BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-017202
Article Type:	Protocol
Date Submitted by the Author:	10-Apr-2017
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Primary Subject Heading:	Evidence based practice
Secondary Subject Heading:	Rehabilitation medicine
Keywords:	chronic low back pain, photobiomodulation therapy, low-level laser therapy, LLLT, PBMT

Effects of photobiomodulation therapy in patients with chronic non-specific low back pain: protocol for a randomized placebo-controlled trial

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Trial registration number: NCT03089424

Funding statement: This work was supported by FAPESP (postdoctoral scholarship of Shaiane Silva Tomazoni) grant number 2016/10265-0.

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Author contributions

SST and LOPC contributed to the concept and design of the study. SST and LOPC established the hypothesis and wrote the original proposal. SST, LCMC, LSG, ACA, DPN, FCM and LOPC contributed significantly in creating the manuscript. LCMC and LOPC performed critical revisions of the manuscript. SST, LCMC, LSG and LOPC wrote the final version of the manuscript. All authors read and approved the final version of the manuscript.

Number of figures and tables: 2 figures and 0 tables.

Conflict of interest: the authors declare no conflict of interest.

ABSTRACT

Introduction: Low back pain (LBP) is one of the largest and most frequent public health problems. LBP is highly associated with absenteeism from work and generates excessive costs for health systems. Photobiomodulation therapy (PBMT) is a frequently used non-pharmacological therapy for the treatment of musculoskeletal disorders. However, there is little high-quality scientific evidence that demonstrates the effectiveness of PBMT in the treatment of patients with chronic LBP in the short, medium, and long term. Therefore, the objective of this clinical trial is to evaluate the effects of PBMT in patients with chronic non-specific LBP in the short, medium, and long term. **Methods and analyses:** This is a prospectively registered, two-arm randomized placebo-controlled trial with blinded patients, assessors and treatment providers. One hundred and forty-eight patients with chronic non-specific LBP will be recruited. Treatment sessions will be provided 3 times a week for 4 weeks (totaling 12 sessions) with patients receiving either placebo or active PBMT. For ethical reasons, all patients, regardless of treatment allocation, will also receive an information booklet based on "The Back Book". Clinical outcomes will be measured at baseline, at the end of treatment, as well as 3, 6, and 12 months after randomization. The primary outcomes will be pain intensity and disability measured after 12 sessions of treatment. The secondary outcomes will be pain intensity and disability measured at 3, 6, and 12 months after randomization, in addition to specific disability and global perceived effect in all time points. **Ethics and dissemination:** The study was approved by the Research Ethics Committee of Universidade Cidade de São Paulo. The results will be disseminated through scientific publications and presentations at national and international scientific meetings. Clinical trial registration number: NCT03089424 (clinicaltrials.gov).

Key-words: chronic low back pain, photobiomodulation therapy, low-level laser therapy, LLLT, PBMT.

Strengths and limitations of this study:

- The present study can be considered to have high methodological quality, since it is a randomized, controlled, and prospectively registered clinical trial.
- One of the strengths of the study is that it is triple-blind, i.e., evaluators, therapists, and patients will be blinded to interventions over the course of the study.

- The sample size was calculated to provide the appropriate statistical power to detect differences in the primary outcomes of the study.
- We believe that our study does not present limitations.

INTRODUCTION

Low back pain (LBP) is one of the greatest and most frequent public health problems, generating high levels of absenteeism at work and excessive costs to health systems (1-3). Recently, LBP was ranked as one of the seven most frequent health problems and as the debilitating symptom that affects the world's population for the largest number of years (4). It is estimated that about 12% of the world's population suffers from LBP (5). The prognosis of this condition is directly related to the duration of symptoms, with less favorable prognoses in patients with chronic LBP (i.e. with a duration of symptoms longer than three months) (6-10). Therefore, the ideal treatment for chronic LBP represents a significant challenge, since there are no treatments that truly minimize the intensity of symptoms. However, several interventions are effective in reducing pain and disability resulting from LBP in the long term (11).

The existing treatments for LBP can be divided into three categories: 1) pharmacological therapies, which trigger several adverse effects with prolonged use (12-14); 2) non-pharmacological therapies, which minimize undesirable effects and are moderately effective in LBP (15); and surgery, used only when conservative treatment is not efficient (16). Several therapies can be used to treat LBP by controlling symptoms, minimizing disability, and improving the patients' quality of life (17).

Photobiomodulation therapy (PBMT) is a non-pharmacological intervention often used in the treatment of musculoskeletal disorders such as LBP (18-21). PBMT consists in applying a non-ionized form of light, which includes laser (light amplification by stimulated emission of radiation), LED (light-emitting diodes), and other lights with a broader spectrum ranging from visible to infrared (22).

Evidence from recent years (18, 23-30) suggests that PBMT triggers positive physiological effects, such as increased microcirculation (31), increased ATP synthesis, stimulation of the mitochondrial respiratory chain (32, 33), stimulation of mitochondrial function (34), and factors that may influence the metabolism of various pathologies. In addition, there is evidence that PBMT reduces the release of reactive oxygen species (ROS) and creatine kinase (CK) activity, in addition to increasing the production of antioxidants and heat shock proteins (35, 36).

Studies have shown the effects of PBMT on LBP. Basford et al. (18) and Gur et al. (19) observed that PBMT appears to be effective in reducing pain and disability triggered by this disorder, while Konstantinovic et al. (20) and Vallone et al. (21) found that PBMT

combined with nonsteroidal anti-inflammatory drugs (NSAIDs) and exercise were efficient in reducing chronic LBP. In a recent systematic review with meta-analysis, Glazov et al. (37) found a clinically significant reduction in chronic LBP in patients treated with PBMT, although a reliable conclusion was hindered by the high heterogeneity in the parameters of therapy application.

Therefore, in spite of the positive results obtained in the aforementioned studies in favor of PBMT, some factors warrant further investigation with high-quality studies on the effects of PBMT applied in isolation in LBP and the ideal parameters of application. Finally there is no placebo-controlled trial that investigated the true efficacy of PBMT in patients with LBP. In view of these issues, the objectives of this study are: 1) to evaluate the short-term effects of PBMT on pain intensity and disability (primary outcomes) in chronic non-specific LBP and 2) to evaluate the medium- and long-term effects of PBMT on pain intensity and general disability (primary outcomes) as well as the short-, medium-, and long-term effects on specific disability and global perceived effect (secondary outcomes) in patients with chronic nonspecific LBP.

METHODS AND ANALYSES

Design

A randomized, triple-blinded (patients, therapists, and outcome assessors), placebo-controlled trial will be performed. The protocol of this study has been prospectively registered on Clinicaltrials.gov (NCT03089424).

Location

The study will be conducted at the Center for Excellence in Clinical Research in Physiotherapy of our institution.

Eligibility criteria

The study assessors will determine whether or not patients will be eligible to participate in the study based on patient history and clinical examination.

Inclusion criteria:

- Patients with non-specific chronic LBP, defined as pain or discomfort between the costal margins and inferior gluteal folds with or without referred pain to the lower limbs;
- Persistent LBP for at least 3 months (38);
- Aged between 18 and 65 years;
- Both genders.

Exclusion criteria:

- Patients with severe skin diseases;
- Patients with LBP associated with nerve root compromise (measured by clinical examination of dermatomes, myotomes, and reflexes);
- Serious spinal pathologies such as fractures, tumors, inflammatory and infectious diseases;
- Decompensated heart disease or metabolic disorders;
- Previous spinal surgery;
- Pregnancy.

Interventions

For ethical reasons, on the first day of treatment, all groups will receive an information booklet on LBP called "The Back Book" (39) based on the recommendations of the European Guidelines (40, 41). The booklet can be accessed freely via internet and it has been translated into Portuguese by our research team. At each treatment session, patients will receive further explanations on the contents of the booklet. There is consistent evidence that *The Back Book* is useful for patients with LBP (42) and it has been used in clinical trials conducted by our research group (43, 44).

Patients will then be randomly allocated to two groups to be submitted to the following interventions:

1. Active PBMT Group: The PBMT will be performed using the Multi Radiance Medical™ Super Pulsed Laser MR4™ console (Solon, OH, USA), with the SE25 (emitter with an area of 4 cm^2) and LaserShower (emitter with an area of 20 cm^2) cluster probes as emitters. Nine sites will be irradiated on the patient's lumbar region: 3 central sites on top of the spinous processes (between T11 and T12, L2 and L3, L5 and S1), using the SE25 (3000 Hz of frequency, 3 minutes of irradiation per site, 24.75 J per site, a totalizing 74.25 J

irradiated from SE25); in the same direction, but laterally, 3 sites on the left and 3 on the right (on the paravertebral muscles), using the LaserShower (1000 Hz of frequency, 3 minutes of irradiation per site, 24.30 J per site, a total of 145.80 J irradiated from LaserShower). Patients will be treated during 12 sessions over a period of four weeks (three sessions/week). At each treatment session, patients will receive a total dose of 220.05 J. At the end of the 12 treatments sessions, patients will receive a total dose of 2640.60 J.

The total treatment time will be 27 minutes per patient. This PBMT application protocol was based on the study of Leal Junior et al. (45). Figure 1 shows the PBMT irradiation sites.

