PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Effects of photobiomodulation therapy in patients with chronic non-specific low back pain: protocol for a randomized placebo-controlled trial
AUTHORS	Tomazoni, Shaiane; Costa, Lucíola; Guimarães, Layana; Araujo, Amanda; Nascimento, Dafne; Medeiros, Flavia; Avanzi, Marina; Costa, Leonardo

VERSION 1 – REVIEW

REVIEWER	Bruno Manfredini Baroni Federal University of Health Sciences of Porto Alegre, Brazil.
REVIEW RETURNED	28-Apr-2017

GENERAL COMMENTS	General comments: I appreciate the opportunity to review this interesting work from a consolidated research group. In summary, this manuscript is a protocol study on the effects of photobiomodulation therapy (PBMT) in patients with chronic non-specific low back pain (LBP). Authors chose an appropriate study design (a prospectively registered, two-arm randomized placebo-controlled trial with blinded patients, assessors and therapists), validated methods for patients' assessment, and a PBMT device previously tested in scientific researches. Effect of PBMT on pain intensity, disability, specific disability and global perceived effect will be measured after 12 sessions of treatment, as well as after 3, 6 and 12 months. Although there is evidence favorable to PBMT in patients with LBP, including a relatively recent meta-analysis (Glazov et al. 2016), authors state that there is still a need for high quality articles on this issue; and this reviewer agree with them. Therefore, this study will improve the current knowledge and contribute to the clinical practice of health professionals involved in the treatment of LBP. However, the manuscript did not make clear some important issues about the protocol, and there are several changes to be made in the manuscript to make this protocol study acceptable for publication in BMJ Open (see specific comments next). Specific comments: Page 3; line 6: I do not agree with the sentence "our study does not present limitations", because all studies have some weakness. PBMT has a well-documented dose-response effect, and other

	parameters (e.g., light source, wavelength, power output, etc.) may significantly affect the treatment success. Thus, some studies have tested more than one treatment dosage to investigate the effects of PBMT on different diseases/injuries. Since previous clinical trials that reported positive effects of PBMT on LBP symptoms have used a range of energy doses and different devices/parameters, there is no consensus about the optimal dosage for LBP. Therefore, the single treatment dosage proposed in this clinical trial could be considered a limitation of this study. Page 4; lines 6-13: Information regarding the high frequency of LBP was repeated in the three sentences. Please, organize this part of the text. Page 4; lines 18-23: There is controversial information here. The first sentence states that “there are no treatments that truly minimize the intensity of symptoms”, while the second sentence says that “several interventions are effective in reducing pain and disability”. Page 4; lines 24-30: Consider add these sentences to the first paragraph, and writing a second paragraph totally dedicated to PBMT and their physiological/therapeutic effects (4th paragraph of the current version of the manuscript). Page 4; lines 35-36: I suggest leaving the clinical trials on PBMT and LBP to the third paragraph. Here, authors should insert as reference the recent clinical guideline by Qaseem et al. (2017). PBMT was cited there as a possible nonpharmacologic treatment for LBP. Qaseem A, Wilt TJ, McLean RM, Forciea MA; Clinical Guidelines Committee of the American College of Physicians. Noninvasive Treatments for Acute, Subacute, and Chronic Low Back Pain: A Clinical Practice Guideline From the American College of Physicians. Ann Intern Med. 2017 Apr 4;166(7):514-530. doi: 10.7326/M16-2367. Epub 2017 Feb 14. Page 4; line 43: There are some misconceptions here. Reference #18 is not an “evidence from recent years” (it was published in 1999), while reference #23 is not related to PBMT. In addition, all studies cited here are focused on therapeutic effects (clinical outcomes) and not physiological effects of PBMT. Please, review this reference list. There are impacting articles in this field that should be cited here (e.g., the systematic review of on LBPT in patients with neck pain, by Chow et al. 2009) Chow RT, Johnson MI, Lopes-Martins RA, Bjordal JM. Efficacy of low-level laser therapy in the management of neck pain: a systematic review and meta-analysis of randomised placebo or active-treatment controlled trials. Lancet. 2009 Dec 5;374(9705):1897-908. Page 4; line 45: Add a reference to “increased ATP synthesis”. There are so many studies on this issue. Page 4; lines 49-53: There are two “in addition” in this sentence. Page 5; line 5: You addressed only trials with positive results in this paragraph. I strongly suggest you include studies that found no additional benefits with PBMT (e.g., Ay et al. 2010) to highlight the conflicting findings in the literature.

