PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	MEASURES OF CENTRAL SENSITISATION AND THEIR MEASUREMENT PROPERTIES IN THE ADULT MUSCULOSKELETAL TRAUMA POPULATION: A PROTOCOL FOR A SYSTEMATIC REVIEW AND DATA SYNTHESIS
AUTHORS	Middlebrook, Nicola; Rushton, Alison; Heneghan, Nicola; Falla, Deborah

VERSION 1 – REVIEW

REVIEWER	Iris Coppieters Vrije Universiteit Brussel, Belgium
REVIEW RETURNED	07-May-2018

GENERAL COMMENTS	The objectives of this systematic review are highly relevant for clinical practice and further research. I believe this systematic review will indeed be an important step towards a more standardised approach of CS assessment which is currently definitely warranted. I have some recommendations to further improve the present protocol: 1) Introduction - page 6 - line 12 to 15: I would add some more examples of chronic pain disorders with evidence for CS reported in literature. For example chronic whiplash associated disorders (Systematic Review: Van Oosterwijck et al 2013). 2) study design - page 9: I would add that you also will not include reviews, systematic reviews and meta-analysis. 3) Study selection - page 11: I would add that any disagreement between the two reviewers will be discussed during a consensus meeting. 4) Risk of bias in individual studies - page 13: I would add clearly that also the risk of bias will be assessed by both reviewers independently and that disagreements will be discussed during a consensus meeting (the % of agreement should also be reported afterwards in the results) and I would add that if no agreement can be made a third expert reviewer will be consulted.

REVIEWER	Ramakrishnan Mani SCHOOL OF PHYSIOTHERAPY UNIVERSITY OF OTAGO DUNEDIN 9054, NEW ZEALAND PO BOX 56, T: 03 479 3485| M: 0211365594 E: ramakrishnan.mani@otago.ac.nz Skype: Ramakrishnan.mani79 Twitter: @Rammani79 W: http://www.otago.ac.nz/physio/about/people/academic/profile/index.html?id=1281 Pain@Otago Research Theme http://www.otago.ac.nz/pain/staff/index.html Yes, I am declaring that I have competing interests

	(professional)..We have published similar reviews recently in 2018 and one is under review in a peer reviewed journal. These reviews have already included some studies (e.g whiplash) that the proposed review is intending to review. 1. Test Procedures to Assess Somatosensory Abnormalities in Individuals with Peripheral Joint Pain: A Systematic Review of Psychometric Properties. Alqarni AM, Manlapaz D, Baxter D, Tumilty S, Mani R Pain Pract. 2018 Jan 19. doi: 10.1111/papr.12680. [Epub ahead of print] 2. Test procedures to assess somatosensory abnormalities in individuals with BACK pain: A systematic review of psychometric properties (ACCEPTED FOR PUBLICATION in Physical Therapy Reviews) 3. Test procedures to assess somatosensory abnormalities in individuals with NECK pain: A systematic review of psychometric properties Physical Therapy Reviews (UNDER REVIEW)
REVIEW RETURNED	19-May-2018

