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)	A study protocol for a randomized controlled trial of ultrasound-guided pulsed radiofrequency of the genicular nerves in the treatment of patients with osteoarthritis knee pain
AUTHORS	Mata, J; Valentí, Pedro; Hernández, Beatriz; Mir, Bartolome; Aguilar, Jose Luis

VERSION 1 - REVIEW

REVIEWER	Gunnvald Kvarstein Te Arctic University of Norway UIT. Clinical studies in Pain Medicine and Interventional Pain Medicine.
REVIEW RETURNED	27-Feb-2017

GENERAL COMMENTS	The authors present a new version of the protocol for the study: "Ultrasound-guided pulsed radiofrequency of the genicular nerves in the treatment of patients with osteoarthritis knee pain: a study protocol for a randomized controlled trial". I have still some comments: In "Introduction" they have omitted the separate paragraph presenting hypotheses. The presentation of aims, however, is not well organized. I would suggest that primary and secondary aims are collected into one single paragraph in the end of "Introduction" with a separate subheading ("Aims"). The presentation of the aim in "Methods" is actually written as a hypothesis, not as an aim. One page 16 they present a stimulation threshold of 0.6V. At page 15 and in previous literature (Rigaud M et al 2008) a critical stimulation threshold to avoid intraneural injection has been given in mA. On page 17, however, they describe a threshold for sensory stimulation with the unit voltage (0.6 V) and not to the amperage or mA. This needs an explanation. On Page 17 the pulsed stimulation is corrected from 240 sec to 8 minutes. The authors present a duration of each pulse at 20 msec followed by a silent period of 480 msec. As one second lasts for 1000 msec, the silent period should be 980 msec, not 480 msec. The description of statistical analyses (page 20) needs to be commented. They plan to perform intra- group comparisons with paired sample T test or Wilkoxon signed rank paired test for continuous variables. Why not by an ANOVA test? An ANOVA analysis would include both inter-group and intra-group comparisons. This should be discussed. They also plan an interim analysis. This will reduce the statistical power and increased the calculated sample size. This needs to be discussed. In Discussion, the authors present studies, discussing the innervation of the knee (Franco C et al 2015 and ultrasound guidance for genicular nerve blocks (Yasar E eet al 2015), and they

	provide a sound explanation for why they chose the protocol by Choi et al. In general, I would suggest the authors to use the term "outcome measure" rather than "outcome".

REVIEWER	Fred R T Nelson, MD Henry Ford Hospital USA
REVIEW RETURNED	19-Apr-2017

GENERAL COMMENTS	I was a bit surprised that this was a review of an institutional review board accepted protocol. Since I am faced with the condition in question on a daily basis I am distinctly biased to promote this type of rigid protocol preparation. This a very nice review paper on how to design a study using the current tools available to guide protocol development. Two basic tolls are the SPIRIT and CONSORT guidelines. The OARSI guidelines are specific for studies on osteoarthritis wherein the other two can be used for a broad range of clinical studies. Although most therapeutic researchers are aware of these tools the paper is a good guide for orthopaedic pain management investigators. I had only a few points of clarification for the authors Title: So that the reader is clear that this is the presentation of a guideline generated protocol and not a presentation of study results change the title Ultrasound-guided pulsed radiofrequency of the genicular nerves in the treatment of patients with osteoarthritis knee pain: a study protocol for a randomized controlled trial to read A study protocol for a randomized controlled trial of ultrasound-guided pulsed radiofrequency of the genicular nerves in the treatment of patients with osteoarthritis knee pain Page 2 line 15 Abstract: This article is entirely devoted to a protocol based on CONSORT, OARSI, and SPIRIT guidelines. For that reason it would be more appropriate to replace the sentence “The purpose of this study is to determine if patients with chronic painful knee osteoarthritis experience meaningful and long-term improvement in pain and function after ultrasound guided pulsed radiofrequency of the genicular nerves.” To read “The purpose of this article is to present a refined protocol to determine if there is long-term improvement in pain and function after ultrasound guided pulsed radiofrequency treatment of the genicular nerves in patients with chronic painful knee osteoarthritis” Page 7 Line 11: I could not figure out if patient selection is only those with pain > 30 mm VAS or > 30% or both. Is there a difference other than one being a measure scale and the other a 10 step Likert? Page 9 line 11: For the double diagnostic block description refer the reader to Figure 2. It is hard to understand what you did for the double block unless you describe each group (starting with a sham and ending with a positive versus stating with a positive and ending with a sham Page 14 line 40: An illustration showing the gross location of these nerves would be useful. Page 19 line 21: Does that mean a difference of 30 mm or 30% between placebo and active groups or from start pain to finish? I question the value of the material for pages 34 - 39 (Numbered 1 – 6). The material is only useful in contest of the full article that you

