PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The reporting of adverse events associated with spinal manipulation in randomized clinical trials: an updated systematic review
AUTHORS	Gorrell, Lindsay; Brown, Benjamin T.; Engel, Roger; Lystad, Reidar

VERSION 1 – REVIEW

REVIEWER	Kranenburg, Hendrikus Hanze University of Applied Sciences, Physiotherapy
REVIEW RETURNED	04-Oct-2022

GENERAL COMMENTS	Thank you for all the work you put in the manuscript which read well. There are some concerns for me in this study. The fact that you consider the 'classic HVLA manual manipulation', the drop-piece-table and mechanical implements all HVLA techniques. And if you do so, I would like to see them as a parameter in the results. Especially, since I read the tendency in the manuscript to not only comment the level of reporting but also to go into the safety of the included techniques. However, if you keep the focus in the manuscript on the original goal of the review (to comment on the level of reporting) it shouldn't be insurmountable. If you would be more interested in the incidence of AE, you must (as you described in the discussion yourself) include other research designs as well. Therefore, I find the statement that "your findings support the literature that SAE are rare" to strong. In line with the previous, with the information you gathered in this study you mustn't want to calculate accurate incidence rates for these techniques since most of the inclusion criteria are set to avoid AE. You chose not to do so "due to the inadequate reporting of the number of manipulations delivered". Statements like the latter two (although the topics are relevant and interesting!) seem inappropriate for this type of design.

REVIEWER	Vining, Robert Palmer College of Chiropractic Center for Chiropractic Research, Research
REVIEW RETURNED	23-Nov-2022

GENERAL COMMENTS	1. Thank you for the opportunity to review the submitted manuscript entitled: The reporting of adverse events associated with spinal manipulation in randomized clinical trials: an updated systematic review. The manuscript is generally well-written. The following comments are designed to improve the submission. 2. I suggest a major revision of the Discussion section of the manuscript. 3. Please avoid using transitional words such as "Interestingly." The

	text should not tell readers what is interesting. Readers should determine what is interesting to them. 4. The Discussion begins with disappointment in adverse event reporting. Instead of communicating the emotion of disappointment, consider the opportunity to explain some of the complexity surrounding adverse event reporting and recommend solutions to current challenges. a. For example, the 1st paragraph states that there have been calls for standardized definitions and classification systems. Instead of ending with that thought, this is an opportunity to point out that until these are developed and broadly accepted, there should be no expectation that reporting will improve on its own. Thus, the text should not communicate disappointment at an unsurprising finding. Though developing standardized definitions and classifications may be beyond the scope of this study, this is an opportunity to suggest a pathway toward achieving these goals. b. Perhaps the biggest opportunity here is to offer practical examples of more ideal adverse event reporting in an appendix. Results from this study further demonstrate that translating standards from CONSORT Harms into good reporting isn't necessarily clear. Consider showing readers what good adverse event reporting looks like. Such examples can include definitions, abstract reporting, results text reporting, results table reporting, etc. Doing so potentially makes this article a practical resource for future trialists, editors, etc. 5. There is a missed opportunity to discuss some important and relevant aspects of adverse event monitoring, grading, and reporting such as: a. Determining relatedness of an adverse event to HVLA spinal manipulation (or other intervention) is not straightforward. HVLA spinal manipulation is often used in research focused on spinal pain, which is known to exist with fluctuating symptoms. Because of the unstable nature of symptoms, some recorded adverse events represent natural symptom drift (thus unrelated). However, unless trials are specifically designed to identify these events (an unfeasible requirement, likely requiring an additional control group) such events are likely to be attributed to HVLA spinal manipulation. Walker et al., demonstrated this concept in a trial entitled: Outcomes of usual chiropractic. The OUCH randomized controlled trial of adverse events. b. This article presents an opportunity to suggest journals consider modifying guidance, word limits, structure, etc. to facilitate better harms reporting in abstracts. For example, journals could consider adding a harms section in abstracts. 6. Recommending researchers report adverse events relative to the number of spinal manipulations to enable post-hoc pooling and risk analysis is more challenging than the current text suggests. For example, several questions arise. What is 1 spinal manipulation (1 visit, 1 HVLA procedure to a specific region, 1 thrust)? Should all spinal manipulations be considered the same (there are many possible HVLA procedures that can be applied to different regions and in different positions)? What type of subgroups should be reported (males, females, age ranges, conditions treated)? Will co-morbid conditions be accounted for in such a risk analysis? Will these risk analyses incorporate adverse events classified as possibly, probably, or definitely related, or some combination thereof? How would natural symptom variation be addressed in the analysis to account for events that cannot be clearly classified as related to HVLA spinal manipulation? If a standardized process is developed, will ethics boards adopt and support researchers in

	these efforts, or will they require monitoring and reporting using different standards? These questions, and more, need answers so researchers can develop monitoring, recording, tracking, grading, analysis, and reporting methods to enable scientifically appropriate post-hoc pooled risk analyses. 7. I strongly suggest removing the speculation that researchers involved with cervical spine manipulation are trying to "prove" safety. Such text is presumptive. There are other possible explanations. 8. In the Conclusion of the abstract and Discussion sections, the text states that the current level of reporting is unacceptable. This begs the question: unacceptable to whom? Consider restating that adverse event reporting is not consistent with established standards. 9. In the Conclusion, instead of ending with recommending researchers adhere to the CONSORT Harms checklist, consider offering practical methods to improve reporting (as suggested earlier). The Harms checklist has been available for several years. If the checklist isn't being adhered to, then reminding readers of its existence is not likely to induce change. Instead, consider offering practical examples of how to translate those standards into manuscript reporting (see comment above suggesting reporting examples as an appendix). In short, consider showing readers what good reporting looks like.

