PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Protocol of the Randomised Placebo Controlled Pilot Trial of the Management of Acute Sciatica (SCIATICA): A Feasibility Study.
AUTHORS	Lassere, Marissa; Johnson, Kent; Thom, Jeanette; Pickard, Grant; Smerdely, Peter

VERSION 1 – REVIEW

REVIEWER	Esther Maas University of British Columbia Canada
REVIEW RETURNED	15-Dec-2017

GENERAL COMMENTS	Summary: This is a protocol of a pilot study that aims to evaluate the feasibility of undertaking a 4-arm randomized controlled comparative effectiveness study of (1) CT-guided peri-neural steroid injection and (2) systemic steroids (tapering dose over 15 days of oral dexamethasone) in a blinded randomized sham and placebo controlled trial. Overall, it will be a very ambitious study, and I praise the authors for setting this up, and first doing a pilot study and publishing the protocol. However, the manuscript has some inconsistencies and requires clarification on a number of issues. Major comments: - The introduction is very elaborate, and gives a complete overview of the existing literature in the field. I praise the authors for that, but some information is redundant and doesn't add to explaining the rationale of the current study. Please shorten this introduction. Examples: o Briefly explain the difference between radiculopathy and sciatica, and state how sciatica is defined in the current study. o The 4th, 5th, and 6th paragraph move back and forth between information about the transforaminal approach, and reviews about epidural steroids in general. I thought this was confusing, and unnecessary long. Try to shorten it, and provide the information for a broader towards a narrower topic. - The description of the four trial arms is confusing. I am aware that this manuscripts will mostly be read my experts in the field, but an inconsistent use of terminology makes reading this manuscript unnecessary complicated. Different terminology is used to explain the interventions and control groups in the text, the figure, and at clinicaltrial.gov. Please explain possible different wordings used to for the treatments, and then continue with 1. I would suggest

	to use the terminology as used at clinicaltrial.gov, unless there's a specific reason not to, or in case something has changed. - What is the rationale for performing an economic evaluation, and especially an economic evaluation with the perspective from the healthcare sector? A lot of questions remain considering the economic evaluation: o Which of the comparisons will be used for the economic evaluation? o When will peri-neural steroid injections or systemic steroids be considered cost-effective? Both are compared to placebo, instead of to usual care (which is more common in economic evaluations), so how will the results be interpreted in terms of cost-effectiveness? o An economic evaluation is not something that can be 'piggybacked' to an RCT. It ideally requires a separate sample size calculation, and specific information on the statistical analyses. Please add this to the current version of the protocol, or mention that this will be explained in the protocol of the full RCT. o The table and clinicaltrial.gov mention that work/health utilization costs are being measured. Which questionnaire will used for this, and how will this be analyzed? - The statistical analysis paragraph is missing information. Although the main aim of this pilot study is to evaluate the feasibility of this study, and determine the sample size of the full RCT, it is mentioned that the effects of treatment on the ODI will be determined. Please add how missing data will be handled, and add on the analyses of the economic evaluation. Minor comments: - First of all, be consistent in the use of terminology considering the interventions and trial arms. In the current version of the manuscript this is confusing. - Please be consistent in the use of abbreviations. Please check the complete manuscript, but these are some examples: o Page 3, line 42: CT & MRI (used without first writing it in full) o Page 4, line 41: IM, IV (used without first writing it in full) o Page 5, line 13: 'randomized controlled trial' is used when RCT is used before o Page 5, line 15: 'computed tomography' is used when CT is used before o Page 6, line 42: FBC, CRP, ESR (used without first writing it in full) o Figure 1: PRO (add abbreviation in legend) o Page 8, line 44: Visual analogue scale; add (VAS) before using the abbreviation in the next line o page 11, line 10: ED (used without first writing it in full) - Which version of the EQ-5D will be used: EQ-5D-3L or EQ-5D-5L? - I would recommend considering to perform a sensitivity analysis to compare QALYs using the EQ-5D and the SF-36 (converted to SF-6D QALY's)

	- Only in the discussion you mention the main comparison is arm 1 – 4; it would have been helpful to mention this earlier in the manuscript - Strength & limitations: Be careful with statement about generalizability in a single center study. I would appreciate some nuance about this statement. - Check for typos: o Page 3, line 23: 'a inception' = 'an inception' o Page 3, line 24: 'at by'