	have reference in 10 and 11.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
In “Introduction" they have omitted the separate paragraph presenting hypotheses.(Page 6)

The paragraph presenting hypotheses has been added in “Introduction” section:
“The primary hypothesis is that ultrasound-guided pulsed radiofrequency of the genicular nerves will mitigate pain and improve function as compared to placebo”.

The presentation of aims, however, is not well organized. I would suggest that primary and secondary aims are collected into one single paragraph in the end of “Introduction” with a separate subheading (“Aims”). The presentation of the aim in “Methods” is actually written as a hypothesis, not as an aim.(Page 7)

The presentation of aims, primary and secondary aims, has been presented in the end of “Introduction” section with a separate subheading (“Aims”).

Aims
The primary outcome will be the change from the baseline of the VAS for pain at the completion of treatment at 12 weeks. Secondary variables to be considered are the following: the change in the secondary efficacy variables from the baseline of the scores for the Goldberg Anxiety and Depression Scale (GADS), changes in pain medication use, changes in functional capacity and stiffness (WOMAC subscales), and VAS scores measured at 1 month, 3 months, 6 months, and 1 year after study commencement.

One page 16 they present a stimulation threshold of 0.6V. At page 15 and in previous literature (Rigaud M et al 2008) a critical stimulation threshold to avoid intraneural injection has been given in mA. On page 17, however, they describe a threshold for sensory stimulation with the unit voltage (0.6 V) and not to the amperage or mA. This needs an explanation.

This is a good point. It is true that a critical stimulation threshold to avoid intraneural injection has been given in mA. Bigeleisen PE, et al (Anesthesiology. 2009; 110(6):1235-43) said that a stimulation current of 0.2 mA or less is reliable to detect intraneural placement of the needle. Furthermore, stimulation currents of more than 0.2 and no more than 0.5 mA could not rule out intraneural position.

The text on page 16 has been modified with a lower limit for the stimulation to avoid potencial intraneural injection: “the nerve will be tested for the absence of fasciculation in the corresponding area of the lower extremity on stimulation of 0,5 mA at 2 Hz, with an impedance value between 300-700 Ω, when needle is judged to be adequately placed by ultrasound, the current intensity (mA) will be reduced at < 0,2 mA”.

On Page 17 the pulsed stimulation is corrected from 240 sec to 8 minutes. The authors present a duration of each pulse at 20 msec followed by a silent period of 480 msec. As one second lasts for 1000 msec, the silent period should be 980 msec, not 480 msec.

Pulsed radiofrequency is the technique whereby radio frequency (RF) oscillations are gated at a rate of pulses per second (cycles per second, defined as a hertz (Hz)). Current of 2 Hz means two cycles per second. (with 20 msec active and 480 msec silent periods per cycle). PRF uses radiofrequency

current in short (20 ms), high-voltage bursts; the “silent” phase (480 ms) of PRF allows time for heat elimination, generally keeping the target tissue below 42° C.