REVIEWER	Daniels, Clinton VA Puget Sound Health Care System, RCS
REVIEW RETURNED	05-Dec-2022

GENERAL COMMENTS	Thank you for the opportunity to review the manuscript titled, "The reporting of adverse events associated with spinal manipulation in randomized clinical trials: an updated systematic review. This was an update of a systematic review published in 2016. The authors registered the protocol on PROSPERO and it was congruent with this manuscript. Strengths of this manuscript are that this was a well-written, well-performed review study, that objectively analyzed results and performed regression analysis to identify predictors, and the authors followed the PRISMA standards for reporting. As the authors acknowledged, due to design improvements, there are some limitations regarding the ability to compare this review's findings to the 2016 review. However, I would like to see more discussion of what has changed, as I found this discussion to be relatively lacking. I would also like to see the authors better outline why the current reporting level of adverse events is "inadequate" and "unacceptable". I hope the following comments will aid the authors in approving their manuscript. Title: Okay Abstract: 1. Page 3, Line 8 - What is an acceptable level of reporting? Clearly closer to 100% is better, but the authors do not provide any kind of reference percentage from studies looking at other interventions as a comparison. Unless the authors can provide this additional context within the manuscript, I would omit the opening sentence and focus more on the change since the 2016 publication. Article summary: 1. 3rd bullet - Recommend omitting the word "Interestingly". Also, why use the word "might" here? Seems your regression analysis indicates there is strong evidence. Consider revising this entire bullet to something like "Reporting of adverse events in RCTs of spinal manipulation are more likely to be reported when chiropractors are delivering the intervention".

	Introduction: 1. Page 5, Lines 13-15 – Is reference 10 the systematic review that is being updated? Please be more clear about this. 2. Page 5, Lines 19-26 – The authors mentioned the temporal association of vertebral artery dissection, however, did not mention any of the more updated population-based studies from the literature. As I am sure the authors are aware, there are now several of these studies that report vascular events occurring at near the same rate following spinal manipulation encounters as following primary care visits. I suggest adding more context to this specific point. 3. Page 5, Lines 51-55 – It is odd to me that the phrasing of the purpose statement does not mention that this is an updated systematic review, as opposed to just indicating you are looking at new data since 2016. Consider revising. Methods: 1. Page 6, Line 19-21 – Can you give an example of what you mean by "mechanical implements"? Are you referring to something handheld like an activator or impulse instrument? 2. Page 6, Line 36 – In the quote, it is confusing that you listed the citation from another source, "…treatment[63].(25))". Please revise. 3. Page 7, Line 3 – Add the citation after "2016 review" to make it more clear where the reader can find the original systematic review. 4. Page 7, Line 18 – Consider changing the word "thrust" to "manipulation" since the operational definition includes "mechanical implements". Results: 1. Page 9, Lines 9-11 – I am not following this comment "…and the removal of records that had been withdrawn by the authors (n=2)." Is this referring to articles that were retracted, or something else? 2. Page 9, Lines 9-13 – This is an impressive volume of full-text articles to screen. Discussion: 1. Page 12, Lines 15-17 – What are the authors basing the opening sentence of the discussion on? Specifically the portion "…remains inadequate." Inadequate compared to what? 2. I recommend starting the discussion section by discussing the answer to your research objective, which was: "to describe if there has been a change in the reporting of adverse events … since 2016." 3. Page 12, Line 31 – I think the authors should remove citation 33 from this statement. While citation 33 by Funabashi et al does call for standardization of terminology, it was also published in late 2021 and therefore unlikely to have been utilized by many (if any) of the published RCTs that met your inclusion criteria. 4. Page 12, Lines 51-53 – "This finding is congruent with the wider published literature discussing adverse events (41-44)." Which finding? Congruent how? Please be more specific so interested readers don't have to dig into the source material to understand the sentence's intent. Please revise for clarity. 5. Page 12, Lines 53-57 – I think this sentence is somewhat misleading. In the 2016 study, only 38.0% (n=140/368) reported adverse events, whereas 61.0% (n=94/154) did so in 2020. So there was approximately a 50% increase in the number of studies providing this information, but the location of where the information dropped slightly from 93.6% (of the 38.0% that reported at all) vs 88.3% (of the 61.0%). So overall a lot more studies reported, but slightly fewer did it in the results section of the paper. 6. Page 13, Lines 3-10 – This sentence is awkwardly phrased. Please revise or break it up for clarity.

	7. Page 14, Lines 12-16 – This sentence is a bit too vague. Please be a little more clear with the argument you are trying to make. 8. Page 14, Lines 16-24 – It doesn't appear to have been studied, but I am curious to see if the adverse event reporting changes at all based on the profession of the study authors vs that of the providers delivering spinal manipulation. For example, would studies of chiropractic spinal manipulation with MDs and PhDs and no chiropractors among the authors have the same/similar adverse event reporting as studies that did include chiropractors in the authorship team). 9. Page 14, Lines 41-43 – Please highlight that this sentence is referring to a secondary analysis of your prior review, and not the prior review itself. I was initially confused by the new reference when referring to your "previous review". Conclusion: 1. Page 16, Line 34-36 – Similar to prior comments, I do not feel that the authors have successfully articulated that adverse event reporting related to spinal manipulation is "unacceptable". Please make this more clear throughout in order to defend this statement in the conclusion. Tables/Figures: 1. In 2020 PRISMA published a flow diagram that is specific to Updated Systematic Reviews that differs from the one in Figure 1. Why did the authors elect to opt for this diagram as opposed to the one specific to Updated reviews? References: Okay Again, thank you for the opportunity to review this manuscript, and I hope the comments are beneficial.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Thank you for all the work you put in the manuscript which read well. There are some concerns for me in this study.

We thank the reviewer for their kind words and have addressed each concern below.

The fact that you consider the 'classic HVLA manual manipulation', the drop-piece-table and mechanical implements all HVLA techniques. And if you do so, I would like to see them as a parameter in the results. Especially, since I read the tendency in the manuscript to not only comment the level of reporting but also to go into the safety of the included techniques. However, if you keep the focus in the manuscript on the original goal of the review (to comment on the level of reporting) it shouldn't be insurmountable.

