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Keywords:	Temporomandibular Joint Dysfunction Syndrome, Cost Effectiveness Analysis, Photobiomodulation Therapy, Pain

PHOTOMODULATION IN THE TREATMENT OF PAIN IN PATIENTS WITH TMD: PROTOCOL FOR COST-EFFECTIVENESS ANALYSIS

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ABSTRACT

Introduction Epidemiological data show that the signs and symptoms of TMD start to become apparent from six years of age, and in adolescence these signs and symptoms are similar to those of adults. The present study aims: to estimate the direct costs of treatment of muscle pain in patients with TMD with low-intensity laser and with occlusal splint and a placebo group; to evaluate the effectiveness of the treatments with low-intensity laser and occlusal splint for muscle pain in patients with TMD; to analyze the cost-effectiveness of the two proposed treatments for pain; and to describe and compare the results of analyses of treatments for pain in patients with TMD.

Methods and analysis It is a prospective trial of clinical and economic analysis.

It will include 45 patients aged between 15 and 25 years with TMD, randomly assigned to a treatment group: G1 (low level laser), G2 (occlusal splint) and G3 (placebo). The analysis will be based on the costs of each treatment during the 12-month period. The outcome for the analysis of the effectiveness will be the pain, measured periodically by means of the clinical examination of the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD). The cost-effectiveness ratio will be calculated using, as endpoints, pain and the calculation of the ratio between the

difference in costs between the groups studied. The evaluation of the impact of the treatment on quality of life will be determined by applying the adapted EuroQol-5D.

Ethics and dissemination Ethics and dissemination This protocol has been ethically approved by the local medical ethical committee Protocol Number: 2.014.339. Results will be submitted to international peer-reviewed journals and presented at international conferences.

Trial registration: NCT01331031

Keywords: Temporomandibular Joint Dysfunction Syndrome, Cost Effectiveness Analysis, Photobiomodulation Therapy, Pain.

Introduction

Temporomandibular disorder (TMD) is a term used to define a number of clinical signs and symptoms that affect the masticatory muscles, the temporomandibular joint (TMJ), and associated structures [1,2,3,4,5,6]. The most common signs and symptoms are sensitivity of the masticatory muscles, pain in one or both of TMJs, limited mandibular movement, articular noises [6,7,8], headache [6,9,10], associated dizziness, hearing loss, and tinnitus may also occur [1,11]. Signs and symptoms of TMD are found in all ages; however, the prevalence of this disorder, considered low in children, increases with age in adolescents and young adults [12,13]. The changes caused by the TMD, especially pain, can interfere in the quality of life of these patients [14].

Various treatment features have been proposed, mainly for pain control, such as occlusal splints, acupuncture, kinesiotherapy, massage therapy, postural training, psychotherapy, joint mobilizations, drug therapy, and laser therapy [15,16]. Low -level laser (LLL) therapy is a non-invasive, non-pharmacological treatment that, according to various studies, has shown beneficial results in the treatment of pain associated with TMD [4,5,6,7,16,17,18,19,20,21,22,23,24]. LLL is a radiation located between the visible and infrared portions of the spectrum of electromagnetic waves, with characteristics of monochromaticity, coherence, one-directionality, and variable wave length [6]. Inflammation modulation and analgesic effects are cited among the therapeutic results of LIL treatment on TMD [5,6,25,22,26].

Low-level laser therapy has demonstrated a capacity to assist in the symptomatic treatment of pain, promoting a considerable degree of comfort for the patient immediately after its application. The main advantage of laser applications in the treatment of TMD is that this type of therapy is non-invasive and low cost, and is currently widely used in dental clinics, reducing the demand for surgery or drugs in the treatment of pain relief and tissue regeneration. The application of laser therapy in patients with TMD has demonstrated the ability to relieve pain within minutes of its application, promoting significant well-being. Moreover, it is an adjuvant pain-relief treatment in which the analgesic action of the laser enables the patient to return to their duties, providing more comfort and a better quality of life [5,6,25,22].

The occlusal splint is a device that is widely used in the treatment of TMD and pain control. The use of an occlusal splint led to improvement after one month and even decreased pain symptoms after one week of use [27]. Therapy with occlusal splints is the most widely used technique in dentistry for the treatment and control of pain in TMDs because it is considered to be a conservative and non-invasive treatment option.