The description of statistical analyses (page 20) needs to be commented. They plan to perform intra-group comparisons with paired sample T test or Wilkoxon signed rank paired test for continuous variables. Why not by an ANOVA test? An ANOVA analysis would include both inter-group and intra-group comparisons. This should be discussed. They also plan an interim analysis. This will reduce the statistical power and increased the calculated sample size. This needs to be discussed.

As we indicated in statistical analysis section, we have planned to perform an ANCOVA (analysis of covariance) to compare difference between groups at 3-months and 1-year after adjusting for baseline values. We think that ANCOVA is the most appropriate analysis in this case because this permits to compare three months and 1 year variables between groups after adjusting for the baseline effect.
To compare differences intra-group (baseline vs. 3-months; baseline vs. 1-year), we also planned to use paired samples tests (such as with paired sample T test or Wilkoxon signed rank paired test)."

With respect interim analyses, we re-adjust the critical value of P according Pocock's method [ref]. According this, two-tailed p value < 0.0294 will be considered statistically significant. Statistical analyses will be performed using SPSS 18.0 (SPSS Inc., Chicago, IL, USA).

Pocock SJ (1977). "Group sequential methods in the design and analysis of clinical trials". Biometrika. 64 (2): 191–9.
Pocock S (2005). "When (not) to stop a clinical trial for benefit". JAMA. 294 (17): 2228–2230. doi:10.1001/jama.294.17.2228 .

Statistical analysis

The primary analysis will be conducted on all outcome data obtained from all participants as randomised and regardless of protocol adherence, i.e. intention to treat analysis.
Data will be presented as mean (standard deviation), median (interquartile range) or number (%). Inter-group comparisons at baseline will be analyzed using independent samples t-test or Mann–Whitney U test for continuous variables and chi square or Fisher’s exact test for categorical variables. Intra-group differences (between baseline and 3-month; between baseline and 1-year) will be evaluated using paired samples t-test or Wilkoxon signed rank paired test for continuous variables and McNemar test for dichotomized variables. Inter-group comparisons at 3-months and at 1-year will be assessed using analysis of covariance and Fisher’s exact test after adjusting changes in categorical and continuous variables for baseline values. Point-biseral (dichotomic data) and Pearson/Spearman (continuous data) correlations coefficients will be computed to assess the relationship between each possible predictor variables at baseline and VAS change at 3-months and at 1-year. Multiple linear regression models will be used to identify baseline predictors of VAS reduction at 3-months and at 1-year. Analysis will be performed using stepwise and backward method for all models.
An interim-analysis will be performed on the primary endpoint when 100% of patients have been randomised and have completed the 3 months follow-up. The interim-analysis will be performed by an independent statistician, blinded for the treatment allocation. The statistician will report to the Research Ethic Committee of the Balearic Islands (RECIB). The RECIB will have unblinded access to all data.

A two-tailed p value < 0.0294 will be considered statistically significant after adjusting according Pocock's method for interim analysis. Statistical analyses will be performed using SPSS 18.0 (SPSS Inc., Chicago, IL, USA).

In general, I would suggest the authors to use the term "outcome measure" rather than "outcome".

The term “outcome” has been changed to “outcome measure” as appropriate.

In Discussion, the authors present studies, discussing the innervation of the knee (Franco C et al 2015 and ultrasound guidance for genicular nerve blocks (Yasar E eet al 2015), and they provide a sound explanation for why they chose the protocol by Choi et al.

We are thankful to the reviewer for the encouraging and positive comments to clarify the manuscript. The suggestions are valuable and very helpful for revising and improving our paper.

Reviewer: 2

Title: So that the reader is clear that this is the presentation of a guideline generated protocol and not a presentation of study results change the title Ultrasound-guided pulsed radiofrequency of the genicular nerves in the treatment of patients with osteoarthritis knee pain: a study protocol for a randomized controlled trial to read A study protocol for a randomized controlled trial of ultrasound-guided pulsed radiofrequency of the genicular nerves in the treatment of patients with osteoarthritis knee pain.