<< Figure 1 >>

2. Placebo PBMT Group: The placebo PBMT will be performed using the Multi Radiance Medical™ Super Pulsed Laser MR4™ console (Solon, OH, USA), with the SE25 (emitter with an area of 4 cm^2) and LaserShower (emitter with an area of 20 cm^2) cluster probes as emitters. Nine sites will be irradiated on the patient's lumbar region: 3 central sites on top of the spinous processes (between T11 and T12, L2 and L3, L5 and S1), using the SE25 (without any dose, 0 J); in the same direction, but laterally, 3 sites on the left and 3 on the right (on the paravertebral muscles), using the LaserShower (without any dose, 0 J). Patients will be treated during 12 sessions over a period of four weeks (three sessions/week). At each treatment session, patients will receive a total dose of 0 J. At the end of the 12 treatments sessions, patients will receive a total dose of 0 J. The placebo mode simulates the pragmatism of clinical practice and increases the credibility of the use of the equipment in relation to the treated patients. The placebo technique has already been widely used in other studies with patients with LBP (44, 46-51), as well as in studies using PBMT (52-54).

Patients will undergo treatment (active PBMT or placebo), according to prior randomization, 3 times a week for 4 consecutive weeks, totaling 12 therapy sessions.

The CONSORT flowchart summarizing experimental procedures and patients are shown in figure 2.

<< Figure 2 >>

Outcomes

Primary and secondary outcomes of the study will be obtained at baseline, at the end of treatment (4 weeks), and 3, 6, and 12 months after randomization. These outcomes will be collected by an assessor who will not be aware of patient allocation to their treatment groups.

The primary outcomes of the study will be:

- Pain intensity measured by the Pain Numerical Rating Scale (55). Pain Numerical Rating Scale evaluates pain intensity levels perceived by the patient on an 11-point scale ranging from 0 to 10, with 0 being "no pain" and 10 "the worst possible pain" (55). Patients will be instructed to score the level of pain intensity based on the last 7 days.
- Disability associated with LBP, as measured by the Roland-Morris Disability Questionnaire (56, 57). The questionnaire consists of 24 items that describe situations that patients may have difficulty performing on a daily basis due to LBP. The greater the number of affirmative answers is, the higher the level of functional disability associated with LBP (55, 57). Patients will be instructed to answer according to their condition on the day of administration of the questionnaire.

The secondary outcomes of the study will be:

- Specific disability, as measured by the Patient-Specific Functional Scale (55). The Patient-Specific Functional Scale is global and can be used for any part of the body. The measurement is done on an 11-point Likert scale for each activity, and the higher the average score is (ranging from 0 and 10 points), the better the patient's ability to perform the activities. The patients will be asked to identify up to three activities that they consider they are incapable of performing or that they have some difficulty performing (55, 58, 59).
- Global perceived effect as measured by the Global Perceived Effect Scale (55). Global Perceived Effect Scale is an 11-point Likert scale, ranging from -5 to +5, that compares the patient's current condition to the onset of symptoms (55). Positive scores represent improvement, while the negative scores represent worsening in relation to the onset of symptoms. Values closer to 5 mean greater intensity of this perception (55).

Sample size

The sample calculation of the study was performed to detect a 1-point difference for the outcome pain intensity (as measured by the Pain Numerical Rating Scale) (55), with an estimated standard deviation of 1.84 points and 4 points for the outcome disability associated with LBP (measured by the Roland-Morris Disability Questionnaire) (56, 57), with an estimated standard deviation of 4.9 points. A statistical power of 80% was considered for the two outcomes, with α of 5% and a possible sample loss of up to 15%. Therefore, a total of 148 patients will be required for the study.

Recruitment

Patients seeking treatment for chronic LBP will be recruited at primary or secondary health services.

Randomization

Prior to initiation of treatment, patients will be randomized into their respective intervention groups. The randomization will be generated by a computer program (Excel Office 2010) and performed by a participating researcher not involved with the recruitment or evaluation of patients. This same researcher will be responsible for programming the PBMT device according to the result of the randomization. The PBMT device used in the present study will make the same sounds regardless of the programmed dose and mode (active PBMT or placebo PBMT). This researcher will be instructed not to disclose the programmed intervention to the therapist or any of the patients and other researchers involved in the study until its completion. Patient and therapist will be blinded throughout the treatment. Concealed allocation will be achieved through the use of sequentially numbered, sealed, and opaque envelopes.

Data collection

The patients will be welcomed by the study's blinded assessor who will determine whether they will be eligible to participate in the study. Subsequently, a file will be completed with the patient's sociodemographic data and clinical history. Next, the primary outcomes and the secondary outcomes of the study will be collected. Then, all eligible patients will be randomized and allocated into two treatment groups: active PBMT or placebo PBMT. At the end of the 12 treatment sessions, the primary and secondary outcomes

of the study participants will be reassessed by the same evaluator who performed the baseline assessment. The 3, 6, and 12-month follow-ups will be performed by telephone by the same evaluator who carried out the other evaluations.

Statistical Analysis

The statistical analysis will be conducted following the principles of intention-to-treat analysis (60). The normality of the data will be tested by visual inspection of histograms and the characterization of the participants will be calculated using descriptive statistical tests. The between-group differences (treatment effects) and their respective 95% confidence intervals will be calculated by using mixed linear models (61) using the group-by-time interaction terms. The analyses will be performed using SPSS version 19.

Ethics

The present study was approved by the Research Ethics Committee of Universidade Cidade de São Paulo (UNICID) under number 1.964.094. All patients eligible for the study will be informed of the objectives and will be required to complete the Informed Consent Form, as determined by Brazilian National Health Council Resolution 196/96.

Dissemination

The study will be disseminated through publication in peer-reviewed international journals, as well as presentations at national and international conferences.

Discussion

Chronic LBP is a condition that is often associated with disability, emotional alterations, and absenteeism from work (8). Since chronic LBP is very prevalent (11), it has a great financial impact, generating high costs, both direct and indirect (62). This fact demonstrates the importance of the constant investigation of more suitable treatments for LBP, aiming at the well-being of the patient and the reduction of expenses for health systems.

PBMT is one of the interventions recommended for the treatment of chronic LBP (63), however, it is a relatively recent therapy given that the first clinical trial investigating its effects on LBP was published in 1999 (18). Since then, some studies have demonstrated the efficacy of PBMT in LBP (19-21). 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.

It is extremely important to carry out studies with high methodological quality aimed at contributing to a better understanding of the effects of PBMT on LBP. Only then will it be possible to determine whether PBMT can be used as one of the treatments of choice for LBP. If the effectiveness of PBMT in LBP is confirmed, it could be used as an alternative method to NSAIDs or opioids, for example, since it causes similar or superior effects to these drugs, shown in other chronic musculoskeletal disorders (64, 65), without the presence of known adverse effects at present. We believe that, by providing relevant and compelling information about PBMT, we will contribute to a safer and more effective clinical practice.

The present study can be considered to have high methodological quality, since it is a randomized, controlled, and prospectively registered clinical trial. In addition, one of the strengths of the study is that it is triple-blind, i.e., evaluators, therapists, and patients will be blinded to interventions over the course of the study. Finally, the sample size was calculated to provide the appropriate statistical power to detect differences in the primary outcomes of the study. Thus, we believe that this study will contribute to the evidence-based practice of PBMT in patients with LBP.

Conflict of interest

The authors declare no conflict of interest.

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FIGURE LEGENDS

Figure 1. PBMT irradiation sites.

Figure 2. Flow diagram of the study.

Figure 1. PBMT irradiation sites.

254x190mm (72 x 72 DPI)

