PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Motor control exercise for symptomatic lumbar disc herniation: Protocol for a systematic review and meta-analysis
AUTHORS	Pourahmadi, Mohammad Reza; Taghipour, Morteza; Ebrahimi Takamjani, Ismail; Sanjari, Mohammad Ali; Mohseni Bandpei, Mohammad; Keshtkar, Abbasali

VERSION 1 - REVIEW

REVIEWER	Jan Hartvigsen University Of Southern Denmark
REVIEW RETURNED	10-May-2016

GENERAL COMMENTS	This is a nice protocol paper for a systematic review however BMJ Open is not the right outlet. I suggest the authors submit to Systematic Reviews, which is a specialty journal that publishes these protocol papers for reviews all the time: http://systematicreviewsjournal.biomedcentral.com/ When the review is complete and the results known, BMJ Open could be a potential target journal depending on the results.

REVIEWER	Peter Michaelson Department of Health Science, Division of Health and Rehabilitation, Luleå University of Technology,Sweden.
REVIEW RETURNED	14-Jun-2016

GENERAL COMMENTS	I agree with the reviewer that the paper is addressing an important issue, and that there is a need for a systematic review covering motor control exercises as intervention for lumbar disc herniation. In overall the protocol is okay written with a good design. However, there are some issues I believe the authors have to address. Abstract That the paper is a systematic review is never mentioned in the Abstract. Introduction First, the Introduction of the paper is somewhat long and imprecise, and should gain of being condensed. The Objective of the study is both clear, and at the same time unclear. The Objective as written in an open way and provides an opportunity for interpretation and flexibility concerning the Control-treatment. Have the authors any idea of how they wish to systemize the Control treatment into separate groups of treatment?, c.f.

exercise, manual therapy, education and so forth? To have a control-group of "other conservative treatment" is imprecise and would provide an inconclusive result

I also see a potential problem with the Intervention group as the review cover both pre- and post-surgery LDH (Population (page 8) and in Objective (page 7)) in the same comparison. It would be better to split the results into two separate analyses, one population with pre-surgery evaluation and one population for post-surgery evaluation when comparing intervention with control-treatment. And maybe also compare motor control exercises to surgery for LDH. Conclusively, specify your Population (page 8) and Objective (page 7) as pre- AND post-surgery groups and maybe also include a comparison of motor control exercises against surgery.

If a comparison against surgery is not included in Objective and Comparators, then there is a problem with the introduction when augmenting for the necessity of this study (page 7, first paragraph). Here the authors' writes about comparison between conservative treatment and surgery, pointing at studies of low quality and methodological shortcoming of previous performed reviews as a objective for performing this study. Also on page 7 (paragraph "Why is it important to this systematic review") discusses the authors the proposed study in relation to previous systematic reviews covering LDH treatment with surgery as reasons for conducting this study. However, surgery as comparator to MCE are not included in the Objective. Either the authors should change their PICO (and Objective) including a comparison between motor control exercises and surgery, or the introduction should be rewritten, excluding the paragraphs using surgery as intervention when motivating this study.

I believe that the diagnostic criteria for Population (page 8, line 41-48) is somewhat unclear. First, the authors state that only participants with a symptomatic LDH will be included (line 41). After that, the next sentence says: "LDH is defined as a herniation of nucleus and/or annulus fibrosis through the tear of annulus fibrous" and "LDH can lead to LBP and or radicular leg pain (symptomatic LDH)". Altogether, does this mean that the inclusion criteria is a patient with a MRI (or CT) verified LDH that also have back pain and radicular leg pain? This has to be clarified.

The primary outcome of the study is okay. Secondary outcomes are more diverse and somewhat multifaceted and I wonder if it is manageable within the study context.