The title has changed in the revised manuscript:

“A study protocol for a randomized controlled trial of ultrasound-guided pulsed radiofrequency of the genicular nerves in the treatment of patients with osteoarthritis knee pain”

Page 2 line 15 Abstract: This article is entirely devoted to a protocol based on CONSORT, OARSI, and SPIRIT guidelines. For that reason, it would be more appropriate to replace the sentence “The purpose of this study is to determine if patients with chronic painful knee osteoarthritis experience meaningful and long-term improvement in pain and function after ultrasound guided pulsed radiofrequency of the genicular nerves.” To read “The purpose of this article is to present a refined protocol to determine if there is long-term improvement in pain and function after ultrasound guided pulsed radiofrequency treatment of the genicular nerves in patients with chronic painful knee osteoarthritis”

The text has been modified: “The purpose of this article is to present a refined protocol to determine if there is long-term improvement in pain and function after ultrasound guided pulsed radiofrequency treatment of the genicular nerves in patients with chronic painful knee osteoarthritis”.

Page 7 Line 11: I could not figure out if patient selection is only those with pain > 30 mm VAS or > 30% or both. Is there a difference other than one being a measure scale and the other a 10 step Likert?

We appreciate this comment of the reviewer. The paragraph has been edited to clarify these points. The sentence has been changed: “pain > 30 mm VAS” has been deleted.
Patients with chronic knee pain with pain intensity of at least 4 out 10 on the VAS on most or all days for more than 3 months are included.
(OARSI Clinical Trials Recommendations: Design, conduct, and reporting of clinical trials for knee osteoarthritis DOI: http://dx.doi.org/10.1016/j.joca.2015.03.005)

The sample size was calculated to detect differences of at least 30% in the pain perception

assessment according to VAS pain intensity (scale of 0 to 100 mm).
Decreases in patients' pain intensity of >30% were considered ''moderately important" improvements, whereas decreases of >50% were considered "substantial" improvements (Dworkin R, et al. Pain 2009; 146:238-244).

Page 9 line 11: For the double diagnostic block description refer the reader to Figure 2. It is hard to understand what you did for the double block unless you describe each group (starting with a sham and ending with a positive versus stating with a positive and ending with a sham

We appreciate this comment of the reviewer. The text in page 9 in the double diagnostic block description has been modified.
We have added: "starting with a sham and ending with a positive versus starting with a positive and ending with a sham".

Page 14 line 40: An illustration showing the gross location of these nerves would be useful.

A figure (figure 3) with the gross location of these nerves has been added

Page 19 line 21: Does that mean a difference of 30 mm or 30% between placebo and active groups or from start pain to finish?

A difference of 30 mm or 30% is between active group and placebo.
Equally important to the determination of the clinical importance of improvements for individual patients is the interpretation of the clinical importance of group differences between treatment and placebo. (Dworkin R, et al. Pain 2009; 146:238-244).
Meta-analysis of OA knee pain trials [Bjordal JM, et al. Eur J Pain 2007; 11:125–38), concluded that the differences in mean response between existing treatments for OA knee pain and placebo never exceeded the threshold of 10 mm for patient reports of a ''minimal perceptible difference" and were always much less than the threshold of 20 mm for an ''important improvement" derived from previous literature.

I question the value of the material for pages 34 - 39 (Numbered 1 – 6). The material is only useful in contest of the full article that you have reference in 10 and 11.

The SPIRIT checklist has been submitted as supplementary material, for the editor and reviewers.