Our inclusion of 'classic HVLA manual manipulation', drop-table and mechanical implements as HVLA techniques is not unique. There is precedent for doing this within the manual therapy literature (1–3) and in commonly cited textbooks (4). Additionally, we do not feel that further analysis of 'classic HVLA manual manipulation' vs 'drop-table' vs 'mechanical implements' as parameters would add benefit to our study as only 5/154 (3.2%) of studies used mechanical implements exclusively which is too few for any meaningful stratified or comparative analyses. Regarding the use of drop-table, there were no studies that exclusively used this technique. Rather, studies incorporated the intervention with other techniques (i.e. manual and/or 'mechanical implements').

We thank the reviewer for the opportunity to focus our manuscript back to the original research question rather than on the incidence/safety data. The manuscript has been edited throughout to address this comment.

If you would be more interested in the incidence of AE, you must (as you described in the discussion yourself) include other research designs as well. Therefore, I find the statement that “your findings support the literature that SAE are rare” to strong.

Again, we thank the reviewer for the opportunity to focus our manuscript back to the original research question. We have edited the manuscript to address feedback provided by all reviewers. The statement that 'our findings support the literature that SAE are rare' has been removed from the Discussion section during this editing. The relevant section now reads (P16, lines 26-28; P17, lines 1-3): *"Due to the methodological design of the review, we are unable to comment on the incidence of adverse events associated with spinal manipulation. Furthermore, RCTs are not necessarily the best research design for collecting data on serious adverse events as they often have strict inclusion criteria and may exclude participants who are at risk of experiencing such events. Additionally, RCTs are powered to detect intervention effects and thus are likely to be underpowered for estimating the risk of serious adverse events.".*

In line with the previous, with the information you gathered in this study you mustn’t want to calculate accurate incidence rates for these techniques since most of the inclusion criteria are set to avoid AE. You chose not to do so “due to the inadequate reporting of the number of manipulations delivered”. Statements like the latter two (although the topics are relevant and interesting!) seem inappropriate for this type of design.

We agree with the reviewer and the Limitations section has been edited to remove the statement 'due to the inadequate reporting of the number of manipulations delivered' and now reads (P18, lines 11-13): *''Secondly, as outlined above, small differences in the methodology between the current and previous reviews (26,58) mean that it is not possible to directly compare all reported findings between the two reviews.".*

Reviewer: 2

1. Thank you for the opportunity to review the submitted manuscript entitled: The reporting of adverse events associated with spinal manipulation in randomized clinical trials: an updated systematic review. The manuscript is generally well-written. The following comments are designed to improve the submission.

We thank the reviewer for their kind words.

2. I suggest a major revision of the Discussion section of the manuscript.

A major revision of the Discussion section has been undertaken incorporating feedback from all 3 reviewers.

3. Please avoid using transitional words such as “Interestingly.” The text should not tell readers what is interesting. Readers should determine what is interesting to them.

We thank the reviewer for this comment and the two instances of the word 'Interestingly' have been removed.

4. The Discussion begins with disappointment in adverse event reporting. Instead of communicating the emotion of disappointment, consider the opportunity to explain some of the complexity surrounding adverse event reporting and recommend solutions to current challenges.

The beginning of the Discussion section has been edited based on this comment and feedback from another reviewer and now reads (P13, lines 3-7): *'' There has been a change in the reporting of adverse events associated with spinal manipulation in RCTs since 2016. Specifically, the percentage of included studies reporting adverse events has increased from 38.0% (2016 study (26))*

to 61.0% (current study). However, the current review highlights that the reporting of adverse events in RCTs involving spinal manipulation as an intervention remains poor and is not consistent with established standards.".

The Discussion section has been further edited to address this comment and now reads (P13, lines 16-27; P14, lines 1-3): *"A recent scoping review explores the complexity of the current literature reporting on adverse events associated with spinal and peripheral joint manipulation and mobilisation (47). Specifically, the authors report that conflicting opinions regarding facets of adverse event definition and classification such as: symptom severity and duration, relatedness to the intervention (e.g., time to onset, tretment provided), action taken to treat the symptoms, expectedness, which profession delivered the intervention and geographical location (with possible medico-legal constraints and/or different expectations of reporting/not reporting) are all factors to reflect on when considering adverse events associated with joint manipulation and mobilisation. In an attempt to address the lack of standardized definitions and classification systems across professions that deliver spinal manipulation, the same authors have conducted an international Delphi study (manuscript in preparation; protocol paper (41)) to determine, by expert consensus a standardised definition and severity classification for adverse events associated with spinal and peripheral joint manipulation and mobilisation. The development and use of such guidelines would would constitute an important step toward uniform reporting the uniform reporting of adverse events associated with spinal manipulation across all stakeholder professions and geographical locations.".*

a. For example, the 1st paragraph states that there have been calls for standardized definitions and classification systems. Instead of ending with that thought, this is an opportunity to point out that until these are developed and broadly accepted, there should be no expectation that reporting will improve on its own. Thus, the text should not communicate disappointment at an unsurprising finding. Though developing standardized definitions and classifications may be beyond the scope of this study, this is an opportunity to suggest a pathway toward achieving these goals.

This feedback has been incorporated into the additional text above (P13, lines 16-27; P14, lines 1-3).

b. Perhaps the biggest opportunity here is to offer practical examples of more ideal adverse event reporting in an appendix. Results from this study further demonstrate that translating standards from CONSORT Harms into good reporting isn't necessarily clear. Consider showing readers what good adverse event reporting looks like. Such examples can include definitions, abstract reporting, results text reporting, results table reporting, etc. Doing so potentially makes this article a practical resource for future trialists, editors, etc.