In the paper, the PEDro –scale are used as a measure of study quality (page 13 line 23 and page 14 line 22). However earlier in the paper the PEDro-scale is defined as a measure for Risk of Bias (paragraph Assessment of Risk of Bias of included studies). The PEDro-scale are usually referred to as to rate quality of randomized trial (c.f. Maher et al. Phys Ther 2003). It would be appropriate if the authors used the same terminology throughout the study, and usually a risk of bias assessment (Furlan 2009) are used together with GRADE assessment of evidence. .

There is a good idea only to include high quality studies (PEDro-rating => 6) (page 12, line 27) when and if possible. However, it is unclear if the statement is for all studies to be included in the paper, or if the statement is valid for each PICO –comparison?

It is unclear what the authors mean with the term limitation in study

design (page 14, line 37) in the paragraph "A summary of findings table". Is limitation in study design the same as Risk of Bias (or Methodological quality) –evaluation of in each evidence (PICO)-grading, and how will the authors address this when using GRADE for establishing the evidence for each main comparison?

REVIEWER	Bruno Saragiotto The George Institute for Global Health, University of Sydney, Australia
REVIEW RETURNED	04-Jul-2016

GENERAL COMMENTS	Thank you for the opportunity to review this manuscript for BMJ open. The protocol of this systematic review is interesting; however, there are some methodological issues that require more information for a decision. Comments are below: - Page 4, line 6: The sentence "for the first time" is unnecessary in this statement. - Page 4, line 22: I don't think this should be included as "Strengths and limitations of this study". Introduction - Overall, the introduction section needs to be more direct and clear. - Page 5, line 53: Not sure about this. These treatments have been shown to be ineffective and are not recommended by the guidelines. This sentence (and references) needs revision. - Page 7, line 8: "However, the study was limited to English-language articles" This is not a good point to use as a limitation of the previous review. The great majority of articles are published in English (and the vastest majority of high-quality research). - Page 7, line 21: What's the link between paediatric patients and this review? The arguments against the previous reviews are weak; maybe it is better just say that they are old-dated and present new trials that were published recently. - Page 8, line 3: The secondary aim does not make much sense as objective. The investigation of heterogeneity should be part of the methods of the review not objective. - Page 8, line 51: The description of the intervention is unclear. What about studies that described the intervention as motor control exercise but omit the principles of motor learning, will be included? If the description is only as "stabilisation exercise or core" will be included? How will the authors deal with different definitions of MCE? - Page 9, line 12: What about adverse events? It is an important outcome (mandatory for all Cochrane reviews for example). - Page 9, line 48: Perhaps it is better to add the search strategy as an appendix. - Page 12, line 12: missing data – what about missing information in the articles (ie, standard deviation, or means). How will the authors deal with that? I think it is better to have a second option if authors do not respond the queries (ie, estimate from other measures?). - Page 12, line 38: "if a large number of high quality studies (≥ 6) will be found based on the PEDro scale during the search, low quality ones will be excluded" – This is a dangerous statement. It is not recommend to exclude low quality trials from the review, instead the authors can perform sensitivity analysis for risk of bias (more appropriated). - Page 12, line 56: "the calculations with a fixed effect model will be repeated using a random effects model as sensitivity analysis". I

	could not understand this statement and the reasons for doing that. Fixed or random effect models should not be used based on the heterogeneity of the data but on the author's assumption that the studies will share a common effect or not. - Page 13, line 10: What if the authors find less than 10 trials to include? Will still use funnel plots? - Page 13, line 53: Heterogeneity is not a reason for not conducting a meta-analysis. This should be downgraded regarding the quality of evidence. - Page 14, line 31: I think the authors should include more details on the quality of evidence assessment. How will they assess each point (ie, risk of bias, indirectness, imprecision, etc).

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Jan Hartvigsen
Institution and Country: University of Southern Denmark, UK
Competing Interests: I have no competing interests
This is a nice protocol paper for a systematic review however BMJ Open is not the right outlet. I suggest the authors submit to Systematic Reviews, which is a specialty journal that publishes these protocol papers for reviews all the time:
http://systematicreviewsjournal.biomedcentral.com/

When the review is complete and the results known, BMJ Open could be a potential target journal depending on the results.