VERSION 2 – REVIEW

REVIEWER	Gunnvald Kvarstein University of Tromsø, the Article University of Norway, Department of Clinical Medicine
REVIEW RETURNED	09-Jun-2017

GENERAL COMMENTS	Page 15: "In the evening of the same day a researcher will call the patient to assess the VAS pain intensity." Is this a prospective assessment or is it based on patient's ability to recall? Page 16 and 19: "30 mm or 30% reduction." Not revised as described in the response letter? Page 15: If the second block assessment is similar to the first one, write "Same assessment protocol as after the 1. diagnostic block". Page 24: Ultrasound guidance and PRF hvae been discussed in the

	Introduction: "too much of the text is a duplication of the paragraphs in the Introduction. Revise. I also recommend a separate paragraph for the discussion of ultrasound guidance and another for PRF. The language needs to be checked for further improvement. Some of the sentences should be written in present tense as the study has not been carried out yet. Page 4. “The study design would /will favour patients that could responded to the treatment (double diagnostic nerve blocks positive to the inclusion) Page 9: Each eligible patient will be randomlyi/randomized twice. Table 1 Pain Page 12: “VAS scores” should be replaced with “VAS pain scores”. I assume this is relevant for the rest of the manuscript. Page 14: The targets included/include the SL, SM and IM genicular nerves Page 14 and 22: The IL genicular nerve did /is not target Page 15: will be made/given/offered a new appointment Page 18: I guess the patients at the 12 month follow up will report the same data as at previous ones. Thus, add “also” in the following sentence: “their expectations for improvement will also be included ..“. Page 19: The presented time points are related to treatment and not commencement of the study Page 19: “allocated” instead of “placed”

REVIEWER	Fred Nelson Henry Ford Hospital Detroit Michigan Wayne State University Medical School Detroit Michigan
REVIEW RETURNED	11-Jun-2017

GENERAL COMMENTS	Thanks for your attention to these details

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Concerning blinding: A patient report of procedural pain should be included as procedural pain may hamper the blinding.

The most common side effect is pain, which is temporary.

A distinction should be made between pain during the procedure and the presence of persistent pain after the procedure.

The procedure does involve injections, so the patient may feel some discomfort. The local anaesthetic is given to make them feel as comfortable as possible. As the electrode is positioned they may feel some of their typical symptoms.

The pain after radiofrequency ablation usually resolves within 48 to 72 hours and can be treated with over-the-counter pain medication, as well as cold packs on the day of the procedure, and hot packs

from the second day onward, until the pain resolves. Some patients may experience slightly increased pain for approximately one to two weeks after the treatment, which should gradually decrease.

Any adverse events will be monitored and reported by researchers at each visit since double diagnostic block. All expected and unexpected adverse events potentially related to the study will be monitored, and their progress will be recorded until resolution.

The researcher executing and supervising the treatments will be blinded to the group allocation. Group allocation will be immediately unblinded if deemed necessary by the chief investigator in the case of serious adverse events potentially related to the study.

Control and real radiofrequency group undergo the same procedure and the possibility of procedural pain is the same in both groups: Radiofrequency (RF) needles and probes will be advanced to each of the target nerves under ultrasound guidance. A 50 Hz-frequency sensorial stimulation is applied with a threshold of < 0.5 mA to identify the nerve position, the current intensity (mA) is reduced at < 0,2 mA. During the sensorial stimulation, the patients are asked if they feel tingling, pain, or discomfort inside the knee. The RF probe is maintained in place until one of those feelings is elicited. In order to avoid inactivating motor nerves, the nerve is tested for the absence of fasciculation in the corresponding area of the lower extremity on stimulation of 0,5 mA at 2 Hz. with an impedance value between 300-700 Ω", when needle is judged to be adequately placed by ultrasound, the current intensity (mA) is reduced at < 0,2 mA. Lidocaine (1 mL of 2%) is injected before activation or simulate activation of the RF generator. The procedure may cause some discomfort or pain in both cases. The pulsed radiofrequency does not produce a lesion in the nerves treated; therefore, procedural pain is a rare event.

Serious adverse effect is considered if this procedural pain increase or does not decrease over time.

Page 15: "In the evening of the same day a researcher will call the patient to assess the VAS

pain intensity." Is this a prospective assessment or is it based on patient's ability to recall?

Pain reduction is observed no later than 30 min after injection, lasting more than 1 or 2 h after lidocaine injection. Patients who have procedures done usually require less than 30 minutes of care by health care professionals before they are discharged to go home.