REVIEWER	Eva Rasmussen Barr Karolinska Institutet ,Department of Neurobiology, Care Sciences and Society, Division of Physiotherapy, Karolinska Institutet, Stockholm, Sweden
REVIEW RETURNED	26-Dec-2017

GENERAL COMMENTS	The authors have undertaken an imporant area to investigate. The research design is intresting and somewhat complicated. I am unsure of the comparisons as they include both active and placebo parts. I have some comments. 1. Pls include recent Cochrane Reviews on the effects of NSAIDs published in 2016, and 2017 on The effects of NSAID in scitatica. One is also published in Spine 2017. 2. I find that a Power calculation should be provided as there are so many comparisons. I understand that this is only a pilot but will it be possible to conduct a trial with so many comparisons? 3. Bullet points - I find that the bullet point on power calculation is neither a strenght nor a limitation. 4. Bullet points - I find that the last two bullet points are not strenght or limitatations but might be part of the discussion.

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1
Reviewer Name: Esther Maas

Institution and Country: University of British Columbia, Canada

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below
Summary:
This is a protocol of a pilot study that aims to evaluate the feasibility of undertaking a 4-arm randomized controlled comparative effectiveness study of (1) CT-guided peri-neural steroid injection and (2) systemic steroids (tapering dose over 15 days of oral dexamethasone) in a blinded randomized sham and placebo controlled trial.
Overall, it will be a very ambitious study, and I praise the authors for setting this up, and first doing a pilot study and publishing the protocol. However, the manuscript has some inconsistencies and requires clarification on a number of issues.

Major comments:
- The introduction is very elaborate, and gives a complete overview of the existing literature in the field. I praise the authors for that, but some information is redundant and doesn't add to explaining the rationale of the current study. Please shorten this introduction. Examples:

o Briefly explain the difference between radiculopathy and sciatica, and state how sciatica is defined in the current study.
We have revised the opening paragraph to clarify the differences between nonprofessional use of the term sciatica and professional use of the terms radicular pain and radiculopathy as best we can, given that there are experts that have strong views on these definitions. We have provided our definition. This study defines the term sciatica as radicular pain with or without radiculopathy from lumbosacral nerve root pathology.

o The 4th, 5th, and 6th paragraph move back and forth between information about the transforaminal approach, and reviews about epidural steroids in general. I thought this was confusing, and unnecessary long. Try to shorten it, and provide the information for a broader towards a narrower topic.

Paragraphs 4, 5, 6 and 7 have been reduced to two paragraphs 4 and 5 (537 to 388 words) and made changes so that the topics change from broad to narrow, as recommended. We have also provided a summary paragraph at end of the introduction that provides the rationale for this pilot/feasibility study.

- The description of the four trial arms is confusing. I am aware that this manuscripts will mostly be read my experts in the field, but an inconsistent use of terminology makes reading this manuscript unnecessary complicated. Different terminology is used to explain the interventions and control groups in the text, the figure, and at clinicaltrial.gov. Please explain possible different wordings used to for the treatments, and then continue with 1. I would suggest to use the terminology as used at clinicaltrial.gov, unless there's a specific reason not to, or in case something has changed.

We revised the manuscript so that all the terminology used to explain the interventions and control groups in the text, the figure, and at clinicaltrial.gov are consistent, including adding the table from clinical trials.gov. The only change from clinical trials.gov is that we have used the term intervention instead of experimental and changed the order of the epidural steroids used so that dexamethasone always appears before betamethasone to reflect that most participants will receive dexamethasone .

- What is the rationale for performing an economic evaluation, and especially an economic evaluation with the perspective from the healthcare sector?

The rationale for undertaking an economic evaluation is to evaluate the feasibility of undertaking a prespecified cost-effectiveness economic evaluation in the main study. In Australia, all drugs and more recently, some procedures, must undergo a cost-effectiveness analysis to determine whether they will be subsidised by the Australian government. This is usually performed from the perspective of the health-care sector rather than from the societal perspective. In this pilot/feasibility study we will ascertain the feasibility of obtaining the outcome (including QALYs) and cost data in a valid manner, determine how much outcome and cost data are missing, and obtain estimates of mean and standard deviation of outcomes and costs.

A lot of questions remain considering the economic evaluation:
o Which of the comparisons will be used for the economic evaluation?

