followed by group discussion. Each document requires two independent votes of “yes” to be included in data extraction. In the case of conflicts, the project leader (a physician with many years of clinical experience in the concussion field) or a third rater not involved in the conflict makes the final decision. Finally, each document has been given labels to reflect important themes in the research. Most documents have received at least one label that match the twelve sections appearing in the Guideline for Concussion/Mild Traumatic Brain Injury and Persistent Symptoms: 3rd Edition.1 For example, a common label has been “diagnosis/assessment of concussion/mTBI,” which is the first section title of the current Guideline. Other labels such as “biomarkers” reflect other themes that may be added to the original twelve sections if the experts deem it appropriate.

Data Collection Process

A standardized data extraction form was created by the investigators in Covidence to ensure relevant data are collected (see next section for Data Items). The raters completed extraction together for several articles per main study design or document type (e.g., intervention, observational, systematic review, qualitative research, clinical practice guideline) in order to enhance inter-rater reliability. Two raters extract data from each included document independently. A third rater completes “consensus” for each article. In Covidence, the consensus rater has the ability to view the original two extractions simultaneously and can then select the best response or can write their own based on the information provided by the raters.

Data Items
The data extraction form has the following sections: document ID (assigned by Covidence); authors; year of publication; title of paper; country in which study was conducted; aim(s) of study related to assessment or treatment; study design; specific design information (e.g., group information, intervention treatment, measurement time points, etc.); relevant outcome measure information; study definition of concussion; number of participants for each group; gender frequencies and percentages for each group; average age and standard deviation for each group; and findings related to assessment or treatment.

Outcomes and Prioritization

Due to the breadth of the present review, no specific outcomes are sought. Any outcomes that contribute to understanding of diagnosis/assessment and treatment of adult concussion is considered relevant.

Risk of Bias in Individual Studies

Risk of bias assessment is currently being conducted at the study or document level (not outcome level). Inter-rater reliability optimization and the rating and consensus procedures are the same as those in data extraction. However, the consensus process only allows the third rater to select a final response due to the nature of the form.

A variety of validated tools have been included in the review. Each tool pertains to the study design or document type. The following tools were included with very minor modifications: Downs and Black scale for health care interventions;\(^3\) the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for observational studies;\(^24\) Critical Appraisal Skills Programme (CASP) for qualitative studies;\(^25\) A MeaSurement Tool to Assess Systematic Reviews (AMSTAR 2) for systematic reviews;\(^26\) and Appraisal of Guidelines for REsearch and Evaluation (AGREE II) for clinical practice guidelines.\(^27\) The
scoring is as follows: Downs and Black (/28); STROBE (/23); CASP (/9); AMSTAR 2 (/20); AGREE II (23 items each scored on a scale ranging from 1 [strongly disagree] to 7 [strongly agree]). The tools are provided in Supplementary Material 3.

**Data Synthesis**

In order for the findings to be translated to recommendations in the living guidelines, over 35 concussion and traumatic brain injury experts from across North America have thus far volunteered to interpret the evidence. Each expert must have peer-reviewed publications about adult concussion and/or be recommended by a current expert panel member. All experts also must be approved by the project leader. Currently, twelve groups covering the sections appearing in the Guideline for Concussion/Mild Traumatic Brain Injury and Persistent Symptoms: 3rd Edition\(^1\) have been created. A minimum of 5 experts have been assigned to domain areas that match their expertise. This number was deemed by consensus to be necessary to reduce bias in decision-making and to encourage discussion. Each expert is also required to declare any conflicts of interest.

The experts deal only with documents related to their domain area. The summarized information from the data extraction form (including risk of bias assessments and full-text copies of each document) is provided to the expert panels. The experts also receive documents/assessments of documents informing the 3rd edition recommendations for that domain area, related guidelines since 2010 (with AGREE II ratings), and a list of relevant evidence for each individual recommendation within a domain area. Ratings for the overall quality of evidence and the strength of recommendation pertaining to only relevant evidence for each recommendation is based on the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach\(^{28,29}\) (see Confidence in Cumulative Evidence section below
for more details). Finally, there are voting options to keep, modify, or delete recommendations based on the new relevant evidence. Space to write a revised recommendation and to propose new recommendations is also provided. Several weeks later, the expert panel meets virtually 1-2 times with a group moderator through a video call to make decisions. Afterwards, results of the meeting(s) are circulated to the entire expert team for feedback. Based on this feedback, the project team makes the necessary revisions. Finally, a round of voting (and feedback) will occur with the entire expert team. See Supplementary Material 4 for the full guideline domain update algorithm.

**Meta-bias(es)**

There are no planned assessments of meta-bias(es) (e.g., publication bias, selective reporting within studies) due to the nature of this review.

**Confidence in Cumulative Evidence**

The GRADE approach is being used to rate the overall quality of relevant evidence informing each recommendation. This approach initially labels randomized controlled trial evidence as high quality and observational study evidence as low quality. Ratings are lowered if there is risk of bias, inconsistency in results, indirectness (i.e., studies not examining interventions, patients, and outcomes of interest), imprecision (e.g., large confidence intervals), and publication bias. Ratings can be elevated if there are large effect sizes, evidence of a dose response gradient, and if all possible confounding would reduce a demonstrated effect or would suggest a spurious effect if no effect was observed. The quality of evidence is rated as very low, low, moderate, or high. We have made an amendment in cases where there is a mix of randomized controlled trials and observational studies informing a recommendation. In these cases, if at least 50% of the studies are randomized controlled trials, the grading will begin at
high quality. Also, we have made the decision that in cases where a recommendation is based on 
expert opinion only, the quality of evidence will be “very low” because it is based on anecdotal 
clinician observation. Each recommendation is also rated as being strong or weak based on a 
cost/benefit analysis. There are four specific factors that determine the strength of 
recommendation: magnitude of the difference between desirable and undesirable effects, quality 
of evidence, the values and preferences of patients, and the resources that need to be expended.

Patient and Public Involvement

Patients or the public are not involved in the design or conduct of the research. However, 
these individuals will be involved in the drafting of guideline recommendations designed for 
clinicians, the production of the patient version of guideline recommendations, and the review of 
resources that accompany the guidelines.

Discussion

Concussion can lead to health issues acutely and in some cases may result in prolonged 
symptoms. There is continued need for up to date guidelines to assist clinicians in managing 
persons with concussion and prolonged symptoms where the complex presentation of symptoms 
can often be challenging for the primary care provider to manage. In addition to this, research 
output in this field is also increasing every year where study quality is typically low, making a 
living systematic review of diagnosis/assessment and treatment of adult concussion necessary.

Although this review has many strengths, it is not without limitations. First, only papers 
published in the English language are being included so other potentially valuable documents 
could be missed. Our multidisciplinary expert team, although large, is also geographically 
limited to North America. Therefore, recommendations included in the living guidelines may not 
reflect the full global perspective. Also, only a minimum of 5 content experts are involved in the
initial examination of the literature and recommendations for each specific domain. Although it would be ideal to include the entire expert team at this phase, it is not feasible because of the workload. Finally, regarding demographics, the review focuses only on adults and on concussion while excluding the pediatric population. The guidelines could potentially be more comprehensive if pediatrics were included but it is not feasible given our infrastructure which is primarily adult expert focussed and there are now available parallel pediatric concussion living guidelines\textsuperscript{30} using similar rigorous approaches which have formal ties to these guidelines.

This continuous review process will greatly benefit clinicians and patients by informing living guidelines that will lead to timely guideline recommendations that over time will have increasing certainty as the evidence improves.

**Ethics and Dissemination:** No ethical approval is necessary because primary data are not collected. The review results will be published in peer-reviewed journals in addition to being on the guidelines website in order to enhance dissemination and implementation. Any important amendments to this protocol will be documented on the guidelines website.

**Authors’ Contributions:** AL (guarantor) and SM were involved in conceptual development, writing, and editing. MTB, DC, LKF, CK, JL, MN, and DV were involved in conceptual development and editing.

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**Competing Interests Statement:** None declared.
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## Completed PRISMA-P 2015 checklist

| Section and topic          | Item No | Checklist item                                                                 | Page and line numbers in manuscript |
|---------------------------|---------|--------------------------------------------------------------------------------|-------------------------------------|
| **Administrative information** |         |                                                                                |                                     |
| Identification            | 1a      | Identify the report as a protocol of a systematic review                       | Page 1, line 1                      |
| Update                    | 1b      | If the protocol is for an update of a previous systematic review, identify as such | Page 2, line 9                      |
| Registration              | 2       | If registered, provide the name of the registry (such as PROSPERO) and registration number | Page 3, line 1                      |
| Contact                   | 3a      | Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author | Page 1, line 2                      |
| Contributions             | 3b      | Describe contributions of protocol authors and identify the guarantor of the review | Page 13, line 2                     |
| Amendments                | 4       | If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments | Page 13, line 13                    |
| Sources                   | 5a      | Indicate sources of financial or other support for the review                  | Page 13, line 18                    |
| Sponsor                   | 5b      | Provide name for the review funder and/or sponsor                              | Page 13, line 18                    |
| Role of sponsor or funder | 5c      | Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol | The funders did not develop the protocol |
| **Introduction**          |         |                                                                                |                                     |
| Rationale                 | 6       | Describe the rationale for the review in the context of what is already known   | Page 4, line 22                     |
| Objectives                | 7       | Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) | Page 5, line 9                      |
| **Methods**               |         |                                                                                |                                     |
| Eligibility criteria      | 8       | Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review | Page 5, line 17                     |
| Information sources       | 9       | Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage | Page 6, line 11                     |
| Search strategy           | 10      | Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated | Page 6, line 19                     |
| Data management           | 11a     | Describe the mechanism(s) that will be used to manage records and data throughout the review | Page 7, line 6                      |
| Selection process         | 11b     | State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) | Page 7, line 10                     |
| Section                              | Code | Description                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Page, Line |
|--------------------------------------|------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|
| Data collection process              | 11c  | Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators                                                                                                                                                                                                                                                                                           | Page 8, line 14 |
| Data items                           | 12   | List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications                                                                                                                                                                                                                                                                                                           | Page 8, line 23 |
| Outcomes and prioritization          | 13   | List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale                                                                                                                                                                                                                                                                                                               | Page 9, line 8 |
| Risk of bias in individual studies   | 14   | Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis                                                                                                                                                                                                                                                                                     | Page 9, line 12 |
| Data synthesis                       | 15a  | Describe criteria under which study data will be quantitatively synthesised                                                                                                                                                                                                                                                                                                                                                                                                       | Data will not be quantitatively synthesised |
|                                      | 15b  | If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I², Kendall’s τ)                                                                                                                                                                                                                                          | N/A        |
|                                      | 15c  | Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)                                                                                                                                                                                                                                                                                                                   | N/A        |
|                                      | 15d  | If quantitative synthesis is not appropriate, describe the type of summary planned                                                                                                                                                                                                                                                                                                                                           | Page 10, line 4 |
| Meta-bias(es)                        | 16   | Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)                                                                                                                                                                                                                                                                                                          | Page 11, line 9 |
| Confidence in cumulative evidence    | 17   | Describe how the strength of the body of evidence will be assessed (such as GRADE)                                                                                                                                                                                                                                                                                                                                                                                                     | Page 11, line 12 |
Initial MEDLINE ALL Search Strategy

1. exp Brain Concussion/
2. Post-Concussion Syndrome/
3. (concuss* or postconcuss*).tw,kw.
4. commotio cerebri.tw,kw.
5. ((post commotion or post head injury) adj2 syndrome*).tw.
6. ((mild or minor or minimal) adj3 (traumatic brain or tbi)).tw.
7. ((tbi or traumatic brain injur*) adj3 symptom*).tw.
8. mtbi.tw,kw. or mild traumatic brain injur*.kw. or minor traumatic brain injur*.kw. or minimal traumatic brain injur*.kw.
9. (brain injur* and rehabilitat*).ti. or Brain Injuries/rh or "Brain Injuries, Traumatic"/rh
10. Craniocerebral Trauma/co
11. exp Brain Injuries/ or Craniocerebral Trauma/ or Head Injuries, Closed/
12. ((following or after or post or persistent or unresolved or delayed or prolong*) adj4 (brain or skull or head or injur*).tw. not (((severe or moderate) adj2 (head or brain or traumatic or tbi)) not (mild or minor)).ti.
13. (following or after or post or persistent or unresolved or delayed or prolong*).tw. and (headache/ or exp headache disorders/)
14. 11 and (12 or 13)
15. or/1-10,14
16. brain injuries/ or brain injuries, traumatic/ or Craniocerebral Trauma/ or Head Injuries, Closed/
17. Post-Traumatic Headache/
18. exp Sleep Wake Disorders/
19. exp Mental Disorders/
20. dizziness/ or vision disorders/
21. Fatigue/
22. Return to Work/ or Return to Sport/
23. Memory Disorders/ or amnesia/
24. cognition disorders/ or cognitive dysfunction/
25. or/17-24
26. 16 and 25
27. (brain injur* adj3 (headache* or cognitive disorder* or sleep disorder* or memory or amnesia or insomnia or mental disorder* or dizziness or vision disorder* or fatigue or "return to work" or "Return to Sport" or psychiatric symptom* or ptsd or post traumatic stress or depression or sleep problem* or cognitive dysfunction)).tw.
28. 26 or 27
29. 15 or 28
30. exp animals/ not humans/
31. (exp child/ or exp infant/) not exp adult/
32. ((child* or infant* or pediatric* or paediatric*) not adult*).ti.
33. or/30-32
34. 29 not 33
35. limit 34 to english language
36. (201706* or 201707* or 201708* or 201709* or 20171* or 2018* or 2019* or 2020*).dt.
37. 35 and 36
Risk of Bias Assessment Tools