Actually a researcher calls the patient to assess the VAS pain intensity between 2 and 3 hours after procedure (the procedure is scheduled in the morning and we have mistranslated 2-3 hours later as "evening").

The paragraph has been changed:

"A researcher calls the patient to assess the VAS pain intensity between 2 and 3 hours after procedure".

Page 16 and 19: "30 mm or 30% reduction." Not revised as described in the response letter?

The sentence has been changed: "pain > 30 mm VAS" has been deleted.

Page 15: If the second block assessment is similar to the first one, write “Same assessment protocol as after the 1. diagnostic block”.

The paragraph has been modified:

“Same assessment protocol as after the first diagnostic block”

Page 24: Ultrasound guidance and PRF have been discussed in the Introduction: "too much of the text is a duplication of the paragraphs in the Introduction. Revise.

Thanks for the recommendation.

These paragraphs have been changed in the Introduction section:

“As opposed to the traditional approach under fluoroscopy, ultrasound allowed the visualization of neurovascular bundles, soft tissue structures and, presumably, more accurate nerve identification [8].

The recommendations for PRF as a treatment of patients with OA knee pain are debated until randomized controlled trials with long-term follow-up confirm the results of current studies”.

I also recommend a separate paragraph for the discussion of ultrasound guidance and another for PRF.

This is changed in the revised manuscript.

The language needs to be checked for further improvement.

Some of the sentences should be written in present tense as the study has not been carried out yet.

Page 4. “The study design would /will favour patients that could respond to the treatment (double diagnostic nerve blocks positive to the inclusion)

The paragraph has been changed:

“The study design favours patients that respond to the treatment (double diagnostic nerve blocks positive to the inclusion) and exclude patients that experience placebo effects or can be resistant to the treatment (double diagnostic nerve blocks negative to the inclusion)”

Page 9: Each eligible patient will be randomlyi/randomized twice.

The text has been modified:

“Each eligible patient will be randomized twice (the randomizer will be otherwise uninvolved in the study)”

Table 1 Pain Page 12: “VAS scores” should be replaced with “VAS pain scores”. I assume this is relevant for the rest of the manuscript.

All the “VAS scores” of the manuscript have been replaced with “VAS pain scores”. (page 7, page 12, page 16 and page 18)

Page 14: The targets included/include the SL, SM and IM genicular nerves

The sentence has been changed:

“The targets include the SL, SM and IM genicular nerves”

Page 14 and 22: The IL genicular nerve did /is not target

The sentences have been changed

Page 15: will be made/given/offered a new appointment.

Patients with a positive response will be given a new appointment in a week.

Page 18: I guess the patients at the 12 month follow up will report the same data as at previous ones. Thus, add “also” in the following sentence: “their expectations for improvement will also be included “.

This is a good point.

The paragraph has been changed:

12th month visit since RF (10th visit)

Thirteen months since baseline, at study completion, questions related to patient satisfaction with the treatment received, and their expectations for improvement will also be included in the questionnaires.

Page 19: The presented time points are related to treatment and not commencement of the study

Thanks. This is a good point, and we have modified accordingly the text in this point:

“VAS pain scores measured at 1 month, 3 months, 6 months, and 1 year after treatment”. (page 7 and page 18)

Page 19: “allocated” instead of “placed”

The sentence has been changed:

“then if they sign an informed consent form, they will be allocated randomly into one of the treatment groups [20].”

Reviewer: 2

We greatly appreciate your thoughtful comments that have helped improve the manuscript. We trust that all of your comments have been addressed accordingly in a revised manuscript.

VERSION 3 – REVIEW

REVIEWER	Gunnvald Kvarstein UiT The Arctic University of Norway, Norway
REVIEW RETURNED	26-Jun-2017

GENERAL COMMENTS	Only two minor comments: Page 4: Move the heading "Aims" to just above the paragraph starting with "The purpose of this study.. " Page 4:Convert exclude to excludes