Although clinical studies have been published that demonstrate the benefits of both LLL treatment and occlusal splints for pain control, neither the cost of TMD in young patients nor the cost-utility of these two treatments has been established. Cost-utility analysis is a method used to compare the benefits and costs of a technology used in healthcare and the benefits are measured in life utility [28].

Methods

Overview

The general purpose of this study is to evaluate the cost-effectiveness of LLL therapy and occlusal splints in the treatment of pain in patients between 15 and 25 years of age with TMD. Because this is a controlled clinical study, and in search of greater transparency and quality of this research and Table 1 provides the enrollment, intervention and assessment schedule following SPIRIT recommendations.

Table 1
Schedule of enrolment, interventions, and assessments of DTM Treatment

	STUDY PERIOD						
	Enrolment	Allocation	Post-allocation				Close-out
			0 Baseline	01 month	03 months	06 months	12 months
ENROLMENT:							
Eligibility screen	X						
Informed consent	X						
Allocation		X					
INTERVENTIONS:							
Low Level laser Therapy			x	x	x	x	x
Occlusal Splint			x	x	x	x	x
Placebo			x	x	x	x	x
ASSESSMENTS:							
Pain			x	x	x	x	x
Quality of life			x	x	x	x	x
Cost							x

* 0 = Baseline, t_1 = 01 month after the treatment, t_2 = 03 months after the treatment, t_3 = 06 months after the treatment, t_4 = 12 months after the treatment

This is a prospective study of clinical and cost approach. Activities will be conducted at the premises of the clinic of the Escola de Odontologia of the Universidade Nove de Julho. The project will follow the regulatory standards for ethics research with humans and will be submitted to the Institutional Review Board of the university. Data collection will begin upon receipt of a favorable opinion and the signing of the informed consent form by the participants and/or their guardians.

Participants

Patients between 15 and 25 years of age selected at the Clinic of the School of Dentistry of UNINOVE will participate in the study. Forty-five patients will be selected, following the sample calculation based on studies with LIL treatment and occlusal splints, using the DINAM 1.0 program (Table 2).

Table 2: Sample calculation

DIMAM 1.0

Sample Sizing

CRITERIA AND PRELIMINARY ESTIMATES:

Level of significance: 5 [%]

Power of the Test: 80 [%]

Standard Deviation (1): 1.9

Standard Deviation (2): 2.8

Experimental Mean (1): 11.9

Experimental Mean (2): 13.4

RESULTS:

Sample size: 15 (each group)

Screening procedures

For a diagnosis of the TMD, the Research Diagnostic Criteria for Temporomandibular Disorders questionnaire (RDC/TMD) [29] will be applied before any intervention. In addition to the questionnaire, a specific clinical examination will be conducted, always by the same previously-trained evaluator, in which the patient will be positioned sitting in a chair, with their feet flat on the floor and the Camper plane parallel to the ground. The exam will consist of palpation of the temporalis, masseter, digastric, and medial pterygoid muscles, palpation of the TMJs, and analysis of mandibular movement, with use of a Digimess® digital pachymeter to measure the vertical and horizontal movements and a stethoscope to check for noises, as well as an investigation of frequent headaches, facial pain, tiredness and difficulty while chewing, bruxism, psychological aspects of adolescence, and para-functional habits.

Pre-clinical trial

Inclusion Criteria: Young people between 15 and 25 years of age with a diagnosis of TMD in group I (myofascial pain in accordance with the RDC-TMD) will be included in the study.

Exclusion Criteria: Individuals with dental-facial anomalies who were in orthodontic or orthopedic treatment of the jaws or in psychological or physical therapy will be

excluded. Individuals who were taking muscle relaxants or anti-inflammatory medications will also be excluded.

Randomization

Participants will be divided into 3 groups, as shown in Table 3.

Table 3. Distribution of participants into research groups

Control	Participants	Therapeutic Intervention
1	15	LLL
2	15	Occlusal Splint
3	15	Placebo

For the random distribution of volunteers with TMD, lots will be drawn using duly sealed brown envelopes. At the beginning of the first evaluation of each patient, an envelope will be opened to determine to which group they will be allocated.