Section 1: Interventions (Downs & Black, 1998)

Supporting text
Enter supporting text about your judgement

1. Is the hypothesis/aim/objective of the study clearly described?

| Yes (1) | No (0) |

Supporting text
Enter supporting text about your judgement

2. Are the main outcomes to be measured clearly described in the Introduction or Methods section?
If the main outcomes are first mentioned in the Results section, the question should be answered no.

| Yes (1) | No (0) |

Supporting text
Enter supporting text about your judgement

3. Are the characteristics of the patients included in the study clearly described?
In cohort studies and trials, inclusion and/or exclusion criteria should be given. In case-control studies, a case-definition and the source for controls should be given.

| Yes (1) | No (0) |

Supporting text
Enter supporting text about your judgement

4. Are the interventions of interest clearly described?
Treatments and placebo (where relevant) that are to be compared should be clearly described.

| Yes (1) | No (0) |

Supporting text
Enter supporting text about your judgement
5. Are the distributions of principal confounders in each group of subjects to be compared clearly described?
A list of principal confounders is provided.

| Yes (2) |
|--------|
| Partially (1) |
| No (0) |

Supporting text
Enter supporting text about your judgement

6. Are the main findings of the study clearly described?
Simple outcome data (including denominators and numerators) should be reported for all major findings so that the reader can check the major analyses and conclusions. (This question does not cover statistical tests which are considered below).

| Yes (1) |
|--------|
| No (0) |

Supporting text
Enter supporting text about your judgement

7. Does the study provide estimates of the random variability in the data for the main outcomes?
In non normally distributed data the inter-quartile range of results should be reported. In normally distributed data the standard error, standard deviation or confidence intervals should be reported. If the distribution of the data is not described, it must be assumed that the estimates used were appropriate and the question should be answered yes.

| Yes (1) |
|--------|
| No (0) |

Supporting text
Enter supporting text about your judgement

8. Have all important adverse events that may be a consequence of the intervention been reported?
This should be answered yes if the study demonstrates that there was a comprehensive attempt to measure adverse events. (A list of possible adverse events is provided).

| Yes (1) |
|--------|
| No (0) |

Supporting text
Enter supporting text about your judgement

9. Have the characteristics of patients lost to follow-up been described?
This should be answered yes where there were no losses to follow-up or where losses to follow-up were so small that findings would be unaffected by their inclusion. This should be answered no where a study does not report the number of patients lost to follow-up.

| Yes (1) |
|--------|
| No (0) |

Supporting text
Enter supporting text about your judgement
10. Have actual probability values been reported (e.g., 0.035 rather than < 0.05) for the main outcomes except where the probability value is less than 0.001?

| Yes (1) | No (0) |
|---------|--------|

Supporting text
Enter supporting text about your judgement

11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?

The study must identify the source population for patients and describe how the patients were selected. Patients would be representative if they comprised the entire source population, an unselected sample of consecutive patients, or a random sample. Random sampling is only feasible where a list of all members of the relevant population exists. Where a study does not report the proportion of the source population from which the patients are derived, the question should be answered as unable to determine.

| Yes (1) | No (0) | Unable to determine (0) |
|---------|--------|------------------------|

Supporting text
Enter supporting text about your judgement

12. Were those subjects who were prepared to participate representative of the entire population from which they were recruited?

The proportion of those asked who agreed should be stated. Validation that the sample was representative would include demonstrating that the distribution of the main confounding factors was the same in the study sample and the source population.

| Yes (1) | No (0) | Unable to determine (0) |
|---------|--------|------------------------|

Supporting text
Enter supporting text about your judgement

13. Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?

For the question to be answered yes the study should demonstrate that the intervention was representative of that in use in the source population. The question should be answered no if, for example, the intervention was undertaken in a specialist centre unrepresentative of the hospitals most of the source population would attend.

| Yes (1) | No (0) | Unable to determine (0) |
|---------|--------|------------------------|

Supporting text
Enter supporting text about your judgement

14. Was an attempt made to blind study subjects to the intervention they have received?

For studies where the patients would have no way of knowing which intervention they received, this should be answered yes.

| Yes (1) | No (0) | Unable to determine (0) |
|---------|--------|------------------------|

Supporting text
Enter supporting text about your judgement
15. Was an attempt made to blind those measuring the main outcomes of the intervention?

|   |   |
|---|---|
| Yes (1) | No (0) |
| Unable to determine (0) |

Supporting text
Enter supporting text about your judgement

16. If any of the results of the study were based on “data dredging”, was this made clear?

Any analyses that had not been planned at the outset of the study should be clearly indicated. If no retrospective unplanned subgroup analyses were reported, then answer yes.

|   |   |
|---|---|
| Yes (1) | No (0) |
| Unable to determine (0) |

Supporting text
Enter supporting text about your judgement

17. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?

Where follow-up was the same for all study patients the answer should be yes. If different lengths of follow-up were adjusted for by, for example, survival analysis the answer should be yes. Studies where differences in follow-up are ignored should be answered no.

|   |   |
|---|---|
| Yes (1) | No (0) |
| Unable to determine (0) |

Supporting text
Enter supporting text about your judgement

18. Were the statistical tests used to assess the main outcomes appropriate?

The statistical techniques used must be appropriate to the data. For example nonparametric methods should be used for small sample sizes. Where little statistical analysis has been undertaken but where there is no evidence of bias, the question should be answered yes. If the distribution of the data (normal or not) is not described it must be assumed that the estimates used were appropriate and the question should be answered yes.

|   |   |
|---|---|
| Yes (1) | No (0) |
| Unable to determine (0) |

Supporting text
Enter supporting text about your judgement

19. Was compliance with the Intervention/s reliable?

Where there was non-compliance with the allocated treatment or where there was contamination of one group, the question should be answered no. For studies where the effect of any misclassification was likely to bias any association to the null, the question should be answered yes.

|   |   |
|---|---|
| Yes (1) | No (0) |
| Unable to determine (0) |

Supporting text
Enter supporting text about your judgement
20. Were the main outcome measures used accurate (valid and reliable)?
For studies where the outcome measures are clearly described, the question should be answered yes. For studies which refer to other work or that demonstrates the outcome measures are accurate, the question should be answered as yes.

|   | Yes (1) | No (0) | Unable to determine (0) |
|---|---------|--------|------------------------|

Supporting text

Enter supporting text about your judgement

21. Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?
For example, patients for all comparison groups should be selected from the same hospital. The question should be answered unable to determine for cohort and case control studies where there is no information concerning the source of patients included in the study.

|   | Yes (1) | No (0) | Unable to determine (0) |
|---|---------|--------|------------------------|

Supporting text

Enter supporting text about your judgement

22. Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?
For a study which does not specify the time period over which patients were recruited, the question should be answered as unable to determine.

|   | Yes (1) | No (0) | Unable to determine (0) |
|---|---------|--------|------------------------|

Supporting text

Enter supporting text about your judgement

23. Were study subjects randomised to intervention groups?
Studies which state that subjects were randomised should be answered yes except where method of randomisation would not ensure random allocation. For example alternate allocation would score no because it is predictable.

|   | Yes (1) | No (0) | Unable to determine (0) |
|---|---------|--------|------------------------|

Supporting text

Enter supporting text about your judgement

24. Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?
All non-randomised studies should be answered no. If assignment was concealed from patients but not from staff, it should be answered no.

|   | Yes (1) | No (0) | Unable to determine (0) |
|---|---------|--------|------------------------|

Supporting text

Enter supporting text about your judgement
25. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?

This question should be answered no for trials if the main conclusions of the study were based on analyses of treatment rather than intention to treat, the distribution of known confounders in the different treatment groups was not described, or the distribution of known confounders differed between the treatment groups but was not taken into account in the analyses. In nonrandomised studies if the effect of the main confounders was not investigated or confounding was demonstrated but no adjustment was made in the final analyses the question should be answered no.

| Yes (1) |
|---------|
| No (0)  |
| Unable to determine (0) |

Supporting text

Enter supporting text about your judgement

26. Were losses of patients to follow-up taken into account?

If the numbers of patients lost to follow-up are not reported, the question should be answered as unable to determine. If the proportion lost to follow-up was too small to affect the main findings, the question should be answered yes.

| Yes (1) |
|---------|
| No (0)  |
| Unable to determine (0) |

Supporting text

Enter supporting text about your judgement

27. Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?

| Yes (1) |
|---------|
| No (0)  |

Supporting text

Enter supporting text about your judgement

Section 2: Observational studies (STROBE; von Elm et al., 2007)

Supporting text

Enter supporting text about your judgement

1. Indicate the study's design with a commonly used term in the title or the abstract.

| Yes (1) |
|---------|
| No (0)  |

Supporting text

Enter supporting text about your judgement

2. Provide in the abstract an informative and balanced summary of what was done and what was found.

| Yes (1) |
|---------|
| No (0)  |

Supporting text

Enter supporting text about your judgement
3. Explain the scientific background and rationale for the investigation being reported.

|   | Yes (1) | No (0) |
|---|---------|--------|

Supporting text
Enter supporting text about your judgement

4. State specific objectives, including any prespecified hypotheses.

|   | Yes (1) | No (0) |
|---|---------|--------|

Supporting text
Enter supporting text about your judgement

5. Present key elements of study design early in the paper.

|   | Yes (1) | No (0) |
|---|---------|--------|

Supporting text
Enter supporting text about your judgement

6. Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection.

|   | Yes (1) | No (0) |
|---|---------|--------|

Supporting text
Enter supporting text about your judgement

7. Cohort study—give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up. Case-control study—give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls. Cross-sectional study—give the eligibility criteria, and the sources and methods of selection of participants.

|   | Yes (1) | No (0) |
|---|---------|--------|

Supporting text
Enter supporting text about your judgement

8. Cohort study—for matched studies, give matching criteria and number of exposed and unexposed. Case-control study—for matched studies, give matching criteria and the number of controls per case.

|   | Yes (1) | No (0) | N/A (1) |
|---|---------|--------|--------|

Supporting text
Enter supporting text about your judgement
9. Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.

|   |   |
|---|---|
| Yes (1) | No (0) |

**Supporting text**
Enter supporting text about your judgement

10. For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group.

|   |   |
|---|---|
| Yes (1) | No (0) |

**Supporting text**
Enter supporting text about your judgement

11. Describe any efforts to address potential sources of bias.

|   |   |
|---|---|
| Yes (1) | No (0) |

**Supporting text**
Enter supporting text about your judgement

12. Explain how the study size was arrived at.

|   |   |
|---|---|
| Yes (1) | No (0) |

**Supporting text**
Enter supporting text about your judgement

13. Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why.

|   |   |
|---|---|
| Yes (1) | No (0) |

**Supporting text**
Enter supporting text about your judgement

14. Describe all statistical methods, including those used to control for confounding.

|   |   |
|---|---|
| Yes (1) | No (0) |

**Supporting text**
Enter supporting text about your judgement
15. Describe any methods used to examine subgroups and interactions.

|   |   |
|---|---|
| Yes (1) |   |
| No (0) |   |
| N/A (1) |   |

**Supporting text**
Enter supporting text about your judgement

16. Explain how missing data were addressed.

|   |   |
|---|---|
| Yes (1) |   |
| No (0) |   |

**Supporting text**
Enter supporting text about your judgement

17. Cohort study—if applicable, explain how loss to follow-up was addressed. Case-control study—if applicable, explain how matching of cases and controls was addressed. Cross-sectional study—if applicable, describe analytical methods taking account of sampling strategy.

|   |   |
|---|---|
| Yes (1) |   |
| No (0) |   |
| N/A (1) |   |

**Supporting text**
Enter supporting text about your judgement

18. Describe any sensitivity analyses.

|   |   |
|---|---|
| Yes (1) |   |
| No (0) |   |
| N/A (1) |   |

**Supporting text**
Enter supporting text about your judgement

19. Report the numbers of individuals at each stage of the study—eg, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed.

|   |   |
|---|---|
| Yes (1) |   |
| No (0) |   |

**Supporting text**
Enter supporting text about your judgement

20. Give characteristics of study participants (eg, demographic, clinical, social) and information on exposures and potential confounders.

|   |   |
|---|---|
| Yes (1) |   |
| No (0) |   |

**Supporting text**
Enter supporting text about your judgement
21. Indicate the number of participants with missing data for each variable of interest.

|           | Yes (1) | No (0) |
|-----------|---------|--------|

Supporting text
Enter supporting text about your judgement

22. Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included.

|           | Yes (1) | No (0) |
|-----------|---------|--------|

Supporting text
Enter supporting text about your judgement

23. Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based.

|           | Yes (1) | No (0) |
|-----------|---------|--------|

Supporting text
Enter supporting text about your judgement

Section 3: Qualitative studies (CASP; 2018)

Supporting text
Enter supporting text about your judgement

1. Was there a clear statement of the aims of the research?

|           | Yes (1) | No (0) |
|-----------|---------|--------|

Supporting text
Enter supporting text about your judgement

2. Is a qualitative methodology appropriate?

HINT: Consider
- if the research seeks to interpret or illuminate the actions and/or subjective experiences of research participants
- is qualitative research the right methodology for addressing the research goal

|           | Yes (1) | No (0) |
|-----------|---------|--------|

Supporting text
Enter supporting text about your judgement
3. Was the research design appropriate to address the aims of the research?

