Author’s response to reviews

Title: Seeking adverse effects in systematic reviews of orthodontic interventions: protocol for a cross-sectional study

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Title: Seeking adverse effects in systematic reviews of orthodontic interventions: protocol for a cross-sectional study
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Journal: Systematic Reviews
Corresponding author: Reint Meursinge Reynders

Dear Dr. Pieper and peer reviewers,

We thank the editor and all 3 reviewers for have taken the time to critically appraise our paper ‘Seeking adverse effects in systematic reviews of orthodontic interventions: protocol for a cross-sectional study’.

These comments were very important for us and we have carefully applied them to improve this manuscript. In the following section we have responded to each of these comments and have highlighted all changes in the manuscript in red.

All authors of this manuscript have participated in addressing these comments and have approved the changes in the final paper. The manuscript is formatted according to the journal guidelines.

We found that at times we had only written ‘adverse effects’ instead of ‘adverse effects of interventions’. We corrected this throughout the manuscript and its related documents.

Sincerely,

Pauline Steegmans, Shandra Bipat, and Reint Meursinge Reynders
Reviewer #1:

The authors plan to investigate the prevalence of systematic reviews of clinical orthodontic interventions that dealt with adverse effects along beneficial effects of those interventions by carrying out a cross-sectional study. The manuscript is well written and addresses a highly important research question, as it is crucial that both, the benefits and harms, of a health care intervention inform the decision-making processes related to it. The planned study ought to have external validity for systematic reviews from the field of orthodontics as both, Cochrane and non-Cochrane reviews, will be included. The authors satisfactorily address how differences that may occur in the study process will be handled, which is particularly important when submitting a manuscript for a study protocol. No major essential revisions are required, but I suggest that the authors undertake the following minor essential revisions:

Response to Reviewer 1:
We thank reviewer 1 for the important issues raised and the kind words. All very very helpful indeed.

Comment 1
Background
L. 91 and l. 101: Instead of 'both outcomes' you should say 'both types of outcomes' to avoid potential confusion.
Response to comment 1
We revised the text accordingly (Lines 90-92).

Comment 2.
L. 100: Please add '(chapter 5.4.1)' after the direct quotation and move the in-text citation that currently stands after 'Cochrane' to the end of that sentence.
Response to comment 2
We revised the text accordingly (Lines 98-100).

Comment 3
Ll. 102-104: This should be moved to the methods section.
Response to comment 3
Adverse effects of interventions are the key topic of our review and we therefore feel that its definition should be presented early on in the manuscript, i.e., in the introduction. We therefore did not follow-up on this suggestion of the reviewer.

Comment 4
Ll. 117-125: This paragraph appears to belong to the methods section as well. Furthermore, I suggest you write 'In our study' or something similar instead of 'In this manuscript'.
Response to comment 4
According to the reviewer’s suggestion we revised ‘In this manuscript’ to ‘In this study’ (Lines 118-119). We did not follow up on the suggestion to move the paragraph starting with ‘In this study we will ………………..our research questions’ to the Methods section. We feel that such a move will jeopardize the flow of our introduction, because our introduction is based on the following 4 paragraph format: paragraph 1: tells the central story of the research study. Paragraph 2: Description of the condition. Paragraph 3: Description of the problem, what has been published on the problem and what is lacking in the literature. Paragraph 4: What is the solution to the problem (conducting this study) and an
explanation why our research questions are valid, important, and for who.

Comment 5
LL. 150-151: I believe the correct way of citing would be to remove citation no. 24 and 25 from the manuscript and only list them in additional file 2 as new citations.
Response to comment 5
We revised this section of the manuscript according to the suggestion of the reviewer (Lines 151-154).

Comment 6
Eligibility criteria: To facilitate reading, I suggest that you re-structure this paragraph, e.g. under each sub-category (study designs, intervention etc.) say: We will include: We will exclude:
Response to comment 6
We revised this section of the manuscript according to the suggestion of the reviewer and agree that this facilitates reading (Lines 156-201).