In this pilot/feasibility study all participants in all study arms have concomitant usual care therapy as directed by the treating physician(s) with analgesics, NSAIDS, pregabalin and physical therapies. None of the comparisons will have valid effectiveness estimates as this is a pilot/feasibility study that is not designed to determine effectiveness. However, the comparisons of interest that will be undertaken are:
Arm 1 to Arm 4 - epidural steroid versus control (usual care alone)
Arm 3 to Arm 4 - oral steroid versus control (usual care alone)
Arm 1 to Arm 3 - epidural steroid versus oral steroid)
(also refer to response to Reviewer 2, Comment 2 on page 5)

o When will peri-neural steroid injections or systemic steroids be considered cost-effective? Both are compared to placebo, instead of to usual care (which is more common in economic evaluations), so how will the results be interpreted in terms of cost-effectiveness?

In this pilot/feasibility study all participants in all study arms have concomitant usual care therapy as directed by the treating physician(s) with analgesics, NSAIDS, pregabalin and physical therapies. Arm 4 is the usual care arm. Also see the response to the above.

o An economic evaluation is not something that can be 'piggybacked' to an RCT. It ideally requires a separate sample size calculation, and specific information on the statistical analyses. Please add this to the current version of the protocol, or mention that this will be explained in the protocol of the full RCT.

The estimates of the sample size in the full RCT will be determined from this pilot/feasibility study and both this and the specific information on the statistical analysis will be explained in the protocol of the full RCT.

o The table and clinicaltrial.gov mention that work/health utilization costs are being measured. Which questionnaire will used for this, and how will this be analyzed?

These costs are determined by the Australian Pharmaceutical Benefits Advisory Committee (PBAC) Manual of Resources items and their associated costs used for economic analyses[1]. The PBAC does not require questionnaires of productivity such as the PRODISQ[2] and similar questionnaires of resource utilization. Our Case Report Form includes days missed from paid employment (if applicable) because of sciatica, use of health services such as doctor, other health-care provider related visits (e.g. acupuncture, chiropractic), injection procedures and neurosurgery. This information will be obtained by interview at each visit. For the analysis will be use the PBAC Guidelines. One of the investigators (KJ) previously performed economic analyses for the PBAC.

- The statistical analysis paragraph is missing information. Although the main aim of this pilot study is to evaluate the feasibility of this study, and determine the sample size of the full RCT, it is mentioned that the effects of treatment on the ODI will be determined. Please add how missing data will be handled, and add on the analyses of the economic evaluation.

This is in the revised manuscript. See sample size and data/statistical analysis plan sections

Minor comments:
- First of all, be consistent in the use of terminology considering the interventions and trial arms. In the current version of the manuscript this is confusing.

We have revised the manuscript to ensure consistency across terminology.

- Please be consistent in the use of abbreviations. Please check the complete manuscript, but these are some examples:
o Page 3, line 42: CT & MRI (used without first writing it in full)
o Page 4, line 41: IM, IV (used without first writing it in full)
o Page 5, line 13: 'randomized controlled trial' is used when RCT is used before
o Page 5, line 15: 'computed tomography' is used when CT is used before
o Page 6, line 42: FBC, CRP, ESR (used without first writing it in full)
o Figure 1: PRO (add abbreviation in legend)
o Page 8, line 44: Visual analogue scale; add (VAS) before using the abbreviation in the next line
o page 11, line 10: ED (used without first writing it in full)

WE have checked for typos and corrected these.

- Which version of the EQ-5D will be used: EQ-5D-3L or EQ-5D-5L?
We are using the EQ-5D-5L.

- I would recommend considering to perform a sensitivity analysis to compare QALYs using the EQ-5D and the SF-36 (converted to SF-6D QALY's)
We have included this in the revision.

- Only in the discussion you mention the main comparison is arm 1 – 4; it would have been helpful to mention this earlier in the manuscript
It is now included in the first paragraph of the methods.

- Strength & limitations: Be careful with statement about generalizability in a single center study. I would appreciate some nuance about this statement.
We have made changes to ensure that are not overstating generalizability.

- Check for typos:
o Page 3, line 23: 'a inception' = 'an inception'
o Page 3, line 24: 'at by'

Reviewer: 2
Reviewer Name: Eva Rasmussen-Barr

Institution and Country: Karolinska Institutet ,Department of Neurobiology, Care Sciences and Society, Division of Physiotherapy, Karolinska Institutet, Stockholm, Sweden

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below
The authors have undertaken an important area to investigate. The research design is interesting and somewhat complicated. I am unsure of the comparisons as they include both active and placebo parts. I have some comments.