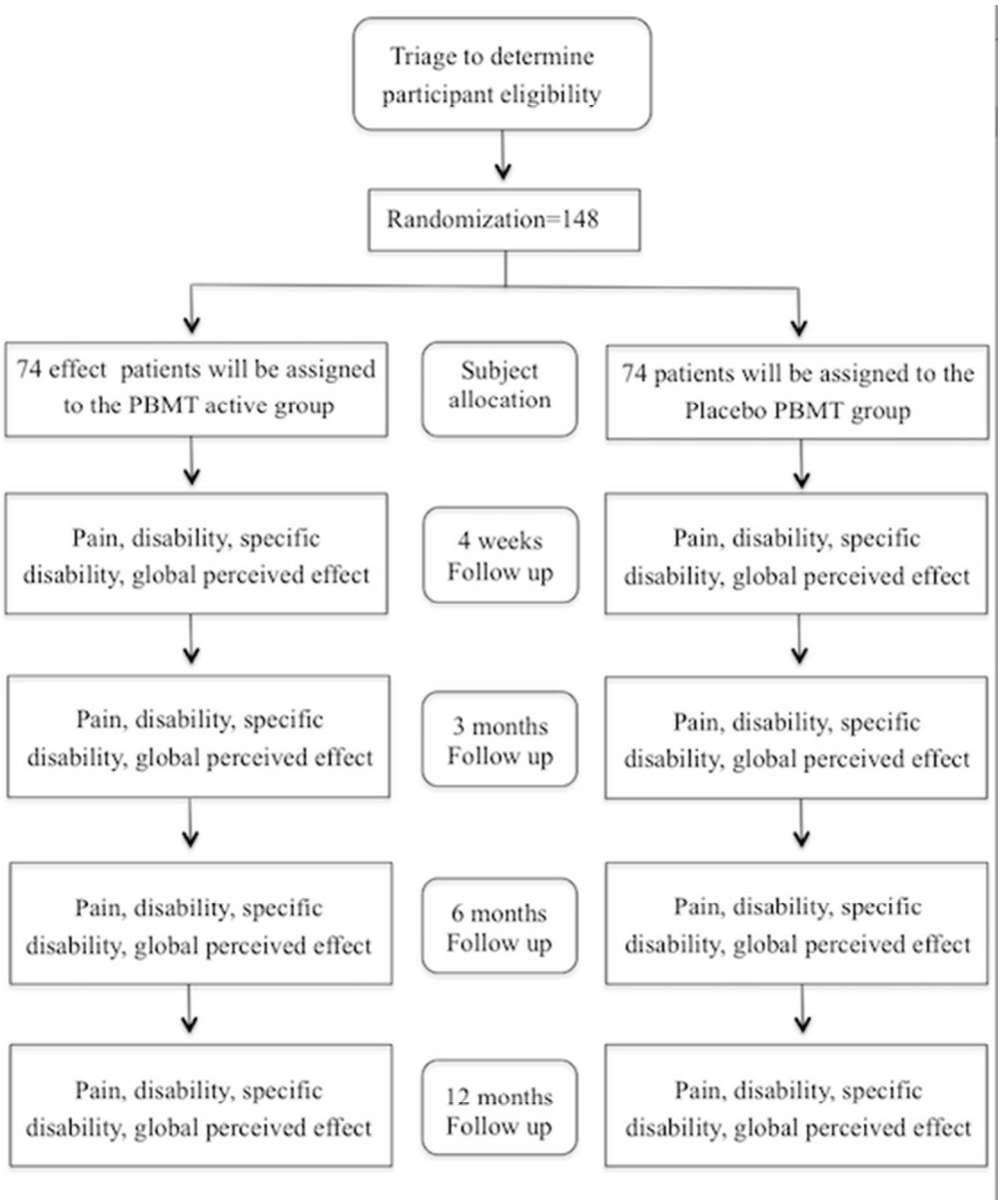

Figure 2. Flow diagram of the study.

197x235mm (72 x 72 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page Number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
	2b	All items from the World Health Organization Trial Registration Data Set	1
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	1
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	1
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	1
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
	6b	Explanation for choice of comparators	7
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5

Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5, 6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6, 7
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	6, 7
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	6, 7
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6, 7
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7, 8
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	8, 9
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	9
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	9
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	9
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	10
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	10
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	-

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	-
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	-
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	-
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	10
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	-
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	-
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	10
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	1
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	10
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	-
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	10
	31b	Authorship eligibility guidelines and any intended use of professional writers	-
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	10

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Effects of photobiomodulation therapy in patients with chronic non-specific low back pain: protocol for a randomized placebo-controlled trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-017202.R1
Article Type:	Protocol
Date Submitted by the Author:	15-Jun-2017
Complete List of Authors:	Tomazoni, Shaiane; Universidade Cidade de Sao Paulo, Masters and Doctoral Programs in Physical Therapy Costa, Lucíola; Universidade Cidade de Sao Paulo, Masters and Doctoral Programs in Physical Therapy Guimarães, Layana; Universidade Cidade de Sao Paulo, Masters and Doctoral Programs in Physical Therapy Araujo, Amanda; Universidade Cidade de Sao Paulo, Masters and Doctoral Programs in Physical Therapy Nascimento, Dafne; Universidade Cidade de Sao Paulo, Masters and Doctoral Programs in Physical Therapy Medeiros, Flavia; Universidade Cidade de Sao Paulo, Masters and Doctoral Programs in Physical Therapy Avanzi, Marina; Universidade Cidade de Sao Paulo, Masters and Doctoral Programs in Physical Therapy Costa, Leonardo; Universidade Cidade de Sao Paulo, Masters and Doctoral Programs in Physical Therapy
Primary Subject Heading:	Evidence based practice
Secondary Subject Heading:	Rehabilitation medicine
Keywords:	chronic low back pain, photobiomodulation therapy, low-level laser therapy, LLLT, PBMT

Effects of photobiomodulation therapy in patients with chronic non-specific low back pain: protocol for a randomized placebo-controlled trial

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Trial registration number: NCT03089424

Funding statement: This work was supported by FAPESP (postdoctoral scholarship of Shaiane Silva Tomazoni) grant number 2016/10265-0.

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Number of figures and tables: 2 figures and 1 table.

Conflict of interest: the authors declare no conflict of interest.

ABSTRACT

Introduction: Low back pain (LBP) is one of the largest and most frequent public health problems worldwide. Photobiomodulation therapy (PBMT) is a frequently used non-pharmacological therapy for the treatment of musculoskeletal disorders. However, there is little high-quality scientific evidence that demonstrates the effectiveness of PBMT in the treatment of patients with chronic LBP in the short, medium, and long term. Therefore, the objective of this clinical trial is to evaluate the effects of PBMT in patients with chronic non-specific LBP in the short, medium, and long term. **Methods and analyses:** This is a prospectively registered, two-arm randomized placebo-controlled trial with blinded patients, assessors and treatment providers. One hundred and forty-eight patients with chronic non-specific LBP will be recruited. Treatment sessions will be provided 3 times a week for 4 weeks (totaling 12 sessions) with patients receiving either placebo or active PBMT. For ethical reasons, all patients, regardless of treatment allocation, will also receive an information booklet based on "The Back Book". Clinical outcomes will be measured at baseline, at the end of treatment, as well as 3, 6, and 12 months after randomization. The primary outcomes will be pain intensity and disability measured after 12 sessions of treatment. The secondary outcomes will be pain intensity and disability measured at 3, 6, and 12 months after randomization, in addition to specific disability and global perceived effect in all time points. **Ethics and dissemination:** The study was approved by the Research Ethics Committee of Universidade Cidade de São Paulo. The results will be disseminated through scientific publications and presentations at national and international scientific meetings. Clinical trial registration number: NCT03089424 (clinicaltrials.gov).

Key-words: chronic low back pain, photobiomodulation therapy, low-level laser therapy, LLLT, PBMT.

Strengths and limitations of this study:

- The present study can be considered to have high methodological quality, since it is a randomized, controlled, and prospectively registered clinical trial.
- One of the strengths of the study is that it is triple-blinded, i.e., outcome assessors, therapists, and patients will be blinded to interventions over the course of the study.
- The sample size was calculated to provide the appropriate statistical power to detect precise differences for the primary outcomes of the study.

- In our study, we will test the effects of a single dose of PBMT (i.e 24 Joules). 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.

INTRODUCTION

Low back pain (LBP) is ranked as one of the most prevalent health problems and is highly associated with disability worldwide (1-4). It is estimated that about 12% of the world's population suffers from LBP (5). Furthermore, LBP generates high levels of work absenteeism and excessive costs to health systems (1, 2). The prognosis of LBP is directly related to the duration of symptoms, with less favorable prognoses in patients with chronic LBP (i.e. with a duration of symptoms longer than three months) (6-10). 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 (11). The existing treatments for LBP can be divided into three categories: 1) pharmacological therapies, which trigger several adverse effects with prolonged use (12-14); 2) non-pharmacological therapies, which minimize undesirable effects and are moderately effective in LBP (15); and surgery, used only when conservative treatment is not efficacious (16). Several therapies can be used to treat LBP by controlling symptoms, minimizing disability, and improving the patients' quality of life (17).

Photobiomodulation therapy (PBMT) is a non-pharmacological intervention often used in the treatment of musculoskeletal disorders such as LBP (18-21). PBMT consists in applying a non-ionized form of light, which includes laser (light amplification by stimulated emission of radiation), LED (light-emitting diodes), and other lights with a broader spectrum ranging from visible to infrared (22). Recent evidence (23-28) suggests that PBMT triggers positive physiological effects, such as increased microcirculation (23), increased ATP synthesis (24, 25) stimulation of the mitochondrial respiratory chain (24, 25), stimulation of mitochondrial function (26), and factors that may influence the metabolism of various pathologies. In addition, there is evidence that PBMT reduces the release of both reactive oxygen species (ROS) and creatine kinase (CK) activity and also increases the production of antioxidants and heat shock proteins (27, 28).

As TFBM has been successfully proved as an effective intervention for neck pain patients (29); it is likely that TFBM could also be a reasonable option for patients with LBP. A range of previous trial have shown the effects of PBMT on acute, subacute and chronic LBP. Basford et al. (18) and Gur et al. (19) observed that PBMT appears to be effective in reducing pain and disability triggered by subacute and chronic LBP respectively. While Konstantinovic et al. (20) and Vallone et al. (21) found that PBMT combined with nonsteroidal anti-inflammatory drugs (NSAIDs) and exercise were efficient in reducing pain

intensity in patients with acute and chronic LBP respectively. In a recent systematic review, Glazov et al. (30) found a clinically significant reduction in pain intensity in chronic LBP in patients treated with PBMT, although a reliable conclusion was hindered by the high heterogeneity in the parameters of therapy application. Furthermore, a recent clinical practice guidelines (31) recommended the use of the PBMT as a possible nonpharmacological treatment for chronic LBP. On the other hand, another trial (32) did not detected differences between PBMT and placebo treatments on pain and disability in mixed sample of 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.

Therefore, in spite of the positive results obtained in the aforementioned studies in favor of PBMT, some factors warrant further investigation with high-quality studies on the effects of PBMT applied in isolation in chronic non-specific LBP. Hence, it is necessary to conduct a high quality, adequately powered, randomized placebo-controlled trial with outcomes been measured at medium-and long-terms. 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, general and specific disability and global perceived effect.