Response: Thank you very much indeed for your positive feedback. We appreciate it a lot. One reason that we didn't submit this protocol to Systematic Reviews is that "article-processing charges" were too high for us to pay and we didn't receive any financial aid.

Reviewer: 2
Reviewer Name: Peter Michaelson
Institution and Country: Department of Health Science, Division of Health and Rehabilitation, Luleå University of Technology, Sweden.
Competing Interests: None declared
I agree with the reviewer that the paper is addressing an important issue, and that there is a need for a systematic review covering motor control exercises as intervention for lumbar disc herniation. In overall the protocol is okay written with a good design.
However, there are some issues I believe the authors have to address.
Abstract
Question 1: That the paper is a systematic review is never mentioned in the Abstract.
Response 1: We mentioned the "systematic review" 3 times in the abstract. We revised the abstract according to the change suggested by the respectable reviewer.
Introduction
Question 2: First, the Introduction of the paper is somewhat long and imprecise, and should gain of being condensed.
Response 2: We removed unnecessary parts and sentences.
Question 3: The Objective of the study is both clear, and at the same time unclear. The Objective as written in an open way and provides an opportunity for interpretation and flexibility concerning the Control-treatment. Have the authors any idea of how they wish to systemize the Control treatment into separate groups of treatment?, c.f. exercise, manual therapy, education and so forth? To have a control-group of "other conservative treatment" is imprecise and would provide an inconclusive result

Response 3: We edited the objective according to Saragiotto et al. (2016)1, Macedo et al. (2016)2, and Yamato et al. (2015)3. We removed the control group. This time we hope this type of writing can convince the reviewer.

References:
1. Saragiotto BT, Maher CG, Yamato TP, et al. Motor control exercise for chronic non-specific low-back pain. The Cochrane Library 2016.
2. Macedo LG, Saragiotto BT, Yamato TP, et al. Motor control exercise for acute non-specific low back pain. The Cochrane Library 2016.
3. Yamato TP, Maher CG, Saragiotto BT, et al. Pilates for low back pain. The Cochrane Library 2015.
Question 4: I also see a potential problem with the Intervention group as the review cover both pre- and post-surgery LDH (Population (page 8) and in Objective (page 7)) in the same comparison. It would be better to split the results into two separate analyses, one population with pre-surgery evaluation and one population for post-surgery evaluation when comparing intervention with control-treatment. And maybe also compare motor control exercises to surgery for LDH. Conclusively, specify your Population (page 8) and Objective (page 7) as pre- AND post-surgery groups and maybe also include a comparison of motor control exercises against surgery.
Response 4: The population and objectives sections were modified according to the change suggested by the respectable reviewer.
Question 5: If a comparison against surgery is not included in Objective and Comparators, then there is a problem with the introduction when augmenting for the necessity of this study (page 7, first paragraph). Here the authors' writes about comparison between conservative treatment and surgery, pointing at studies of low quality and methodological shortcoming of previous performed reviews as a objective for performing this study. Also on page 7 (paragraph "Why is it important to this systematic review") discusses the authors the proposed study in relation to previous systematic reviews covering LDH treatment with surgery as reasons for conducting this study. However, surgery as comparator to MCE are not included in the Objective. Either the authors should change their PICO (and Objective) including a comparison between motor control exercises and surgery, or the introduction should be rewritten, excluding the paragraphs using surgery as intervention when motivating this study.
Response 5: "Surgery" has been added in the Comparators section.