Procedures

Treatment with LLL

For the LLL Therapy, a gallium-aluminum-arsenide (GaAIAs) laser, model Twin Flex Evolution ®, from MM Optics, will be used. The laser therapy sessions will be performed in a reserved room, annexed to the dental clinic offices, free from sound interference. At the time of application, only the volunteer to be treated and the professional responsible will be present, both wearing special glasses for eye protection. The tip of the laser will be coated with disposable transparent plastic (PVC) (to avoid cross-contamination and for reasons of hygiene) and the facial site to be irradiated will be cleansed with 70% alcohol. During the applications the patient will remain seated, with the Frankfurt plane parallel to the ground.

Twelve laser applications will be applied as initial treatment, with 2 sessions per week. A wave length of 780 nm, with an energy density of 25 J/cm2, a power of 50 mW and power density of 1.25 W/cm2, will be used for a duration of 20 seconds per point, resulting in a total energy of 1J per point. The laser will be applied at each point, using a conventional tip in contact with the skin, thus considering an area of 0.04 cm^2, in

accordance with the protocol [8,16]. The laser will be applied to 3 points of the masseter muscle (upper, middle, and lower bundles) and 1 point in the anterior temporalis on each side of the face [16]. After the first 12 sessions, the protocol will be conducted the same way, twice a month.

Placebo group

For the placebo group, all the measures described for the group 1 (LIL) will be adopted, however the laser equipment will remain switched off.

Treatment with Oclusal Splints

The group undergoing treatment with occlusal splints will be instructed to use the device during sleep, 8 hours per night, for a period of 12 months. The splints will be made following the principles established by literature [1]. Participants will be molded with alginate to obtain models. In the upper model, a 2 mm acetate splint will be made, to be later replaced with acrylic resin [31], and these splints will be adjusted in centric relation, to promote occlusal stability and disocclusion guide. Weekly follow-up and adjustments will be performed during the evaluation period, until the completion of treatment [31].

Evaluation of pain

Muscle pain will be analyzed by clinical criteria of the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD). The clinical examination will be conducted periodically, and the parameters for analysis will be at intervals of 1, 3, 6 and 12 months.

Evaluation of the impact of the treatment on quality of life

To assess the impact of treatment on the quality of life of the participants, the EQ-5D will be used, which is a generic instrument for assessing quality of life related to health, developed in Europe, translated and validated for several languages, including Portuguese [35]. Because it was developed for the purpose of determining a single

cardinal indicator of the state of health, it can be used for both clinical evaluation and economic evaluation.

For this type of study, it is important that the instrument is short and simple, and represents dimensions relating to quality of life and health status [36]. Currently, the original version is called EQ-5D-3L, as another version, EQ- 5D-5L, was launched. EQ-5D-3L is composed of two stages, a questionnaire and a visual analogue scale (VAS). The questionnaire contains five questions that evaluate the domains mobility, personal care, usual activities, pain or discomfort and anxiety/depression. For each question, patients are asked to select the option that best reflects their conditions, selecting from three alternatives. The first alternative indicates the absence of problems, the second indicates some problems, and the third, severe problems. The instrument will be applied at intervals of 1, 3, 6 and 12 months after treatment. The responses will be compared intra-groups (same subject in the different intervals) and between groups.

Cost Analysis

This phase of the study will consist in the quantification of resources, i.e. determining the frequency of use of resources and materials during the treatment. The units used to quantify the direct costs consumed are physical units such as consultation time, number of sessions, equipment used, and materials consumed. These data will be collected using a specific form. In this phase, the prospective method of quantification of resources will be used which, according literature [34], is a method that collects information on resources according to a prior plan, in conjunction with clinical study. The consumption is recorded as the actions occur. The resources will be attributed a value, and the cost of each treatment determined for each participant, for 12 months, in each group studied.

Organization and statistical treatment of the Data

The numerical data are described by mean and standard deviation or median and interquartile range (IQR) when the distribution is not presented as normal. The categorical variables are described by means of absolute frequencies and percentages. The measure of outcome used in this study will be the cost ratio and the effectiveness evaluated by muscle pain reported by the patient.