METHODS AND ANALYSES

Design

A randomized, triple-blinded (patients, therapists, and outcome assessors), placebo-controlled trial will be performed. The protocol of this study has been prospectively registered on Clinicaltrials.gov (NCT03089424).

Location

The study will be conducted at the Center for Excellence in Clinical Research in Physiotherapy of Universidade Cidade de São Paulo, Brazil.

Eligibility criteria

The study assessors will determine whether or not patients will be eligible to participate in the study based on patient history and clinical examination.

Inclusion criteria:

- Patients with non-specific chronic LBP, defined as pain or discomfort between the costal margins and inferior gluteal folds with or without referred pain to the lower limbs;
- Persistent LBP for at least 3 months (33);
- Aged between 18 and 65 years;
- Both genders.

Exclusion criteria:

- Patients with severe skin diseases (e.g., skin cancer, erysipelas, severe eczema, severe dermatitis, severe psoriasis and severe hives lupus);
- Patients with LBP associated with nerve root compromise (measured by clinical examination of dermatomes, myotomes, and reflexes) (34, 35);
- Serious spinal pathologies such as fractures, tumors, inflammatory and infectious diseases;
- Decompensated heart disease or metabolic disorders;
- Previous spinal surgery;
- Pregnancy.

Interventions

For ethical reasons, on the first day of treatment, all groups will receive an information booklet on LBP called "The Back Book" (36) based on the recommendations of the European Guidelines (35, 37). The booklet can be accessed freely via internet and it has been translated into Portuguese by our research team. At each treatment session, patients will receive further explanations on the contents of the booklet. There is consistent evidence that *The Back Book* is useful for patients with LBP (38) and it has been used in clinical trials conducted by our research group (39, 40).

Patients will then be randomly allocated to two groups to be submitted to the active PBMT or Placebo interventions. The active and placebo PBMT will be performed using the same device and the irradiated sites will be the same in both therapies. 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 (41), the patients will not able to know if active or placebo PBMT will be administered. The device was previously coded as active or placebo modes, and only one researcher not involved in the randomization, treatment and evaluation is aware of these codes. Patients will undergo treatment (active PBMT or placebo), according to prior randomization, 3 times a week (with a minimal interval of 24 hours) for 4 consecutive weeks, totaling 12 therapy sessions. The choice of treatment frequency was based on Basford et al. (18). The total treatment (active PBMT or placebo) time will be 27 minutes per patient. 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. Intervention specifications:

1. Active PBMT Group: The PBMT will be performed using the Multi Radiance Medical™ Super Pulsed Laser MR4™ console (Solon, OH, USA), with the SE25 (emitter with an area of 4 cm^2) and LaserShower (emitter with an area of 20 cm^2) cluster probes as emitters. Nine sites will be irradiated on the patient's lumbar region. PBMT irradiation sites were chosen based on previous studies (18-21) and in order to cover the largest possible area of the lumbar spine: 3 central sites on top of the spinous processes (between T11 and T12, L2 and L3, L5 and S1), using the SE25 (3000 Hz of frequency, 3 minutes of irradiation per site, 24.75 J per site, a totalizing 74.25 J irradiated from SE25); in the same direction, but laterally, 3 sites on the left and 3 on the right (on the paravertebral muscles), using the LaserShower (1000 Hz of frequency, 3 minutes of irradiation per site, 24.30 J per site, a total of 145.80 J irradiated from LaserShower). At each treatment session, patients will receive a total dose of 220.05 J. At the end of the 12 treatments sessions, patients will receive a total dose of 2640.60 J. Table 1 shows parameters for SE25™ and LaserShower™ cluster probe.

This PBMT application protocol was based on the study of Leal Junior et al. (42). Figure 1 shows the PBMT irradiation sites.

Table 1. Parameters for SE25™ and LaserShower™ cluster probe.

	SE25™	LaserShower™
Number of lasers	1 Super-pulsed infrared	4 Super-pulsed infrared
Wavelength (nm)	905 (±1)	905 (±1)
Frequency (Hz)	3000	1000
Peak power (W) - each	25	12.5
Average mean optical output (mW) - each	7.5	1.25
Power density (mW/cm^2) - each	17.05	2.84
Energy density (J/cm^2) - each	3.07	0.511
Dose (J) - each	1.35	0.225
Spot size of laser (cm^2) - each	0.44	0.44
Number of red LEDs	4 Red	4 Red
Wavelength of red LEDs (nm)	640 (±10)	640 (±10)
Frequency (Hz)	2	2
Average optical output (mW) - each	15	15
Power density (mW/cm^2) - each	16.67	16.67
Energy density (J/cm^2) - each	3	3
Dose (J) - each	2.7	2.7
Spot size of red LED (cm^2) - each	0.9	0.9
Number of infrared LEDs	4 Infrared	4 Infrared
Wavelength of infrared LEDs (nm)	875 (±10)	875 (±10)
Frequency (Hz)	16	16
Average optical output (mW) - each	17.5	17.5
Power density (mW/cm^2) - each	19.44	19.44
Energy density (J/cm^2) - each	3.5	3.5
Dose (J) - each	3.15	3.15
Spot Size of LED (cm^2) - each	0.9	0.9
Magnetic Field (mT)	35	35
Irradiation time per site (sec)	180	180
Total dose per site (J)	24.75	24.30
Aperture of device (cm^2)	4	20
Application mode	Cluster probe held stationary in skin contact with a 90-degree angle and slight pressure	Cluster probe held stationary in skin contact with a 90-degree angle and slight pressure

<< Figure 1 >>

2. Placebo PBMT Group: The placebo PBMT will be delivered using the same device that active PBMT, but without any emission of therapeutic dose. Patients will receive a total dose of 0 J in placebo mode. The placebo mode simulates the pragmatism of clinical practice and increases the credibility of the use of the equipment in relation to the treated

patients. The placebo technique has already been widely used in other studies with patients with LBP (40, 43-48), as well as in studies using PBMT (41, 49, 50).

We will use two different emitters in PBMT (active or placebo) 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 cm^2), 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 analgesic effects (51, 52). 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 cm^2), 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 (24, 25), an increase in microcirculation (23) 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 (42), however the frequencies and doses were adapted for back pain patients.

The CONSORT flowchart summarizing experimental procedures and patients are shown in figure 2.

<< Figure 2 >>

Outcomes

Primary outcomes of the study will be obtained at baseline and immediately after the last treatment session (4 weeks). Secondary outcomes of the study will be obtained at baseline, at the end of treatment (4 weeks), and 3, 6, and 12 months after randomization. These outcomes will be collected by an assessor who will not be aware of patient allocation to their treatment groups.

The primary outcomes of the study will be:

- Pain intensity measured by the Pain Numerical Rating Scale (53). Pain Numerical Rating Scale evaluates pain intensity levels perceived by the patient on an 11-point

scale ranging from 0 to 10, with 0 being "no pain" and 10 "the worst possible pain" (53). Patients will be instructed to score the level of pain intensity based on the last 7 days.

- Disability associated with LBP, as measured by the Roland-Morris Disability Questionnaire (54, 55). The questionnaire consists of 24 items that describe situations that patients may have difficulty performing on a daily basis due to LBP. The greater the number of affirmative answers is, the higher the level of functional disability associated with LBP (53, 55). Patients will be instructed to answer according to their condition on the day of administration of the questionnaire.

The secondary outcomes of the study will be:

- Specific disability, as measured by the Patient-Specific Functional Scale (53). The Patient-Specific Functional Scale is global and can be used for any part of the body. The measurement is done on an 11-point Likert scale for each activity, and the higher the average score is (ranging from 0 and 10 points), the better the patient's ability to perform the activities. The patients will be asked to identify up to three activities that they consider they are incapable of performing or that they have some difficulty performing (53, 56, 57).
- Global perceived effect as measured by the Global Perceived Effect Scale (53). Global Perceived Effect Scale is an 11-point Likert scale, ranging from -5 to +5, that compares the patient's current condition to the onset of symptoms (53). Positive scores represent improvement, while the negative scores represent worsening in relation to the onset of symptoms. Values closer to 5 mean greater intensity of this perception (53).
- Pain intensity measured by the Pain Numerical Rating Scale (53).
- Disability associated with LBP, as measured by the Roland-Morris Disability Questionnaire (54, 55).

Sample size

The sample calculation of the study was performed to detect a 1-point difference for the outcome pain intensity (as measured by the Pain Numerical Rating Scale) (53), with an estimated standard deviation of 1.84 points and 4 points for the outcome disability associated with LBP (measured by the Roland-Morris Disability Questionnaire) (54, 55), with an estimated standard deviation of 4.9 points. A statistical power of 80% was considered for the

two outcomes, with α of 5% and a possible sample loss of up to 15%. Therefore, a total of 148 patients will be required for the study.

Recruitment

Patients seeking treatment for chronic LBP will be recruited at primary or secondary care health services. We will partner with supervising clinicians at primary and secondary health services so that they will refer chronic non-specific LBP patients to our study for treatment.

Randomization

Prior to initiation of treatment, patients will be randomized into their respective intervention groups. The randomization will be generated by a computer program (Excel Office 2010) and performed by a participating researcher not involved with the recruitment or evaluation of patients. This same researcher will be responsible for programming the PBMT device according to the result of the randomization. The PBMT device used in the present study will make the same sounds regardless of the programmed dose and mode (active PBMT or placebo PBMT). This researcher will be instructed not to disclose the programmed intervention to the therapist or any of the patients and other researchers involved in the study until its completion. Patient and therapist will be blinded throughout the treatment. Concealed allocation will be achieved through the use of sequentially numbered, sealed, and opaque envelopes.