	Ay S, Doğan SK, Evcik D. Is low-level laser therapy effective in acute or chronic low back pain? Clin Rheumatol. 2010 Aug;29(8):905-10. Page 5; lines 15-18: This is not true. For instance, the study conducted by Konstantinovic et al. (2010) is a placebo-controlled trial. Therefore, this rationale cannot be used to justify the present study. Page 5; lines 18-27: The objectives are a little confusing. Maybe you should use a single sentence, as reported in the Abstract. Page 5; first paragraph: In view of the evidence on PBMT in LPB patients, including a meta-analysis (Glazov et al. 2016), the justification for this study needs to be improved. In my opinion, the high methodological quality of this study design, the large sample size and the measures at medium- and long-term periods are the strengths of this study and should be highlighted. Page 6; line 15: Add examples of severe skin diseases. Page 6; lines 17-18: Provide references on the clinical exam you will adopt. Page 6; Interventions: PBMT studies usually present a table/figure/box with the treatment parameters. This information summarized in a quick-access location is very useful for readers. You can even add this information to figure 1. Page 6; Intervention: Please, provide a rationale for using the SE25 probe on the spinous process and the LaserShower probe on the paravertebral muscles. Page 7; lines 23-43: You do not need to repeat all characteristics of PBMT devices. But you should make clear whether placebo application will be applied with the device turned off or there is a “placebo mode” available at the own equipment. Page 7; lines 45-46: Provide additional information about the choice by 4 treatment weeks and 3 weekly sessions. In additional, what is the minimal interval between sessions? Page 7; Intervention: What is the patient positioning during PBMT/placebo application? Page 7; Intervention: You did not explain how the therapist (responsible for PBMT application) will be blinded on the treatment performed by each patient. Page 8, lines 5-6: How long does it take between the last treatment session and the post-intervention assessment? When post-intervention assessment is performed immediately after the last treatment session, acute effects of PBMT possibly act as a confounding factor. For instance, patient may be under the analgesic effect of the PBMT application for minutes/hours after the treatment session, and this transitory relief of pain influencing his/her responses on Pain Numerical Rating Scale. Page 8; line 10: Description of primary and secondary outcomes is

	different from the abstract. Page 9; lines 20-22: Please, provide additional information regarding the patients' recruitment. Will the researchers be within the health service to recruit patients? Or will the clinicians be responsible to select patients? Page 10; lines 5-6: Provide information related to the reliability of these assessments performed by telephone. Page 11; lines 6-8: "[…] some studies have demonstrated the efficacy of PBMT in LBP". There are studies with negative results too (e.g., Ay et a. 2010). You should address these conflicting findings in this part of the text. Page 11; lines 8-11: If the low methodological quality of the previous studies is a justifying to carry out this clinical trial, their weak points should be highlighted here. The reader needs to know the novelty of this study. Page 11; Discussion: You did not write any comment on the dose-response effect of PBMT. Studies with positive results in the literature used dissimilar equipment, emitting sources, energy doses, etc. Thus, how do you know that parameters proposed in this study are the most adequate for treating patients with LBP? I suggest you address the issue "PBMT parameters" and the inconsistencies on the optimal parameters for LBP in one paragraph of the discussion section. In addition, the use of a single dosage of PBMT in this trial should be mentioned as a limitation of the study.

REVIEWER	Vanessa Milanese Holanda Beneficência Portuguesa of São Paulo Hospital Brazil
REVIEW RETURNED	29-Apr-2017

GENERAL COMMENTS	This is an interesting and well described clinical study protocol. I would suggest to explain better why the targets T11-T12, L2-L3 and L5-S1 were chosen. There are no results available. Some of the information provided in the manuscript is redundant publication. It is very similar with the information available at the clinicaltrials.gov Please, consider a new submission including the results (or some part of them).

REVIEWER	Paul F. White, PhD, MD Cedars-Sinai Medical Center in Los Angeles, CA Consultant to Phoenix Thera-lase Systems LLC, Dallas TX
REVIEW RETURNED	14-May-2017

GENERAL COMMENTS	I could not find the Results section. The author's description of the laser device needs to provide more details. Although it could be improved, the English writing style is surprisingly good. The study design is excellent and would provide important information on cold laser therapy for the medical community.

VERSION 1 – AUTHOR RESPONSE

Reviewer #1
Bruno Manfredini Baroni

Comments to the Author:
I appreciate the opportunity to review this interesting work from a consolidated research group. In summary, this manuscript is a protocol study on the effects of photobiomodulation therapy (PBMT) in patients with chronic non-specific low back pain (LBP). Authors chose an appropriate study design (a prospectively registered, two-arm randomized placebo-controlled trial with blinded patients, assessors and therapists), validated methods for patients' assessment, and a PBMT device previously tested in scientific researches. Effect of PBMT on pain intensity, disability, specific disability and global perceived effect will be measured after 12 sessions of treatment, as well as after 3, 6 and 12 months. Although there is evidence favorable to PBMT in patients with LBP, including a relatively recent meta-analysis (Glazov et al. 2016), authors state that there is still a need for high quality articles on this issue; and this reviewer agree with them. Therefore, this study will improve the current knowledge and contribute to the clinical practice of health professionals involved in the treatment of LBP. However, the manuscript did not make clear some important issues about the protocol, and there are several changes to be made in the manuscript to make this protocol study acceptable for publication in BMJ Open (see specific comments next).
We appreciate your kind and constructive comments. We have made all recommended changes and answered all questions.