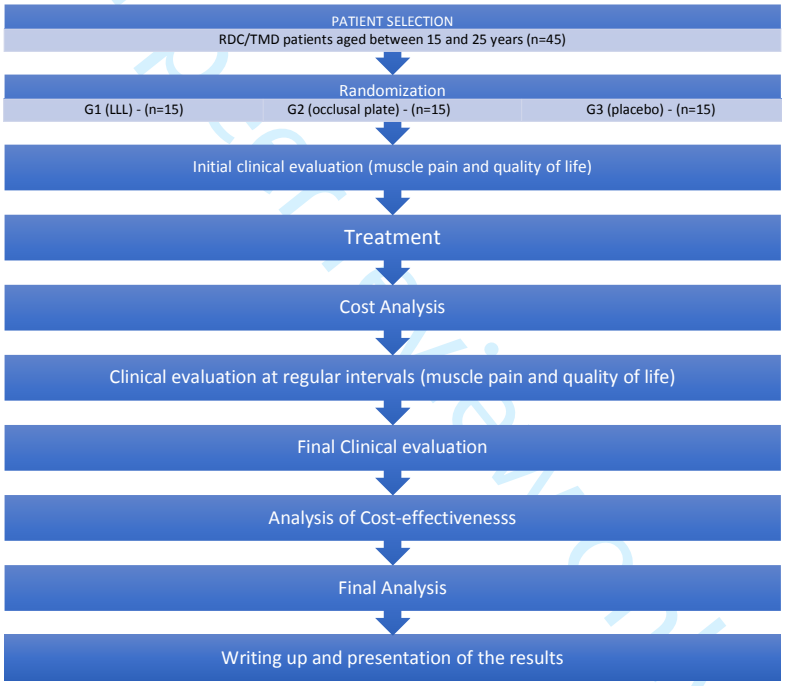
Measurement of costs: Monetary Units (C)

Measurement of Effects (effectiveness): PAIN

Analyses: $(C_{G1}/PAIN_{G1})$-$(C_{G2}/PAIN_{G2})$

CE (cost-effectiveness) = $(C_{G1} - C_{G2})/ (PAIN_{G1} - PAIN_{G2})$

The data will be tabulated and processed in SPSS for Windows. Descriptive statistics will be performed, for presentation of the distribution of the variables. To evaluate the association of categorical variables, the Chi-squared and Fisher's exact test will be used; for the comparison of means, the Student t-test and analysis of variance (ANOVA) will be used, and for the correlation analysis between continuous variables, Pearson's correlation test will be applied. A significance level of 95% ($p<0.05$) will be considered. The study will follow the flow chart presented in Figure 1.



Discussion

The TMD is the most common orofacial pain and the Myogenic TMD is the frequent subtype. As TMD can be self-limiting, and the patient's complaints about: pain, loss of function and trismus, the TMD causes a decrease in quality of life [37,38,39]. Due of this, is very import to know how treatment (Occlusal Splint or LLL Therapy) is more cost-effectiveness to TDM pain.

The Therapy with an occlusal splint is commonly used as a basic TMD treatment in the dental practice, because their manufacturing making is simple, have a low cost, are

reversible and have obtain a high prevalence of outcome in the treatment of the most painfull symptoms of TDM [40,41].

Low-level laser has been used to control pain in TMD and clinical studies have reported favorable results [4,5,6,7,16,17,18,19,20,21,23,24,26]. However, the relationship between the cost of treatment and its effectiveness has not been established in the literature. Clinical and economic data evaluated together can serve as a support for decision making in choosing a treatment or a new protocol to provide optimum conditions for affected patients.

Cost-effectiveness analysis has been used when costs are a crucial factor to choose certain product or technology. It has been considered the most suitable method to compare two or more alternatives regarding a new technology in health. Thus, in health, the economic analysis represents the evaluation of choice alternatives for allocation of resources. It has great importance, since it evaluates and compares alternatives and facilitates the use and a proper allocation of resources for spheres that may have greater benefits regarding reduction of morbidity costs or greater clinical effect[42].

The development of a clinical and economic trial of treatments for control of muscle pain in patients with TMD provides relevant information for clinical decision making and choosing new care protocols for inclusion. Through this study, we hope to: Obtain data related to the direct costs of treatments with LLL therapy and occlusal splints in the treatment of muscle pain in patients with TMD. Determine the ratio between the cost and effectiveness of treatments, considering pain as the endpoint for measuring effectiveness, and define the impact of the treatments evaluated to the quality of life of patients with TMD.

Contributors: Substantial contributions to the conception: APTS and LJM. Design of the work: CLHG, APTS and LJM. Drafting the work: APTS and LJM. Revising the work: APTS, CLHG, KPSF, SKB, RAMF, ACRTH, SFM and LJM. Final approval of the work: SKB, KPSF, APTS and LJM.