While we appreciate this suggestion from the reviewer, this information is already provided in the 2004 CONSORT Harms guidelines (Appendix 2) and we feel that it would be redundant to provide the same information as an appendix in this review. Furthermore, an update to these guidelines is in preparation from the CONSORT Harms Working Group (personal correspondence and https://methods.cochrane.org/adverseeffects/news/consort-harms-update**). However, we have more strongly directed readers to the current CONSORT Harms guidelines (P14, lines 5-12):** *"However, until this work is published, the 2004 CONSORT Harms extension provides a checklist of items to include and specific examples of good reporting (Appendix 2) when reporting on harms (adverse events) in RCTs (24). Furthermore, it appears that an update to this guideline is emergent (25). It is hoped that these* updated *guidelines will ensure that authors and journal editors alike are both aware and implement better harms reporting in the future. We strongly encourage researchers and journal editors alike to read and use the most recent CONSORT Harms checklist during all phases of study development, data collection, manuscript preparation, submission and during the review process."*

5. There is a missed opportunity to discuss some important and relevant aspects of adverse event monitoring, grading, and reporting such as:
    a. Determining relatedness of an adverse event to HVLA spinal manipulation (or other intervention) is not straightforward. HVLA spinal manipulation is often used in research focused on spinal pain, which is known to exist with fluctuating symptoms. Because of the unstable nature of symptoms, some recorded adverse events represent natural symptom drift (thus unrelated). However, unless trials are specifically designed to identify these events (an unfeasible requirement, likely requiring an additional control group) such events are likely to be attributed to HVLA spinal manipulation. Walker et al., demonstrated this concept in a trial entitled: Outcomes of usual chiropractic. The OUCH randomized controlled trial of adverse events.

A paragraph has been added to the Discussion section which we feel addresses this comment (P13, lines 16-27; P14, lines 1-3): *"A recent scoping review explores the complexity of the current literature reporting on adverse events associated with spinal and peripheral joint manipulation and mobilisation (47). Specifically, the authors report that conflicting opinions regarding facets of adverse event definition and classification such as: symptom severity and duration, relatedness to the intervention (e.g., time to onset, treatment provided), action taken to treat the symptoms, expectedness, which profession delivered the intervention and geographical location (with possible medico-legal constraints and/or different expectations of reporting/not reporting) are all factors to reflect on when considering adverse events associated with joint manipulation and mobilisation. In an attempt to address the lack of standardized definitions and classification systems across professions that deliver spinal manipulation, the same authors have conducted an international Delphi study (manuscript in preparation; protocol paper (41)) to determine, by expert consensus a standardised definition and severity classification for adverse events associated with spinal and peripheral joint manipulation and mobilisation. The development and use of such guidelines would constitute an important step toward uniform reporting of adverse events associated with spinal manipulation across all stakeholder professions and geographical locations.".*

    b. This article presents an opportunity to suggest journals consider modifying guidance, word limits, structure, etc. to facilitate better harms reporting in abstracts. For example, journals could consider adding a harms section in abstracts.

This information has been consolidated from two existing paragraphs and expanded upon in the Discussion section which now reads (P15, lines 10-23): *"Furthermore, the responsibility for improved reporting of adverse events falls not only to authors but also to journal editors and custodians of clinical trial registries to ensure that adverse events are adequately reported i.e., using the most recent CONSORT Harms extension guidelines (24), alongside efficacy/effectiveness data prior to publication (25,46,54). Manuscript reviewers and journal editors must be aware of the current best-practices for the reporting of harms (24) and enforce these guidelines duing peer review processes of both protocol and end-of-study results papers. However, this may not be as straight-forward as it appears. Despite this, there is a need for improved reporting of adverse events in RCTs that include spinal manipulation as an intervention and a first step would be for journals to incorporate clear instructions on harms reporting in their guidelines and instructions to authors. As a second step, journal editors may facilitate this process by limiting publication to only those studies that adhere to the current guidelines for the reporting of harms in RCTs that include spinal manipulation as an intervention.".*

6. Recommending researchers report adverse events relative to the number of spinal manipulations to enable post-hoc pooling and risk analysis is more challenging than the current text suggests. For example, several questions arise. What is 1 spinal manipulation (1 visit, 1 HVLA procedure to a specific region, 1 thrust)? Should all spinal manipulations be considered the same (there are many possible HVLA procedures that can be applied to different regions and in different positions)? What type of subgroups should be reported (males, females, age ranges, conditions treated)? Will co-morbid conditions be accounted

for in such a risk analysis? Will these risk analyses incorporate adverse events classified as possibly, probably, or definitely related, or some combination thereof? How would natural symptom variation be addressed in the analysis to account for events that cannot be clearly classified as related to HVLA spinal manipulation? If a standardized process is developed, will ethics boards adopt and support researchers in these efforts, or will they require monitoring and reporting using different standards? These questions, and more, need answers so researchers can develop monitoring, recording, tracking, grading, analysis, and reporting methods to enable scientifically appropriate post-hoc pooled risk analyses.

We disagree with the reviewer that reporting the number of spinal manipulations delivered to a participant in a research study is challenging. Put simply, if a spinal manipulation is delivered to a participant, irrespective of the type of spinal manipulation (e.g., manual HVLA, drop-table, mechanical implement etc), or the region to which it is delivered (e.g., cervical, thoracic etc), it should be noted on the data collection form and should be reported alongside any results using data from that study. This includes any 'multiple thrust attempts' which we argue should be enumerated. Additionally, the type of spinal manipulation should always be recorded and reported. Ideally, the dosage of all manipulations delivered in all studies would be quantified using some force/pressure measuring system and thus, it would be very apparent during data analysis how many manipulations had been delivered. However, this suggestion is perhaps unfeasible due to cost and equipment availability restrictions.

Regarding post-hoc pooling and risk analysis, we agree with the reviewer that it is not simple (with examples of possible challenges listed above). However, we argue that there should be steps taken towards addressing this important issue – this problem may be difficult to solve, but that cannot be an excuse for not trying. As outlined above, it is not difficult to report how many manipulations were delivered to each participant and this is, at a very basic level, perhaps the first step towars the calculation of adverse events incidence rates in RCTs involving spinal manipulation.

Regarding a standardized process, the development and implementation of minimum standards for reporting harms in research papers does not preclude ethics boards from having additional requirements for the purpose of approving and monitoring research projects.

7. I strongly suggest removing the speculation that researchers involved with cervical spine manipulation are trying to “prove” safety. Such text is presumptive. There are other possible explanations.