HINT: Consider
• if the researcher has justified the research design (e.g. have they discussed how they decided which method to use)

| Yes (1) | No (0) |

Supporting text
Enter supporting text about your judgement

4. Was the recruitment strategy appropriate to the aims of the research?

HINT: Consider
• if the researcher has explained how the participants were selected
• if they explained why the participants they selected were the most appropriate to provide access to the type of knowledge sought by the study
• if there are any discussions around recruitment (e.g. why some people chose not to take part)

| Yes (1) | No (0) |

Supporting text
Enter supporting text about your judgement

5. Was the data collected in a way that addressed the research issue?

HINT: Consider
• if the setting for the data collection was justified
• if it is clear how data were collected (e.g. focus group, semi-structured interview etc.)
• if the researcher has justified the methods chosen
• if the researcher has made the methods explicit (e.g. for interview method, is there an indication of how interviews are conducted, or did they use a topic guide)
• if methods were modified during the study, if so, has the researcher explained how and why
• if the form of data is clear (e.g. tape recordings, video material, notes etc.)
• if the researcher has discussed saturation of data

| Yes (1) | No (0) |

Supporting text
Enter supporting text about your judgement

6. Has the relationship between researcher and participants been adequately considered?

HINT: Consider
• if the researcher critically examined their own role, potential bias and influence during (a) formulation of the research questions (b) data collection, including sample recruitment and choice of location
• How the researcher responded to events during the study and whether they considered the implications of any changes in the research design

| Yes (1) | No (0) |

Supporting text
Enter supporting text about your judgement
7. Have ethical issues been taken into consideration?

HINT: Consider

- If there are sufficient details of how the research was explained to participants for the reader to assess whether ethical standards were maintained
- If the researcher has discussed issues raised by the study (e.g., issues around informed consent or confidentiality or how they have handled the effects of the study on the participants during and after the study)
- If approval has been sought from the ethics committee

| Yes (1) | No (0) |
|---------|--------|

Supporting text

Enter supporting text about your judgement

8. Was the data analysis sufficiently rigorous?

HINT: Consider

- If there is an in-depth description of the analysis process
- If thematic analysis is used, if so, is it clear how the categories/themes were derived from the data
- Whether the researcher explains how the data presented were selected from the original sample to demonstrate the analysis process
- If sufficient data are presented to support the findings
- To what extent contradictory data are taken into account
- Whether the researcher critically examined their own role, potential bias and influence during analysis and selection of data for presentation

| Yes (1) | No (0) |
|---------|--------|

Supporting text

Enter supporting text about your judgement

9. Is there a clear statement of findings?

HINT: Consider whether

- If the findings are explicit
- If there is adequate discussion of the evidence both for and against the researcher’s arguments
- If the researcher has discussed the credibility of their findings (e.g., triangulation, respondent validation, more than one analyst)
- If the findings are discussed in relation to the original research question

| Yes (1) | No (0) |
|---------|--------|

Supporting text

Enter supporting text about your judgement

Section 4: Systematic reviews (AMSTAR 2; Shea et al., 2017)

Supporting text

Enter supporting text about your judgement

1. Did the research questions and inclusion criteria for the review include the components of PICO?

For Yes:
- Population
- Intervention
- Comparator group
- Outcome

| Yes (1) | No (0) |
|---------|--------|

Supporting text

Enter supporting text about your judgement
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?

For Partial Yes:
The authors state that they had a written protocol or guide that included ALL the following:
- review question(s)
- a search strategy
- inclusion/exclusion criteria
- a risk of bias assessment

For Yes:
As for partial yes, plus the protocol should be registered and should also have specified:
- a meta-analysis/synthesis plan, if appropriate, and
- a plan for investigating causes of heterogeneity
- justification for any deviations from the protocol

| Yes (2) |
|---------|
| Partial Yes (1) |
| No (0) |

Supporting text
Enter supporting text about your judgement

3. Did the review authors explain their selection of the study designs for inclusion in the review?

For Yes, the review should satisfy ONE of the following:
- Explanation for including only RCTs
- OR Explanation for including only non-RCTs
- OR Explanation for including both RCTs and non-RCTs

| Yes (1) |
|---------|
| No (0) |

Supporting text
Enter supporting text about your judgement

4. Did the review authors use a comprehensive literature search strategy?

For Partial Yes (all the following):
- searched at least 2 databases (relevant to research question)
- provided key word and/or search strategy
- justified publication restrictions (eg, language)

For Yes, should also have (all the following):
- searched the reference lists/bibliographies of included studies
- searched trial/study registries
- included/consulted content experts in the field
- where relevant, searched for grey literature
- conducted search within 24 months of completion of the review

| Yes (2) |
|---------|
| Partial Yes (1) |
| No (0) |

Supporting text
Enter supporting text about your judgement
5. Did the review authors perform study selection in duplicate?
For Yes, either ONE of the following:
- at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include
- OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 per cent), with the remainder selected by one reviewer

| Yes (1) | No (0) |

Supporting text
Enter supporting text about your judgement

6. Did the review authors perform data extraction in duplicate?
For Yes, either ONE of the following:
- at least two reviewers achieved consensus on which data to extract from included studies
- OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 per cent), with the remainder extracted by one reviewer

| Yes (1) | No (0) |

Supporting text
Enter supporting text about your judgement

7. Did the review authors provide a list of excluded studies and justify the exclusions?
For Partial Yes:
- provided a list of all potentially relevant studies that were read in full text form but excluded from the review
- Justified the exclusion from the review of each potentially relevant study

| Yes (2) | Partial Yes (1) | No (0) |

Supporting text
Enter supporting text about your judgement

8. Did the review authors describe the included studies in adequate detail?
For Partial Yes (ALL the following):
- described populations
- described interventions
- described comparators
- described outcomes
- described research designs
For Yes, should also have ALL the following:
- described population in detail
- described intervention and comparator in detail (including doses where relevant)
- described study’s setting
- timeframe for follow-up

| Yes (2) | Partial Yes (1) | No (0) |

Supporting text
Enter supporting text about your judgement

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9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review (RCTs only)?

**RCTs**
For Partial Yes, must have assessed RoB from:
- uncontrolled allocation, and
- lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all cause mortality).
For Yes, must also have assessed RoB from:
- allocation sequence that was not truly random, and
- selection of the reported result from among multiple measurements or analyses of a specified outcome

| Yes (2) |
|---------|
| Partial Yes (1) |
| No (0) |

10. Did the review authors report on the sources of funding for the studies included in the review?

For Yes
- Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information but it was not reported by study authors also qualifies

| Yes (1) |
|---------|
| No (0) |

Supporting text
Enter supporting text about your judgement

11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?

**RCTs**
For Yes:
- The authors justified combining the data in a meta-analysis
- AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present
- AND investigated the causes of any heterogeneity

| Yes (1) |
|---------|
| No (0) |

For NRSI
For Yes:
- The authors justified combining the data in a meta-analysis
- AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available
- AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review

For other studies
For Yes:
- Use appropriate criteria from above points.

| Yes (1) |
|---------|
| No (0) |

No meta-analysis (1)
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?
   For Yes:
   □ Included only low risk of bias RCTs
   □ OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect
   □ Yes (1)
   □ No (0)
   □ No meta-analysis (1)

Supporting text
Enter supporting text about your judgement

13. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?
   For Yes:
   □ There was no significant heterogeneity in the results
   □ OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review
   □ Yes (1)
   □ No (0)

Supporting text
Enter supporting text about your judgement

14. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?
   For Yes:
   □ Performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias
   □ Yes (1)
   □ No (0)
   □ No meta-analysis (1)

Supporting text
Enter supporting text about your judgement

15. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?
   For Yes:
   □ The authors reported no competing interests OR
   □ The authors described their funding sources and how they managed potential conflicts of interest
   □ Yes (1)
   □ No (0)

Supporting text
Enter supporting text about your judgement

Section 5: Guidelines (AGREE II; 2017)
A score of 1 should be given when there is no information that is relevant to the AGREE II item, if the concept is very poorly reported, or if the authors state explicitly that criteria were not met.
A score of 7 should be given if the quality of reporting is exceptional and where the full criteria and considerations articulated in the User's Manual have been met.

Supporting text
Enter supporting text about your judgement
*Supporting text boxes were present on the actual form but have been omitted from the following items to save space. Also, the scale has been omitted from items 2-23 for the same reason.

1. The overall objective(s) of the guideline is (are) specifically described.

   Item content includes the following CRITERIA:
   • health intent(s) (i.e., prevention, screening, diagnosis, treatment, etc.)
   • expected benefit or outcome
   • target(s) (e.g., patient population, society)

   Additional CONSIDERATIONS:
   • Is the item well written? Are the descriptions clear and concise?
   • Is the item content easy to find in the guideline?

   | 1 (Strongly Disagree) |
   | 2 | 3 | 4 |
   | 5 | 6 | 7 (Strongly Agree) |

2. The health question(s) covered by the guideline is (are) specifically described.

   Item content includes the following CRITERIA:
   • target population
   • intervention(s) or exposure(s)
   • companions (if appropriate)
   • outcome(s)
   • health care setting or context

   Additional CONSIDERATIONS:
   • Is the item well written? Are the descriptions clear and concise?
   • Is the item content easy to find in the guideline?
   • Is there enough information provided in the question(s) for anyone to initiate the development of a guideline on this topic or to understand the patients/populations and contexts profiled in the guideline?

3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.

   How to Rate:
   Item content includes the following CRITERIA:
   • target population, gender and age
   • clinical condition (if relevant)
   • severity/stage of disease (if relevant)
   • comorbidities (if relevant)
   • excluded populations (if relevant)

   Additional CONSIDERATIONS:
   • Is the item well written? Are the descriptions clear and concise?
   • Is the item content easy to find in the guideline?
   • Is the population information specific enough so that the correct and eligible individuals would receive the action recommended in the guideline?

4. The guideline development group includes individuals from all relevant professional groups.

   This item refers to the professionals who were involved at some stage of the development process. This may include members of the steering group, the research team involved in selecting and reviewing the evidence and individuals involved in formulating the final recommendations. This item excludes individuals who have externally reviewed the guideline (see item 13). This item excludes target population representation (see item 5). Information about the composition, discipline, and relevant expertise of the guideline development group should be provided.

5. The views and preferences of the target population (patients, public, etc.) have been sought.

   Item content includes the following CRITERIA:
   • statement of type of strategy used to capture patients’/public’s views and preferences (e.g., participation in the guideline development group, literature review of values and preferences)
   • methods by which preferences and views were sought (e.g., data from literature, surveys, focus groups)
   • outcomes/information gathered on patient/public information
   • description of how the information gathered was used to inform the guideline development process and/or formation of the recommendations

   Additional CONSIDERATIONS:
   • Is the item well written? Are the descriptions clear and concise?
   • Is the item content easy to find in the guideline?
6. The target users of the guideline are clearly defined.
   - clear description of intended guideline audience (e.g. specialists, family physicians, patients, clinical or
     institutional leaders/administrators)
   - description of how the guideline may be used by its target audience (e.g., to inform clinical decisions, to
     inform policy, to inform standards of care)
   Additional CONSIDERATIONS:
   - Is the item well written? Are the descriptions clear and concise?
   - Is the item content easy to find in the guideline?
   - Are the target users appropriate for the scope of the guideline?

7. Systematic methods were used to search for evidence.
   Details of the strategy used to search for evidence should be provided including search terms used, sources
   consulted, and dates of the literature covered. Sources may include electronic databases (e.g. MEDLINE, EMBASE, CINAHL), databases of systematic reviews (e.g. the Cochrane Library, DARE), handsearching journals, reviewing conference proceedings, and other guidelines (e.g. the US National Guideline Clearinghouse, the German Guidelines Clearinghouse). The search strategy should be as comprehensive as
   possible and executed in a manner free from potential biases and sufficiently detailed to be replicated.