Data collection

The patients will be welcomed by the study's blinded assessor who will determine whether they will be eligible to participate in the study. Subsequently, a file will be completed with the patient's sociodemographic data and clinical history. Next, the primary outcomes and the secondary outcomes of the study will be collected. Then, all eligible patients will be randomized and allocated into two treatment groups: active PBMT or placebo PBMT. At the end of the 12 treatment sessions, the primary and secondary outcomes of the study participants will be reassessed by the same evaluator who performed the baseline assessment. The 3, 6, and 12-month follow-ups will be performed by telephone by the same evaluator who carried out the other evaluations. All of the questionnaires that will

be used in the present study have been fully tested for their measurement properties (53, 55). These measurement properties were also tested over the phone. Therefore, we are confident that the assessments are reliable.

Statistical Analysis

The statistical analysis will be conducted following the principles of intention-to-treat analysis (58). The normality of the data will be tested by visual inspection of histograms and the characterization of the participants will be calculated using descriptive statistical tests. The between-group differences (treatment effects) and their respective 95% confidence intervals will be calculated by using mixed linear models (59) using the group-by-time interaction terms. The analyses will be performed using SPSS version 19.

Ethics

The present study was approved by the Research Ethics Committee of Universidade Cidade de São Paulo (UNICID) under number 1.964.094. All patients eligible for the study will be informed of the objectives and will be required to complete the Informed Consent Form, as determined by Brazilian National Health Council Resolution 196/96.

Dissemination

The study will be disseminated through publication in peer-reviewed international journals, as well as presentations at national and international conferences.

Discussion

Chronic LBP is a condition that is often associated with disability, emotional alterations, and absenteeism from work (8). Since chronic LBP is very prevalent (11), it has a great financial impact, generating high costs, both direct and indirect (60). This fact demonstrates the importance of the constant investigation of more suitable treatments for LBP, aiming at the well-being of the patient and the reduction of expenses for health systems.

PBMT is one of the interventions recommended for the treatment of chronic LBP (31), however, it is a relatively recent therapy given that the first clinical trial investigating its effects on LBP was published in 1999 (18). 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 (32), some studies have demonstrated the efficacy of PBMT in chronic and acute LBP (18-21). 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 (18-21, 32); have a small sample size (18, 19, 21, 32) and have high risk of bias. In addition, none of the studies were either triple blinded or were analyzed using intention to treat principles.

It is extremely important to carry out studies with high methodological quality aimed at contributing to a better understanding of the effects of PBMT on LBP. Only then will it be possible to determine whether PBMT can be used as one of the treatments of choice for LBP. If the effectiveness of PBMT in LBP is confirmed, it could be used as an alternative method to NSAIDs or opioids, for example, since it causes similar or superior effects to these drugs, shown in other chronic musculoskeletal disorders (61, 62), without the presence of known adverse effects at present. We believe that, by providing relevant and compelling information about PBMT, we will contribute to a safer and more effective clinical practice.

Nevertheless, it is important to highlight that 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 (52). In addition, the power and time of irradiation are also extremely important parameters to obtain better results with the PBMT (63). 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 (42) and took into consideration the dosage recommended by World Association for Laser Therapy (WALT) (63). Therefore, although we believe that the dosage chosen for the present study is the most likely to be effective in triggering the expected results, a limitation of our study is that we will test only one dose of PBMT.

The present study can be considered to have high methodological quality, since it is a randomized, controlled, and prospectively registered clinical trial. In addition, one of the strengths of the study is that it is triple-blinded, i.e., evaluators, therapists, and patients will be blinded to interventions over the course of the study. Finally, the sample size was calculated to provide the appropriate statistical power to detect precise differences in the primary outcomes of the study. Therefore, we believe that this study will contribute to the evidence-based practice of PBMT in patients with chronic LBP.

Author contributions

SST and LOPC contributed to the concept and design of the study. SST and LOPC established the hypothesis and wrote the original proposal. SST, LCMC, LSG, ACA, DPN, FCM, MAA and LOPC contributed significantly in creating the manuscript. LCMC and LOPC performed critical revisions of the manuscript. SST, LCMC and LOPC wrote the final version of the manuscript. All authors read and approved the final version of the manuscript.

Conflict of interest

The authors declare no conflict of interest.

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FIGURE LEGENDS

Table 1. Parameters for SE25™ and LaserShower™ cluster probe.

Figure 1. PBMT irradiation sites.

Figure 2. Flow diagram of the study.

Figure 1. PBMT irradiation sites.

109x158mm (300 x 300 DPI)

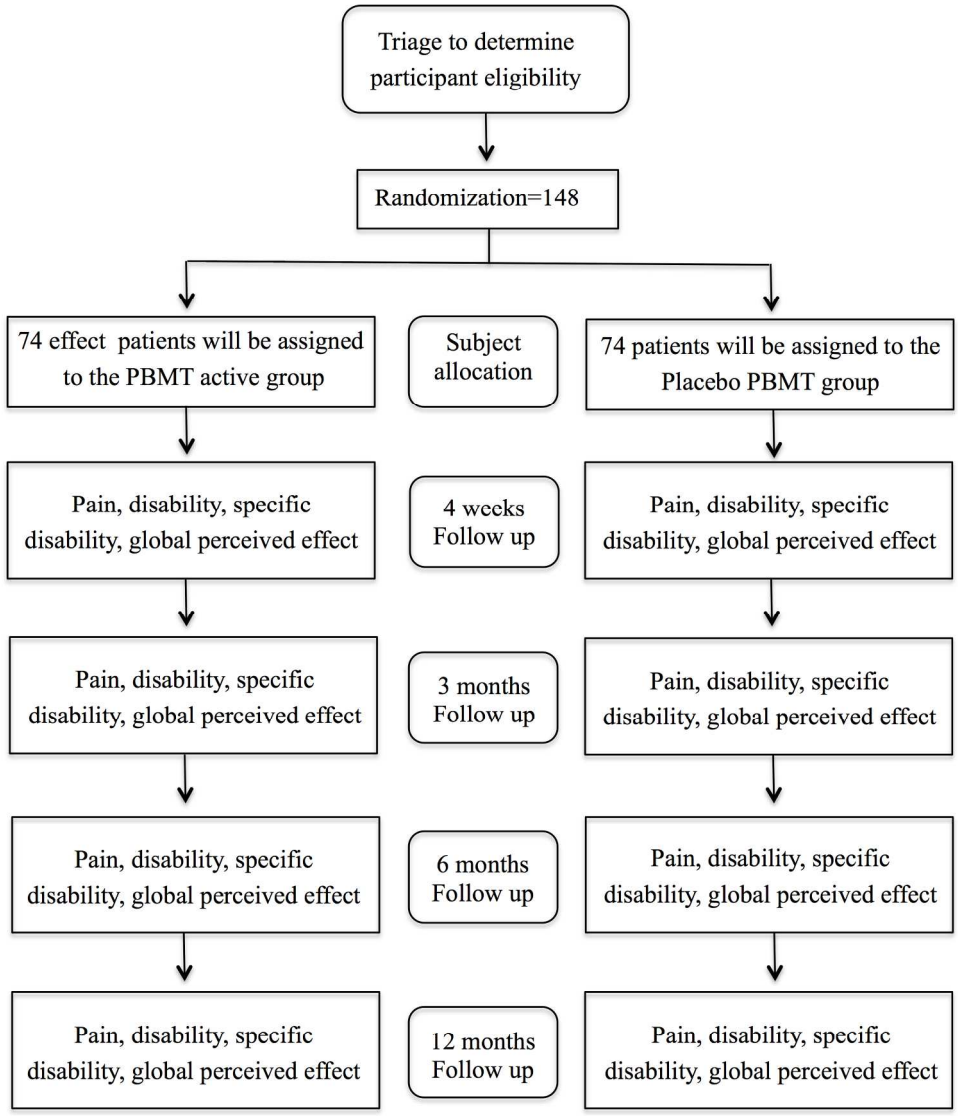

Figure 2. Flow diagram of the study.

197x227mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page Number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
	2b	All items from the World Health Organization Trial Registration Data Set	1
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	1
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	1
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	1
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
	6b	Explanation for choice of comparators	7
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5, 6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6, 7
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	6, 7
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	6, 7
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6, 7
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7, 8
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	8, 9
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	9

Methods: Assignment of interventions (for controlled trials)

Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	9
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	9
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	10
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	10
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	-

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	-
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	-
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	-
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	10
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	-
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	-
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	10
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	1
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	10
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	-
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	10
	31b	Authorship eligibility guidelines and any intended use of professional writers	-
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	10

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Effects of photobiomodulation therapy in patients with chronic non-specific low back pain: protocol for a randomized placebo-controlled trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-017202.R2
Article Type:	Protocol
Date Submitted by the Author:	04-Aug-2017
Complete List of Authors:	Tomazoni, Shaiane; Universidade Cidade de Sao Paulo, Masters and Doctoral Programs in Physical Therapy Costa, Lucíola; Universidade Cidade de Sao Paulo, Masters and Doctoral Programs in Physical Therapy Guimarães, Layana; Universidade Cidade de Sao Paulo, Masters and Doctoral Programs in Physical Therapy Araujo, Amanda; Universidade Cidade de Sao Paulo, Masters and Doctoral Programs in Physical Therapy Nascimento, Dafne; Universidade Cidade de Sao Paulo, Masters and Doctoral Programs in Physical Therapy Medeiros, Flavia; Universidade Cidade de Sao Paulo, Masters and Doctoral Programs in Physical Therapy Avanzi, Marina; Universidade Cidade de Sao Paulo, Masters and Doctoral Programs in Physical Therapy Costa, Leonardo; Universidade Cidade de Sao Paulo, Masters and Doctoral Programs in Physical Therapy
Primary Subject Heading:	Evidence based practice
Secondary Subject Heading:	Rehabilitation medicine
Keywords:	chronic low back pain, photobiomodulation therapy, low-level laser therapy, LLLT, PBMT

Effects of photobiomodulation therapy in patients with chronic non-specific low back pain: protocol for a randomized placebo-controlled trial

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Trial registration number: NCT03089424

Funding statement: This work was supported by FAPESP (postdoctoral scholarship of Shaiane Silva Tomazoni) grant number 2016/10265-0.