Specific Comments
Review 1.
Page 3; line 6: I do not agree with the sentence "our study does not present limitations", because all studies have some weakness. PBMT has a well-documented dose-response effect, and other parameters (e.g., light source, wavelength, power output, etc.) may significantly affect the treatment success. Thus, some studies have tested more than one treatment dosage to investigate the effects of PBMT on different diseases/injuries. Since previous clinical trials that reported positive effects of PBMT on LBP symptoms have used a range of energy doses and different devices/parameters, there is no consensus about the optimal dosage for LBP. Therefore, the single treatment dosage proposed in this clinical trial could be considered a limitation of this study.
We agree with you. We added the following information to the strengths and limitations section: In our study, we will test the effects of a single dose of PBMT (24 J). PBMT is known to present a biphasic dose-response pattern, i.e., within a therapeutic window (dosage range) the effects of biostimulation can be observed. However, if dosages below or above this window are used, these effects may not be observed.

Therefore, the application of only one dose of PBMT may be considered a limitation of this trial. However, in order to minimize this limitation, we based the choice of our parameters using the best evidence available (1).

Review 2.
Page 4; lines 6-13: Information regarding the high frequency of LBP was repeated in the three sentences. Please, organize this part of the text.
Thank you for your comment. We organized this section as suggested. Furthermore, we added the following information to the Introduction section: "Low back pain (LBP) is ranked as one of the most frequent health problems and is highly associated with disability worldwide (2-5). It is estimated that about 12% of the world's population suffers from LBP (6). Furthermore, LBP generates high levels of work absenteeism and excessive costs to health systems (2,3)".

Review 3.

Page 4; lines 18-23: There is controversial information here. The first sentence states that “there are no treatments that truly minimize the intensity of symptoms”, while the second sentence says that “several interventions are effective in reducing pain and disability”.
We have rewritten this sentence to clarify the idea as suggested. Furthermore, we added the following information to the Introduction section: “Therefore, the ideal treatment for chronic LBP represents a significant challenge, since there are no treatments that cure persistent LBP. However, several interventions provide low to moderate effects in reducing pain and disability on this population (7)”.

Review 4.
Page 4; lines 24-30: Consider add these sentences to the first paragraph, and writing a second paragraph totally dedicated to PBMT and their physiological/therapeutic effects (4th paragraph of the current version of the manuscript).
We appreciate the reviewer’s suggestion and the changes were made.

Review 5.
Page 4; lines 35-36: I suggest leaving the clinical trials on PBMT and LBP to the third paragraph. Here, authors should insert as reference the recent clinical guideline by Qaseem et al. (2017). PBMT was cited there as a possible nonpharmacologic treatment for LBP.
We appreciate reviewer’s suggestion to insert Qaseem et al. as one of the references. In current version of our manuscript we have included in the discussion the reference suggested by you. Furthermore, we added the following information to the Introduction section: “Furthermore, a recent clinical practice guidelines (8) recommended the use of the PBMT as a possible nonpharmacological treatment for chronic LBP”.

Review 6.
Page 4; line 43: There are some misconceptions here. Reference #18 is not an “evidence from recent years” (it was published in 1999), while reference #23 is not related to PBMT. In addition, all studies cited here are focused on therapeutic effects (clinical outcomes) and not physiological effects of PBMT. Please, review this reference list. There are impacting articles in this field that should be cited here (e.g., the systematic review of on LBPT in patients with neck pain, by Chow et al. 2009).
1. We agree with the reviewer that there has been a mistake, and some references did not match with the information contained in the sentence. All these issues are now fixed. Furthermore, we added the following correction of references in Discussion section: “Recent evidence (9-14)…”

2. We appreciate the reviewer’s suggestion and we added the systematic review of on PBMT in patients with neck pain, by Chow et al., 2009. Furthermore, we added the following information to the Introduction section: “As TFBM has been successfully proved as an effective intervention for neck pain patients (15) and it is likely that TFBM could also be a reasonable option for patients with LBP.”

Review 7.
Page 4; line 45: Add a reference to “increased ATP synthesis”. There are so many studies on this issue.
Thank you for this comment. We added the reference to “increased ATP synthesis”: “… increased ATP synthesis (10,11)…

Review 8.
Page 4; lines 49-53: There are two “in addition” in this sentence.
We appreciate the reviewer’s comments, and the pertinent changes were made.