Comment 7
L. 199: Did you mean that you will search eligible systematic reviews in the Cochrane Database of Systematic reviews and through the journals websites when saying 'we will manually search'? Please specify.
Response to comment 7
Thank you very much for pointing this out. We specified this according to the suggestion of the reviewer (Lines 204-205).

Comment 8
LL. 199-200: You should briefly state why you will only include systematic reviews published in the past 10 years (although you pick up this matter again in the limitations section).
Response to comment 8
Again thank you very much for pointing this out. We explained this in the manuscript, i.e., our starting date coincides with the launch of PRISMA, i.e., 21 July 2009. We modified our starting date of the searches to the first of August 2009 and will search until 31 July 2019 (Lines 211-213).

Comment 9
L. 215 and 224: Please specify how you would contact the review authors, e.g. 'via email'.
Response to comment 9
We specified this according to the suggestions of the reviewer (Lines 221-223).

Comment 10
L. 221: Did you mean 'screened' when saying 'hand searched'? Please specify.
Response to comment 10
We mean ‘screened’ and specified this in the manuscript (Lines 228-230).

Comment 11
Strengths: For better readability, you should restructure this rather long sentence and consider making it multiple sentences.
Response to comment 11
We implemented this suggestion (Lines 298-304).

Comment 12
Funding. Please further specify this (with regards to the protocol and the study you plan).
Response to comment 12
We revised the funding section according to the reviewer’s suggestion (Lines 356-358).

Comment 13
Reference no. 6 does not appear in the text and is the same as reference no. 26. Please remove reference no. 6 and correct the following references accordingly.
Response to comment 13
Thank you for pointing this out. We made the necessary corrections.

Comment 14
Abstract. L. 42 (as well as l. 111 and l. 315): Instead of 'medical trial' I suggest you write 'clinical trial' to be consistent with the commonly used terminology.
Response to comment 14
We implemented this suggestion (Lines 42, 112, 322).

Comment 15
Keywords. The comma after 'interventions' should be a semicolon.
Response to comment 15
We corrected this (Lines 68-69).

Comment 16
Methods. L. 159: Please add a comma after 'Qualitative'.
Response to comment 16
We corrected this (Line 162).

Comment 17
Information sources: The bullet point at that paragraph seems unnecessary and can be removed.
Response to comment 17
We corrected this (Lines 204).

Comment 18
Ll. 199-200: To be consistent, you should say 31 December 2018 instead of December 31, 2018.
Response to comment 18
We modified the dates as explained under comment 8 (Lines 210-213).

Comment 19
Ll. 218-219: Maybe change wording to 'extracted into' instead of 'uploaded to'.
Response to comment 19
We revised this according to the reviewer’s suggestion (Lines 225-226).

Comment 20
LL. 226-227: I suggest you change 'studies/study' to 'systematic review(s)' to be consistent.
Response to comment 20
We revised this according to the reviewer’s suggestion (Lines 236-237).

Comments 21 and 22
Figure 1. Step 5: You could delete the 'of' here. Step 6: You could delete 'in the eligible systematic reviews' here.
Response to comments 21 and 22
We revised this in Figure 1 according to the reviewer’s suggestion.

Reviewer #2

Comment 1
The protocol indicates that AEs in orthodontics interventions are sought, however it is unclear why SRs of adverse events of interventions are excluded entirely?
Response to comment 1
This is an important point indeed. Our original plan was to assess reporting of adverse effects in SRs of adverse effects. We changed direction after prioritization of research questions and decided to address the questions of this manuscript first. Our next study will focus on SRs of adverse effects.

Comment 2
Is the population of interest adults or paediatrics or both?
Response to comment 2
Thank you very much for this comment. We created an additional subheading ‘Participants’ under the eligibility criteria that clarifies this issue (Lines 165-171).