Roles of study sponsor and funders: FAPESP has no role in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities.

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Number of figures and tables: 2 figures and 1 table.

Conflict of interest: the authors declare no conflict of interest.

ABSTRACT

Introduction: Low back pain (LBP) is one of the largest and most frequent public health problems worldwide. Photobiomodulation therapy (PBMT) is a frequently used non-pharmacological therapy for the treatment of musculoskeletal disorders. However, there is little high-quality scientific evidence that demonstrates the effectiveness of PBMT in the treatment of patients with chronic LBP in the short, medium, and long term. Therefore, the objective of this clinical trial is to evaluate the effects of PBMT in patients with chronic non-specific LBP in the short, medium, and long term. **Methods and analyses:** This is a prospectively registered, two-arm randomized placebo-controlled trial with blinded patients, assessors and treatment providers. One hundred and forty-eight patients with chronic non-specific LBP will be recruited. Treatment sessions will be provided 3 times a week for 4 weeks (totaling 12 sessions) with patients receiving either placebo or active PBMT. For ethical reasons, all patients, regardless of treatment allocation, will also receive an information booklet based on "The Back Book". Clinical outcomes will be measured at baseline, at the end of treatment, as well as 3, 6, and 12 months after randomization. The primary outcomes will be pain intensity and disability measured after 12 sessions of treatment. The secondary outcomes will be pain intensity and disability measured at 3, 6, and 12 months after randomization, in addition to specific disability and global perceived effect in all time points. **Ethics and dissemination:** The study was approved by the Research Ethics Committee of Universidade Cidade de São Paulo. The results will be disseminated through scientific publications and presentations at national and international scientific meetings. Clinical trial registration number: NCT03089424 (clinicaltrials.gov).

Key-words: chronic low back pain, photobiomodulation therapy, low-level laser therapy, LLLT, PBMT.

Strengths and limitations of this study:

- The present study can be considered to have high methodological quality, since it is a randomized, controlled, and prospectively registered clinical trial.
- One of the strengths of the study is that it is triple-blinded, i.e., outcome assessors, therapists, and patients will be blinded to interventions over the course of the study.
- The sample size was calculated to provide the appropriate statistical power to detect precise differences for the primary outcomes of the study.

- In our study, we will test the effects of a single dose of PBMT (i.e 24 Joules). 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 available evidence.

INTRODUCTION

Low back pain (LBP) is ranked as one of the most prevalent health problems and is highly associated with disability worldwide (1-4). It is estimated that about 12% of the world's population suffers from LBP (5). Furthermore, LBP generates high levels of work absenteeism and excessive costs to health systems (1, 2). The prognosis of LBP is directly related to the duration of symptoms, with less favorable prognoses in patients with chronic LBP (i.e. with a duration of symptoms longer than three months) (6-10). 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 (11). The existing treatments for LBP can be divided into three categories: 1) pharmacological therapies, which trigger several adverse effects with prolonged use (12-14); 2) non-pharmacological therapies, which minimize undesirable effects and are moderately effective in LBP (15); and surgery, used only when conservative treatment is not efficacious (16). Several therapies can be used to treat LBP by controlling symptoms, minimizing disability, and improving the patients' quality of life (17).

Photobiomodulation therapy (PBMT) is a non-pharmacological intervention often used in the treatment of musculoskeletal disorders such as LBP (18-21). PBMT consists in applying a non-ionized form of light, which includes laser (light amplification by stimulated emission of radiation), LED (light-emitting diodes), and other lights with a broader spectrum ranging from visible to infrared (22). Recent evidence (23-28) suggests that PBMT triggers positive physiological effects, such as increased microcirculation (23), increased ATP synthesis (24, 25) stimulation of the mitochondrial respiratory chain (24, 25), stimulation of mitochondrial function (26), and factors that may influence the metabolism of various pathologies. In addition, there is evidence that PBMT reduces the release of both reactive oxygen species (ROS) and creatine kinase (CK) activity and also increases the production of antioxidants and heat shock proteins (27, 28).

As PBMT has been successfully proved as an effective intervention for neck pain patients (29); it is likely that PBMT could also be a reasonable option for patients with LBP. A range of previous trial have shown the effects of PBMT on acute, subacute and chronic LBP. Basford et al. (18) and Gur et al. (19) observed that PBMT appears to be effective in reducing pain and disability triggered by subacute and chronic LBP respectively. While Konstantinovic et al. (20) and Vallone et al. (21) found that PBMT combined with nonsteroidal anti-inflammatory drugs (NSAIDs) and exercise were efficient in reducing pain

intensity in patients with acute and chronic LBP respectively. In a recent systematic review, Glazov et al. (30) found a clinically significant reduction in pain intensity in chronic LBP in patients treated with PBMT, although a reliable conclusion was hindered by the high heterogeneity in the parameters of therapy application. Furthermore, a recent clinical practice guidelines (31) recommended the use of the PBMT as a possible nonpharmacological treatment for chronic LBP. On the other hand, another trial (32) did not detected differences between PBMT and placebo treatments on pain and disability in mixed sample of 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.

Therefore, in spite of the positive results obtained in the aforementioned studies in favor of PBMT, some factors warrant further investigation with high-quality studies on the effects of PBMT applied in isolation in chronic non-specific LBP. Hence, it is necessary to conduct a high quality, adequately powered, randomized placebo-controlled trial with outcomes been measured at medium-and long-terms. 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, general and specific disability and global perceived effect.

METHODS AND ANALYSES

Design

A randomized, triple-blinded (patients, therapists, and outcome assessors), placebo-controlled trial will be performed. The protocol of this study has been prospectively registered on Clinicaltrials.gov (NCT03089424).

Study setting

The study will be conducted at the Center for Excellence in Clinical Research in Physiotherapy of Universidade Cidade de São Paulo, Brazil.

Eligibility criteria

The study assessors will determine whether or not patients will be eligible to participate in the study based on patient history and clinical examination.

Inclusion criteria:

- Patients with non-specific chronic LBP, defined as pain or discomfort between the costal margins and inferior gluteal folds with or without referred pain to the lower limbs;
- Persistent LBP for at least 3 months (33);
- Aged between 18 and 65 years;
- Both genders.

Exclusion criteria:

- Patients with severe skin diseases (e.g., skin cancer, erysipelas, severe eczema, severe dermatitis, severe psoriasis and severe hives lupus);
- Patients with LBP associated with nerve root compromise (measured by clinical examination of dermatomes, myotomes, and reflexes) (34, 35);
- Serious spinal pathologies such as fractures, tumors, inflammatory and infectious diseases;
- Decompensated heart disease or metabolic disorders;
- Previous spinal surgery;
- Pregnancy.

Interventions

For ethical reasons, on the first day of treatment, all groups will receive an information booklet on LBP called "The Back Book" (36) based on the recommendations of the European Guidelines (35, 37). The booklet can be accessed freely via internet and it has been translated into Portuguese by our research team. At each treatment session, patients will receive further explanations on the contents of the booklet. There is consistent evidence that *The Back Book* is useful for patients with LBP (38) and it has been used in clinical trials conducted by our research group (39, 40).

Patients will then be randomly allocated to two groups to be submitted to the active PBMT or Placebo interventions. The active and placebo PBMT will be performed using the same device and the irradiated sites will be the same in both therapies. 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 (41), the patients will not able to know if active or placebo PBMT will be administered. The device was previously coded as active or placebo modes, and only one researcher not involved in the randomization, treatment and evaluation is aware of these codes. Patients will undergo treatment (active PBMT or placebo), according to prior randomization, 3 times a week (with a minimal interval of 24 hours) for 4 consecutive weeks, totaling 12 therapy sessions. The choice of treatment frequency was based on Basford et al. (18). The total treatment (active PBMT or placebo) time will be 27 minutes per patient. 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. Intervention specifications:

1. Active PBMT Group: The PBMT will be performed using the Multi Radiance Medical™ Super Pulsed Laser MR4™ console (Solon, OH, USA), with the SE25 (emitter with an area of 4 cm^2) and LaserShower (emitter with an area of 20 cm^2) cluster probes as emitters. Nine sites will be irradiated on the patient's lumbar region. PBMT irradiation sites were chosen based on previous studies (18-21) and in order to cover the largest possible area of the lumbar spine: 3 central sites on top of the spinous processes (between T11 and T12, L2 and L3, L5 and S1), using the SE25 (3000 Hz of frequency, 3 minutes of irradiation per site, 24.75 J per site, a totalizing 74.25 J irradiated from SE25); in the same direction, but laterally, 3 sites on the left and 3 on the right (on the paravertebral muscles), using the LaserShower (1000 Hz of frequency, 3 minutes of irradiation per site, 24.30 J per site, a total of 145.80 J irradiated from LaserShower). At each treatment session, patients will receive a total dose of 220.05 J. At the end of the 12 treatments sessions, patients will receive a total dose of 2640.60 J. Table 1 shows parameters for SE25™ and LaserShower™ cluster probe.