This sentence has been edited and now reads (P16, lines 12-15): *"Furthermore, while there is no obvious reason why studies in which spinal manipulation was delivered by a chiropractor would be more likely to report on adverse events, it is possible that this finding could be explained by a desire to provide evidence to refute critics of the intervention who claim that spinal manipulation, specifically that delivered to the cervical spine, is unsafe (56,57).".*

8. In the Conclusion of the abstract and Discussion sections, the text states that the current level of reporting is unacceptable. This begs the question: unacceptable to whom? Consider restating that adverse event reporting is not consistent with established standards.

The Abstract Conclusion has been edited considering feedback from all reviewers (and directly addressing this comment and now reads (P3, lines 2-6): *"While the current level of reporting of adverse events associated with spinal manipulation in RCTs has increased since our 2016 publication on the same topic, the level remains low and inconsistent with established standards. As such, it is imperative for authors, journal editors and administrators of clinical trial registries to ensure there is more balanced reporting of both benefits and harms in RCTs involving spinal manipulation.".*

The Conclusion has been edited considering feedback from all reviewers (and directly addressing this comment) and now reads (P18, lines 16-24): *"While the current level of reporting of adverse events associated with spinal manipulation in RCTs has increased since our 2016 publication on the same topic, the level remains low and inconsistent with established standards. As such, it is imperative for authors, journal editors and administrators of clinical trial registries to ensure there is more balanced reporting of both benefits and harms of spinal manipulation in RCTs involving spinal manipulation. We strongly recomend that authors adhere to the most recent CONSORT Harms checklist when reporting their results and advocate for the creation of standardized definitions and classification systems relating to adverse events in manual therapy. This will facilitate the future pooling of adverse events data across all professions utilizing spinal manipulation and improve the ability to calculate incidence rates for the different levels of adverse events.".*

9. In the Conclusion, instead of ending with recommending researchers adhere to the CONSORT Harms checklist, consider offering practical methods to improve reporting (as suggested earlier). The Harms checklist has been available for several years. If the checklist isn't being adhered to, then reminding readers of its existence is not likely to induce change. Instead, consider offering practical examples of how to translate those standards into manuscript reporting (see comment above suggesting reporting examples as an appendix). In short, consider showing readers what good reporting looks like.

The Conclusion has been edited considering feedback from all reviewers (please see above response). As mentioned previously in our response to point 4b, we feel that it is beyond the scope of this manuscript to provide this information (especially in the Conclusion) and that this information will be forthcoming in the near future.

Reviewer: 3

Thank you for the opportunity to review the manuscript titled, "The reporting of adverse events associated with spinal manipulation in randomized clinical trials: an updated systematic review. This was an update of a systematic review published in 2016. The authors registered the protocol on PROSPERO and it was congruent with this manuscript. Strengths of this manuscript are that this was a well-written, well-performed review study, that objectively analyzed results and performed regression analysis to identify predictors, and the authors followed the PRISMA standards for reporting. As the authors acknowledged, due to design improvements, there are some limitations regarding the ability to compare this review's findings to the 2016 review. However, I would like to see more discussion of what has changed, as I found this discussion to be relatively lacking. I would also like to see the authors better outline why the current reporting level of adverse events is "inadequate" and "unacceptable". I hope the following comments will aid the authors in approving their manuscript.
We thank the reviewer for their kind words.

Title: Okay

Abstract:

1. Page 3, Line 8 - What is an acceptable level of reporting? Clearly closer to 100% is better, but the authors do not provide any kind of reference percentage from studies looking at other interventions as a comparison. Unless the authors can provide this additional context within the manuscript, I would omit the opening sentence and focus more on the change since the 2016 publication.

The Abstract Conclusion has been edited considering feedback from all reviewers and now reads (P3, lines 2-6): *"While the current level of reporting of adverse events associated with spinal manipulation in RCTs has increased since our 2016 publication on the same topic, the level remains low and inconsistent with established standards. As such, it is impertive for authors, journal editors and administrators of clinical trial registries to ensure there is more balanced reporting of both benefits and harms of spinal manipulation in RCTs involving spinal manipulation.".*

Article summary:

1. 3rd bullet - Recommend omitting the word “Interestingly”. Also, why use the word “might” here? Seems your regression analysis indicates there is strong evidence. Consider revising this entire bullet to something like “Reporting of adverse events in RCTs of spinal manipulation are more likely to be reported when chiropractors are delivering the intervention”.

This section has been completely re-written in response to a request made by the Editor. As such, this point is no longer included in this section which now reads (P3, lines 11-14):

- This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines (1)
- *The search strategy was inclusive of professions that deliver spinal manipulation*
- *The search included several databases relevant to manual therapy*
- *Due to heterogeneity of reporting of adverse events, only descriptive statistics were used to describe domains of interest*

Introduction:

1. Page 5, Lines 13-15 – Is reference 10 the systematic review that is being updated? Please be more clear about this.

This reference (10) has been edited to the following study: Funabashi M, Pohlman KA, Goldsworthy R, Lee A, Tibbles A, Mior S, et al. Beliefs, perceptions and practices of chiropractors and patients about mitigation strategies for benign adverse events after spinal manipulation therapy. Chiropr Man Ther. 2020;28(1):46.

2. Page 5, Lines 19-26 – The authors mentioned the temporal association of vertebral artery dissection, however, did not mention any of the more updated population-based studies from the literature. As I am sure the authors are aware, there are now several of these studies that report vascular events occurring at near the same rate following spinal manipulation encounters as following primary care visits. I suggest adding more context to this specific point.

The Introduction section has been edited to include the following text (P5, lines 11-21): *"Indeed, synthesis of the current literature suggests that there is no evidence for cervical spine manipulation causing cervical artery dissection (14). Additionally, several large population-based studies have reported that there is no difference in risk of cervical artery dissection following visits to a chiropractor compared to those occurring following a visit to a primary care provider (15,16) or, in those who received cervical spinal manipulation compared to matched controls (17,18). Furthermore, recent biomechanical studies report that head angular displacements and vertebral artery length changes are small during cervical spine manipulation thrusts (19) and that the vertebral artery does not experience longitudinal force during cervical spine manipulation (20). Despite this literature, the serious nature of such events that are temporally associated with cervical spine manipulation makes it imperative that the circumstances surrounding such events are reported transparently."*

3. Page 5, Lines 51-55 – It is odd to me that the phrasing of the purpose statement does not mention that this is an updated systematic review, as opposed to just indicating you are looking at new data since 2016. Consider revising.

