

## 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

<b>TITLE (PROVISIONAL)</b>	Surgical versus Conservative Treatment for Lumbar Disc Herniation: A Prospective Cohort Study
<b>AUTHORS</b>	Gugliotta, Marinella; da Costa, Bruno; Dabis, Essam; Theiler, Robert; Jüni, Peter; reichenbach, stephan; Landolt, Hans; Hasler, Paul

### VERSION 1 - REVIEW

<b>REVIEWER</b>	Katarina Silverplats Department of Orthopaedic, Sahlgrenska University Hospital Swedish Armed Forces/Centre of Defence Medicine
<b>REVIEW RETURNED</b>	21-Jun-2016

<b>GENERAL COMMENTS</b>	<p>1. p.4 l.53 Aim of the study is to compare the effect of surgical and conservative treatment on sciatica symptom severity and quality of life in patients with lumbar disc herniation. The aim is not answered in the results and conclusions. What about radiculopathy symptoms after surgery or conservative treatment? Quality of life? In abstract there is a different aim based on "symptomatic lumbar disc herniation".</p> <p>2. p.2 l.16 Primary outcomes were pain. What kind of pain? Leg pain, back pain? What about quality of life? When it is one of your question in the aim, I would like to have it as a primary outcome as well.</p> <p>6. Outcomes are defined as primary and secondary, but do not reflect the aim. Is it back pain or leg pain in NASS? I think it must be explained in the method part. And SF-36 if it is used as outcome parameters for quality of life, it should be considered as an primary outcome.</p> <p>9. The results and conclusion do not give answerers to the aim.</p> <p>11. I miss in conclusion any discussion about quality of life. In "conclusions" p.2 l.40 "surgical treatment provided faster relief from back pain symptoms in patients with lumbar disc herniation". For me this is not a conclusion to your aim. Back pain is not a symptom that require surgery, or? So for me this information is unnecessary. You should lift up your own results reflected to your questions.</p> <p>P. 5 l. 22. How long was the duration of symptoms of back pain, leg pain or other symptoms before they underwent surgery?</p> <p>P.6 l.18. What do you mean with "treatment failed", in what way?</p> <p>P.9 l.52 Why did patients drop out? Was it just cross-over or just lost-to-follow-up?</p>
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<b>REVIEWER</b>	Wilco C. Peul Leiden University Medical Center, Netherlands
<b>REVIEW RETURNED</b>	03-Jul-2016

<b>GENERAL COMMENTS</b>	<p>Your elegantly described cohort did indeed repeat the results of some of the rct's. Some of these had a timing design and not cross over as you did write down.</p> <p>Your manuscript would gain more strength if you would emphasize on the fact that you describe regular care, without a clinical trial design, and within this regular care you do find similar outcomes compare to the usa SPORT and the Netherlands Sciatica trial.</p> <p>Some critical points should be taken care of.</p> <ul style="list-style-type: none"> <li>-the baseline duration of sciatica complaints is not mentioned anywhere. Is the basis of the comparison!</li> <li>-although it seems clear which question you do want to answer, it is not clear from the introduction. Did your study want to repeat the rct s in regular clinical life? Or did you want to test the generilisability of these earlier studies? As it it s not completely clear the used methods are not necessary to answer a question. Why not studying longitudinally 2 large observational cohorts, comparing surgery and prolonged conservative treatment.</li> </ul> <p>To conclude. With some important adjustments and adding some new value to the readers it might be interesting for the general public. If not it is prably okay for a specialistic journal</p>
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### VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Katarina Silverplats

Institution and Country: Department of Orthopaedic, Sahlgrenska University Hospital, Swedish Armed Forces/Centre of Defence Medicine Competing Interests: None declared

1. Reviewers' Comment: p.4 l.53 Aim of the study is to compare the effect of surgical and conservative treatment on sciatica symptom severity and quality of life in patients with lumbar disc herniation. The aim is not answered in the results and conclusions. What about radiculopathy symptoms after surgery or conservative treatment? Quality of life? In abstract there is a different aim based on "symptomatic lumbar disc herniation".

Authors' Reply: In our manuscript, we used the NASS questionnaire to assess sciatica symptoms severity. The NASS questionnaire addresses pain, neurogenic symptoms, and limitation of physical function, and results are reported in the results section. Quality of life was assessed using the 36-Item Short-Form Health Survey (SF-36) and results are also reported in the results section. The conclusions of our article reflect the findings of the pre-defined primary outcome, which is back pain.