1. Pls include recent Cochrane Reviews on the effects of NSAIDs published in 2016, and 2017 on The effects of NSAID in sciatica. One is also published in Spine 2017.
Both are now included.

2. I find that a Power calculation should be provided as there are so many comparisons. I understand that this is only a pilot but will it be possible to conduct a trial with so many comparisons?
There are 6 possible comparisons in a 4 arm trial. However, generally controlling for type 1 error rate is not needed when several different experimental arms are compared with the control [3], [4], [5]. Therefore no multiplicity adjustment is needed for:
Comparison I: Arm 1 versus Arm 4 (epidural steroid is superior to control).
Comparison II: Arm 2 versus Arm 4 (epidural saline is superior to control).
Comparison III: Arm 3 versus Arm 4 (oral steroid is superior to control).
However, in order to proceed to the following comparison:
Comparison IV: Arm 1 versus Arm 3 (epidural steroid is superior to oral steroids, we must first demonstrate that Comparisons I and III were statistical significant, and there must be a type 1 error adjustment, for which there are several methods published [5], [6]. If we would like to determine whether epidural steroid is non-inferior to oral steroids, then the ignorable difference must also be prespecified. The pilot/feasibility study will provide data that will be helpful in determining these sample size calculations.

3. Bullet points - I find that the bullet point on power calculation is neither a strength nor a limitation.
We have removed this bullet point.

4. Bullet points - I find that the last two bullet points are not strength or limitations but might be part of the discussion.
No discussion is permitted in BMJ Open. We have removed the last bullet and modified the 4th bullet to include patients.

1. Commonwealth of Australia as represented by the Department of Health. Guidelines for preparing a submission to the Pharmaceutical Benefits Advisory Committee (Version 5.0). https://pbacpbsgovau/content/information/files/pbac-guidelines-version-5pdf 2016
2. Koopmanschap MA. PRODISQ: a modular questionnaire on productivity and disease for economic evaluation studies. Expert review of pharmacoeconomics & outcomes research 2005;5(1):23-8 doi: 10.1586/14737167.5.1.23[published Online First: Epub Date]|.
3. Proschan MA, Waclawiw MA. Practical guidelines for multiplicity adjustment in clinical trials. Controlled clinical trials 2000;21(6):527-39
4. Baron G, Perrodeau E, Boutron I, et al. Reporting of analyses from randomized controlled trials with multiple arms: a systematic review. BMC medicine 2013;11:84 doi: 10.1186/1741-7015-11-84[published Online First: Epub Date]|.
5. Wason JM, Stecher L, Mander AP. Correcting for multiple-testing in multi-arm trials: is it necessary and is it done? Trials 2014;15:364 doi: 10.1186/1745-6215-15-364[published Online First: Epub Date]|.
6. Bender R, Lange S. Adjusting for multiple testing--when and how? Journal of clinical epidemiology 2001;54(4):343-9

FORMATTING AMENDMENTS (if any)
Required amendments will be listed here; please include these changes in your revised version:

VERSION 2 – REVIEW

REVIEWER	Esther Maas University of British Columbia, Vancouver, Canada
REVIEW RETURNED	22-Feb-2018

GENERAL COMMENTS	Dear authors, Thank you for considering my comments on the first submission. You have addressed most of the concerns from both reviewers very clearly. Also, the included table with the description of the trial arms is very helpful and a good addition to the paper. I only have three points that I would like to see clarified further: 1. As requested by the editor, you removed the word 'effectiveness' from the title and throughout the study. However, in the body of the text you replace this with 'efficacy'. However, doing a pilot/feasability study where all participants have concomitant usual care (which is required for the economic evaluation as well), is not an efficacy study. This is a feasibility study to inform the RCT in which you will investigate the effectiveness and cost-effectiveness of transforaminal epidural steroid versus systemic steroids. Please adjust this throughout the manuscript. 2. In the description of the statistical analysis plan, you state: "The random-effects portion of the model specifies that months are a random effect. Analyses will be undertaken unadjusted and adjusted for medication use and other covariates." If I am correct, each measurement (so time) is a level, and not the months. Secondly, I would like to see a clearer description of the choice of covariates. Will you predefine the covariates, or base them on the differences found in this feasability study? 3. In the economic evaluation description, you state that you will evaluate the incremental cost per ODI or QALY. I assume you will evaluate the incremental cost per point on the ODI or per 10 points?