We have chosen not to edit the purpose statement as we believe it is accurate as it is currently written. Considering that the Title, Conclusion of the Abstract and the Strengths and Limitations section all mention our previous review and that the search was somewhat expanded from that used in our 2016 publication, we feel that it is unnecessary to provide this information in our purpose statement.

Methods:

1. Page 6, Line 19-21 – Can you give an example of what you mean by “mechanical implements”? Are you referring to something handheld like an activator or impulse instrument?

This clarification has been made and the sentence now reads (P6, line 16): *"For the purposes of this review, spinal manipulation delivered using drop-piece-table and mechanical implements (e.g. Activator instrument) were considered HVLA procedures (29)."*

2. Page 6, Line 36 – In the quote, it is confusing that you listed the citation from another source, “…treatment[63].(25))”. Please revise.

This clarification has been made and the sentence now reads (P6, lines 26-27; P7, lines 1-6): *"To be classified as reporting on adverse events "directly", a study must have provided explicit description of their operational definition of an adverse event (e.g. "In the current study, an adverse event was defined as a sequelae of 1-week duration with any symptom perceived as distressing and unacceptable to the patient that required further treatment [excerpt from reference 63]." (33)), and/or how data on adverse events were measured (e.g. "Active and passive surveillance methods were used to collect information on adverse events." (34)), and/or provide a substantial description of adverse events observed during data collection (35,36)."*

3. Page 7, Line 3 – Add the citation after “2016 review” to make it more clear where the reader can find the original systematic review.

The reference has been added and the sentence now reads (P7, line 12): *"Consistent with the 2016 review (26), RCTs reporting original data on spinal manipulation as either the sole intervention, or as the sole intervention in a comparator group, delivered by any regulated health professional, and published in English, were eligible for inclusion."*

4. Page 7, Line 18 – Consider changing the word “thrust” to “manipulation” since the operational definition includes “mechanical implements”.

This change has been made and the sentence now reads (P7, line 19): *"Studies were also excluded if it was unclear if the intervention being delivered involved an HVLA manipulation."*

Results:

1. Page 9, Lines 9-11 – I am not following this comment “…and the removal of records that had been withdrawn by the authors (n=2).” Is this referring to articles that were retracted, or something else?

Yes, your interpretation was correct. This sentence has been edited and now reads (P9, line 15): *"A total of 3,363 unique records remained after de-duplication (n=2,034) and the removal of retracted articles (n=2)."*

2. Page 9, Lines 9-13 – This is an impressive volume of full-text articles to screen.

We thank the reviewer for their kind words.

Discussion:

1. Page 12, Lines 15-17 – What are the authors basing the opening sentence of the discussion on? Specifically the portion "…remains inadequate." Inadequate compared to what?

This sentence has been edited and now reads (P13, lines 5-7): "*However, the current review highlights that the reporting of adverse events in RCTs involving spinal manipulation as an intervention remains poor and is not consistent with established standards."***.**

2. I recommend starting the discussion section by discussing the answer to your research objective, which was: "to describe if there has been a change in the reporting of adverse events … since 2016."

The Discussion section has been edited to provide a direct answer to the research question as suggested by the reviewer and this section now reads (P13, lines 3-7): *"There has been a change in the reporting of adverse events associated with spinal manipulation in randomized controlled trials (RCTs) since 2016. Specifically, the percentage of included studies reporting adverse events has increased from 38.0% (2016 study (26)) to 61.0% (current study). However, the current review highlights that the reporting of adverse events in RCTs involving spinal manipulation as an intervention remains poor and is not consistent with established standards.".*

3. Page 12, Line 31 – I think the authors should remove citation 33 from this statement. While citation 33 by Funabashi et al does call for standardization of terminology, it was also published in late 2021 and therefore unlikely to have been utilized by many (if any) of the published RCTs that met your inclusion criteria.

This reference has been removed.

4. Page 12, Lines 51-53 – "This finding is congruent with the wider published literature discussing adverse events (41-44)." Which finding? Congruent how? Please be more specific so interested readers don't have to dig into the source material to understand the sentence's intent. Please revise for clarity.

These two sentences have been edited for clarity and now read (P14, lines 16-18): *"Despite this, the current reporting on adverse events in the title/abstract of RCTs utilizing spinal manipulation remains poor, a finding that is also present in the wider published medical literature discussing adverse events (49–52)."*

5. Page 12, Lines 53-57 – I think this sentence is somewhat misleading. In the 2016 study, only 38.0% (n=140/368) reported adverse events, whereas 61.0% (n=94/154) did so in 2020. So there was approximately a 50% increase in the number of studies providing this information, but the location of where the information dropped slightly from 93.6% (of the 38.0% that reported at all) vs 88.3% (of the 61.0%). So overall a lot more studies reported, but slightly fewer did it in the results section of the paper.

Additional information has been added to the beginning of this sentence to prevent any confusion. This sentence now reads (P14, lines 18-21): *"Despite an overall increase in the number of studies reporting on adverse events in RCT involving spinal manipulation (38.0-61.0%, 2016 (26) to current), adverse events reporting in the results section has decreased (93.6% vs 88.3%) over the past 6 years and remains lower than that in the wider published literature (50,53)."*

6. Page 13, Lines 3-10 – This sentence is awkwardly phrased. Please revise or break it up for clarity.

This sentence has been edited and now reads (P14, lines 23-27): *" Furthermore, an important source of information for the formulation of a considered evidence-based risk-benefit analysis for the use of spinal manipulation as a treatment option by both clinician and patient (49,52) is transparent data reporting on both the efficacy and adverse events occurring in RCTs involving spinal manipulation."*

7. Page 14, Lines 12-16 – This sentence is a bit too vague. Please be a little more clear with the argument you are trying to make.