8. The criteria for selecting the evidence are clearly described.
   Criteria for including/excluding evidence identified by the search should be provided. These criteria should be explicitly described and reasons for including and excluding evidence should be
   clearly stated. For example, guideline authors may decide to only include evidence from randomized clinical trials and to exclude articles not written in English.

9. The strengths and limitations of the body of evidence are clearly described.
   Statements highlighting the strengths and limitations of the evidence should be provided. This ought to include explicit descriptions - using informal or formal tools/methods - to assess and
describe the risk of bias for
   individual studies and/or for specific outcomes and/or explicit commentary of the body of evidence aggregated across all studies. This may be presented in different ways, for example: using
tables commenting on different quality domains, an application of a formal instrument or strategy (e.g., Jadad scale, GRADE method); or descriptions in the text.

10. The methods for formulating the recommendations are clearly described.
    A description of the methods used to formulate the recommendations and how final decisions were arrived at should be provided. For example, methods may include a voting system, informal consensus, and formal consensus techniques (e.g., Delphi, Glasier techniques). Areas of disagreement and methods of resolving them
    should be specified.

11. The health benefits, side effects, and risks have been considered in formulating the recommendations.
    The guideline should consider health benefits, side effects, and risks when formulating the recommendations. For example, a guideline on the management of breast cancer may include a
discussion on the overall effects
    on various final outcomes. These may include: survival, quality of life, adverse effects, and symptom management or a discussion comparing one treatment option to another. There should be
    evidence that these issues have been addressed.

12. There is an explicit link between the recommendations and the supporting evidence.
    An explicit link between the recommendations and the evidence on which they are based should be included in the guideline. The guideline user should be able to identify the components of
    the body of evidence relevant to each recommendation.

13. The guideline has been externally reviewed by experts prior to its publication.
    A guideline should be reviewed externally before it is published. Reviewers should not have been involved in the guideline development group. Reviewers should include experts in the clinical
    area as well as some
    methodological experts. Target population (patients, public) representatives may also be included. A description of the methodology used to conduct the external review should be presented,
    which may include a
    list of the reviewers and their affiliation.

14. A procedure for updating the guideline is provided.
    Guidelines need to reflect current research. A clear statement about the procedure for updating the guideline should be provided. For example, a timescale has been given or a standing panel
    is established who receives
    regularly updated literature searches and makes changes as required.

15. The recommendations are specific and unambiguous.
    A recommendation should provide a concrete and precise description of which option is appropriate in which
    situation and in what population group, as informed by the body of evidence.
    • An example of a specific recommendation: Antibiotics should be prescribed in children two years or older with a diagnosis of acute otitis media if the pain lasts longer than three days or if
      the pain increases after the consultation despite adequate treatment with painkillers; in these cases, amoxicillin should be given for 7 days (supplied with a dosage scheme).
    • An example of a vague recommendation: Antibiotics are indicated for cases with an abnormal or complicated course.

    It is important to note that in some instances, evidence is not always clear-cut and there may be uncertainty about the best care option(s). In this case, the uncertainty should be stated in the
    guideline.

16. The different options for management of the condition or health issue are clearly presented.
    A guideline that targets the management of a disease should consider the different possible options for
    screening, prevention, diagnosis or treatment of the condition it covers. These possible options should be
    clearly stated in the guideline. For example, a recommendation on the management of depression may contain the following treatment alternatives:
    a. Treatment with TCA
    b. Treatment with SSRI
    c. Psychotherapy
    d. Combination of pharmacological and psychological therapy

17. Key recommendations are easily identifiable.
    Users should be able to find the most relevant recommendations easily. These recommendations answer the main question(s) that have been covered by the guideline and can be identified in
    different ways. For example,
    they can be summarized in a box, typed in bold, underlined or presented as flow charts or algorithms.
18. The guideline describes facilitators and barriers to its application.

There may be existing facilitators and barriers that will impact the application of guideline recommendations.
For example:
- A guideline on stroke may recommend that care should be coordinated through stroke units and stroke services. There may be a special funding mechanism in the region to enable the formation of stroke units.
- A guideline on diabetes in primary care may require that patients are seen and followed up in diabetic clinics. There may be an insufficient number of clinicians available in a region to enable clinics to be established.

19. The guideline provides advice and/or tools on how the recommendations can be put into practice.

For a guideline to be effective it needs to be disseminated and implemented with additional materials. For example, these may include: a summary document, a quick reference guide, educational tools, results from a pilot test, patient leaflets, or computer support. Any additional materials should be provided with the guideline.

20. The potential resource implications of applying the recommendations have been considered.

The recommendations may require additional resources in order to be applied. For example, there may be a need for more specialized staff, new equipment, and expensive drug treatment. These may have cost implications for health care budgets. There should be a discussion in the guideline of the potential impact of the recommendations on resources.

21. The guideline presents monitoring and/or auditing criteria.

Measuring the application of guideline recommendations can facilitate their ongoing use. This requires clearly defined criteria that are derived from the key recommendations in the guideline. The criteria may include process measures, behavioural measures, clinical or health outcome measures. Examples of monitoring and audit criteria are:
- Haemoglobin A1c should be ≥ 8.0.
- The level of diastolic blood pressure should be ≥ 95 mmHg.
- 80% of the population aged 50 years should receive colorectal cancer screening rates using fecal occult blood tests.
- If complaints of acute otitis media last longer than three days, amoxicillin should be prescribed.

22. The views of the funding body have not influenced the content of the guideline.

Many guidelines are developed with external funding (e.g., government, professional associations, charity organizations, pharmaceutical companies). Support may be in the form of financial contribution for the complete development, or for parts of it (e.g., printing of the guidelines). There should be an explicit statement that the views or interests of the funding body have not influenced the final recommendations.

23. Competing interests of guideline development group members have been recorded and addressed.

There are circumstances when members of the development group may have competing interests. For example, this would apply to a member of the development group whose research on the topic covered by the guideline is also funded by a pharmaceutical company. There should be an explicit statement that all group members have declared whether they have any competing interests.

Item content includes the following CRITERIA:
- description of the types of competing interests considered
- methods by which potential competing interests were sought
- description of the competing interests
- description of how the competing interests influenced the guideline process and development of recommendations

Additional CONSIDERATIONS:
- Is the item well written? Are the descriptions clear and concise?
- Is the item content easy to find in the guideline?
- What measures were taken to minimize the influence of competing interests on guideline development or formulation of the recommendations?
Guideline Domain Update Algorithm

1. Panel meetings (3-4 weeks)

2. Optional feedback by entire team (2 weeks)
   - Kept recommendations
   - Modified recommendations (minor changes)
   - Modified (major changes), deleted, or new recommendations

3. Revisions by project team (1 week)
   - Revisions based on comments

4. Feedback and vote by entire team (2 weeks)
   - Available for viewing/to be published

5. Clean-up by project team (1 week)
   - Publish (80% approval)
   - Delete if non-important recommendation
   - Revisions/back to step 4

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# Protocol for a living systematic review for the management of concussion in adults

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Protocol for a living systematic review for the management of concussion in adults

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Word count: 3,156
Abstract

Introduction: Concussion/mild traumatic brain injury (mTBI) often presents initially with disabling symptoms that resolve, but for an unfortunate minority some of these symptoms may become prolonged. Although research into diagnosis and interventions for concussion is increasing, study quality overall remains low. A living systematic review that is updated as evidence becomes available is the ideal research activity to inform a living guideline targeting clinicians and patients. The purpose of this paper is to present the protocol of an ongoing living systematic review for the management of adult concussion that will inform living guidelines building off the Guideline for Concussion/Mild Traumatic Brain Injury and Persistent Symptoms: 3rd Edition.

Methods and Analysis: The preferred reporting items for systematic review and meta-analysis-protocol (PRISMA-P) guidelines were followed in the reporting of this systematic review protocol. We are including English peer-reviewed observational studies, trials, qualitative studies, systematic reviews, and clinical practice guidelines related to diagnosis/assessment or treatment of adult concussion. Future searches will be conducted at minimum every six months using the following databases: MEDLINE ALL, EMBASE, Cochrane, PsycInfo, and CINAHL. The data are managed in the Covidence website. Screening, data extraction, and risk of bias assessments are being done through multiple raters working independently. Multiple validated tools are being used to assess risk of bias, and the tool applied matches the document or study design (e.g., Downs and Black scale for health care interventions). Many concussion experts in various clinical disciplines from across North America have volunteered to examine the evidence in order to make recommendations for the living guidelines.
Ethics and Dissemination: The PROSPERO registration number is: CRD42022301786. No ethical approval is necessary because primary data are not collected. The results will be disseminated through peer-reviewed publications and on the living guidelines website once built.

Strengths and Limitations of this Study

- Frequent searches will ensure the accompanying adult concussion living guidelines are up to date.
- There is a large multidisciplinary concussion expert team who have volunteered to interpret the evidence.
- The review focuses only on adults while excluding the pediatric population which is a limitation.
- The review is limited to documents published in the English language.
- Perspectives of the expert team is geographically limited to North America and may not reflect the full global perspective.
Introduction

Concussion/mTBI describes an acute neurophysiological event related to a mechanical energy applied to the head, neck or body (with transmitting forces to the brain), such as from sudden acceleration, deceleration, rotational forces, or repetitive subconcussive hits. All concussions are considered to be a mTBI; however, mTBI can differ from concussion when there is evidence of brain injury on conventional neuroimaging or there is persistent neurologic deficit. Concussion can cause meaningful morbidity, with many persons who have sustained a concussion suffering from prolonged symptoms for years post-injury. Concussion is also among the most common neurological conditions with an estimated annual incidence of 503 per 100,000 in the United States based on emergency department data, and even higher estimates of up to 1,153 per 100,000 if community-based concussions are taken into account. Therefore, effective diagnosis/assessment and treatment is critical.

Systematic reviews provide the best evidence available, and there are many that focus on concussion management. However, systematic review currency and accuracy is challenged by the increasing rate of research output. People might consider conducting a traditional systematic review update, but these updates tend to be inefficient because a new team often needs to be assembled for each update meaning the “institutional memory” of the original team is lost. Living systematic reviews may be an effective solution. A living systematic review is defined as: “a systematic review that is continually updated, incorporating relevant new evidence as it becomes available” (p. 24). In addition to pushing the limits of currency and accuracy, living systematic reviews provide an a priori commitment to a frequency of review giving predictability to end users such as clinicians. Applying a living systematic review process to concussion diagnosis/assessment and treatment is appropriate given that research output in this
particular field is increasing every year\textsuperscript{16} and certainty in much of the existing evidence is low,\textsuperscript{1} making frequent updates necessary.

A living systematic review is the ideal research activity to inform living guidelines. Guidelines are normally developed to support clinicians and their patients in making choices to optimize outcomes.\textsuperscript{17} Living guidelines are: “an optimization of the guideline development process to allow updating of individual recommendations as soon as relevant new evidence becomes available”\textsuperscript{18} (p. 47). There have been a few guidelines published on adult concussion (e.g., \textsuperscript{1,19,20}). However, no group or organization has developed living guidelines to address all aspects of diagnosis/assessment and treatment of concussion in adults. The purpose of this paper is to present the protocol of an ongoing living systematic review for the management of adult concussion (e.g., diagnosis, initial management, post-traumatic headache, return to activity) that will inform living guidelines building off the Guideline for Concussion/Mild Traumatic Brain Injury and Persistent Symptoms: 3rd Edition.\textsuperscript{1}

**Methods and Analysis**

The PRISMA-P guidelines\textsuperscript{2} (see Supplementary Material 1 for the completed checklist) were followed in the reporting of this systematic review protocol.

**Eligibility Criteria**

The inclusion criteria are: studies related to concussion diagnosis/assessment or treatment; at least 50% of sample has concussion (e.g., a Glasgow Coma Scale score of 13-15,\textsuperscript{21} confirmation through a standardized concussion assessment tool, diagnosis by a physician or nurse practitioner) in cases where one group is analyzed; at least 50% of the sample is 18 years of age or older; and the sample is human. Peer-reviewed observational studies (cross-sectional, cohort, case-control), clinical trials, qualitative studies, systematic reviews, and clinical practice
guidelines are included. Documents are limited to English language and publication from May 2017 because that covers literature that did not inform the Guideline for Concussion/Mild Traumatic Brain Injury and Persistent Symptoms: 3rd Edition.¹

The exclusion criteria are: studies that focus on moderate or severe TBI (i.e., a Glasgow Coma Scale score of less than 13); more than 50% of sample has moderate or severe TBI in cases where one group is analyzed; more than 50% of sample is under 18 years of age; and the sample is not human. Case reports/n of 1 studies, non-systematic reviews, conference abstracts/presentations, theses, non-peer-reviewed articles (e.g., newspaper articles), letters or commentaries, addendums/errata, and book chapters are excluded. Documents not available in English, published before May 2017, or originating from grey literature are also not included.