GENERAL COMMENTS	Abstract: It is a well written abstract for a review protocol. Avoid the repetition statement on PRISMA. Instead write it as, the protocol is informed and reported in line with…
	Aims are not specific to the outcome of the review, I recommend to state the aim of the study is to establish the level of evidence on the measurement properties of CS measures…Stage-1 is not really a aim for this review, the final outcome should be the aim, of course that would be achieved through identifying studies and evaluating the measures used in the study….
	Introduction: See above comment regarding study aims..
	The sentence begins with Furthermore, measures… is not clear, please clarify, how the ICF framework is related to the focus of this review on outcome measures? CS measures probably belong to impairment (body function) of the ICF model, however it is not clearly reported in the literature.
	Please summaries the findings and methodologies used in the published systematic reviews on PMP measures of central sensitization/somatosensory abnormalities. [Alqarni et al 2018; Moloney N et al 2011, 2012]. How this systematic review would build on these existing reviews in terms of studies included and the methodologies used to develop level of evidence of related measures identified in this proposed review.
	Please provide an expanded background on MSK trauma and the focus of measures chosen in this review. Although there were some information and clinical outcomes, I would suggest including some specific focus on pain mechanisms in this population.
	I have some concerns in using the COSMIN tool, which was originally developed for PROMS, it is not really straightforward in applying it to assess studies that measurement properties of QST and other related measures. Particularly, the criteria on sample size, would score most of the studies that will be included as 'poor', I would like to see an amended version for the tool that would be applicable for assessing relevant studies, it may be applicable for CSI, but not may be for other studies (non-questionnaire based outcome measures). Please indicate which constructs may not be applicable for QST based studies, for example IRT based assessment criteria is not applicable.
	Please adapt the File 3: COSMIN Definitions and Criteria for the purpose of the study. There are tools that can be used to assess reliability and validity of the studies on measurement properties. Please include a statement how the agreement between raters will be determined.

	Second stage of the review is not clear; please clarify, whether those outcome measures identified in the stage-1 will need to have their measurement properties established in the same population (MSK trauma) or any other population.
	I am not clear with the proposed criteria/methods, "the secondary search will be widened to general musculoskeletal conditions or healthy subjects but findings will be evaluated and synthesised separately. If this was carried out, how it would be different from the exiting reviews in this area? Then it would be a redundant review. Please clarify.
	Please explain how these criteria of GRADE will be assed against studies on measurement properties. Particularly, inconsistency, imprecision and Indirectness will be assessed.

REVIEWER	Catherine Doody University College Dublin, Ireland
REVIEW RETURNED	24-May-2018

GENERAL COMMENTS	This is a well written protocol and should be of interest to the readership of BMJ Open. The authors have given considerable thought to the overall protocol methodololgy and have approached this in a systematic manner.
	My comments relate to the likely heterogenicity of study population for the review, in addition to the problems currently with identifying features of CS in individulas and the significant limitations of the current measures used for same.
	It could be argued that central sensitization is a construct as such, as opposed to a diagnostic label. The various measures to assess Central sensitization are in the main assessing pain hypersensitivity. As such suggest this be included in the language around CS throughtout the manuscript. For example in Line 12 suggest 'Features of' be inserted before CS.
	The literature currently suggests that central sensitization contributes to the pain phenotype in people with predominently chronic pain conditions e.g. fibromyalgia, OA, CNSLBP, chronic neck pain, TMJ, patellofemoral pain syndrome etc. However even in these populations it is currently unclear what are the definitive diagnostic criteria for determining the presence of central sensitization.
	In relaition to the chosen population for this current review MSK trauma, the presence of CS less well documented. MSK trauma also encompasses a very wide / large variety of conditions, ranging from acute to complex chronic conditions.
	Consideration should be given to the broadness of this term, with view to refining and narrowing it further prior to commencing the review. The search as currently outlined may result in very disperate literature with may present significant challenges for evaluation and synthesis of this literature. For example acute trauma will be included in addition to more chronic complex post traumatic conditions, with whiplash being specified.
	In adidtion could the authors further justify why the have selected MSK Trauma?

Could they provide further details on the specific inclusion criteria for their study popluation? Ideally to include all of the specific conditions, which could be also reflected in an expanded search string.

In the context of the term MSK trauma, could the authors clarify how they will interpret 'trauma'? Will this exclude chronic conditions for example shoulder impingement syndrome which it has been suggested may result from microtrauma over a long period of time, (similarly achilles tendinopaty, patellofemoral pain syndrome may result from micro-trauma secondary to changes in biomechanics etc)?

Page 11, line 1 the authors specify that the search may be widened to include general MSK conditions, or health subjects, please clarify further what specific general MSK conditions will be included within this additional very broad term. Clarify why health subjects will be included?