This sentence has been edited and now reads (P16, lines 8-11): *" This disconnect between the publication of studies with better methodological quality in higher impact journals is also seen in the medical literature. Specifically, a previous study reported that there were methodological weaknesses in 184 studies published in 2015-2016 by four of the top ranked general medical journals (BMJ, JAMA, Lancet, and NEJM) (54)."*

8. Page 14, Lines 16-24 – It doesn't appear to have been studied, but I am curious to see if the adverse event reporting changes at all based on the profession of the study authors vs that of the providers delivering spinal manipulation. For example, would studies of chiropractic spinal manipulation with MDs and PhDs and no chiropractors among the authors have the same/similar adverse event reporting as studies that did include chiropractors in the authorship team).

We agree with the reviewer that this would indeed be an interesting topic. One of the authors has recently conducted a Delphi consensus study (manuscript in preparation) that aimed to establish a standardized adverse event definition and classification system that can be prospectively used across multiple professions utilizing spinal and peripheral joint manipulation and mobilization (scoping review used in round 2 of the Delphi (5); protocol paper for the Delphi (6)). It is this author's experience that there are very different definitions, classification systems and expectations surrounding what constitutes an adverse event (and subsequently the reporting of these events) across professions and also between different stakeholders (e.g. clinicians, researchers, patients, educators etc). Results reporting the proportions of studies in which spinal manipulation was delivered by different clinicians have been added to the Results section. Specifically, Table 1 (P10, lines 14-15) and the following text (P9, lines 22-27; P10, line 1): *"Of these 94 studies, 36 (38.3%) directly reported on adverse events, with studies in which spinal manipulation was delivered by a chiropractor most frequently reporting this data (n=17; 47.2%, Table 1). Indirect reporting occurred in 58 studies (61.7%), with studies in which spinal manipulation was delivered by a physiotherapist being the most frequent (n=29; 50.0%, see Table 1). Of the 60 studies (39.0%) that did not report on adverse events, studies in which spinal manipulation was delivered by a physiotherapist were the most frequent (n=28; 46.7%, see Table 1)."*

9. Page 14, Lines 41-43 – Please highlight that this sentence is referring to a secondary analysis of your prior review, and not the prior review itself. I was initially confused by the new reference when referring to your "previous review".

This clarification has been made and the sentence now reads (P16, lines 23-24): *"This hypothesis is supported by a secondary analysis of our previous review which reported that the region treated was not a significant predictor for reporting on adverse events (58)."*

Conclusion:

1. Page 16, Line 34-36 – Similar to prior comments, I do not feel that the authors have successfully articulated that adverse event reporting related to spinal manipulation is

"unacceptable". Please make this more clear throughout in order to defend this statement in the conclusion.

The Conclusion has been edited considering feedback from all reviewers and now reads (P18, lines 16-24): *"While the current level of reporting of adverse events associated with spinal manipulation in RCTs has increased since our 2016 publication on the same topic, the level remains low and inconsistent with established standards. As such, it is imperative for authors, journal editors and administrators of clinical trial registries to ensure there is more balanced reporting of both benefits and harms of spinal manipulation in RCTs involving spinal manipulation. We strongly recommend that authors adhere to the most recent CONSORT Harms checklist when reporting their results and advocate for the creation of standardized definitions and classification systems relating to adverse events in manual therapy. This will facilitate the future pooling of adverse events data across all professions utilizing spinal manipulation and improve the ability to calculate incidence rates for the different levels of adverse events.".*

Tables/Figures:

1. In 2020 PRISMA published a flow diagram that is specific to Updated Systematic Reviews that differs from the one in Figure 1. Why did the authors elect to opt for this diagram as opposed to the one specific to Updated reviews?

The 2020 PRISMA flow diagram for updated systematic reviews is not appropriate for this systematic review because the current search strategy and databases searched were different to those used in the initial review. Furthermore, we did not include any of the studies reported on in the initial review in this update. We have clarified this point in the Methodology, Study selection process section (P8, lines 2-3): *"Duplicate records and records included in the 2016 review were removed before title and abstract screening."*

References: Okay

References:

1. Beliveau PJH, Wong JJ, Sutton DA, Simon NB, Bussières AE, Mior SA, et al. The chiropractic profession: a scoping review of utilization rates, reasons for seeking care, patient profiles, and care provided. Chiropractic & Manual Therapies. 2017 Nov 22;25(35).

2. Pickar J. Neurophysiological effects of spinal manipulation. The spine journal : official journal of the North American Spine Society. 2002 Oct;2(5):357–71.

3. Gorrell LM, Beath K, Engel RM. Manual and instrument applied cervical manipulation for mechanical neck pain: a randomized controlled trial. Journal of Manipulative & Physiological Therapeutics. 2016;39(5):319–29.

4. Bergmann T. Chiropractic Technique Principles and Procedures. 3rd ed. Missouri: Elselvier Mosby, USA; 2011.

5. Funabashi M, Gorrell LM, Pohlman KA, Bergna A, Heneghan NR. Definition and classification for adverse events following spinal and peripheral joint manipulation and mobilization: A scoping review. PLOS ONE. 2022 Jul 15;17(7):e0270671.

6. Funabashi M, Pohlman KA, Gorrell LM, Salsbury SA, Bergna A, Heneghan NR. Expert consensus on a standardised definition and severity classification for adverse events associated with spinal and peripheral joint manipulation and mobilisation: protocol for an international e-Delphi study. BMJ Open. 2021 Nov 1;11(11):e050219.

VERSION 2 – REVIEW

REVIEWER	Kranenburg, Hendrikus

	Hanze University of Applied Sciences, Physiotherapy
REVIEW RETURNED	20-Mar-2023

GENERAL COMMENTS	Thank you for reviewing this work.