Comment 3
What is the rationale for the time-frame of SRs published between 2009 to 2018?
Response to comment 3
Thank you very much for pointing this out. Reviewer 1 asked the same question (See comment 8 for Reviewer 1) (Lines 211-213).

Comment 4
Unclear if both English and non-English are included; if only English, have the authors considered selective reporting or publication bias?
Response to comment 4
This is not an issue, because all included journals are those with the highest impact factor and all are published in English.

Comment 5
Exposure time may impact on the rate of AEs reported; how do the authors intend to minimize differences in exposure time of these interventions used across the studies especially where data pooling will be undertaken.
Response to comment 5
Exposure time is indeed an important point and shorter exposure times could result in less or even no adverse effects. However, this problem does not affect any of our research questions. This research study is about seeking or reporting of adverse effects or not seeking or reporting of adverse effects regardless of the characteristics or intensity of the adverse effects.

Comment 6
What is the criteria for the choice of the 5 leading orthodontic journals chosen/selected? I.e. based on impact factor, etc or otherwise?
Response to comment 6
Thank you very much for pointing this out. We addressed this issue in the manuscript (Lines 204-207).

Comment 7
Line 224: "Authors suspect of multiple publications of the same systematic review will be contacted" -
What is the rationale of this at the first instance? Also, how do the authors intend to choose which review of the multiple publication to choose without compromising consistency in study selection?
Response to comment 7
Thank you for pointing this out. We have addressed this issue in further detail (Lines 232-234).

Comment 8
Line 247 "We will also score additional adverse effects of orthodontic interventions that are identified..." What do the authors mean by 'score'? i.e. do the authors anticipate to "weight" the AEs or otherwise?
Response to comment 8
This is an important issue and we revised the manuscript accordingly (Lines 257-260).

Comment 9
Are there any differences or similarities across the 5 leading journals relative to how AEs are reported or otherwise? If so, how does this impact on the potential generalisability of the study results?
Response to comment 9
This is indeed an interesting issue that we like to explore. Our planned outcomes are presented in a summary of findings table (Table 3) and are also calculated for each individual journal separately (See section Outcomes and statistical analyses).

Comment 10
Lines 310 and 311: In this research study we will assess whether adverse effects were sought and reported in both Cochrane and non-Cochrane systematic reviews of orthodontic interventions. Do the authors intend to include relatively similar number of these reviews to allow for a fair comparison between the Cochrane vs non-Cochrane or otherwise?
Response to comment 10
This is also an important question, but unfortunately Cochrane reviews of orthodontic interventions are few in numbers and a fair comparison is not expected.

Reviewer #3:
The paper addresses an interesting topic, is quite rare identify studies that properly evaluate adverse effects in orthodontics. So first of all, my congratulations to explore such issue.

Response to reviewer 3: We thank you for these words

Comment 1
My major concern is about possibility of selection bias due to eligibility criteria stated and the reason to select just the fifth most important journals of orthodontics. There is no clear justification of why the fifth leading journals based on citation reports by Clarivate Analytics and Cochrane database were selected as information source. I'm questioning this, because there are important general dentistry journals or even journals focused only on Systematic Reviews (i.e. this journal in question, Systematic Reviews is not included) and could provide important information. Orthodontics intervention systematic reviews are not only published in this journal, so there is a clear selection bias problem.
Response to comment 1
Thank you very much for bringing up this issue (See also comment 6 of reviewer 2). The selection of these 5 studies was based on impact factor. We included this rationale in the manuscript. (Lines 204-207). We agree that including all systematic reviews of orthodontic interventions in our sample would be interesting. However, selecting a sample of leading journals of a particular field is common practice
in cross-sectional studies in biomedicine. Findings from such studies represent the quality of outcomes of the best journals in a particular field and journals with lower impact factors can take notice. Findings on leading journals in a field usually also have a high external validity for the stakeholders in that field of specialty. If the results of our study will be optimistic, we will definitely perform an additional similar study that takes into account all journals. At this moment this would be a waste, particularly in the context that many systematic reviews are not conducted nor reported according to the highest standards (Ioannidis JP. The Mass Production of Redundant, Misleading, and Conflicted Systematic Reviews and Meta-analyses. Milbank Q. 2016 Sep;94(3):485-514.). It is also important to note that our protocol has been designed for a cross-sectional study and not for a systematic review.