It is noted that the Cosmin tool is designed for evaluating the content validity of patient reported outcome measures. Could the authors clarify how it will be used for more objective measures such as QST?

In relation to the outcome measures could the authors clarify what specific measures they will include in relation to QST? Suggest explain further Page 8 Line 55/56 where QST is referred to as a single measure. Will QST for example measures of include tactile allodynia, secondary punctate or pressure hyperalgesia, enhanced temporal summation? Will fMRI be included?

Further disucssion could be included areound the complexity of identifying CS, some features of CS, e.g. pain hypersensitivity by itself is not necessarity indicitative of CS. Further discussion could be included to explore the difficulty of identifying CS.

Pg 9 Line 1 Clarify further what the authors mean by measures to evaluate symptoms of CS, please clarify specfic measures.

Page 10 Search strategy
Cosmin state that 'studies on measurement properties are sometimes difficult to find in Pubmed or other databases due to poor indexing, large variation in terminology, and poor reporting of measurement properties. Therefore we developed two search filters for finding studies on measurement properties in Pubmed', clarify if these filters will be used?

Will a sub-group analysis be undertaken for example in relation to the different conditions included under MSK trauma? Or possibly in relation to the different outcome measures e.g. PROM / objective measures?

The discussion could be expanded to include further discussion in relaiton to some of the issues outlined above.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1 Comments	Author Responses

1. Introduction - page 6 - line 12 to 15: I would add some more examples of chronic pain disorders with evidence for CS reported in literature. For example, chronic whiplash associated disorders (Systematic Review: Van Oosterwijck et al 2013).	Thank you for this suggestion, further examples of disorders have been added to this section with the additional reference suggested (page 6).
2. Study design - page 9: I would add that you also will not include reviews, systematic reviews and meta-analysis.	Thank you for highlighting this, it has been updated to reflect this in the study design section (page 9-10).
3. Study selection - page 11: I would add that any disagreement between the two reviewers will be discussed during a consensus meeting.	We have added an additional sentence as suggested (page 12).
4. Risk of bias in individual studies - page 13: I would add clearly that also the risk of bias will be assessed by both reviewers independently and that disagreements will be discussed during a consensus meeting (the % of agreement should also be reported afterwards in the results) and I would add that if no agreement can be made a third expert reviewer will be consulted.	Thank you for highlighting this, an additional paragraph has been added to this section to reflect this (page 13-14).
Reviewer 2 Comments	**Author Responses**
1. Abstract: It is a well written abstract for a review protocol. Avoid the repetition statement on PRISMA. Instead write it as, the protocol is informed and reported in line with…	Thank you - the abstract has been updated to avoid repetition around PRISMA.
2. Aims are not specific to the outcome of the review, I recommend to state the aim of the study is to establish the level of evidence on the measurement properties of CS measures…Stage-1 is not really a aim for this review, the final outcome should be the aim, of course that would be achieved through identifying studies and evaluating the measures used in the study….	Due to the multiple measures being used in this area with no current gold standard identified, summarising the current measures being used was identified as a beneficial aim of this review. The wording of the aims in the abstract and introduction however, have been amended to make the primary aims clearer to the reader as suggested.
3. Introduction: See above comment regarding study aims.. The sentence begins with Furthermore, measures… is not clear, please clarify, how the ICF framework is related to the focus of this review on outcome measures? CS measures probably belong to impairment (body function) of the ICF model, however it is not clearly reported in the literature.	Thank you for highlighting this, the wording around ICF has been amended in the text (page 5).
4. Please summaries the findings and methodologies used in the published systematic reviews on PMP measures of central sensitization/somatosensory abnormalities. [Alqarni et al 2018;	We have added a paragraph to reflect the points raised here (page 7) adding the recent reviews stated and highlighting specifically the main difference between this review (focus on musculoskeletal trauma and using updated risk