Review 9.
Page 5; line 5: You addressed only trials with positive results in this paragraph. I strongly suggest you include studies that found no additional benefits with PBMT (e.g., Ay et al. 2010) to highlight the

conflicting findings in the literature.
We appreciate reviewer's suggestion to insert the conflicting findings in the literature. In current version of our manuscript we have included in the discussion a sentence about these conflicting findings: "On the other hand, Ay et al. (16) did not detected differences between PBMT and placebo treatments on pain and disability in patients with acute and chronic LBP associated with lumbar disk degeneration. These findings show that there are still conflicts in the literature about PBMT in LBP. Therefore high quality and adequately powered trials are strongly needed".

Review 10.
Page 5; lines 15-18: This is not true. For instance, the study conducted by Konstantinovic et al. (2010) is a placebo-controlled trial. Therefore, this rationale cannot be used to justify the present study.
We appreciate the reviewer's comment, however, the Konstantinovic study was carried out in patients with acute low back pain associated with radiculopathy, unlike our study, which will be conducted in patients with chronic non-specific low back pain. However, the study by Ay et al. (16) is a placebo-controlled trial in a mixed sample of patients with acute and chronic LBP. Therefore, we followed the suggestion of the reviewer and we will not use this justification in our introduction.

Review 11.
Page 5; lines 18-27: The objectives are a little confusing. Maybe you should use a single sentence, as reported in the Abstract.
We appreciate the reviewer's comments, and the pertinent changes were made. Furthermore, we added the following information to the Introduction section: "Therefore, the objective of this study is to evaluate the effects of PBMT against placebo in patients with chronic non-specific LBP in the short, medium, and long term for the outcomes of pain intensity, disability associated with LBP, specific disability and global perceived effect."

Review 12.
Page 5; first paragraph: In view of the evidence on PBMT in LPB patients, including a meta-analysis (Glazov et al. 2016), the justification for this study needs to be improved. In my opinion, the high methodological quality of this study design, the large sample size and the measures at medium- and long-term periods are the strengths of this study and should be highlighted.
We appreciate reviewer's suggestion and have rewritten this sentence to improve the justification for this study. Furthermore, we added the following information to the Introduction section: "… In view of these issues, it is necessary to conduct a high quality, adequately powered, randomized placebo-controlled trial with outcomes been measured at medium-and long-terms… ".

Review 13.
Page 6; line 15: Add examples of severe skin diseases.
We added the following information to the exclusion criteria: "Patients with severe skin diseases (e.g., skin cancer, erysipelas, severe eczema, severe dermatitis, severe psoriasis and severe hives lupus)".

Review 14.
Page 6; lines 17-18: Provide references on the clinical exam you will adopt.
We added the reference as requested.

Review 15.
Page 6; Interventions: PBMT studies usually present a table/figure/box with the treatment parameters. This information summarized in a quick-access location is very useful for readers. You can even add this information to figure 1.

We appreciate reviewer's suggestion to insert a table with the treatment parameters. We insert a table in the "interventions' section".

Review 16:
Page 6; Intervention: Please, provide a rationale for using the SE25 probe on the spinous process and the LaserShower probe on the paravertebral muscles.
We appreciate the reviewer's comments. We added the following information to the "interventions section": "We will use two different emitters because we have different objectives in each application area, which consequently require different mechanisms of action. We will use the SE25 emitter on the spinous processes in order to inhibit pain. Considering the smaller area of this emitter (4 cm2), the power density will be increased, which will consequently induce the triggering of inhibitory effects, such as a decrease in the axonal flow and thus providing potential analgesic effects (17, 18). In addition, the higher frequency used in this emitter will also increase the number of photons that will reach the target tissue, which will also promote the triggering of inhibitory effects and consequent analgesic effect. For the erector spinae muscles, we will use the LaserShower 50 (LS50) emitter in order to promote photobiostimulatory effects, considering the larger area of the device (20 cm2), with consequent lower power density. In addition, this emitter has a lower frequency, which will consequently decrease the number of photons delivered to the target tissue. With these factors, we believe that we will promote an increase in the production of ATP (10, 11), an increase in microcirculation (9) and consequently a decrease in muscle fatigue and stiffness. This therapeutic strategy using different emitters and different frequencies showed positive effects in the reduction of nonspecific knee pain in a previous study that used this same PBMT device and these same emitters (1), however the frequencies and doses were adapted for back pain patients."

Review 17.
Page 7; lines 23-43: You do not need to repeat all characteristics of PBMT devices. But you should make clear whether placebo application will be applied with the device turned off or there is a "placebo mode" available at the own equipment.
Thank you for this comment. We added the following information to the interventions' section: "The placebo PBMT will be delivered using the same device that active PBMT, but without any emission of therapeutic dose".