To address the reviewer's comments we added the following information to the Outcome Measures section on page 6:

"Sciatica symptom severity was assessed using the North American Spine Society (NASS) questionnaire, and quality of life was assessed using the 36-Item Short-Form Health Survey (SF-36)."

We also added further information to the aim in our abstract:

"We sought to compare short- and long-term effectiveness of surgical and conservative treatment in sciatica symptom severity and quality of life in patients with lumbar disc herniation."

2. Reviewers' Comment: p.2 l.16 Primary outcomes were pain. What kind of pain? Leg pain, back pain? What about quality of life? When it is one of your question in the aim, I would like to have it as a primary outcome as well.

Authors' Reply: The pre-defined primary outcome was back pain. We amended the text to clarify this where needed. It is important that the outcome was pre-specified, and we would therefore not be able to change it at this point.

3. Reviewers' Comment: Outcomes are defined as primary and secondary, but do not reflect the aim. Is it back pain or leg pain in NASS? I think it must be explained in the method part. And SF-36 if it is used as outcome parameters for quality of life, it should be considered as an primary outcome.

Authors' Reply: We have clarified this issue as explained in the reply to comment #1 of this reviewer.

4. Reviewers' Comment: The results and conclusion do not give answers to the aim.

Authors' Reply: We have clarified this issue as explained in the reply to comment #1 of this reviewer. Results presented come from questionnaires that assessed symptoms severity and quality of life, as outlined in the aims, and conclusions were based on the primary outcome.

5. Reviewers' Comment: I miss in conclusion any discussion about quality of life. In "conclusions" p.2 l.40 "surgical treatment provided faster relief from back pain symptoms in patients with lumbar disc herniation". For me this is not a conclusion to your aim. Back pain is not a symptom that require surgery, or? So for me this information is unnecessary. You should lift up your own results reflected to your questions.

Authors' Reply: As previously explained, our conclusions were based on our primary outcome. As the primary outcome was pre-specified, we would unfortunately not be able to change it at this point.

6. Reviewers' Comment: P. 5 l. 22. How long was the duration of symptoms of back pain, leg pain or other symptoms before they underwent surgery?

Authors' Reply: This information was not systematically entered in our registry at baseline, so we are unfortunately not able to report it. The lack of sound information on length of symptoms duration at baseline is a limitation of our registry, and thus of our study.

7. Reviewers' Comment: P.6 l.18. What do you mean with "treatment failed", in what way?

Authors' Reply: Given the pragmatic nature of our study, which is based on a routine clinical practice registry, there was no single definition of treatment failure. Thus, treatment failure was assessed on a case-by-case basis, and was determined by patients and clinicians as an insufficient improvement in patient's symptoms and quality of life. To address the reviewers comment, we adapted the text as following (page 6, parag 2):

"If conservative treatment failed, which was ascertained on a case-by-case basis, surgery was provided as an option."

8. Reviewers' Comment: P.9 l.52 Why did patients drop out? Was it just cross-over or just lost-to-follow-up?

Authors' Reply: Patients dropped out due to loss to follow-up. This is now described in page 10, parag 1:

"Moreover, a significant number of patients dropped out of our study due to loss to follow-up, especially by latter time points. We conducted multiple imputation as an attempt to include in our

analysis patients with missing outcome data, however no statistical technique is likely to completely solve the problem of missing data, and it is always better to have observed data as opposed to imputed data for all patients included in the analysis.”

Reviewer: 2

Reviewer Name: Wilco C. Peul

Institution and Country: Leiden University Medical Center, Netherlands Competing Interests: None

1. Reviewers' Comment: Dear authors, Your elegantly described cohort did indeed repeat the results of some of the rct's. Some of these had a timing design and not cross over as you did write down.

Authors' Reply: Many thanks for your kind remark. There seems to be a misunderstanding regarding our use of the “cross-over” terminology. We actually did not say that the RCT's had a cross-over design. We said that there was a large proportion of patients who crossed over from conservative to surgical treatment. What was meant is that patients that were randomly allocated to receive conservative treatment in those RCTs, actually received surgical treatment, indicating that randomization was not respected and bias possibly took place. To clarify this, we modified the text as following (page 4, parag 3):

“A large proportion of patients randomly allocated to conservative treatment in randomized controlled trials (RCTs) actually received surgical treatment (26–54%),...”

2. Reviewers' Comment: Your manuscript would gain more strength if you would emphasize on the fact that you describe regular care, without a clinical trial design, and within this regular care you do find similar outcomes compare to the usa SPORT and the Netherlands Sciatica trial.