Information Sources

The search strategy (see next section) was originally created in April 2020 for the MEDLINE ALL database in collaboration with a librarian at a research-intensive hospital. The strategy was then peer-reviewed by another librarian at a separate hospital according to the PRESS guideline.²² The PRESS guideline is a checklist of topics that information specialists should consider when evaluating an electronic search strategy. The strategy was approved with minor revisions. EMBASE, Cochrane, PsycInfo, and CINAHL databases are also being searched using the strategy.

Search Strategy

An initial search was completed at the beginning of April 2020 covering May 2017 to the end of March 2020. That search yielded 19,745 results. The search was updated to cover recent literature published April 2020 to the end of March 2021. The new search yielded 5,071 results, meaning the total number of search results was 24,816. The full search strategy for the initial
MEDLINE ALL search has been reported in Supplementary Material 2 as an example. The next search will cover literature published from April 2021 to the end of February 2022 (search to be conducted on March 1, 2022). After this next search, consistent with living systematic review recommendations, the search is planned to repeat every six months at minimum to capture recent literature.

Data Management

The search results are being imported into the Covidence systematic review website. This website automatically removes duplicates, and provides the opportunity for screening, data extraction, and risk of bias assessments with multiple raters.

Selection Process

After duplicates from the initial searches were removed by Covidence, 16,086 documents remained (11,916 from the initial search and 4,170 from the updated search). At the title and abstract screening phase, raters select “yes,” “no,” or “maybe.” A rating of “maybe” is selected when there is not enough information to choose “yes.” However, a “maybe” rating does allow the document to move to the full-text screening phase.

For this first phase of screening, a test set of 100 references was exported from Covidence into an Excel file. All raters independently provided a vote for each document as a calibration training exercise. All votes were compiled on the spreadsheet and discussions were held to determine a consensus vote (as required) for each study. The actual screening was then started in Covidence in dual-screen mode (i.e., two votes were needed per document), until approximately 1,200 documents were completed. There was less than a 10% conflict rate, and any conflicts were resolved through discussion with the final decision being made by a senior researcher. Since the team has demonstrated satisfactory inter-rater reliability, only one vote is
now needed from raters to decide whether documents should move to the full-text screening phase.

Regarding full-text screening, a test set of documents (n = 50) was first exported as a training exercise for the raters (conflict rate was less than 20%), followed by group discussion. Each document requires two independent votes of “yes” to be included in data extraction. In the case of conflicts, the project leader (a physician with many years of clinical experience in the concussion field) or a third rater not involved in the conflict makes the final decision. Finally, each document has been given labels to reflect important themes in the research. Most documents have received at least one label that match the twelve sections appearing in the Guideline for Concussion/Mild Traumatic Brain Injury and Persistent Symptoms: 3rd Edition.¹ For example, a common label has been “diagnosis/assessment of concussion/mTBI,” which is the first section title of the current Guideline. Other labels such as “biomarkers” reflect other themes that may be added to the original twelve sections if the experts deem it appropriate.

Data Collection Process

A standardized data extraction form was created by the investigators in Covidence to ensure relevant data are collected (see next section for Data Items). The raters completed extraction together for several articles per main study design or document type (e.g., intervention, observational, systematic review, qualitative research, clinical practice guideline) in order to enhance inter-rater reliability. Two raters extract data from each included document independently. A third rater completes “consensus” for each article. In Covidence, the consensus rater has the ability to view the original two extractions simultaneously and can then select the best response or can write their own based on the information provided by the raters.

Data Items
The data extraction form has the following sections: document ID (assigned by Covidence); authors; year of publication; title of paper; country in which study was conducted; aim(s) of study related to assessment or treatment; study design; specific design information (e.g., group information, intervention treatment, measurement time points, etc.); relevant outcome measure information; study definition of concussion; number of participants for each group; gender frequencies and percentages for each group; average age and standard deviation for each group; and findings related to assessment or treatment.

Outcomes and Prioritization

Due to the breadth of the present review, no specific outcomes are sought. Any outcomes that contribute to understanding of diagnosis/assessment and treatment of adult concussion is considered relevant.

Risk of Bias in Individual Studies

Risk of bias assessment is currently being conducted at the study or document level (not outcome level). Inter-rater reliability optimization and the rating and consensus procedures are the same as those in data extraction. However, the consensus process only allows the third rater to select a final response due to the nature of the form.

A variety of validated tools have been included in the review. Each tool pertains to the study design or document type. The following tools were included with very minor modifications: Downs and Black scale for health care interventions; an amalgamation of items adopted from the Joanna Briggs Institute (JBI) critical appraisal tools for observational studies; Critical Appraisal Skills Programme (CASP) for qualitative studies; A MeaSurement Tool to Assess Systematic Reviews (AMSTAR 2) for systematic reviews; and Appraisal of Guidelines for REsearch and Evaluation (AGREE II) for clinical practice guidelines. The scoring is as
follows: Downs and Black (/28); JBI (/16); CASP (/9); AMSTAR 2 (/20); AGREE II (23 items each scored on a scale ranging from 1 [strongly disagree] to 7 [strongly agree]). The tools are provided in Supplementary Material 3.

Data Synthesis

In order for the findings to be translated to recommendations in the living guidelines, over 35 concussion and traumatic brain injury experts from across North America have thus far volunteered to interpret the evidence. Each expert must have peer-reviewed publications about adult concussion and/or be recommended by a current expert panel member. All experts also must be approved by the project leader. Currently, twelve groups covering the sections appearing in the Guideline for Concussion/Mild Traumatic Brain Injury and Persistent Symptoms: 3rd Edition have been created. A minimum of 5 experts have been assigned to domain areas that match their expertise. This number was deemed by consensus to be necessary to reduce bias in decision-making and to encourage discussion. Each expert is also required to declare any conflicts of interest.

The experts deal only with documents related to their domain area. The summarized information from the data extraction form (including risk of bias assessments and full-text copies of each document) is provided to the expert panels. The experts also receive documents/assessments of documents informing the 3rd edition recommendations for that domain area, related guidelines since 2010 (with AGREE II ratings), and a list of relevant evidence for each individual recommendation within a domain area. Ratings for the overall quality of evidence and the strength of recommendation pertaining to only relevant evidence for each recommendation is based on the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach (see Confidence in Cumulative Evidence section below.
for more details). Finally, there are voting options to keep, modify, or delete recommendations based on the new relevant evidence. Space to write a revised recommendation and to propose new recommendations is also provided. Several weeks later, the expert panel meets virtually 1-2 times with a group moderator through a video call to make decisions. Afterwards, results of the meeting(s) are circulated to the entire expert team for feedback. Based on this feedback, the project team makes the necessary revisions. Finally, a round of voting (and feedback) will occur with the entire expert team. See Supplementary Material 4 for the full guideline domain update algorithm.

**Meta-bias(es)**

There are no planned assessments of meta-bias(es) (e.g., publication bias, selective reporting within studies) due to the nature of this review.

**Confidence in Cumulative Evidence**

The GRADE approach is being used to rate the overall quality of relevant evidence informing each recommendation. This approach initially labels randomized controlled trial evidence as high quality and observational study evidence as low quality. Ratings are lowered if there is risk of bias, inconsistency in results, indirectness (i.e., studies not examining interventions, patients, and outcomes of interest), imprecision (e.g., large confidence intervals), and publication bias. Ratings can be elevated if there are large effect sizes, evidence of a dose response gradient, and if all possible confounding would reduce a demonstrated effect or would suggest a spurious effect if no effect was observed. The quality of evidence is rated as very low, low, moderate, or high. We have made an amendment in cases where there is a mix of randomized controlled trials and observational studies informing a recommendation. In these cases, if at least 50% of the studies are randomized controlled trials, the grading will begin at
high quality. Also, we have made the decision that in cases where a recommendation is based on
expert opinion only, the quality of evidence will be “very low” because it is based on anecdotal
clinician observation. Each recommendation is also rated as being strong or weak based on a
cost/benefit analysis. There are four specific factors that determine the strength of
recommendation: magnitude of the difference between desirable and undesirable effects, quality
of evidence, the values and preferences of patients, and the resources that need to be expended.

Patient and Public Involvement

Patients or the public are not involved in the design or conduct of the research. However,
these individuals will be involved in the drafting of guideline recommendations designed for
clinicians, the production of the patient version of guideline recommendations, and the review of
resources that accompany the guidelines.

Discussion

Concussion can lead to health issues acutely and in some cases may result in prolonged
symptoms. There is continued need for up to date guidelines to assist clinicians in managing
persons with concussion and prolonged symptoms where the complex presentation of symptoms
can often be challenging for the primary care provider to manage. In addition to this, research
output in this field is also increasing every year where study quality is typically low, making a
living systematic review of diagnosis/assessment and treatment of adult concussion necessary.

Although this review has many strengths, it is not without limitations. First, only papers
published in the English language are being included so other potentially valuable documents
could be missed. Our multidisciplinary expert team, although large, is also geographically
limited to North America. Therefore, recommendations included in the living guidelines may not
reflect the full global perspective. Also, only a minimum of 5 content experts are involved in the
For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

initial examination of the literature and recommendations for each specific domain. Although it would be ideal to include the entire expert team at this phase, it is not feasible because of the workload. Finally, regarding demographics, the review focuses only on adults and on concussion while excluding the pediatric population. The guidelines could potentially be more comprehensive if pediatrics were included but it is not feasible given our infrastructure which is primarily adult expert focussed and there are now available parallel pediatric concussion living guidelines using similar rigorous approaches which have formal ties to these guidelines.

This continuous review process will greatly benefit clinicians and patients by informing living guidelines that will lead to timely guideline recommendations that over time will have increasing certainty as the evidence improves.

**Ethics and Dissemination:** No ethical approval is necessary because primary data are not collected. The review results will be published in peer-reviewed journals in addition to being on the guidelines website in order to enhance dissemination and implementation. Any important amendments to this protocol will be documented on the guidelines website.

**Authors’ Contributions:** AL (guarantor) and SM were involved in conceptual development, writing, and editing. MTB, DC, LKF, CK, JL, MN, and DV were involved in conceptual development and editing.

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**Competing Interests Statement:** None declared.
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| Section and topic          | Item No | Checklist item                                                                 | Page and line numbers in manuscript |
|---------------------------|---------|--------------------------------------------------------------------------------|--------------------------------------|
| Administrative information|         |                                                                                  |                                      |
| Identification            | 1a      | Identify the report as a protocol of a systematic review                        | Page 1, line 1                       |
| Update                    | 1b      | If the protocol is for an update of a previous systematic review, identify as    | Page 2, line 9                       |
|                           |         | such                                                                            |                                      |
| Registration              | 2       | If registered, provide the name of the registry (such as PROSPERO) and registration number | Page 3, line 1                       |
| Contact                   | 3a      | Provide name, institutional affiliation, e-mail address of all protocol authors;  | Page 1, line 2                       |
|                           |         | provide physical mailing address of corresponding author                        |                                      |
| Contributions             | 3b      | Describe contributions of protocol authors and identify the guarantor of the     | Page 13, line 2                      |
|                           |         | review                                                                           |                                      |
| Amendments                | 4       | If the protocol represents an amendment of a previously completed or published   | Page 13, line 13                     |
|                           |         | protocol, identify as such and list changes; otherwise, state plan for          |                                      |
|                           |         | documenting important protocol amendments                                        |                                      |
| Sources                   | 5a      | Indicate sources of financial or other support for the review                   | Page 13, line 18                     |
| Sponsor                   | 5b      | Provide name for the review funder and/or sponsor                               | Page 13, line 18                     |
| Role of sponsor or funder | 5c      | Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in      | The funders did not develop the      |
|                           |         | developing the protocol                                                         | protocol                             |
| Introduction              |         |                                                                                  |                                      |
| Rationale                 | 6       | Describe the rationale for the review in the context of what is already known    | Page 4, line 22                      |
| Objectives                | 7       | Provide an explicit statement of the question(s) the review will address with    | Page 5, line 9                       |
|                           |         | reference to participants, interventions, comparators, and outcomes (PICO)       |                                      |
| Methods                   |         |                                                                                  |                                      |
| Eligibility criteria      | 8       | Specify the study characteristics (such as PICO, study design, setting, time     | Page 5, line 17                      |
|                           |         | frame) and report characteristics (such as years considered, language,           |                                      |
|                           |         | publication status) to be used as criteria for eligibility for the review        |                                      |
| Information sources       | 9       | Describe all intended information sources (such as electronic databases, contact | Page 6, line 11                      |
|                           |         | with study authors, trial registers or other grey literature sources) with        |                                      |
|                           |         | planned dates of coverage                                                       |                                      |
| Search strategy           | 10      | Present draft of search strategy to be used for at least one electronic          | Page 6, line 19                      |
|                           |         | database, including planned limits, such that it could be repeated               |                                      |
| Data management           | 11a     | Describe the mechanism(s) that will be used to manage records and data           | Page 7, line 6                       |
|                           |         | throughout the review                                                           |                                      |
| Selection process         | 11b     | State the process that will be used for selecting studies (such as two            | Page 7, line 10                      |
|                           |         | independent reviewers) through each phase of the review (that is, screening,     |                                      |
|                           |         | eligibility and inclusion in meta-analysis)                                      |                                      |
| Section                          | Item | Description                                                                 | Page, line |
|---------------------------------|------|-----------------------------------------------------------------------------|-----------|
| Data collection process         | 11c  | Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators | 8, 14     |
| Data items                      | 12   | List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications | 8, 23     |
| Outcomes and prioritization     | 13   | List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale | 9, 8      |
| Risk of bias in individual studies | 14   | Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis | 9, 12     |
| Data synthesis                  | 15a  | Describe criteria under which study data will be quantitatively synthesised | Data will not be quantitatively synthesised |
|                                 | 15b  | If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I², Kendall’s τ) | N/A       |
|                                 | 15c  | Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) | N/A       |
|                                 | 15d  | If quantitative synthesis is not appropriate, describe the type of summary planned | 10, 4     |
| Meta-bias(es)                   | 16   | Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) | 11, 9     |
| Confidence in cumulative evidence | 17   | Describe how the strength of the body of evidence will be assessed (such as GRADE) | 11, 12    |
Initial MEDLINE ALL Search Strategy