Review 18.
Page 7; lines 45-46: Provide additional information about the choice by 4 treatment weeks and 3 weekly sessions. In additional, what is the minimal interval between sessions?
1. We based our study on Basford et al. (19) for the choice of frequency for the PBMT treatment. Although the studies performed with PBMT for LBP used different treatment frequencies (20-22), we took into account the frequency that is most feasible for clinical practice.

Furthermore, we added the following information in the Methods section: The choice of treatment frequency was based on Basford et al. (19).

2. The minimum interval between sessions was determined from the Albuquerque-Pontes study (11), which determined that the effects of PBMT on biostimulation of cytochrome C oxidase start within 5 minutes after irradiation and remain for up to 24 hours. Therefore, in order not to deliver an excessive dose of PBMT, we will observe a minimum interval of 24 hours between treatment sessions. Furthermore, we added the following information to the Methods section: "… according to prior randomization, 3 times a week (with a minimal interval of 24 hours) for 4 consecutive weeks, totaling 12 therapy sessions."

Review 19.
Page 7; Intervention: What is the patient positioning during PBMT/placebo application?
We appreciate the reviewer's comments, and we added this information in the methods section: "The

patients will be positioned preferably in prone. However, in specific cases where patients do not tolerate this position due to pain, we will respect the patient's preferred positioning."

Review 20.
Page 7; Intervention: You did not explain how the therapist (responsible for PBMT application) will be blinded on the treatment performed by each patient.
We appreciate reviewer's comments and we added this information in the methods section: "The active and placebo PBMT will be performed using the same device and the irradiated sites will be the same in both groups. To ensure blinding for therapists and patients, the device will emit the same sounds and the same information on the display regardless of the programmed mode (active or placebo). Furthermore, because the device produces a nonsignificant amount of heat (23), the patients will not able to know if active or placebo PBMT will be administered. The device was previously coded as active or placebo mode, and only one researcher not involved in the randomization, treatment and evaluation is aware of these codes."

Review 21.
Page 8, lines 5-6: How long does it take between the last treatment session and the post-intervention assessment? When post-intervention assessment is performed immediately after the last treatment session, acute effects of PBMT possibly act as a confounding factor. For instance, patient may be under the analgesic effect of the PBMT application for minutes/hours after the treatment session, and this transitory relief of pain influencing his/her responses on Pain Numerical Rating Scale.
The assessment after 12 sessions of treatment will be performed immediately after the last treatment session. Although we know that PBMT can trigger acute effects, the Numerical Pain Scale will measure the average pain of the last 7 days, not the pain at the moment the questionnaire is applied. Therefore, this will reduce the chance that this possible analgesic effect may be a possible confounding factor. In addition, we believe that assessment on the last day of treatment contributes to a lower sample loss, since the patient does not have to return another day just for reassessment.

Review 22.
Page 8; line 10: Description of primary and secondary outcomes is different from the abstract.
We appreciate the reviewer's comments, and the pertinent changes were made in both Methods and Analysis sections.

Review 23.
Page 9; lines 20-22: Please, provide additional information regarding the patients' recruitment. Will the researchers be within the health service to recruit patients? Or will the clinicians be responsible to select patients?

We appreciate the reviewer's comments, and we added this information in the methods section: "We will partner with supervising clinicians at primary and secondary care health services so that they will refer chronic non-specific LBP patients to our study for treatment."

Review 24.
Page 10; lines 5-6: Provide information related to the reliability of these assessments performed by telephone.
All of the questionnaires that will be used in the present study have been fully tested for their measurement properties (24, 25). These measurement properties were also tested over the phone. Therefore, we are confident that the assessments are reliable. In addition, conducting follow-ups via telephone reduces sample loss, since the patient does not have to travel solely for reassessments. It is important to point out that large and important studies worldwide carry out this technique of follow-up via phone call (26, 27, 28) proving to be a well-established and effective method of measuring outcomes in the medium and long term. Furthermore, our research group has performed more than

10 clinical trials using this method (29-33) without any problems with reliability.

Review 25.
Page 11; lines 6-8: “[…] some studies have demonstrated the efficacy of PBMT in LBP”. There are studies with negative results too (e.g., Ay et a. 2010). You should address these conflicting findings in this part of the text.
We appreciate the reviewer’s comments and the pertinent changes were made, including this confliting findings. Furthermore, we added the following information to the Discussion section: “Since then, there are still conflicts in the literature about PBMT in LBP. Although there is evidence that PBMT is no better than placebo treatment on pain and disability in a mixed sample of patients with acute and chronic LBP (16), some studies have demonstrated the efficacy of PBMT in chronic and acute LBP (19-22). Nevertheless, there are still issues to be clarified about its efficacy, as there are no high-quality methodological studies that test PBMT versus placebo in chronic LBP patients.”