Ethics approval and consent to participate: This study was approved the Nove de Julho University Ethics Committee - Protocol Number: 2.014.339. All participants will provide informed consent before participating in this study.

Availability of data and materials: Not appropriate. This paper is a protocol description and does not contain any data.

Competing interest: The authors have no conflict of interest, financial or otherwise to declare.

Data sharing statement: The original protocol and substantive amendments are available. These were available for the included authors and the local medical ethical committee.

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AUTHORSHIP STATEMENT

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All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript. Furthermore, each author certifies that this material or similar material has not been and will not be submitted to or published in any other publication before its appearance in the BMJ Open.

Authorship contributions

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This statement is signed by all the authors

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PHOTOMODULATION IN THE TREATMENT OF PAIN IN PATIENTS WITH TEMPOROMANDIBULAR DISORDER: PROTOCOL FOR COST-EFFECTIVENESS ANALYSIS

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ABSTRACT

Introduction Epidemiological data show that the signs and symptoms of Temporomandibular disorder (TMD) start to become apparent from six years of age, and in adolescence these signs and symptoms are similar to those of adults. The present study aims: to estimate the direct costs in the treatment of chronic muscle pain in patients with TMD with photobiomodulation therapy and with occlusal splint and a placebo group; to evaluate the effectiveness of the treatments with photobiomodulation therapy and occlusal splint for muscle pain in patients with TMD; to analyze the cost-effectiveness of the two proposed treatments for pain; and to describe and compare the results of analyses of treatments for pain in patients with TMD.

Methods and analysis It is a prospective trial of clinical and economic analysis.

It will include 45 patients aged between 15 and 25 years with TMD, randomly assigned to a treatment group: G1 (photobiomodulation), G2 (occlusal splint) and G3 (placebo). The analysis will be based on the costs of each treatment during the 12-month period. The outcome for the analysis of the effectiveness will be the pain, measured periodically by means of the clinical examination of the Research Diagnostic Criteria

for Temporomandibular Disorders (RDC/TMD). The cost-effectiveness ratio will be calculated using, as endpoints, pain and the calculation of the ratio between the difference in costs between the groups studied. The evaluation of the impact of the treatment on quality of life will be determined by applying the adapted EuroQol-5D.

Ethics and dissemination Ethics and dissemination This protocol has been ethically approved by the local medical ethical committee Protocol Number: 2.014.339. Results will be submitted to international peer-reviewed journals and presented at international conferences.

Trial registration: NCT03096301

Keywords: Temporomandibular Disorder, Temporomandibular Joint Dysfunction Syndrome, Cost Effectiveness Analysis, Photobiomodulation Therapy, Pain.

Introduction

Temporomandibular disorder (TMD) is a term used to define a number of clinical signs and symptoms that affect the masticatory muscles, the temporomandibular joint (TMJ), and associated structures. [1-6] The most common signs and symptoms are sensitivity of the masticatory muscles, pain in one or both of TMJs, limited mandibular movement, articular noises [6-8] headache [6 9 10], associated dizziness, hearing loss, and tinnitus may also occur. [1 11] Signs and symptoms of TMD are found in all ages; however, the prevalence of this disorder, considered low in children, increases with age in adolescents and young adults. [12 13] The changes caused by the TMD, especially pain, can interfere in the quality of life of these patients. [14]

Various treatment features have been proposed, mainly for pain control, such as occlusal splints, acupuncture, kinesiotherapy, massage therapy, postural training, psychotherapy, joint mobilizations, drug therapy, and laser therapy. [15 16] Photobiomodulation therapy is a non-invasive, non-pharmacological treatment that, according to various studies, has shown beneficial results in the treatment of pain associated with TMD. [4-7 16-24] Photobiomodulation is a radiation located between the visible and infrared portions of the spectrum of electromagnetic waves, with characteristics of monochromaticity, coherence, one-directionality, and variable wave length. [6] Inflammation modulation and analgesic effects are cited among the therapeutic results of Photobiomodulation treatment on TMD.[5 6 22 25 26]

therapy has demonstrated a capacity to assist in the symptomatic treatment of pain, promoting a considerable degree of comfort for the patient immediately after its application. The main advantage of laser applications in the treatment of TMD is that this type of therapy is non-invasive and low cost, and is currently widely used in dental clinics, reducing the demand for surgery or drugs in the treatment of pain relief and tissue regeneration. The application of laser therapy in patients with TMD has demonstrated the ability to relieve pain within minutes of its application, promoting significant well-being. Moreover, it is an adjuvant pain-relief treatment in which the analgesic action of the laser enables the patient to return to their duties, providing more comfort and a better quality of life. [5 6 22 25]