Question 6: I believe that the diagnostic criteria for Population (page 8, line 41-48) is somewhat unclear. First, the authors state that only participants with a symptomatic LDH will be included (line 41). After that, the next sentence says: "LDH is defined as a herniation of nucleus and/or annulus fibrosis through the tear of annulus fibrous" and "LDH can lead to LBP and or radicular leg pain (symptomatic LDH)". Altogether, does this mean that the inclusion criteria is a patient with a MRI (or CT) verified LDH that also have back pain and radicular leg pain? This has to be clarified.
Response 6: We revised and re-wrote the population part again and according to previous related papers.
Question 7: The primary outcome of the study is okay. Secondary outcomes are more diverse and somewhat multifaceted and I wonder if it is manageable within the study context.
Response 7: We selected secondary outcomes based on primary studies. We believe that there are sufficient number of studies for the secondary outcomes and it is possible to perform meta-analyses for their results separately. However, we will try our best to manage the secondary outcomes within our systematic review.
Question 8: In the paper, the PEDro –scale are used as a measure of study quality (page 13 line 23 and page 14 line 22). However earlier in the paper the PEDro-scale is defined as a measure for Risk of Bias (paragraph Assessment of Risk of Bias of included studies). The PEDro-scale are usually referred to as to rate quality of randomized trial (c.f. Maher et al. Phys Ther 2003). It would be appropriate if the authors used the same terminology throughout the study, and usually a risk of bias assessment (Furlan 2009) are used together with GRADE assessment of evidence.

Response 8: We edited the paragraph. We removed the PEDro scale and replaced it with the risk of bias assessment form described by Furlan et al.1 Furthermore, we tried to use the same terminology and maintain the consistency in writing styles throughout the revised version of the manuscript.

Reference:
1. Furlan AD, Pennick V, Bombardier C, et al. 2009 updated method guidelines for systematic reviews in the Cochrane Back Review Group. Spine 2009;34(18):1929-41.
Question 9: There is a good idea only to include high quality studies (PEDro-rating => 6) (page 12, line 27) when and if possible. However, it is unclear if the statement is for all studies to be included in the paper, or if the statement is valid for each PICO –comparison?
Response 9: Another reviewer of this paper believe that it is dangerous to exclude low quality studies. He stated that "… It is not recommended to exclude low quality trials from the review, instead the authors can perform sensitivity analysis for risk of bias (more appropriated) …". Therefore, we decided to include studies based on the PICO criteria and perform sensitivity analysis for RoB of included articles.

Question 10: It is unclear what the authors mean with the term limitation in study design (page 14, line 37) in the paragraph "A summary of findings table". Is limitation in study design the same as Risk of Bias (or Methodological quality) –evaluation of in each evidence (PICO)-grading, and how will the authors address this when using GRADE for establishing the evidence for each main comparison?
Response 10: According to GRADE handbook (SA version) - GDT - Guideline Development Tool (http://gdt.guidelinedevelopment.org/app/handbook/handbook.html#h.gwd531rylwaj):
"… 5.2.1 Study limitations (Risk of Bias [RoB]):
Limitations in the study design and execution may bias the estimates of the treatment effect. Our confidence in the estimate of the effect and in the following recommendation decreases if studies suffer from major limitations. The more serious the limitations are, the more likely it is that the quality of evidence will be downgraded. Numerous tools exist to evaluate the risk of bias in randomized trials and observational studies…" In this review, RoB among the included studies will be assessed with a RoB assessment form described by Furlan et al.
If: RoB: low ◊ GRADE assessment of study limitations: No serious limitations, do not downgrade
If: RoB: Unclear ◊ GRADE assessment of study limitations: No serious limitations, do not downgrade (Consideration: potential limitations are unlikely to lower confidence in the estimate of effect) OR Serious limitations, downgrade one level (Consideration: potential limitations are likely to lower confidence in the estimate of effect)
If: RoB: high ◊ GRADE assessment of study limitations: Serious limitations, downgrade one level OR Very serious limitations, downgrade two levels

The authors would like to thank you for your insightful and detailed comments on our paper. We hope that the point-by-point responses and the revised version of our paper meet your requirement.
Reviewer: 3
Reviewer Name: Bruno Saragiotto
Institution and Country: The George Institute for Global Health, University of Sydney, Australia
Competing Interests: None
Thank you for the opportunity to review this manuscript for BMJ open. The protocol of this systematic review is interesting; however, there are some methodological issues that require more information for a decision. Comments are below:

Question 1: Page 4, line 6: The sentence "for the first time" is unnecessary in this statement.
Response 1: The sentence was removed according to the change suggested by the respectable

reviewer.