	Moloney N et al 2011, 2012]. How this systematic review would build on these existing reviews in terms of studies included and the methodologies used to develop level of evidence of related measures identified in this proposed review.	of bias tools)
5.	Please provide an expanded background on MSK trauma and the focus of measures chosen in this review. Although there were some information and clinical outcomes, I would suggest including some specific focus on pain mechanisms in this population.	We have added further information around the development of a mechanistic approach in musculoskeletal trauma with additional references to reflect this on page 6. Further information then follows this on page 6/7 focusing on the various methods currently used in musculoskeletal trauma population.
6.	I have some concerns in using the COSMIN tool, which was originally developed for PROMS, it is not really straightforward in applying it to assess studies that measurement properties of QST and other related measures. Particularly, the criteria on sample size, would score most of the studies that will be included as 'poor', I would like to see an amended version for the tool that would be applicable for assessing relevant studies, it may be applicable for CSI, but not may be for other studies (non-questionnaire based outcome measures). Please indicate which constructs may not be applicable for QST based studies, for example IRT based assessment criteria is not applicable.	Thank you for the comments regarding the COSMIN tool. The updated COSMIN risk of bias tool for systematic reviews will be used for this review which is an updated version in which the sample size limitation has been removed. A sentence has been added in the introduction (page 7) which introduces the new tool at an earlier stage in the protocol.
7.	Please adapt the File 3: COSMIN Definitions and Criteria for the purpose of the study. There are tools that can be used to assess reliability and validity of the studies on measurement properties.	We have assumed this is in relation to the word PROM being used specifically and therefore have amended the supplementary document 3 to reflect this.
8.	Please include a statement how the agreement between raters will be determined.	We have added further information in the study selection section to address this comment (page 12).
9.	Second stage of the review is not clear; please clarify, whether those outcome measures identified in the stage-1 will need to have their measurement properties established in the same population (MSK trauma) or any other population.	Thank you for highlighting this. The wording of this section has been revised to make this clearer (page 11). The second part of the search will focus on the outcome measures that have been identified as being used in the musculoskeletal trauma population from the first search. The second stage of the search will focus on measurement properties specifically tested on musculoskeletal trauma but will be widened to include musculoskeletal conditions; this will allow us to evaluate the measurement properties if a limited number of articles are

	returned specifically on the trauma population.
10. I am not clear with the proposed criteria/methods, "the secondary search will be widened to general musculoskeletal conditions or healthy subjects but findings will be evaluated and synthesised separately. If this was carried out, how it would be different from the exiting reviews in this area? Then it would be a redundant review. Please clarify.	We hope the points made above regarding the searches have helped clarify this. The main aim of this review is to evaluate measurement properties of measures specifically used in the musculoskeletal trauma population and to identify which measures are being used, however if limited results specifically on trauma are retrieved, the search will be widened to include musculoskeletal conditions. This review will differ from earlier published reviews as it will be current with an updated search and using a new refined risk of bias tool
11. Please explain how these criteria of GRADE will be assed against studies on measurement properties. Particularly, inconsistency, imprecision and Indirectness will be assessed.	Thank you for raising this point. Alongside the new COSMIN risk of bias tool, guidelines in conducting systematic reviews were published (Prinsen et. al. 2018) in which GRADE has been adapted for this purpose. We will be following these guidelines in this review.
Reviewer 3 Comments	**Author Responses**
1. It could be argued that central sensitization is a construct as such, as opposed to a diagnostic label. The various measures to assess Central sensitization are in the main assessing pain hypersensitivity. As such suggest this be included in the language around CS throughout the manuscript. For example in Line 12 suggest 'Features of' be inserted before CS.	Thank you for raising this point – wording has been adapted throughout to reflect this and the concept of CS as a construct has been added on page 6.
2. The literature currently suggests that central sensitization contributes to the pain phenotype in people with predominantly chronic pain conditions e.g. fibromyalgia, OA, CNSLBP, chronic neck pain, TMJ, patellofemoral pain syndrome etc. However even in these populations it is currently unclear what are the definitive diagnostic criteria for determining the presence of central sensitization.	Thank you for this observation and we agree with the point made.
3. In relation to the chosen population for this current review MSK trauma, the presence of CS less well documented. MSK trauma also encompasses a very wide / large variety of conditions, ranging from acute to complex chronic conditions. Consideration should be given to the broadness of this term, with view to refining and narrowing it further	This is a good point which we recognise could be a potential challenge especially with mixed aetiology. Previous systematic reviews in this area have addressed this issue by stating that musculoskeletal trauma needed to be 90% musculoskeletal in nature (Clay et al. 2010), excluding moderate to severe brain injury, burns to more than 30% of the body and self-injurious