1. exp Brain Concussion/
2. Post-Concussion Syndrome/
3. (concuss* or postconcuss*).tw,kw.
4. commotio cerebri.tw,kw.
5. ((post commotion or post head injury) adj2 syndrome*).tw.
6. ((mild or minor or minimal) adj3 (traumatic brain or tbi)).tw.
7. ((tbi or traumatic brain injur*) adj3 symptom*).tw.
8. mtbi.tw,kw. or mild traumatic brain injur*.kw. or minor traumatic brain injur*.kw. or minimal traumatic brain injur*.kw.
9. (brain injur* and rehabilitat*).ti. or Brain Injuries/rh or "Brain Injuries, Traumatic"/rh
10. Craniocerebral Trauma/co
11. exp Brain Injuries/ or Craniocerebral Trauma/ or Head Injuries, Closed/
12. ((following or after or post or persistent or unresolved or delayed or prolong*) adj4 (brain or skull or head or injur*)).tw. not (((severe or moderate) adj2 (head or brain or traumatic or tbi)) not (mild or minor)).ti.
13. (following or after or post or persistent or unresolved or delayed or prolong*).tw. and (headache/ or exp headache disorders/)
14. 11 and (12 or 13)
15. or/1-10,14
16. brain injuries/ or brain injuries, traumatic/ or Craniocerebral Trauma/ or Head Injuries, Closed/
17. Post-Traumatic Headache/
18. exp Sleep Wake Disorders/
19. exp Mental Disorders/
20. dizziness/ or vision disorders/
21. Fatigue/
22. Return to Work/ or Return to Sport/
23. Memory Disorders/ or amnesia/
24. cognition disorders/ or cognitive dysfunction/
25. or/17-24
26. 16 and 25
27. (brain injur* adj3 (headache* or cognitive disorder* or sleep disorder* or memory or amnesia or insomnia or mental disorder* or dizziness or vision disorder* or fatigue or "return to work" or "Return to Sport" or psychiatric symptom* or ptsd or post traumatic stress or depression or sleep problem* or cognitive dysfunction)).tw.
28. 26 or 27
29. 15 or 28
30. exp animals/ not humans/
31. (exp child/ or exp infant/) not exp adult/
32. ((child* or infant* or pediatric* or paediatric*) not adult*).ti.
33. or/30-32
34. 29 not 33
35. limit 34 to english language
36. (201706* or 201707* or 201708* or 201709* or 20171* or 2018* or 2019* or 2020*).dt.
37. 35 and 36
# Risk of Bias Assessment Tools

## Section 1: Interventions (Downs & Black, 1998)

### Supporting text

Enter supporting text about your judgement

| 1. Is the hypothesis/aim/objective of the study clearly described? |
|---|
| Yes (1) |
| No (0) |

### Supporting text

Enter supporting text about your judgement

| 2. Are the main outcomes to be measured clearly described in the Introduction or Methods section? |
|---|
| Yes (1) |
| No (0) |

### Supporting text

Enter supporting text about your judgement

| 3. Are the characteristics of the patients included in the study clearly described? |
|---|
| Yes (1) |
| No (0) |

### Supporting text

Enter supporting text about your judgement

| 4. Are the interventions of interest clearly described? |
|---|
| Yes (1) |
| No (0) |

### Supporting text

Enter supporting text about your judgement

| 5. Are the baseline characteristics of the study groups clearly described? |
|---|
| Yes (1) |
| No (0) |

### Supporting text

Enter supporting text about your judgement

| 6. Are the methods for measurement of outcomes clearly described? |
|---|
| Yes (1) |
| No (0) |

### Supporting text

Enter supporting text about your judgement

| 7. Is the follow-up of all participants completed? |
|---|
| Yes (1) |
| No (0) |

### Supporting text

Enter supporting text about your judgement

| 8. Is the intervention delivered as intended? |
|---|
| Yes (1) |
| No (0) |

### Supporting text

Enter supporting text about your judgement

| 9. Are the results of the study clearly described? |
|---|
| Yes (1) |
| No (0) |

### Supporting text

Enter supporting text about your judgement

| 10. Is the analysis of data appropriate? |
|---|
| Yes (1) |
| No (0) |

### Supporting text

Enter supporting text about your judgement

| 11. Are the conclusions of the study clearly described? |
|---|
| Yes (1) |
| No (0) |

### Supporting text

Enter supporting text about your judgement

| 12. Is the study free from bias? |
|---|
| Yes (1) |
| No (0) |
5. Are the distributions of principal confounders in each group of subjects to be compared clearly described?
A list of principal confounders is provided.

|   |   |
|---|---|
| Yes (2) | |
| Partially (1) | |
| No (0) | |

**Supporting text**
Enter supporting text about your judgement

6. Are the main findings of the study clearly described?
Simple outcome data (including denominators and numerators) should be reported for all major findings so that the reader can check the major analyses and conclusions. (This question does not cover statistical tests which are considered below).

|   |   |
|---|---|
| Yes (1) | |
| No (0) | |

**Supporting text**
Enter supporting text about your judgement

7. Does the study provide estimates of the random variability in the data for the main outcomes?
In non normally distributed data the inter-quartile range of results should be reported. In normally distributed data the standard error, standard deviation or confidence intervals should be reported. If the distribution of the data is not described, it must be assumed that the estimates used were appropriate and the question should be answered yes.

|   |   |
|---|---|
| Yes (1) | |
| No (0) | |

**Supporting text**
Enter supporting text about your judgement

8. Have all important adverse events that may be a consequence of the intervention been reported?
This should be answered yes if the study demonstrates that there was a comprehensive attempt to measure adverse events. (A list of possible adverse events is provided).

|   |   |
|---|---|
| Yes (1) | |
| No (0) | |

**Supporting text**
Enter supporting text about your judgement

9. Have the characteristics of patients lost to follow-up been described?
This should be answered yes where there were no losses to follow-up or where losses to follow-up were so small that findings would be unaffected by their inclusion. This should be answered no where a study does not report the number of patients lost to follow-up.

|   |   |
|---|---|
| Yes (1) | |
| No (0) | |

**Supporting text**
Enter supporting text about your judgement
10. Have actual probability values been reported (e.g., 0.035 rather than < 0.05) for the main outcomes except where the probability value is less than 0.001?

|   |   |
|---|---|
| Yes (1) | No (0) |

Supporting text
Enter supporting text about your judgement

11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?

The study must identify the source population for patients and describe how the patients were selected. Patients would be representative if they comprised the entire source population, an unselected sample of consecutive patients, or a random sample. Random sampling is only feasible where a list of all members of the relevant population exists. Where a study does not report the proportion of the source population from which the patients are derived, the question should be answered as unable to determine.

|   |   |
|---|---|
| Yes (1) | No (0) |
| Unable to determine (0) |

Supporting text
Enter supporting text about your judgement

12. Were those subjects who were prepared to participate representative of the entire population from which they were recruited?

The proportion of those asked who agreed should be stated. Validation that the sample was representative would include demonstrating that the distribution of the main confounding factors was the same in the study sample and the source population.

|   |   |
|---|---|
| Yes (1) | No (0) |
| Unable to determine (0) |

Supporting text
Enter supporting text about your judgement

13. Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?

For the question to be answered yes the study should demonstrate that the intervention was representative of that in use in the source population. The question should be answered no if, for example, the intervention was undertaken in a specialist centre unrepresentative of the hospitals most of the source population would attend.

|   |   |
|---|---|
| Yes (1) | No (0) |
| Unable to determine (0) |

Supporting text
Enter supporting text about your judgement

14. Was an attempt made to blind study subjects to the intervention they have received?

For studies where the patients would have no way of knowing which intervention they received, this should be answered yes.

|   |   |
|---|---|
| Yes (1) | No (0) |
| Unable to determine (0) |

Supporting text
Enter supporting text about your judgement
15. Was an attempt made to blind those measuring the main outcomes of the intervention?

| Yes (1) | No (0) | Unable to determine (0) |
|---------|--------|-------------------------|

Supporting text
Enter supporting text about your judgement

16. If any of the results of the study were based on “data dredging”, was this made clear?

Any analyses that had not been planned at the outset of the study should be clearly indicated. If no retrospective unplanned subgroup analyses were reported, then answer yes.

| Yes (1) | No (0) | Unable to determine (0) |
|---------|--------|-------------------------|

Supporting text
Enter supporting text about your judgement

17. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?

Where follow-up was the same for all study patients the answer should be yes. If different lengths of follow-up were adjusted for by, for example, survival analysis the answer should be yes. Studies where differences in follow-up are ignored should be answered no.

| Yes (1) | No (0) | Unable to determine (0) |
|---------|--------|-------------------------|

Supporting text
Enter supporting text about your judgement

18. Were the statistical tests used to assess the main outcomes appropriate?

The statistical techniques used must be appropriate to the data. For example nonparametric methods should be used for small sample sizes. Where little statistical analysis has been undertaken but where there is no evidence of bias, the question should be answered yes. If the distribution of the data (normal or not) is not described it must be assumed that the estimates used were appropriate and the question should be answered yes.

| Yes (1) | No (0) | Unable to determine (0) |
|---------|--------|-------------------------|

Supporting text
Enter supporting text about your judgement

19. Was compliance with the Intervention/s reliable?

Where there was non compliance with the allocated treatment or where there was contamination of one group, the question should be answered no. For studies where the effect of any misclassification was likely to bias any association to the null, the question should be answered yes.

| Yes (1) | No (0) | Unable to determine (0) |
|---------|--------|-------------------------|

Supporting text
Enter supporting text about your judgement
20. Were the main outcome measures used accurate (valid and reliable)?
For studies where the outcome measures are clearly described, the question should be answered yes. For studies which refer to other work or that demonstrates the outcome measures are accurate, the question should be answered as yes.

|   |   |
|---|---|
| Yes (1) |   |
| No (0) |   |
| Unable to determine (0) |   |

Supporting text

Enter supporting text about your judgement

21. Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?
For example, patients for all comparison groups should be selected from the same hospital. The question should be answered unable to determine for cohort and case control studies where there is no information concerning the source of patients included in the study.

|   |   |
|---|---|
| Yes (1) |   |
| No (0) |   |
| Unable to determine (0) |   |

Supporting text

Enter supporting text about your judgement

22. Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?
For a study which does not specify the time period over which patients were recruited, the question should be answered as unable to determine.

|   |   |
|---|---|
| Yes (1) |   |
| No (0) |   |
| Unable to determine (0) |   |

Supporting text

Enter supporting text about your judgement

23. Were study subjects randomised to intervention groups?
Studies which state that subjects were randomised should be answered yes except where method of randomisation would not ensure random allocation. For example alternate allocation would score no because it is predictable.

|   |   |
|---|---|
| Yes (1) |   |
| No (0) |   |
| Unable to determine (0) |   |

Supporting text

Enter supporting text about your judgement

24. Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?
All non-randomised studies should be answered no. If assignment was concealed from patients but not from staff, it should be answered no.

|   |   |
|---|---|
| Yes (1) |   |
| No (0) |   |
| Unable to determine (0) |   |

Supporting text

Enter supporting text about your judgement
Section 2: Observational studies

Observational Studies Risk of Bias Assessment Tool: An Amalgamation of Items Adopted from the Joanna Briggs Institute (JBI) Critical Appraisal Tools

*Each item below will be applied to observational studies meeting inclusion criteria. The scoring options are: Yes (1), No (0), Unclear (0), and N/A (1).

**Items adopted from JBI cross-sectional studies assessment tool:**

1. **Were the criteria for inclusion in the sample clearly defined?**

The authors should provide clear inclusion and exclusion criteria that they developed prior to recruitment of the study participants. The inclusion/exclusion criteria should be specified (e.g., risk, stage of disease progression) with sufficient detail and all the necessary information critical to the study.

2. **Were the study subjects and the setting described in detail?**
The study sample should be described in sufficient detail so that other researchers can determine if it is comparable to the population of interest to them. The authors should provide a clear description of the population from which the study participants were selected or recruited, including demographics, location, and time period.