Question 2: Page 4, line 22: I don't think this should be included as "Strengths and limitations of this study".
Response 2: The bullet has been removed.
Introduction
Question 3: Overall, the introduction section needs to be more direct and clear.
Response 3: Unnecessary parts and sentences have been removed.
Question 4: Page 5, line 53: Not sure about this. These treatments have been shown to be ineffective and are not recommended by the guidelines. This sentence (and references) needs revision.
Response 4: The sentences were edited and revised.

Question 5: Page 7, line 8: "However, the study was limited to English-language articles" This is not a good point to use as a limitation of the previous review. The great majority of articles are published in English (and the vastest majority of high-quality research).
Response 5: The sentence was revised.

Question 6: Page 7, line 21: What's the link between paediatric patients and this review? The arguments against the previous reviews are weak; maybe it is better just say that they are old-dated and present new trials that were published recently.
Response 6: We removed that paper from the revised version of the manuscript.

Question 7: Page 8, line 3: The secondary aim does not make much sense as objective. The investigation of heterogeneity should be part of the methods of the review not objective.
Response 7: We edited the objective according to Saragiotto et al. (2016)1, Macedo et al. (2016)2, and Yamato et al. (2015)3.

References:
1. Saragiotto BT, Maher CG, Yamato TP, et al. Motor control exercise for chronic non-specific low-back pain. The Cochrane Library 2016.
2. Macedo LG, Saragiotto BT, Yamato TP, et al. Motor control exercise for acute non-specific low back pain. The Cochrane Library 2016.
3. Yamato TP, Maher CG, Saragiotto BT, et al. Pilates for low back pain. The Cochrane Library 2015.

Question 8: Page 8, line 51: The description of the intervention is unclear. What about studies that described the intervention as motor control exercise but omit the principles of motor learning, will be included? If the description is only as "stabilisation exercise or core" will be included? How will the authors deal with different definitions of MCE?
Response 8: The invaluable comment of the respectable editor is highly appreciated. The description of the intervention was modified by further explanation.

Question 9: Page 9, line 12: What about adverse events? It is an important outcome (mandatory for all Cochrane reviews for example).
Response 9: We added adverse events in the secondary outcomes.

Question 10: Page 9, line 48: Perhaps it is better to add the search strategy as an appendix.
Response 10: We added the search syntax as an APPENDIX.
Question 11: Page 12, line 12: missing data – what about missing information in the articles (ie, standard deviation, or means). How will the authors deal with that? I think it is better to have a second option if authors do not respond the queries (ie, estimate from other measures?).
Response 11: The paragraph entitled "dealing with missing data" has been revised and modified.
Question 12: Page 12, line 38: "if a large number of high quality studies (≥ 6) will be found based on

the PEDro scale during the search, low quality ones will be excluded" – This is a dangerous statement. It is not recommend to exclude low quality trials from the review, instead the authors can perform sensitivity analysis for risk of bias (more appropriated).

Response 12: We will not exclude low quality trials. As you recommended, we will perform sensitivity analysis for RoB. Thank you very much for your interesting suggestion.

Question 13: Page 12, line 56: "the calculations with a fixed effect model will be repeated using a random effects model as sensitivity analysis". I could not understand this statement and the reasons for doing that. Fixed or random effect models should not be used based on the heterogeneity of the data but on the author's assumption that the studies will share a common effect or not.

Response 13: The paragraph entitled "assessment of heterogeneity" has been edited and modified.