	prior to commencing the review. The search as currently outlined may result in very disparate literature with may present significant challenges for evaluation and synthesis of this literature. For example acute trauma will be included in addition to more chronic complex post traumatic conditions, with whiplash being specified.	injury (Rosenbloom, 2013). Further detail has been added in the inclusion/exclusion criteria (pg 8) to reflect this point.
4.	In addition could the authors further justify why they have selected MSK Trauma? Could they provide further details on the specific inclusion criteria for their study population? Ideally to include all of the specific conditions, which could be also reflected in an expanded search string.	There is currently a gap in the evidence base around musculoskeletal trauma despite some subgroups having been extensively studied. With an increase in interest and studies following major musculoskeletal trauma and all using multiple measures to evaluate pain there is a need to synthesis the evidence base and work towards a standardised approach. Further detail to reflect this has now been added (page 7)
5.	In the context of the term MSK trauma, could the authors clarify how they will interpret 'trauma'? Will this exclude chronic conditions for example shoulder impingement syndrome which it has been suggested may result from microtrauma over a long period of time, (similarly achilles tendinopathy, patellofemoral pain syndrome may result from micro-trauma secondary to changes in biomechanics etc)?	We will define trauma in this review as an injury resulting from a traumatic event, for example an RTC. This is clarified in the population inclusion criteria (page 8), therefore chronic conditions that have resulted from microtrauma will not fit with these criteria and would be excluded.
6.	Page 11, line 1 the authors specify that the search may be widened to include general MSK conditions, or health subjects, please clarify further what specific general MSK conditions will be included within this additional very broad term. Clarify why health subjects will be included?	Thank you for raising this point, further detail has been added to clarify the term MSK conditions (page 11.) In relation to the inclusion of healthy subjects in this review; high quality studies have been conducted evaluating measurement properties of measures which can inform clinical practice/future studies, therefore would be of benefit to include in this review. We have added an additional sentence in the manuscript to reflect this point raised. (page 11)
7.	It is noted that the Cosmin tool is designed for evaluating the content validity of patient reported outcome measures. Could the authors clarify how it will be used for more objective measures such as QST?	We acknowledge and agree with this point. The updated COSMIN Risk of Bias tool for systematic reviews will be used in this review. The tool will be adapted where necessary to evaluate non patient reported outcome measures. Although this new tool and the previous tool were designed for PROMs, it has been used to measure all types of outcome