REVIEWER	Vining, Robert Palmer College of Chiropractic Center for Chiropractic Research, Research
REVIEW RETURNED	03-Mar-2023

GENERAL COMMENTS	1. Please consider revising the final paragraph of the Introduction to establish rationale for the study. Currently, the text states: “While there has been an improvement in the reporting of adverse events since the publication of the 2004 extension, reporting remains insufficient (25), especially for RCTs that involve spinal manipulation (26).” As written, the text reads like a conclusion, inadvertently leading readers to ask: “Why conduct the study if reporting is known to be insufficient?” In reviewing the references, however, it appears that the text is attempting to communicate 2 unwritten thoughts that should be explicitly stated to help readers better follow the rationale: 1. That reporting remains insufficient in general for randomized controlled trials; and 2. That a prior review published in 2016 clarified that the same is true for spinal manipulation. Then the final sentence would make sense. 2. Very minor point: Because data are plural, consider revising occurrences of “this data” to “these data” where present in the manuscript. 3. The Discussion text suggesting spinal manipulation by chiropractors is more often reported to refute critics who claim the intervention as unsafe is not supported by study data. This conjecture should be removed. 4. Discussion text suggests that reporting the number of spinal manipulations delivered in a study “…would allow for inter-disciplinary calculation of incidence rates…” The statement seems to presume that all relevant studies similarly employ spinal manipulation as a solitary intervention. It doesn’t seem to account for studies using multimodal approaches, the wide variety of conditions studied and manipulative procedures used, other co-occurring interventions, (e.g., biomechanical tests) used in some studies, or appropriately analyzing pooled data. Please consider either removing this text to avoid oversimplifying the related issues or clarifying that though there are many factors to consider beyond reporting the number spinal manipulations, such reporting can be a step forward. 5. Please recheck appendix naming. Should there be 4 appendices in the revision? In the revised submission, there was no appendix displaying the 2004 CONSORT Harms extension as described in the 3rd paragraph of the Discussion.

REVIEWER	Daniels, Clinton VA Puget Sound Health Care System, RCS
REVIEW RETURNED	29-Mar-2023

GENERAL COMMENTS	The authors have thoroughly and satisfactorily addressed all of my concerns. Very well done.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Thank you for reviewing this work.

We thank the reviewer for their time re-reviewing our manuscript.

Reviewer: 2

We thank the reviewer for their time re-reviewing our manuscript.

1. Please consider revising the final paragraph of the Introduction to establish rationale for the study. Currently, the text states: “While there has been an improvement in the reporting of adverse events since the publication of the 2004 extension, reporting remains insufficient (25), especially for RCTs that involve spinal manipulation (26).” As written, the text reads like a conclusion, inadvertently leading readers to ask: “Why conduct the study if reporting is known to be insufficient?” In reviewing the references, however, it appears that the text is attempting to communicate 2 unwritten thoughts that should be explicitly stated to help readers better follow the rationale: 1. That reporting remains insufficient in general for randomized controlled trials; and 2. That a prior review published in 2016 clarified that the same is true for spinal manipulation. Then the final sentence would make sense.

We have edited the Introduction to read (P6, lines 4-8): *"However, reporting of adverse events in RCTs in the wider medical literature remains insufficient since the publication of the 2004 extension (25), a finding that is also evident in RCTs that involve spinal manipulation (26). Thus, the objective of this review was to describe if there has been a change in the reporting of adverse events associated with spinal manipulation in RCTs since 2016."*

2. Very minor point: Because data are plural, consider revising occurrences of “this data” to “these data” where present in the manuscript.

We thank the reviewer for their attention to detail. This change has been made throughout the manuscript.

3. The Discussion text suggesting spinal manipulation by chiropractors is more often reported to refute critics who claim the intervention as unsafe is not supported by study data. This conjecture should be removed.

We have edited the Discussion section to read (P16, lines 12-16): *"Furthermore, while there is no obvious reason why studies in which spinal manipulation was delivered by a chiropractor would be more likely to report on adverse events, possible reasons for this finding could include that chiropractors are more likely to deliver cervical spine manipulation in general and/or that due to perceived 'risks' of cervical spine manipulation, other professions choose not to conduct trials investigating this intervention."*

4. Discussion text suggests that reporting the number of spinal manipulations delivered in a study “…would allow for inter-disciplinary calculation of incidence rates…” The statement seems to presume that all relevant studies similarly employ spinal manipulation as a solitary intervention. It doesn’t seem to account for studies using multimodal approaches, the wide variety of conditions studied and manipulative procedures used, other co-occurring interventions, (e.g., biomechanical tests) used in some studies, or appropriately analyzing pooled data. Please consider either removing this text to avoid oversimplifying the related issues or clarifying that though there are many factors to

consider beyond reporting the number spinal manipulations, such reporting can be a step forward.

The word 'would' has been changed to 'could' in the relevant Discussion section (P17, lines 5 & 17).

Furthermore, the following text has been added to the Discussion section (P17, lines 8-13): *"We acknowledge that the calculation of accurate incidence rates is not straight-forward. Indeed, factors such as the use of different spinal manipulation techniques, how to parse out adverse events attributable to different interventions (e.g. orthopaedic testing, soft tissue treatment or exercise) and how to amalgamate reports on different cohorts (e.g. neck vs. low back pain) must all be considered. While this task seems insurmountable, consistent reporting of the number of spinal manipulations delivered to every participant in RCTs is the first step towards this goal. To this end, the number of spinal manipulationselivered was only available in 75 (48.7%) of the included studies."*

5. Please recheck appendix naming. Should there be 4 appendices in the revision? In the revised submission, there was no appendix displaying the 2004 CONSORT Harms extension as described in the 3rd paragraph of the Discussion.

We have clarified this sentence to indicate that it is Appendix 2 of the cited 2004 CONSORT Harms extension that we are referring to (P14, lines 5-7): *"However, until this work is published, Appendix 2 of the 2004 CONSORT Harms extension (24) provides a checklist of items to include and specific examples of good reporting when reporting on harms (adverse events) in RCTs."*

Reviewer: 3

The authors have thoroughly and satisfactorily addressed all of my concerns. Very well done.

We thank the reviewer for their kind words and time re-reviewing our manuscript.

VERSION 3 – REVIEW

REVIEWER	Vining, Robert Palmer College of Chiropractic Center for Chiropractic Research, Research
REVIEW RETURNED	03-Apr-2023

GENERAL COMMENTS	All comments are satisfactorily addressed. I have no further substantive comments to offer.