Authors' Reply: We now emphasize throughout the manuscript that our data is based on regular care. We also made this clearer in the discussion section (page 9, parag 3):

“Interestingly, results of our observational cohort conducted in a routine care setting more closely resemble those reported by previous RCTs.”

3. Reviewers' Comment: Some critical points should be taken care of.

-the baseline duration of sciatica complaints is not mentioned anywhere. Is the basis of the comparison!

Authors' Reply: This information was not systematically entered in our registry at baseline, so we are unfortunately not able to report it. The lack of sound information on length of symptoms duration at baseline is a limitation of our registry, and thus of our study.

4. Reviewers' Comment: -although it seems clear which question you do want to answer, it is not clear from the introduction. Did your study want to repeat the rct s in regular clinical life? Or did you want to test the generalisability of these earlier studies? As it is not completely clear the used methods are not necessary to answer a question. Why not studying longitudinally 2 large observational cohorts, comparing surgery and prolonged conservative treatment.

Authors' Reply: The question we wanted to answer is whether surgery is better than conservative

treatment to improve sciatica symptom severity and quality of life in patients with lumbar disk herniation, as describe in the end of our introduction section. However, the methods used are novel, and strengthens the findings from previous RCTs, which could in theory be not representative of a routine clinical setting. Our data collected from routine clinical care has a higher external validity, and the use of inverse probability weighting to mimick an RCT and minimize confounding increases internal validity. To address the reviewer’s comment, we have further clarified this on page 4, parag 3: “Observational cohort studies have typically differed in important baseline prognostic indicators between treatment group and their results were thus more prone to confounding. A large proportion of patients randomly allocated to conservative treatment in randomized controlled trials (RCTs), which are less prone to generate confounded results, actually received surgical treatment (26–54%), and some researchers have questioned whether patients willing to participate in RCTs of surgery are representative of patients commonly seen in clinical practice.

In order to present results that are more representative of routine clinical care while minimizing the risk of confounded results, we conducted a properly sized observational cohort study in a routine clinical setting using consecutive sampling, in which baseline differences in prognostic indicators were accounted for in an analysis with inverse probability weighting closely mimicking an RCT, with the aim of comparing the effect of surgical and conservative treatment on sciatica symptom severity and quality of life in patients with lumbar disc herniation.”

5. Reviewers' Comment: To conclude. With some important adjustments and adding some new value to the readers it might be interesting for the general public. If not it is prably okay for a specialistic journal

### VERSION 2 – REVIEW

<b>REVIEWER</b>	Wilco C. Peul Leiden University Medical Center
<b>REVIEW RETURNED</b>	03-Sep-2016

<b>GENERAL COMMENTS</b>	The authors did a good job on answering our questions. One part is still is in conflict with my scientific opinion, however, but seems difficult to address by the authors. That is the remark about the cross-over of patients in the RCT's. 2 RCT's had delayed surgery after a prolonged period of conservative treatment in their design. In other words, these patients did not cross-over. But again in a cohort study this is better addressed. without the correction there is a wrong statement here. But I can live with that and react as one of the PI's of the original study !
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### VERSION 2 – AUTHOR RESPONSE

Reviewer: 2

Reviewer Name: Wilco C. Peul

Institution and Country: Leiden University Medical Center, The Netherlands Competing Interests: None

1. Reviewer's Comment: The authors did a good job on answering our questions. One part is still is in conflict with my scientific opinion, however, but seems difficult to address by the authors. That is the remark about the cross-over of patients in the RCT's. 2 RCT's had delayed surgery after a prolonged period of conservative treatment in their design. In other words, these patients did not cross-over. But again in a cohort study this is better addressed. without the correction there is a wrong statement here. But I can live with that and react as one of the

PI's of the original study !

Authors' reply: We thank Prof. Peul for insisting on this important issue. I (BRDC) completely missed the point and failed to properly address his comment on the previous revision. We rectified the sentence and citations (please see full manuscript for citations) as following (page 4, parag. 3):

“Randomized controlled trials (RCTs) are less prone to generate confounded results. However, in RCTs comparing surgical with conservative treatment, a large proportion of patients randomly allocated to conservative treatment actually received surgical treatment right after randomization or after an initial period of conservative treatment (26–54%). Therefore, RCTs are actually mainly comparing early surgery with conservative treatment and delayed surgery in selected patients, as was referred to by Peul et al. In addition, some researchers have questioned whether patients willing to participate in RCTs of surgery versus conservative treatment are representative of patients commonly seen in clinical practice”.