Question 14: Page 13, line 10: What if the authors find less than 10 trials to include? Will still use funnel plots?

Response 14: We will not assess reporting bias when less than 10 studies are included.

Question 15: Page 13, line 53: Heterogeneity is not a reason for not conducting a meta-analysis. This should be downgraded regarding the quality of evidence.

Response 15: We stated that "If sufficient homogenous primary studies are available we will conduct a meta-analysis".1-4 However we edited the sentence according to respectable reviewver.

References:
1. Saragiotto BT, Maher CG, Yamato TP, et al. Motor control exercise for chronic non-specific low-back pain. The Cochrane Library 2016.
2. Macedo LG, Saragiotto BT, Yamato TP, et al. Motor control exercise for acute non-specific low back pain. The Cochrane Library 2016.
3. Yamato TP, Maher CG, Saragiotto BT, et al. Pilates for low back pain. The Cochrane Library 2015.
4. Cramer H, Haller H, Lauche R, Dobos G. Mindfulness-based stress reduction for low back pain. A systematic review. BMC Complement Altern Med. 2012;12: 162.

Question 16: Page 14, line 31: I think the authors should include more details on the quality of evidence assessment. How will they assess each point (ie, risk of bias, indirecteness, imprecision, etc).

Response 16: We added more information on the quality of evidence assessment in the revised version of the manuscript.

After working hard on revising the manuscript according to the changes suggested by the respectable reviewer, we hope that the point-by-point responses and the revised version of our paper meet your requirement. Thank you very much for your very helpful and constructive comments, which we indeed appreciated.

VERSION 2 – REVIEW

REVIEWER	Bruno Saragiotto The George Institute for Global Health, Australia
REVIEW RETURNED	27-Jul-2016

GENERAL COMMENTS	I would like to thank the authors for their hard work on implementing all my suggestions; the quality of the review will be much better now. It is really important to work hard on the protocol so that can guide the process of the systematic review. It is a really good protocol now and the authors will end up with a high quality review. I just have two

	final comments to add that I would like to see it done before acceptance. 1) I did not think the authors should change their risk of bias assessment to the Cochrane tool. The PEDro scale is the most reliable and validity scale for methodological quality (better validity than Cochrane tool), and has the advantage of downloading the scores from the PEDro website, so I don't see a point to use this tool, unless it is a Cochrane review. 2) I think the GRADE assessment need more details; perhaps in an appendix the author can describe the domains and how to assess each of them.

VERSION 2 – AUTHOR RESPONSE

Reviewer Name: Bruno Saragiotto
Institution and Country: The George Institute for Global Health, Australia
Competing Interests: None
I would like to thank the authors for their hard work on implementing all my suggestions; the quality of the review will be much better now. It is really important to work hard on the protocol so that can guide the process of the systematic review. It is a really good protocol now and the authors will end up with a high quality review. I just have two final comments to add that I would like to see it done before acceptance.
Thank you very much indeed for your positive feedback. We appreciate it a lot. The quality of this protocol has been greatly improved.
Question 1: I did not think the authors should change their risk of bias assessment to the Cochrane tool. The PEDro scale is the most reliable and validity scale for methodological quality (better validity than Cochrane tool), and has the advantage of downloading the scores from the PEDro website, so I don't see a point to use this tool, unless it is a Cochrane review.
Response 1: In the first version of the manuscript, we selected the PEDro scale. In the first revision, a respectable reviewer asked us to replace the PEDro scale with a RoB assessment tool described by Furlan et al. However, in this revision we changed the RoB assessment tool to the PEDro scale, according to the change suggested by the respectable reviewer.
Question 2: I think the GRADE assessment need more details; perhaps in an appendix the author can describe the domains and how to assess each of them.
Response 2: We added more details about the domains and their assessment in Appendix 2.
The authors would like to thank you for your insightful and detailed comments on our paper. We hope that the point-by-point responses and the revised version of our paper meet your requirement.