Review 26.
Page 11; lines 8-11: If the low methodological quality of the previous studies is a justifying to carry out this clinical trial, their weak points should be highlighted here. The reader needs to know the novelty of this study.
We appreciate the reviewer’s comments and the pertinent changes were made: “Nevertheless, there are still issues to be clarified about its efficacy, as there are no high-quality methodological studies that test PBMT versus placebo in LBP patients. To date, studies evaluating the effects of PBMT on chronic non-specific LBP have not been prospectively registered (16, 19-22) and have a small sample size (16, 19, 20, 22) and high risk of bias. In addition, none of the studies were triple blinded and none of the data analyses were carried using intention to treat principles.

Review 27.
Page 11; Discussion: You did not write any comment on the dose-response effect of PBMT. Studies with positive results in the literature used dissimilar equipment, emitting sources, energy doses, etc. Thus, how do you know that parameters proposed in this study are the most adequate for treating patients with LBP? I suggest you address the issue “PBMT parameters” and the inconsistencies on the optimal parameters for LBP in one paragraph of the discussion section. In addition, the use of a single dosage of PBMT in this trial should be mentioned as a limitation of the study.
We appreciate the reviewer’s comments and we added the following information to the Discussion section: PBMT presents a biphasic dose-response pattern, i.e., within a therapeutic window (dose range) the biostimulation effects can be seen. Very low doses may not trigger responses in the irradiated tissue, whereas very high doses may cause inhibition (34). In addition, the power and time of irradiation are also extremely important parameters to obtain better results with the PBMT (35).

Therefore, the choice of PBMT parameters is essential for obtaining positive results and represents an important challenge in treating any musculoskeletal disorder. To date, there is great heterogeneity in the parameters of PBMT used for the treatment of LBP, and it is not possible to conclude the best dose for the treatment of this disorder. Thus, our parameters were adapted from the best evidence available (1) and took into consideration the dosage recommended by WALT (35). Thus, although we believe that the dosage chosen for the present study will be effective in triggering the expected results, a limitation of our study is that we will test only one dose of PBMT.

Reviewer #2
Vanessa Milanese Holanda
Comments to the Author

Please leave your comments for the authors below.
Review 1.
This is an interesting and well described clinical study protocol.

We appreciate the reviewer's comments.

Review 2.
I would suggest to explain better why the targets T11-T12, L2-L3 and L5-S1 were chosen.
We appreciate the reviewer's comments and we added this information in the paper:
PBMT irradiation sites were chosen based on previous studies (19-22), and in order to cover the largest possible area of the lumbar spine.

Review 3.
There are no results available.
We appreciate the reviewer's comments, but according SPIRIT (Standard Protocol Items: Recommendations for interventional Trials) the protocol of a clinical trial is essential for study conduct, review, reporting and interpretation. Researchers use protocols to document plans for study conduct at all stages from participant recruitment to results dissemination (36). To help improve the quality and content of protocols, an international group developed the SPIRIT 2013 Statement (36, 37), that provides recommendations for a minimum set of scientific, ethical, and administrative elements that should be addressed in a clinical trial protocol. The items that must be included are: 1. Administrative information; 2. Introduction; 3. Methods: participants, interventions, outcomes; 4. Methods: assignment of interventions; 4. Methods: data collection, management, analysis; 5. Methods: monitoring; 6. Ethics and Dissemination; 7. Appendices. The BMJ Open recommends that we use SPIRIT 2013 Statement as guidance. Since the present study is a protocol, we do not have results available at this time. However, in the future, after completing the data collection, we will publish a new article with our results.

Review 4.
Some of the information provided in the manuscript is redundant publication. It is very similar with the information available at the clinicaltrials.gov. Please, consider a new submission including the results (or some part of them).
We appreciate the reviewer's comments,
We wish to point out that the journal's standards strongly recommend that the study be recorded prospectively (38). In the registry (clinicaltrials.gov website), we have to present the methods of the study, consequently the information will be similar in the protocol, but more complete. However, according to BMJ Open standards, the publication of protocols is important because "publishing study protocols enables researchers and funding bodies to stay up to date in their fields by providing exposure to research activity that may not otherwise be widely publicised. This can help prevent unnecessary duplication of work and will hopefully enable collaboration.

Publishing protocols in full also makes available more information than is currently required by trial registries and increases transparency, making it easier for others (editors, reviewers and readers) to see and understand any deviations from the protocol that occur during the conduct of the study."

Reviewer #3
Paul F. White, PhD, MD

Please leave your comments for the authors below

Review 1.
I could not find the Results section.
We appreciate the reviewer's comments. Please, see reviewer #3, second comment.

Review 2.
The author's description of the laser device needs to provide more details.
We appreciate reviewer's comments and we insert a table in the "interventions", with more information

about laser device and parameters: table 1 (parameters SE25 and LaserShower emitter).

Review 3:
Although it could be improved, the English writing style is surprisingly good.
We really appreciate reviewer's comments.

Review 4:
The study design is excellent and would provide important information on cold laser therapy for the medical community.
We really appreciate reviewer's comments.