This PBMT application protocol was based on the study of Leal Junior et al. (42). Figure 1 shows the PBMT irradiation sites.

Table 1. Parameters for SE25™ and LaserShower™ cluster probe.

	SE25™	LaserShower™
Number of lasers	1 Super-pulsed infrared	4 Super-pulsed infrared
Wavelength (nm)	905 (±1)	905 (±1)
Frequency (Hz)	3000	1000
Peak power (W) - each	25	12.5
Average mean optical output (mW) - each	7.5	1.25
Power density (mW/cm^2) - each	17.05	2.84
Energy density (J/cm^2) - each	3.07	0.511
Dose (J) - each	1.35	0.225
Spot size of laser (cm^2) - each	0.44	0.44
Number of red LEDs	4 Red	4 Red
Wavelength of red LEDs (nm)	640 (±10)	640 (±10)
Frequency (Hz)	2	2
Average optical output (mW) - each	15	15
Power density (mW/cm^2) - each	16.67	16.67
Energy density (J/cm^2) - each	3	3
Dose (J) - each	2.7	2.7
Spot size of red LED (cm^2) - each	0.9	0.9
Number of infrared LEDs	4 Infrared	4 Infrared
Wavelength of infrared LEDs (nm)	875 (±10)	875 (±10)
Frequency (Hz)	16	16
Average optical output (mW) - each	17.5	17.5
Power density (mW/cm^2) - each	19.44	19.44
Energy density (J/cm^2) - each	3.5	3.5
Dose (J) - each	3.15	3.15
Spot Size of LED (cm^2) - each	0.9	0.9
Magnetic Field (mT)	35	35
Irradiation time per site (sec)	180	180
Total dose per site (J)	24.75	24.30
Aperture of device (cm^2)	4	20
Application mode	Cluster probe held stationary in skin contact with a 90-degree angle and slight pressure	Cluster probe held stationary in skin contact with a 90-degree angle and slight pressure

<< Figure 1 >>

2. Placebo PBMT Group: The placebo PBMT will be delivered using the same device that active PBMT, but without any emission of therapeutic dose. Patients will receive a total dose of 0 J in placebo mode. The placebo mode simulates the pragmatism of clinical practice and increases the credibility of the use of the equipment in relation to the treated

patients. The placebo technique has already been widely used in other studies with patients with LBP (40, 43-48), as well as in studies using PBMT (41, 49, 50).

We will use two different emitters in PBMT (active or placebo) 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 cm^2), 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 analgesic effects (51, 52). 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 cm^2), 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 (24, 25), an increase in microcirculation (23) 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 (42), however the frequencies and doses were adapted for back pain patients.

Outcomes and blinding

Primary outcomes of the study will be obtained at baseline and immediately after the last treatment session (4 weeks). Secondary outcomes of the study will be obtained at baseline, at the end of treatment (4 weeks), and 3, 6, and 12 months after randomization. These outcomes will be collected by an assessor who will not be aware of patient allocation to their treatment groups.

The primary outcomes of the study will be:

- Pain intensity measured by the Pain Numerical Rating Scale (53). Pain Numerical Rating Scale evaluates pain intensity levels perceived by the patient on an 11-point scale ranging from 0 to 10, with 0 being "no pain" and 10 "the worst possible pain"

(53). Patients will be instructed to score the level of pain intensity based on the last 7 days.

- Disability associated with LBP, as measured by the Roland-Morris Disability Questionnaire (54, 55). The questionnaire consists of 24 items that describe situations that patients may have difficulty performing on a daily basis due to LBP. The greater the number of affirmative answers is, the higher the level of functional disability associated with LBP (53, 55). Patients will be instructed to answer according to their condition on the day of administration of the questionnaire.

The secondary outcomes of the study will be:

- Specific disability, as measured by the Patient-Specific Functional Scale (53). The Patient-Specific Functional Scale is global and can be used for any part of the body. The measurement is done on an 11-point Likert scale for each activity, and the higher the average score is (ranging from 0 and 10 points), the better the patient's ability to perform the activities. The patients will be asked to identify up to three activities that they consider they are incapable of performing or that they have some difficulty performing (53, 56, 57).
- Global perceived effect as measured by the Global Perceived Effect Scale (53). Global Perceived Effect Scale is an 11-point Likert scale, ranging from -5 to +5, that compares the patient's current condition to the onset of symptoms (53). Positive scores represent improvement, while the negative scores represent worsening in relation to the onset of symptoms. Values closer to 5 mean greater intensity of this perception (53).
- Pain intensity measured by the Pain Numerical Rating Scale (53).
- Disability associated with LBP, as measured by the Roland-Morris Disability Questionnaire (54, 55).

Participant timeline

The CONSORT flowchart summarizing experimental procedures and patients are shown in figure 2.

<< Figure 2 >>

Sample size

The sample calculation of the study was performed to detect a 1-point difference for the outcome pain intensity (as measured by the Pain Numerical Rating Scale) (53), with an estimated standard deviation of 1.84 points and 4 points for the outcome disability associated with LBP (measured by the Roland-Morris Disability Questionnaire) (54, 55), with an estimated standard deviation of 4.9 points. A statistical power of 80% was considered for the two outcomes, with α of 5% and a possible sample loss of up to 15%. Therefore, a total of 148 patients will be required for the study.

Recruitment

Patients seeking treatment for chronic LBP will be recruited at primary or secondary care health services. We will partner with supervising clinicians at primary and secondary health services so that they will refer chronic non-specific LBP patients to our study for treatment.

Randomization

Prior to initiation of treatment, patients will be randomized into their respective intervention groups. The randomization will be generated by a computer program (Excel Office 2010) and performed by a participating researcher not involved with the recruitment or evaluation of patients. This same researcher will be responsible for programming the PBMT device according to the result of the randomization. The PBMT device used in the present study will make the same sounds regardless of the programmed dose and mode (active PBMT or placebo PBMT). This researcher will be instructed not to disclose the programmed intervention to the therapist or any of the patients and other researchers involved in the study until its completion. Patient and therapist will be blinded throughout the treatment. Concealed allocation will be achieved through the use of sequentially numbered, sealed, and opaque envelopes.

Data collection

The patients will be welcomed by the study's blinded assessor who will determine whether they will be eligible to participate in the study. Subsequently, a file will be

completed with the patient's sociodemographic data and clinical history. Next, the primary outcomes and the secondary outcomes of the study will be collected. Then, all eligible patients will be randomized and allocated into two treatment groups: active PBMT or placebo PBMT. At the end of the 12 treatment sessions, the primary and secondary outcomes of the study participants will be reassessed by the same evaluator who performed the baseline assessment. The 3, 6, and 12-month follow-ups will be performed by telephone by the same evaluator who carried out the other evaluations. All of the questionnaires that will be used in the present study have been fully tested for their measurement properties (53, 55). These measurement properties were also tested over the phone. Therefore, we are confident that the assessments are reliable.

Statistical Analysis

The statistical analysis will be conducted following the principles of intention-to-treat analysis (58). The normality of the data will be tested by visual inspection of histograms and the characterization of the participants will be calculated using descriptive statistical tests. The between-group differences (treatment effects) and their respective 95% confidence intervals will be calculated by using mixed linear models (59) using the group-by-time interaction terms. The analyses will be performed using SPSS version 19.

Ethics

The present study was approved by the Research Ethics Committee of Universidade Cidade de São Paulo (UNICID) under number 1.964.094. All patients eligible for the study will be informed by study assessors of the objectives and will be required to complete the Informed Consent Form (appendix 1), as determined by Brazilian National Health Council Resolution 196/96.

Research personnel will take all appropriate and customary steps to ensure that data remain secure and that patient privacy and confidentiality will be maintained.

Dissemination Policy

The study will be disseminated through publication in peer-reviewed international journals, as well as presentations at national and international conferences.

Discussion

Chronic LBP is a condition that is often associated with disability, emotional alterations, and absenteeism from work (8). Since chronic LBP is very prevalent (11), it has a great financial impact, generating high costs, both direct and indirect (60). This fact demonstrates the importance of the constant investigation of more suitable treatments for LBP, aiming at the well-being of the patient and the reduction of expenses for health systems.

PBMT is one of the interventions recommended for the treatment of chronic LBP (31), however, it is a relatively recent therapy given that the first clinical trial investigating its effects on LBP was published in 1999 (18). 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 (32), some studies have demonstrated the efficacy of PBMT in chronic and acute LBP (18-21). 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 (18-21, 32); have a small sample size (18, 19, 21, 32) and have high risk of bias. In addition, none of the studies were either triple blinded or were analyzed using intention to treat principles.