		measures when modified.
8.	In relation to the outcome measures could the authors clarify what specific measures they will include in relation to QST? Suggest explain further Page 8 Line 55/56 where QST is referred to as a single measure. Will QST for example measures of include tactile allodynia, secondary punctate or pressure hyperalgesia, enhanced temporal summation? Will fMRI be included?	We will include all measures under the term QST which can include thermal testing or pressure, vibration etc. To make this clearer to the reader, further elaboration around the term QST has been added (page 9).
9.	Further discussion could be included around the complexity of identifying CS, some features of CS, e.g. pain hypersensitivity by itself is not necessarily indicative of CS. Further discussion could be included to explore the difficulty of identifying CS.	We agree with the point raised here. Please see point 13 on how this has been updated and reflected in the manuscript.
10.	Pg 9 Line 1 Clarify further what the authors mean by measures to evaluate symptoms of CS, please clarify specific measures.	We have now added an example of a measure which we hope makes this clearer on page 9.
11.	Page 10 Search strategy Cosmin state that 'studies on measurement properties are sometimes difficult to find in Pubmed or other databases due to poor indexing, large variation in terminology, and poor reporting of measurement properties. Therefore we developed two search filters for finding studies on measurement properties in Pubmed', clarify if these filters will be used?	Thank you for raising this issue. We will include the use of the search filter for Pubmed and EMBASE in which it has been adapted for. A sentence has been added on page 11 to reflect this.
12.	Will a sub-group analysis be undertaken for example in relation to the different conditions included under MSK trauma? Or possibly in relation to the different outcome measures e.g. PROM / objective measures?	We will be subgrouping per outcome measure per measurement property rather than to different conditions within the trauma population due to heterogeneity of the trauma population. This is summarised on page 14.
13.	The discussion could be expanded to include further discussion in relation to some of the issues outlined above.	Thank you for raising this point, we have now added further discussion around the challenges of CS, which further addresses points raised in point 9.

VERSION 2 – REVIEW

REVIEWER	Iris Coppieters Vrije Universiteit Brussel, Belgium
REVIEW RETURNED	23-Jul-2018

GENERAL COMMENTS	1. Introduction - page 6: Thank you for adding further examples of disorders. However, I would change chronic whiplash disorders into chronic whiplash associated disorders. Please change 'has' into 'have' in the following sentence: Features of CS has been identified... 2. The authors have made all relevant additions and changes

	according to my comments. I have no further comments. The revised protocol is improved compared to the previous version of the protocol.

REVIEWER	Ramakrishnan Mani SENIOR LECTURER, CENTRE FOR HEALTH, ACTIVITY AND REHABILITATION RESEARCH, SCHOOL OF PHYSIOTHERAPY, UNIVERSITY OF OTAGO, DUNEDIN, NEW ZEALAND.
REVIEW RETURNED	30-Jul-2018

GENERAL COMMENTS	Please add few sentences indicating central sensitization is a component of altered body structure and function that are commonly seen in MSK trauma populations (e.g. whiplash). At the moment, the reader cannot see the pain mechanisms based assessment under the ICF framework. "Furthermore, measures which incorporate the main components of the International Classification of Functioning, Disability and Health (ICF) such as body function and body structure allowing a more holistic approach in assessing patients."

REVIEWER	Catherine Doody University College Dublin, Ireland
REVIEW RETURNED	27-Jul-2018

GENERAL COMMENTS	Suggest to reword inserted line on page 6 to omit "the true underlying pathophysiological cause of CS is still unknown". In relation to the chosen population for the review, the search strategy while adjusted somewhat may result in very disparate literature, which may be challenging for subsequent evaluation and synthesis. Suggest that this be refined further to include the major specific MSK trauma conditions of interest. Have the authors run any preliminary searches? Apologies I cannot locate the new definition of trauma to include 'injury result from a traumatic event, for example RCT on page 8 in the red/ highlighted section on the amended manuscript? It is noted that the authors propose to adapt the COSMIN Risk of Bias tool, can the authors include some comment in relation to the number of adaptations that will be necessary and any likely effects in relation to the overall validity of the tool? Could the authors please indicate where they have included an expanded discussion on the complexity of identifying features of CS (point 9 and 13).

VERSION 2 – AUTHOR RESPONSE

Reviewer 1 Comments	Author Responses
1. Introduction - page 6: Thank you for adding further examples of disorders. However, I would change chronic whiplash disorders into chronic whiplash associated disorders. Please change 'has' into 'have' in the following sentence: Features of CS has been	Thank you for your comments – this has been amended as suggested on page 6.

identified...	
2. The authors have made all relevant additions and changes according to my comments. I have no further comments. The revised protocol is improved compared to the previous version of the protocol.	