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Esther Maas

Institution and Country: University of British Columbia, Vancouver, Canada

Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below
Dear authors,

Thank you for considering my comments on the first submission. You have addressed most of the concerns from both reviewers very clearly. Also, the included table with the description of the trial arms is very helpful and a good addition to the paper. I only have three points that I would like to see clarified further:

1. As requested by the editor, you removed the word 'effectiveness' from the title and throughout the study. However, in the body of the text you replace this with 'efficacy'. However, doing a pilot/feasability study where all participants have concomitant usual care (which is required for the economic evaluation as well), is not an efficacy study. This is a feasibility study to inform the RCT in which you will investigate the effectiveness and cost-effectiveness of transforaminal epidural steroid versus systemic steroids. Please adjust this throughout the manuscript.

Thank you for bringing our attention. We have removed the word efficacy from all places that refers to our feasibility study. The word efficacy only appears in the descriptions in the background of previous research.

2. In the description of the statistical analysis plan, you state: "The random-effects portion of the model specifies that months are a random effect. Analyses will be undertaken unadjusted and adjusted for medication use and other covariates." If I am correct, each measurement (so time) is a level, and not the months.
Yes this is correct it's the measurement at each time. The software that I use specifies the time interval in the command codes which here is months. I will correct this in the manuscript to clarify.

Secondly, I would like to see a clearer description of the choice of covariates. Will you predefine the covariates, or base them on the differences found in this feasibility study?

The other covariates are predefined and are now specified in the manuscript. Essentially they are:
- presence of a definite motor radiculopathy or not
- days from onset of sciatica pain to delivery of the intervention,
- whether the imaging demonstrates (a) a prolapsed disc, (b) a sequestered disc or (c) a extruded disc fragment,
- whether imaging demonstrates bony/osteophytic narrowing of the neural exit foramen or not,
- age

3. In the economic evaluation description, you state that you will evaluate the incremental cost per ODI or QALY. I assume you will evaluate the incremental cost per point on the ODI or per 10 points?

In this feasibility study we will do it on cost per point rather than categorising the ODI over a 10 point scale.

VERSION 3 – REVIEW

REVIEWER	Esther Maas University of British Columbia, Canada
REVIEW RETURNED	06-Apr-2018

GENERAL COMMENTS	Dear authors, Thank you for revising my comments in the previous reviews. I only have 2 minor comments that came up while reading the current version of the manuscript: 1. The description of the random-effects model is still hard to follow. Probably I am confused because you mention that the random-effects portion of the model is time measured each month. However, if I look at Table 2, the measurements are weekly for the first period and 6-weekly at the long-term follow-up. So does the software you are using specify the monthly time frames? This still requires a bit more clarification. I made a suggestion for the description of the random-effects model: "The random-effect portion of the model is time, which here is each measurement, treated in the model as monthly time intervals" (?) Please adjust, or further clarify the use of monthly time frames in the random-effects model. Thank you. 2. The first sentence in the paragraph "Patient and Public Involvement" incudes twice 'in the'. This is just a typo, but please correct.

VERSION 3 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1
Reviewer Name: Esther Maas
Institution and Country: University of British Columbia, Canada

Please leave your comments for the authors below
Dear authors,

Thank you for revising my comments in the previous reviews. I only have 2 minor comments that came up while reading the current version of the manuscript:

1. The description of the random-effects model is still hard to follow. Probably I am confused because you mention that the random-effects portion of the model is time measured each month. However, if I look at Table 2, the measurements are weekly for the first period and 6-weekly at the long-term follow-up. So does the software you are using specify the monthly time frames? This still requires a bit more clarification. I made a suggestion for the description of the random-effects model: "The random-effect portion of the model is time, which here is each measurement, treated in the model as monthly time intervals" (?) Please adjust, or further clarify the use of monthly time frames in the random-effects model. Thank you.
Thank you. We have made the changes you have suggested.

"We will also use a multilevel linear mixed model to evaluate the ODI. In this linear mixed model, the intercept, treatment arm, time(weeks) and treatment arm by time (weeks) interaction are a fixed effect and intercept and time (weeks) are a random effect. This allows individual random variation around the change in ODI over time as well as around the intercept."

2. The first sentence in the paragraph "Patient and Public Involvement" incudes twice 'in the'. This is just a typo, but please correct.

We have deleted the second "in the"