It is extremely important to carry out studies with high methodological quality aimed at contributing to a better understanding of the effects of PBMT on LBP. Only then will it be possible to determine whether PBMT can be used as one of the treatments of choice for LBP. If the effectiveness of PBMT in LBP is confirmed, it could be used as an alternative method to NSAIDs or opioids, for example, since it causes similar or superior effects to these drugs, shown in other chronic musculoskeletal disorders (61, 62), without the presence of known adverse effects at present. We believe that, by providing relevant and compelling information about PBMT, we will contribute to a safer and more effective clinical practice.

Nevertheless, it is important to highlight that 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 (52). In addition, the power and time of irradiation are also extremely important parameters to obtain better results with the PBMT (63). 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 (42) and took into consideration the dosage recommended by World Association for Laser Therapy (WALT) (63). Therefore, although we believe that the dosage chosen for the present study is the most likely to be effective in triggering the expected results, a limitation of our study is that we will test only one dose of PBMT.

The present study can be considered to have high methodological quality, since it is a randomized, controlled, and prospectively registered clinical trial. In addition, one of the strengths of the study is that it is triple-blinded, i.e., evaluators, therapists, and patients will be blinded to interventions over the course of the study. Finally, the sample size was calculated to provide the appropriate statistical power to detect precise differences in the primary outcomes of the study. Therefore, we believe that this study will contribute to the evidence-based practice of PBMT in patients with chronic LBP.

Author contributions

SST and LOPC contributed to the concept and design of the study. SST and LOPC established the hypothesis and wrote the original proposal. SST, LCMC, LSG, ACA, DPN, FCM, MAA and LOPC contributed significantly in the development of the manuscript. LCMC and LOPC performed critical revisions of the manuscript. SST, LCMC and LOPC wrote the final version of the manuscript. All authors read and approved the final version of the manuscript.

Conflict of interest

The authors declare no conflict of interest.

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FIGURE LEGENDS

Table 1. Parameters for SE25™ and LaserShower™ cluster probe.

Figure 1. PBMT irradiation sites.

Figure 2. Flow diagram of the study.

Appendix 1. Model consent form

Figure 1. PBMT irradiation sites.

109x158mm (300 x 300 DPI)

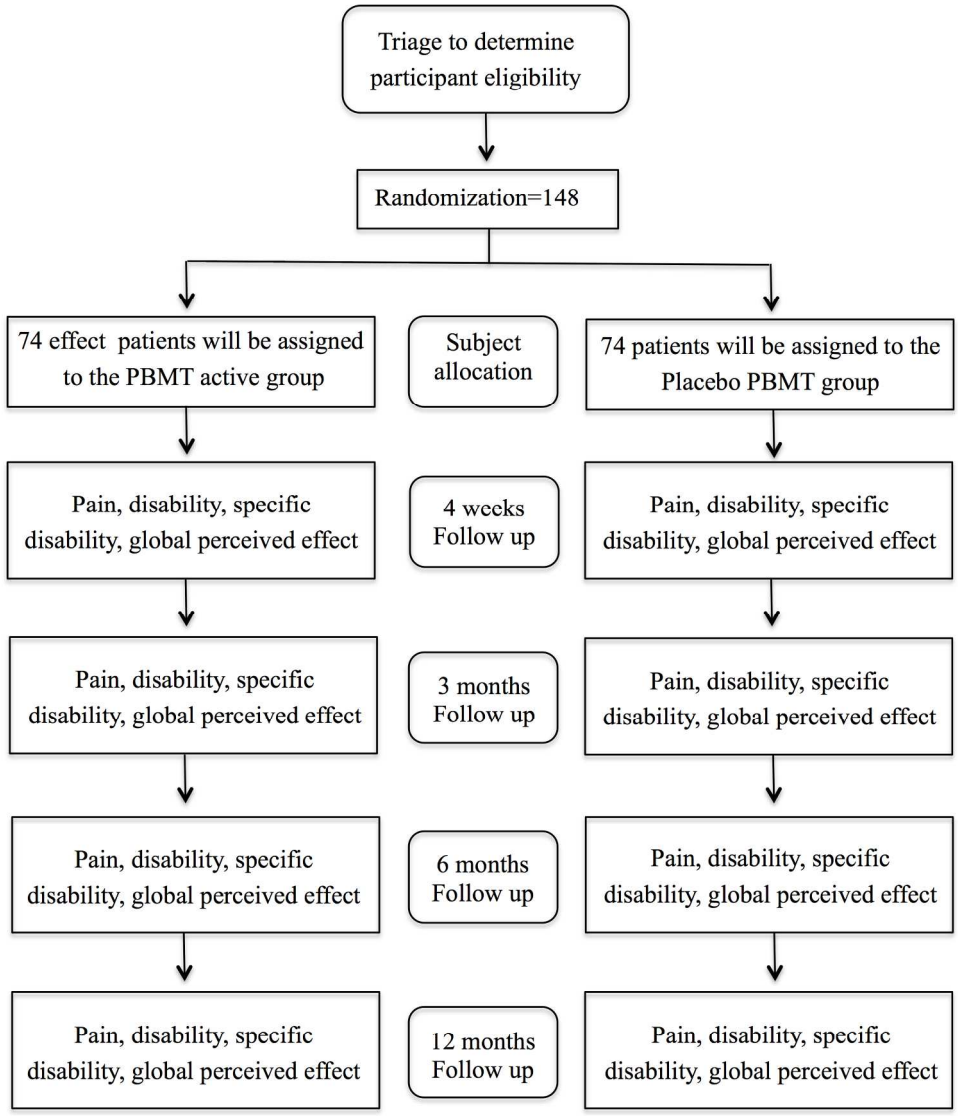

Figure 2. Flow diagram of the study.

197x227mm (300 x 300 DPI)

Informed Consent Form

To Mr./Mrs. _____

ID no. _____, born in _____,

gender _____, home address _____

_____

_____

You have been invited to participate in the study titled: *"Effects of photobiomodulation therapy in patients with chronic non-specific low back pain: a randomized placebo-controlled trial"*. This trial aims to evaluate the efficacy of photobiomodulation therapy (PBMT) in patients with non-specific chronic low back. In order to participate, you will be firstly screened by one of the researchers, who will determine if you are eligible for the study. If so, you will you respond a number of scales and questionnaires that measure intensity of your low back pain, disability, and impression of recovery since the onset of your symptoms. At the initial assessment, you will be asked to perform some movements of your spine and some tests will be carried out to better understand your clinical condition. You may feel some discomfort during and after the assessment, which tends to improve in the short term. The researchers involved in this study will take all necessary care to minimize these possible discomforts. After the assessment, you will be randomly allocated to two possible interventions: 1) active PBMT (therapy with a light with special properties capable of penetrating the tissues of your body and triggering therapeutic effects) or 2) placebo PBMT (therapy with a light having special properties capable of penetrating the tissues of your body and triggering therapeutic effects, applied at a very low dose below the therapeutic dose). You will not be able to identify which intervention you will be receiving. For safety reasons, during the application of the therapies, you must wear special, dark, protective goggles that will block the passage of light. This equipment will be provided by the therapist. Wearing these glasses will protect your eyes from direct contact with the light, thus avoiding possible damage to your eyesight. If you feel any discomfort during therapy, please notify the therapist and request immediate interruption of the application. In addition, regardless of the group to which you will be allocated, you will also receive an information booklet designed specifically for patients with low back pain (there are several studies that demonstrate the effectiveness of this booklet in patients with low back pain). In addition, you will be free to clarify any questions at each session with your therapist. The treatment will last 12 sessions (3 sessions weekly, for 4 weeks,

lasting 30 minutes each). After the end of treatment, you will be reassessed by the same therapist who evaluated you initially. This therapist will contact you at 3, 6, and 12 months after the beginning of the treatment to measure your symptoms.

Any clarifications can be provided by the chief investigator, Leonardo Oliveira Pena Costa, at Rua Cesário Galeno, 448, Tatuapé or via telephone on (11) 2178-1564.

We guarantee the confidentiality of all the information collected and you may withdraw your consent at any time, without any penalty or loss of benefit.

I hereby attest that I have been informed and fully understand the objectives of this study, the techniques and procedures I will receive, and the risks and discomforts that may occur. I have received guarantee of total confidentiality and of obtaining further clarification whenever I wish. Therefore, I agree to voluntarily participate in this study and I understand that I may withdraw my consent at any time without any penalty or loss of benefit (if the subject is enrolled in the Institution where the research is being conducted).

Date: __ / _ / __

_____

Signature of study participant or legal representative

_____

Chief investigator

I, Leonardo Oliveira Pena Costa, chief investigator of the study *"Effects of photobiomodulation therapy in patients with chronic non-specific low back pain: a randomized placebo-controlled trial"* hereby declare that I have obtained the free consent of this study participant (or his or her legal representative) to conduct this study.

Date: __ / __ / ___

_____

Signature of the chief investigator

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page Number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
	2b	All items from the World Health Organization Trial Registration Data Set	1
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	1
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	1
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	1
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
	6b	Explanation for choice of comparators	5
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6, 7
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	6, 7
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	6
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6, 7
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9, 10
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	11

Methods: Assignment of interventions (for controlled trials)

Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	11

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	11
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	11
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	11
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	11
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9, 10
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11, 12
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11, 12
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	-
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	12
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	-

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	-
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	-
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	-
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	12
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	-
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	12
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	-
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	12
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	1
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	10
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	-
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	12
	31b	Authorship eligibility guidelines and any intended use of professional writers	-
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	-

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.