Reviewer 2 Comments	**Author Responses**
1. Please add few sentences indicating central sensitization is a component of altered body structure and function that are commonly seen in MSK trauma populations (e.g. whiplash).	Thank you for your suggestions, please see comment below for further information
2. At the moment, the reader cannot see the pain mechanisms based assessment under the ICF framework. "Furthermore, measures which incorporate the main components of the International Classification of Functioning, Disability and Health (ICF) such as body function and body structure allowing a more holistic approach in assessing patients."	Thank you for your comment – as you are aware there are 4 main domains within the ICF. The main point of this sentence was to highlight that certain outcome measures such as the NRS only focus on one domain of the ICF i.e. body function. As this section comes before the introduction of CS, we have not expanded on features of CS being related to the ICF domains specifically. Wehave reworded this section on page 5 to make the above point clearer to the reader.

Reviewer 3 Comments	**Author Responses**
1. Suggest to reword inserted line on page 6 to omit "the true underlying pathophysiological cause of CS is still unknown".	Thank you for your suggestion; thissentence has been reworded on page 6.
2. In relation to the chosen population for the review, the search strategy while adjusted somewhat may result in very disparate literature, which may be challenging for subsequent evaluation and synthesis. Suggest that this be refined further to include the major specific MSK trauma conditions of interest. Have the authors run any preliminary searches?	Thank you for your comments. The preliminary searches have been conducted and minor amendments to the search strategy have been made to exclude two terms (pain measurement and hypersensitivity removed to ensure the search results were relevant) (see supplementary file 2). From the scoping searches conducted, with the exception of whiplash, the majority of studies use the broader term of musculoskeletal trauma to encompass multiple injuries such as fractures, soft tissue injury etc rather than focusing on a particular subcategory. Therefore the decision was made to keep a broader term in the first stage of the search. Previous systematic reviews such as Rosenbloom et al 2013 and Clay et al. 2010, 2012, Khan et al 2012 have used this strategy successfully with no adverse issues reported for the search strategy.Furthermore, the synthesis of data will focus more around the measurement properties of the outcome measures identified rather than the condition/type of trauma.

3.	Apologies I cannot locate the new definition of trauma to include 'injury result from a traumatic event, for example RCT on page 8 in the red/ highlighted section on the amended manuscript?	Thank you for highlighting this. The definition of trauma is located on page 8 and we have now added an additional sentence to clarify examples of traumatic events. "For the purpose of this review, musculoskeletal trauma will be defined as: any musculoskeletal structure e.g. bones, joints, ligaments, tendons and muscles that surround these structures involved in a traumatic injury. Examples of a traumatic injury include road traffic collisions, falls and gunshot and stab wounds".
4.	It is noted that the authors propose to adapt the COSMIN Risk of Bias tool, can the authors include some comment in relation to the number of adaptations that will be necessary and any likely effects in relation to the overall validity of the tool?	Thank you for your feedback. It is envisaged that minimum adaptations will be required as most questions can be applied for non-PROM's – for example the reliability questions can be applied to quantitativesensory testing measures i.e. PPT as well as PROM's. The COSMIN group also recommend adaptations for other measures if needed (Prinsen et al 2018). Furthermore, the previous COSMIN tool in which this new improved tool was developed was adapted with no issues with regarding validity. An additional sentence on page 14 to support this.
5.	Could the authors please indicate where they have included an expanded discussion on the complexity of identifying features of CS (point 9 and 13).	The discussion was expanded on page 14 under clinical implications of the study. The concept of features of CS was introduced in the introduction (page 6) as well as thewording throughout the manuscript referring to CS as features of CS. In addition to make the challenges around the concept of CS and features of CS clearer, we have added further clarification on page 14 to further highlight this point and make this clearer for the reader.