References:

1. Leal-Junior EC, Johnson DS, Saltmarche A, Demchak T. Adjunctive use of combination of super-pulsed laser and light-emitting diodes phototherapy on nonspecific knee pain: double-blinded randomized placebo-controlled trial. Lasers Med Sci. 2014:29;1839-47.

2. Tulder MV. Chapter 1. European guidelines. Eur Spine J 2006;15:134-35.

3. Academia Americana De Cirurgiões Ortopédicos (American Academy Of Orthopaedic Surgeons). US Bone and Joint Decade - The Burden of Musculoskeletal Diseases in the United States. Rosemont, IL, USA, 2008.

4. Dagenais S, Caro J, Haldeman SA. systematic review of low back pain cost of illness studies in the United States and internationally. Spine J. 2008;8:8-20.

5. Murray CJ, Lopez AD. Measuring the global burden of disease. N Engl J Med. 2013;369:448-457.

6. Hoy D, Bain C, Williams G, March L, Brooks P, Blyth F, et al. A systematic review of the global prevalence of low back pain. Arthritis Rheum. 2012;64:2028-37.

7. Maher C, Underwood M, Buchbinder R. Non-specific low back pain. Lancet. 2017;389:736-47.

8. Qaseem A, Wilt TJ, McLean RM, Forciea MA. Clinical Guidelines Committee of the American College of Physicians. Noninvasive Treatments for Acute, Subacute, and Chronic Low Back Pain: A Clinical Practice Guideline From the American College of Physicians.

Ann Intern Med. 2017;166:514-530.

9. Tullberg M, Alstergren PJ, Ernberg MM. Effects of low-power laser exposure on masseter muscle pain and microcirculation. Pain. 2003;105:89-96.

10. Silveira PC, Silva LA, Fraga DB, Freitas TP, Streck EL, Pinho R. Evaluation of mitochondrial respiratory chain activity in muscle healing by low-level laser therapy. J Photochem Photobiol B. 2009;4:89-92

11. Albuquerque-Pontes GM, Vieira RP, Tomazoni SS, Caires CO, Nemeth V, Vanin AA, et al. Effect of pre-irradiation with different doses, wavelengths, and application intervals of low-level laser therapy on cytochrome c oxidase activity in intact skeletal muscle of rats. Lasers Med Sci. 2015;30:59-66.

12. Xu X, Zhao X, Liu TC, Pan H. Low-intensity laser irradiation improves the mitochondrial dysfunction of C2C12 induced by electrical stimulation. Photomed Laser Surg. 2008;26:197-202.

13. Avni D, Levkovitz S, Maltz L, Oron U. Protection of skeletal muscles from ischemic injury: low-level laser therapy increases antioxidant activity. Photomed Laser Surg. 2005;23:273-277.

14. Rizzi CF, Mauriz JL, Freitas Corrêa DS, Moreira AJ, Zettler CG, Filippin LI, et al. Effects of low-level laser therapy (LLLT) on the nuclear factor (NF)-kappaB signaling pathway in traumatized muscle. Lasers Surg Med. 2006;38:704-13.

15. Chow RT, Johnson MI, Lopes-Martins RA, Bjordal JM. Efficacy of low-level laser therapy in the management of neck pain: a systematic review and meta-analysis of randomised placebo or active-treatment controlled trials. Lancet. 2009;4:1897-908.

16. Ay S, Doğan SK, Evcik D. Is low-level laser therapy effective in acute or chronic low back pain? Clin Rheumatol. 2010;29:905-10.

17. Huang YY, Sharma SK, Carrol J, Hamblin MR. Biphasic dose response in low level light therapy – an update. Dose Response. 2011;9:602-618.

18. Chow R, Armati P, Laakso EL, Bjordal JM, Baxter GD. Inhibitory effects of laser irradiation on peripheral mammalian nerves and relevance to analgesic effects: a systematic review. Photomed Laser Surg. 2011;29:365-81.

19. Basford JR, Sheffield CG, Harmsen WS. Laser therapy: a randomized, controlled trial of the effects of low-intensity Nd:YAG laser irradiation on musculoskeletal back pain. Arch Phys Med Rehabil. 1999;80:647-52.

20. Gur A, Karakoc M, Cevik R, Nas K, Sarac AJ, Karakoc M. Efficacy of low power laser therapy and exercise on pain and functions in chronic low back pain. Lasers Surg Med. 2003;32:233-38.

21. Konstantinovic LM, Kanjuh ZM, Milovanovic AN, Cutovic MR, Djurovic AG, Savic VG, et al. Acute low back pain with radiculopathy: a double-blind, randomized, placebo-controlled study. Photomed Laser Surg. 2010;28:553-60.