3. Was the exposure measured in a valid and reliable way?

The study should clearly describe the method of measurement of exposure. Assessing validity requires that a 'gold standard' is available to which the measure can be compared. The validity of exposure measurement usually relates to whether a current measure is appropriate or whether a measure of past exposure is needed.

Reliability refers to the processes included in an epidemiological study to check repeatability of measurements of the exposures. These usually include intra-observer reliability and inter-observer reliability.

4. Were objective, standard criteria used for measurement of the condition?

It is useful to determine if patients were included in the study based on either a specified diagnosis or definition. This is more likely to decrease the risk of bias. Characteristics are another useful approach to matching groups, and studies that did not use specified diagnostic methods or definitions should provide evidence on matching by key characteristics.

5. Were confounding factors identified?

Confounding has occurred where the estimated intervention exposure effect is biased by the presence of some difference between the comparison groups (apart from the exposure investigated/of interest). Typical confounders include baseline characteristics, prognostic factors, or concomitant exposures (e.g. smoking). A confounder is a difference between the comparison groups and it influences the direction of the study results. A high quality study at the level of cohort design will identify the potential confounders and measure them (where possible). This is difficult for studies where behavioral, attitudinal or lifestyle factors may impact on the results.

6. Were strategies to deal with confounding factors stated?

Strategies to deal with effects of confounding factors may be dealt within the study design or in data analysis. By matching or stratifying sampling of participants, effects of confounding factors can be adjusted for. When dealing with adjustment in data analysis, assess the statistics used in the study. Most will be some form of multivariate regression analysis to account for the confounding factors measured.

7. Were the outcomes measured in a valid and reliable way?

Read the methods section of the paper. If for e.g. lung cancer is assessed based on existing definitions or diagnostic criteria, then the answer to this question is likely to be yes. If lung cancer is assessed using observer reported, or self-reported scales, the risk of over- or under-
reporting is increased, and objectivity is compromised. Importantly, determine if the measurement tools used were validated instruments as this has a significant impact on outcome assessment validity.

Having established the objectivity of the outcome measurement (e.g. lung cancer) instrument, it’s important to establish how the measurement was conducted. Were those involved in collecting data trained or educated in the use of the instrument/s? (e.g. radiographers). If there was more than one data collector, were they similar in terms of level of education, clinical or research experience, or level of responsibility in the piece of research being appraised?

8. Was appropriate statistical analysis used?

As with any consideration of statistical analysis, consideration should be given to whether there was a more appropriate alternate statistical method that could have been used. The methods section should be detailed enough for reviewers to identify which analytical techniques were used (in particular, regression or stratification) and how specific confounders were measured.

For studies utilizing regression analysis, it is useful to identify if the study identified which variables were included and how they related to the outcome. If stratification was the analytical approach used, were the strata of analysis defined by the specified variables? Additionally, it is also important to assess the appropriateness of the analytical strategy in terms of the assumptions associated with the approach as differing methods of analysis are based on differing assumptions about the data and how it will respond.

**Items adopted from JBI case series studies assessment tool:**

4. Did the case series have consecutive inclusion of participants?

Studies that indicate a consecutive inclusion are more reliable than those that do not. For example, a case series that states ‘we included all patients (24) with osteosarcoma who presented to our clinic between March 2005 and June 2006’ is more reliable than a study that simply states ‘we report a case series of 24 people with osteosarcoma.’

6. Was there clear reporting of the demographics of the participants in the study?

The case series should clearly describe relevant participant’s demographics such as the following information where relevant: participant’s age, sex, education, geographic region, ethnicity, time period, education.

8. Were the outcomes or follow-up results of cases clearly reported?

The results of any intervention or treatment should be clearly reported in the case series. A good case study should clearly describe the clinical condition post-intervention in terms of the presence or lack of symptoms. The outcomes of management/treatment when presented as images or figures can help in conveying the information to the reader/clinician. It is important that adverse events are clearly documented and described, particularly a new or unique condition
is being treated or when a new drug or treatment is used. In addition, unanticipated events, if any
that may yield new or useful information should be identified and clearly described.

**Items adopted from JBI case control studies assessment tool:**

1. Were the groups comparable other than presence of disease in cases or absence of disease in
controls?

The control group should be representative of the source population that produced the cases. This
is usually done by individual matching; wherein controls are selected for each case on the basis
of similarity with respect to certain characteristics other than the exposure of interest. Frequency
or group matching is an alternative method. Selection bias may result if the groups are not
comparable.

**Items adopted from JBI cohort studies assessment tool:**

2. Were the exposures measured similarly to assign people to both exposed and unexposed
groups?

A high quality study at the level of cohort design should mention or describe how the exposures
were measured. The exposure measures should be clearly defined and described in detail. This
will enable reviewers to assess whether or not the participants received the exposure of interest.

6. Were the groups/participants free of the outcome at the start of the study (or at the moment of
 exposure)?

The participants should be free of the outcomes of interest at the start of the study. Refer to the
‘methods’ section in the paper for this information, which is usually found in descriptions of
participant/sample recruitment, definitions of variables, and/or inclusion/exclusion criteria.

8. Was the follow up time reported and sufficient to be long enough for outcomes to occur?

The appropriate length of time for follow up will vary with the nature and characteristics of the
population of interest and/or the intervention, disease or exposure. To estimate an appropriate
duration of follow up, read across multiple papers and take note of the range for duration of
follow up. The opinions of experts in clinical practice or clinical research may also assist in
determining an appropriate duration of follow up. For example, a longer timeframe may be
needed to examine the association between occupational exposure to asbestos and the risk of
lung cancer. It is important, particularly in cohort studies that follow up is long enough to enable
the outcomes. However, it should be remembered that the research question and outcomes being
examined would probably dictate the follow up time.

9. Was follow up complete, and if not, were the reasons to loss to follow up described and
explored?
It is important in a cohort study that a greater percentage of people are followed up. As a general guideline, at least 80% of patients should be followed up. Generally a dropout rate of 5% or less is considered insignificant. A rate of 20% or greater is considered to significantly impact on the validity of the study. However, in observational studies conducted over a lengthy period of time a higher dropout rate is to be expected. A decision on whether to include or exclude a study because of a high dropout rate is a matter of judgement based on the reasons why people dropped out, and whether dropout rates were comparable in the exposed and unexposed groups.

Reporting of efforts to follow up participants that dropped out may be regarded as an indicator of a well conducted study. Look for clear and justifiable description of why people were left out, excluded, dropped out etc. If there is no clear description or a statement in this regards, this will be a 'No'.

Section 3: Qualitative studies (CASP; 2018)

1. Was there a clear statement of the aims of the research?

   | Yes (1) | No (0) |

2. Is a qualitative methodology appropriate?

   HINT: Consider
   * if the research seeks to interpret or illuminate the actions and/or subjective experiences of research participants
   * is qualitative research the right methodology for addressing the research goal

   | Yes (1) | No (0) |

3. Was the research design appropriate to address the aims of the research?

   HINT: Consider
   * if the researcher has justified the research design (e.g. have they discussed how they decided which method to use)

   | Yes (1) | No (0) |
4. Was the recruitment strategy appropriate to the aims of the research?

HINT: Consider
• If the researcher has explained how the participants were selected
• If they explained why the participants they selected were the most appropriate to provide access to the type of knowledge sought by the study
• If there are any discussions around recruitment (e.g. why some people chose not to take part)

| Yes (1) | No (0) |

Supporting text
Enter supporting text about your judgement

5. Was the data collected in a way that addressed the research issue?

HINT: Consider
• If the setting for the data collection was justified
• If it is clear how data were collected (e.g. focus group, semi-structured interview etc.)
• If the researcher has justified the methods chosen
• If the researcher has made the methods explicit (e.g. for interview method, is there an indication of how interviews are conducted, or did they use a topic guide)
• If methods were modified during the study, if so, has the researcher explained how and why
• If the form of data is clear (e.g. tape recordings, video material, notes etc.)
• If the researcher has discussed saturation of data

| Yes (1) | No (0) |

Supporting text
Enter supporting text about your judgement

6. Has the relationship between researcher and participants been adequately considered?

HINT: Consider
• If the researcher critically examined their own role, potential bias and influence during (a) formulation of the research questions (b) data collection, including sample recruitment and choice of location
• How the researcher responded to events during the study and whether they considered the implications of any changes in the research design

| Yes (1) | No (0) |

Supporting text
Enter supporting text about your judgement

7. Have ethical issues been taken into consideration?

HINT: Consider
• If there are sufficient details of how the research was explained to participants for the reader to assess whether ethical standards were maintained
• If the researcher has discussed issues raised by the study (e.g. issues around informed consent or confidentiality or how they have handled the effects of the study on the participants during and after the study)
• If approval has been sought from the ethics committee

| Yes (1) | No (0) |

Supporting text
Enter supporting text about your judgement
8. Was the data analysis sufficiently rigorous?

HINT: Consider

- If there is an in-depth description of the analysis process
- If thematic analysis is used, if so, is it clear how the categories/themes were derived from the data
- Whether the researcher explains how the data presented were selected from the original sample to demonstrate the analysis process
- If sufficient data are presented to support the findings
- To what extent contradictory data are taken into account
- Whether the researcher critically examined their own role, potential bias and influence during analysis and selection of data for presentation

|        | Yes (1) | No (0) |
|--------|---------|--------|

Supporting text

Enter supporting text about your judgement

9. Is there a clear statement of findings?

HINT: Consider whether

- If the findings are explicit
- If there is adequate discussion of the evidence both for and against the researcher's arguments
- If the researcher has discussed the credibility of their findings (e.g. triangulation, respondent validation, more than one analyst)
- If the findings are discussed in relation to the original research question

|        | Yes (1) | No (0) |
|--------|---------|--------|

Supporting text

Enter supporting text about your judgement

Section 4: Systematic reviews (AMSTAR 2; Shea et al., 2017)

Supporting text

Enter supporting text about your judgement

1. Did the research questions and inclusion criteria for the review include the components of PICO?

For Yes:
- Population
- Intervention
- Comparator group
- Outcome

|        | Yes (1) | No (0) |
|--------|---------|--------|

Supporting text

Enter supporting text about your judgement
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?

For Partial Yes:
The authors state that they had a written protocol or guide that included ALL the following:
- review question(s)
- a search strategy
- inclusion/exclusion criteria
- a risk of bias assessment

For Yes:
As for partial yes, plus the protocol should be registered and should also have specified:
- a meta-analysis/synthesis plan, if appropriate, and
- a plan for investigating causes of heterogeneity
- justification for any deviations from the protocol

|   | Yes (2) |
|---|---------|
|   | Partial Yes (1) |
|   | No (0) |

Supporting text
Enter supporting text about your judgement

3. Did the review authors explain their selection of the study designs for inclusion in the review?

For Yes, the review should satisfy ONE of the following:
- Explanation for including only RCTs
- OR Explanation for including only NRIS
- OR Explanation for including both RCTs and NRIS

|   | Yes (1) |
|---|---------|
|   | No (0) |

Supporting text
Enter supporting text about your judgement

4. Did the review authors use a comprehensive literature search strategy?

For Partial Yes (all the following):
- searched at least 2 databases (relevant to research question)
- provided key word and/or search strategy
- justified publication restrictions (eg, language)

For Yes, should also have (all the following):
- searched the reference lists/bibliographies of included studies
- searched trial/study registries
- included/consulted content experts in the field
- where relevant, searched for grey literature
- conducted search within 24 months of completion of the review

|   | Yes (2) |
|---|---------|
|   | Partial Yes (1) |
|   | No (0) |

Supporting text
Enter supporting text about your judgement
5. Did the review authors perform study selection in duplicate?