Comment 2
Second, it is not clear if just interventions reviews that stated in their objectives the assessment of adverse effects or all intervention reviews will be included, it also could generate selection bias and must be clear.
Response to comment 2
In the eligibility criteria of our cross-sectional study we have stated that systematic reviews of orthodontic intervention will be eligible. Whether adverse effects were defined as a research objective in these reviews was not listed in our manuscript as an eligibility criteria. Actually this is one of our research questions: Was seeking of adverse effects of interventions defined as a research objective of the review?

Comment 3
Introduction. I suggest to the authors point some possible adverse effects that are slightly or highly common in orthodontics treatments that could appear in the systematic reviews. The statement of possible effects that could be found will strengthen the introduction.
Response to comment 3
This point is addressed by the inclusion of table 2, which lists adverse effects in orthodontics.

Comment 4
I suggest removing the last phrase from the first paragraph of the introduction (pag. 4 line 92). A similar statement was written in the fourth one (pag. 5 line 117).
Response to comment 4
The purpose of the opening paragraph of the introduction of a research study is to capture the readers’ attention and explain the objectives of the paper. Eliminating the last phrase of the first paragraph will eliminate the objectives and we have therefore not followed up on this suggestion.

Comment 5
Methods. Besides the definition of intervention review is in the Glossary of term (Figure 1). More than just the definition of systematic review, the definition of intervention review must be present in the subsection "Study designs" in page 6 or 7.
Response to comment 5
Thank you for bringing this point to our attention. We have included this (Lines 158-160).

Comment 6
I suggest viewing the general comment about the statement "Systematic reviews that focus exclusively on adverse effects of interventions will be excluded" must be reviewed. I suggest removing it, and that kind of reviews must be included due to the possibility of underestimate the prevalence if those articles be excluded.
Response to comment 6
We have addressed this issue under comment 1 of reviewer 2.

Comment 7
Information Source. I suggest viewing the general comment about the journal selection. It must to be modify and well written.
Response to comment 7
We revised the section information sources (Lines 204-213).

Comment 8
Study records. In the Data management subsection, the item about disagreement of eligibility criteria my suggestion is that Persistent disagreements be solved by a third person since the methodologist already be part of the one reviewer. It is clear that will be a discussion first, but after reading the entire paragraph it sounds that RMR decision will be the majority, what is not so appropriate since this reviewer will conduct the first selection and data extraction.
Response to comment 8
Thank you very much for pointing this out. SB is the appropriate methodologist that will be consulted in the case of disagreements. We revised the manuscript accordingly (Lines 223-224).

Comment 9
In the Scoring adverse effects of orthodontic intervention subsection, according to the table 2, that is based in Proteasa et al. (ref. 20) study, pain is not included as adverse effect. Pain could lead to drop-outs in the intervention and it is and adverse effect of an orthodontic treatment. In my opinion, It is mandatory the inclusion of "pain" as additional adverse effect. If this inclusion not be done, will be necessary a strong justification of its absence.
Response to comment 9
Thank you very much for pointing this out. We addressed this comment (Lines 120-122) and (Lines 257-260).

Comment 10
Discussion. The limitation 1, related to the use of the 5 leading it is correct, but not justify the exclusion of other journals, limiting and creating a clear underestimate of the prevalence. Furthermore, the present study is a protocol, if a clear bias was already identified to develop a high-quality study, bias must be avoided. So I strongly recommended the inclusion of other journals eliminating this underestimation and consequently this limitation.
Response to comment 10
We have addressed this issue