22. Vallone F, Benedicenti S, Sorrenti E, Schiavetti I, Angiero F. Effect of diode laser in the treatment of patients with nonspecific chronic low back pain: a randomized controlled trial. Photomed Laser Surg. 2014;32:490-94.

23. Grandinétti V Dos S, Miranda EF, Johnson DS, De Paiva PR, Tomazoni SS, Vanin AA, et al. The thermal impact of phototherapy with concurrent super-pulsed lasers and red and infrared LEDs on human skin. Lasers Med Sci. 2015;30:1575-81.

24. Costa LO, Maher CG, Latimer J, Ferreira PH, Ferreira ML, Pozzi GC, et al. Clinimetric testing of three self-report outcome measures for low back pain patients in Brazil: which one is the best? Spine (Phila Pa 1976). 2008;33:2459-63.

25. Costa LO, Maher CG, Latimer J, Ferreira PH, Pozzi GC, Ribeiro RN. Psychometric characteristics of the Brazilian-Portuguese versions of the Functional Rating Index and the Roland Morris Disability Questionnaire. Spine (Phila Pa 1976). 2007;32:1902-07.

26. Hancock MJ, Maher CG, Latimer J, McLachlan AJ, Cooper CW, Day RO et al. Assessment of diclofenac or spinal manipulative therapy, or both, in addition to recommended first-line treatment for acute low back pain: a randomised controlled trial. Lancet. 2007;370:1638-43.

27. Williams CM, Maher CG, Latimer J, McLachlan AJ, Hancock MJ, Day RO et al. Efficacy of paracetamol for acute low-back pain: a double-blind, randomised controlled trial. Lancet. 2014;384:1586-96.

28. Mathieson S, Maher CG, McLachlan AJ, Latimer J, Koes BW, Hancock MJ et al. Trial of Pregabalin for Acute and Chronic Sciatica. N Engl J Med. 2017;376:1111-1120.

29. de Oliveira RF, Liebano RE, Costa Lda C, Rissato LL, Costa LO. Immediate effects of region-specific and non-region-specific spinal manipulative therapy in patients with chronic low back pain: a randomized controlled trial. Phys Ther. 2013;93:748-56.

30. da Luz MA Jr, Costa LO, Fuhro FF, Manzoni AC, Oliveira NT, Cabral CM. Effectiveness of mat Pilates or equipment-based Pilates exercises in patients with chronic nonspecific low back pain: a randomized controlled trial. Phys Ther. 2014;94:623-31.

31. Parreira Pdo C, Costa Lda C, Takahashi R, Hespanhol Junior LC, Luz Junior MA, Silva TM et al. Kinesio taping to generate skin convolutions is not better than sham taping for people with chronic non-specific low back pain: a randomised trial. J Physiother. 2014;60:90-6.

32. Luz Júnior MA, Sousa MV, Neves LA, Cezar AA, Costa LO. Kinesio Taping® is not better than placebo in reducing pain and disability in patients with chronic non-specific low back pain: a randomized controlled trial. Braz J Phys Ther. 2015;19:482-90.

33. Garcia AN, Hancock M, Costa LCM, De Souza, FS, Gomes GVFO, Almeida MO, et al. Efficacy of the mechanical diagnosis and therapy in patients with chronic nonspecific low back pain: a randomized placebo controlled trial. 2017; Brit J Sports Med [in press]

34. Huang YY, Sharma SK, Carrol J, Hamblin MR. Biphasic dose response in low level light therapy – an update. Dose Response. 2011;9:602-618.

35. World Association for Laser Therapy - WALT (2010): Dosage recommendations. Recommended treatment doses for low level laser therapy. Available in: http://www.walt.nu/dosage-recommendations.html. Accessed May 30, 2017.

36. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K et al., SPIRIT 2013 statement: defining standard protocol items for clinical trials. Ann Intern Med. 2013;158:200-7.

37. Chan AW, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin JA et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. BMJ. 2013;346:e7586.

38. Viergever RF, Li K. Trends in global clinical trial registration: an analysis of numbers of registered clinical trials in different parts of the world from 2004 to 2013. BMJ Open. 2015;5:e008932.

VERSION 2 – REVIEW

REVIEWER	Bruno Manfredini Baroni Universidade Federal de Ciências da Saúde de Porto Alegre, Brazil
REVIEW RETURNED	01-Jul-2017

GENERAL COMMENTS	Congratulations to the authors. I wish you success in conducting the experiment. Obs.: a single detail, change TFBM for PBMT at the introduction section (twice, lines 48-49).

VERSION 2 – AUTHOR RESPONSE

Reviewer #1
Bruno Manfredini Baroni

Comments to the Author:
Congratulations to the authors.
I wish you success in conducting the experiment.
Obs.: a single detail, change TFBM for PBMT at the introduction section (twice, lines 48-49).

We appreciate the reviewer's comments, and we have made the recommended changes.