For Yes, either ONE of the following:
- at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include
- OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 per cent), with the remainder selected by one reviewer

| Yes (1) |
| No (0) |

Supporting text
Enter supporting text about your judgement

6. Did the review authors perform data extraction in duplicate?

For Yes, either ONE of the following:
- at least two reviewers achieved consensus on which data to extract from included studies
- OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 per cent), with the remainder extracted by one reviewer

| Yes (1) |
| No (0) |

Supporting text
Enter supporting text about your judgement

7. Did the review authors provide a list of excluded studies and justify the exclusions?

For Partial Yes:
- provided a list of all potentially relevant studies that were read in full text form but excluded from the review
- Justified the exclusion from the review of each potentially relevant study

| Yes (2) |
| Partial Yes (1) |
| No (0) |

Supporting text
Enter supporting text about your judgement

8. Did the review authors describe the included studies in adequate detail?

For Partial Yes (ALL the following):
- described populations
- described interventions
- described comparators
- described outcomes
- described research designs
- described population in detail
- described intervention and comparator in detail (including doses where relevant)
- described study’s setting
- timeframe for follow-up

| Yes (2) |
| Partial Yes (1) |
| No (0) |

Supporting text
Enter supporting text about your judgement
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review (RCTs only)?

| RCTs | For Partial Yes, must have assessed RoB from: |
|------|---------------------------------------------|
|      | - lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all cause mortality). |
|      | For Yes, must also have assessed RoB from: |
|      | - allocation sequence that was not truly random, and |
|      | - selection of the reported result from among multiple measurements or analyses of a specified outcome |

| NRSI | For Partial Yes, must have assessed RoB from: |
|------|-----------------------------------------------|
|      | - from confounding, and |
|      | - from selection bias |
|      | For Yes, must also have assessed RoB: |
|      | - methods used to ascertain exposures and outcomes, and |
|      | - selection of the reported result from among multiple measurements or analyses of a specified outcome |

|  | Yes (2) |
|---|---------|
|  | Partial Yes (1) |
|  | No (0) |

10. Did the review authors report on the sources of funding for the studies included in the review?

|   | For Yes |
|---|---------|
|   | Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information but it was not reported by study authors also qualifies |
|   | Yes (1) |
|   | No (0) |

Supporting text

Enter supporting text about your judgement

11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?

| RCTs | For Yes: |
|------|----------|
|      | - The authors justified combining the data in a meta-analysis |
|      | - AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present |
|      | - AND investigated the causes of any heterogeneity |

| NRSI | For Yes: |
|------|----------|
|      | - The authors justified combining the data in a meta-analysis |
|      | - AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available |
|      | - AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review |

| For other studies | For Yes: |
|-------------------|---------|
|                   | - Use appropriate criteria from above points. |
|                   | Yes (1) |
|                   | No (0) |
|                   | No meta-analysis (1) |
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?

For Yes:
- □ Included only low risk of bias RCTs
- □ OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect

| Yes (1) | No (0) | No meta-analysis (1) |

Supporting text
Enter supporting text about your judgement

13. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?

For Yes:
- □ There was no significant heterogeneity in the results
- □ OR heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review

| Yes (1) | No (0) |

Supporting text
Enter supporting text about your judgement

14. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?

For Yes:
- □ Performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias

| Yes (1) | No (0) | No meta-analysis (1) |

Supporting text
Enter supporting text about your judgement

15. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

For Yes:
- □ The authors reported no competing interests
- □ OR The authors described their funding sources and how they managed potential conflicts of interest

| Yes (1) | No (0) |

Supporting text
Enter supporting text about your judgement

Section 5: Guidelines (AGREE II; 2017)
A score of 1 should be given when there is no information that is relevant to the AGREE II item, if the concept is very poorly reported, or if the authors state explicitly that criteria were not met.
A score of 7 should be given if the quality of reporting is exceptional and where the full criteria and considerations articulated in the User’s Manual have been met.

Supporting text
Enter supporting text about your judgement
*Supporting text boxes were present on the actual form but have been omitted from the following items to save space. Also, the scale has been omitted from items 2-23 for the same reason.

1. The overall objective(s) of the guideline is (are) specifically described.

   Item content includes the following CRITERIA:
   - health intent(s) (i.e., prevention, screening, diagnosis, treatment, etc.)
   - expected benefit or outcome
   - target(s) (e.g., patient population, society)
   
   Additional CONSIDERATIONS:
   - Is the item well written? Are the descriptions clear and concise?
   - Is the item content easy to find in the guideline?

| 1 (Strongly Disagree) |
|-----------------------|
| 2                     |
| 3                     |
| 4                     |
| 5                     |
| 6                     |
| 7 (Strongly Agree)    |

2. The health question(s) covered by the guideline is (are) specifically described.

   Item content includes the following CRITERIA:
   - target population
   - intervention(s) or exposure(s)
   - companions (if appropriate)
   - outcome(s)
   - health care setting or context
   
   Additional CONSIDERATIONS:
   - Is the item well written? Are the descriptions clear and concise?
   - Is the item content easy to find in the guideline?
   - Is there enough information provided in the question(s) for anyone to initiate the development of a guideline on this topic or to understand the patients/populations and contexts profiled in the guideline?

3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.

   How to Rate:
   Item content includes the following CRITERIA:
   - target population, gender and age
   - clinical condition (if relevant)
   - severity/stage of disease (if relevant)
   - comorbidities (if relevant)
   - excluded populations (if relevant)
   
   Additional CONSIDERATIONS:
   - Is the item well written? Are the descriptions clear and concise?
   - Is the item content easy to find in the guideline?
   - Is the population information specific enough so that the correct and eligible individuals would receive the action recommended in the guideline?

4. The guideline development group includes individuals from all relevant professional groups.

   This item refers to the professionals who were involved at some stage of the development process. This may include members of the steering group, the research team involved in selecting and reviewing the evidence and individuals involved in formulating the final recommendations. This item excludes individuals who have externally reviewed the guideline (see Item 13). This item excludes target population representation (see item 5). Information about the composition, discipline, and relevant expertise of the guideline development group should be provided.

5. The views and preferences of the target population (patients, public, etc.) have been sought.

   Item content includes the following CRITERIA:
   - statement of type of strategy used to capture patients'/public's views and preferences (e.g., participation in the guideline development group, literature review of values and preferences)
   - methods by which preferences and views were sought (e.g., evidence from literature, surveys, focus groups)
   - outcomes/information gathered on patient/public information
   - description of how the information gathered was used to inform the guideline development process and/or formation of the recommendations
   
   Additional CONSIDERATIONS:
   - Is the item well written? Are the descriptions clear and concise?
   - Is the item content easy to find in the guideline?
6. The target users of the guideline are clearly defined.
   - clear description of intended guideline audience (e.g. specialists, family physicians, patients, clinical or
     institutional leaders/administrators)
   - description of how the guideline may be used by its target audience (e.g., to inform clinical decisions, to
     inform policy, to inform standards of care)
   - Additional considerations:
     - Is the item well written? Are the descriptions clear and concise?
     - Is the item content easy to find in the guideline?
     - Are the target users appropriate for the scope of the guideline?

7. Systematic methods were used to search for evidence.

Details of the strategy used to search for evidence should be provided including search terms used, sources
consulted, and dates of the literature covered. Sources may include electronic databases (e.g. MEDLINE, EMBASE, CINAHL), databases of systematic reviews (e.g. the Cochrane Library, DARE), handsearching journals, reviewing conference proceedings, and other guidelines (e.g. the US National Guideline Clearinghouse, the German Guidelines Clearinghouse). The search strategy should be as comprehensive as possible and executed in a manner free from potential biases and sufficiently detailed to be replicated.

8. The criteria for selecting the evidence are clearly described.

Criteria for including/excluding evidence identified by the search should be provided. These criteria should be explicitly described and reasons for including and excluding evidence should be clearly stated. For example, guideline authors may decide to only include evidence from randomized clinical trials and to exclude articles not written in English.

9. The strengths and limitations of the body of evidence are clearly described.

Statements highlighting the strengths and limitations of the evidence should be provided. This ought to include explicit descriptions of the strengths and weaknesses of the body of evidence aggregated across all studies. The method of assessment should include different quality domains, the application of a formal instrument or strategy (e.g., Jadad scale, GRADE method), and any discussion comparing one treatment option to another. There should be evidence that these issues have been addressed.

10. The methods for formulating the recommendations are clearly described.

A description of the methods used to formulate the recommendations and how final decisions were arrived at should be provided. For example, methods may include a voting system, informal consensus, and formal consensus techniques (e.g., Delphi, giardia techniques). Areas of disagreement and methods of resolving them should be specified.

11. The health benefits, side effects, and risks have been considered in formulating the recommendations.

The guideline should consider health benefits, side effects, and risks when formulating the recommendations. For example, a guideline on the management of breast cancer may require a discussion on the overall effects on various final outcomes. These may include: survival, quality of life, adverse effects, and symptom management or a discussion comparing one treatment option to another. There should be evidence that these issues have been addressed.

12. There is an explicit link between the recommendations and the supporting evidence.

An explicit link between the recommendations and the evidence on which they are based should be included in the guideline. The guideline user should be able to identify the components of the body of evidence relevant to each recommendation.

13. The guideline has been externally reviewed by experts prior to its publication.

A guideline should be reviewed externally before it is published. Reviewers should not have been involved in the guideline development group. Reviewers include experts in the clinical area as well as some methodological experts. Target population (patients, public) representatives may also be included. A description of the methodology used to conduct the external review should be presented, which may include a list of the reviewers and their affiliation.

14. A procedure for updating the guideline is provided.

Guidelines need to reflect current research. A clear statement about the procedure for updating the guideline should be provided. For example, a timescale has been given or a standing panel is established who receives regularly updated literature searches and makes changes as required.

15. The recommendations are specific and unambiguous.

A recommendation should provide a concrete and precise description of which option is appropriate in which situation and in what population group, as informed by the body of evidence.

   - An example of a specific recommendation is: Antibiotics should be prescribed in children two years or older with a diagnosis of acute otitis media if the pain lasts longer than three days or if the pain increases after the consultation despite adequate treatment with painkillers; in these cases, amoxicillin should be given for 7 days (supplied with a dosage scheme).
   - An example of a vague recommendation is: Antibiotics are indicated for cases with an abnormal or complicated course.

It is important to note that in some instances, evidence is not always clear cut and there may be uncertainty about the best care option(s). In this case, the uncertainty should be stated in the guideline.

16. The different options for management of the condition or health issue are clearly presented.

A guideline that targets the management of a disease should consider the different possible options for screening, prevention, diagnosis, treatment, or management of the condition it covers. These possible options should be clearly presented in the guideline. For example, a recommendation on the management of depression may contain the following treatment alternatives:

   a. Treatment with TCA
   b. Treatment with SSRIs
   c. Psychotherapy
   d. Combination of pharmacological and psychological therapy

17. Key recommendations are easily identifiable.

Users should be able to find the most relevant recommendations easily. These recommendations answer the main question(s) that have been covered by the guideline and can be identified in different ways. For example, they can be summarized in a box, typed in bold, underlined or presented as flow charts or algorithms.
18. The guideline describes facilitators and barriers to its application.

There may be existing facilitators and barriers that will impact the application of guideline recommendations.

For example:

i. A guideline on stroke may recommend that care should be coordinated through stroke units and stroke services. There may be a special funding mechanism in the region to enable the formation of stroke units.

ii. A guideline on diabetes in primary care may require that patients are seen and followed up in diabetics clinics. There may be an insufficient number of clinicians available in a region to enable clinics to be established.

19. The guideline provides advice and/or tools on how the recommendations can be put into practice.

For a guideline to be effective it needs to be disseminated and implemented with additional materials. For example, these may include: a summary document, a quick reference guide, educational tools, results from a pilot test, patient leaflets, or computer support. Any additional materials should be provided with the guideline.

20. The potential resource implications of applying the recommendations have been considered.

The recommendations may require additional resources in order to be applied. For example, there may be a need for more specialized staff, new equipment, and expensive drug treatment. These may have cost implications for health care budgets. There should be a discussion in the guideline of the potential impact of the recommendations on resources.

21. The guideline presents monitoring and/or auditing criteria.

Measuring the application of guideline recommendations can facilitate their ongoing use. This requires clearly defined criteria that are derived from the key recommendations in the guideline. The criteria may include process measures, behavioural measures, clinical or health outcome measures. Examples of monitoring and audit criteria are:

- The HbA1c should be < 8.0%.
- The level of diastolic blood pressure should be < 95 mmHg.
- 80% of the population aged 50 years should receive colorectal cancer screening rates using fecal occult blood tests.
- If complaints of acute otitis media last longer than three days, amoxicillin should be prescribed.

22. The views of the funding body have not influenced the content of the guideline.

Many guidelines are developed with external funding (e.g. government, professional associations, charity organizations, pharmaceutical companies). Support may be in the form of financial contribution for the complete development, or for parts of it (e.g., printing of the guidelines). There should be an explicit statement that the views or interests of the funding body have not influenced the final recommendations.

23. Competing interests of guideline development group members have been recorded and addressed.

There are circumstances when members of the development group may have competing interests. For example, this would apply to a member of the development group whose research on the topic covered by the guideline is also funded by a pharmaceutical company. There should be an explicit statement that all group members have declared whether they have any competing interests.

Item content includes the following CRITERIA:

- description of the types of competing interests considered
- methods by which potential competing interests were sought
- description of the competing interests
- description of how the competing interests influenced the guideline process and development of recommendations

Additional CONSIDERATIONS:

- Is the item well written? Are the descriptions clear and concise?
- Is the item content easy to find in the guideline?
- What measures were taken to minimize the influence of competing interests on guideline development or formulation of the recommendations?
Guideline Domain Update Algorithm

1. Panel meetings (3-4 weeks)

2. Optional feedback by entire team (2 weeks)
   - Kept recommendations
   - Modified recommendations (minor changes)
   - Modified (major changes), deleted, or new recommendations

3. Revisions by project team (1 week)
   - Revisions based on comments

4. Feedback and vote by entire team (2 weeks)
   - Available for viewing/to be published

5. Clean-up by project team (1 week)
   - Publish (80% approval)
   - Delete if non-important recommendation
   - Revisions/back to step 4