The occlusal splint is a device that is widely used in the treatment of TMD and pain control. The use of an occlusal splint led to improvement after one month and even decreased pain symptoms after one week of use. [27] Therapy with occlusal splints is the most widely used technique in dentistry for the treatment and control of pain in TMDs because it is considered to be a conservative and non-invasive treatment option.

Although clinical studies have been published that demonstrate the benefits of both Photobiomodulation treatment and occlusal splints for pain control, neither the cost of TMD in young patients nor the cost-utility of these two treatments has been established. Cost-utility analysis is a method used to compare the benefits and costs of a technology used in healthcare and the benefits are measured in life utility. [28]

Methods

Overview

The general purpose of this study is to evaluate the cost-effectiveness of Photobiomodulation therapy and occlusal splints in the treatment of pain in patients between 15 and 25 years of age with TMD. Because this is a controlled clinical study, and in search of greater transparency and quality of this research and Table 1 provides the enrollment, intervention and assessment schedule following SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) recommendations.

Table 1
Schedule of enrolment, interventions, and assessments of TMD Treatment

	STUDY PERIOD						
	Enrolment	Allocation	Post-allocation				Close-out
			0 Baseline	01 month	03 months	06 months	12 months
ENROLMENT:							
Eligibility screen	X						
Informed consent	X						
Allocation		X					
INTERVENTIONS:							
Photobiomodulation Therapy			x	x	x	x	x
Occlusal Splint			x	x	x	x	x
Placebo			x	x	x	x	x
ASSESSMENTS:							
Pain			x	x	x	x	x
Quality of life			x	x	x	x	x
Cost							x

* 0 = Baseline, t_1 = 01 month after the treatment, t_2 = 03 months after the treatment, t_3 = 06 months after the treatment, t_4 = 12 months after the treatment

This is a prospective study of clinical and cost approach. Activities will be conducted at the premises at the Clinic of the School of Dentistry of Universidade Nove de Julho (UNINOVE). The project will follow the regulatory standards for ethics research with humans and will be submitted to the Institutional Review Board of the university. Data collection will begin upon receipt of a favorable opinion and the signing of the informed consent form by the participants and/or their guardians.

Participants

Patients between 15 and 25 years of age selected at the Clinic of the School of Dentistry of Universidade Nove de Julho (UNINOVE) will participate in the study. Forty-five patients will be selected, following the sample calculation based on studies with

photobiomodulation treatment and occlusal splints, using the DINAM 1.0 program (Table 2).

The sample calculation was based on a previous literature review and will only be included in the sample, patients with chronic myofascial pain.

Table 2: Sample calculation

DIMAM 1.0 Sample Sizing	
CRITERIA AND PRELIMINARY ESTIMATES:	
Level of significance: 5 [%]	
Power of the Test: 80 [%]	
Standard Deviation (1): 1.9	
Standard Deviation (2): 2.8	
Experimental Mean (1): 11.9	
Experimental Mean (2): 13.4	
RESULTS:	
Sample size: 15 (each group)	

Screening procedures

For a diagnosis of the TMD, the Research Diagnostic Criteria for Temporomandibular Disorders questionnaire (RDC/TMD) [29] will be applied before any intervention. In addition to the questionnaire, a specific clinical examination will be conducted, always by the same previously-trained evaluator, in which the patient will be positioned sitting in a chair, with their feet flat on the floor and the Camper plane parallel to the ground. The exam will consist of palpation of the temporalis, masseter, digastric, and medial pterygoid muscles, palpation of the TMJs, and analysis of mandibular movement, with use of a Digimess® digital pachymeter to measure the vertical and horizontal movements and a stethoscope to check for noises, as well as an investigation of frequent headaches, facial pain, tiredness and difficulty while chewing, bruxism, psychological aspects of adolescence, and para-functional habits. The RDC/TMD questionnaire will be responsible to indicate the diagnosis for myofascial TMD and clinical examination form analyzes the mandibular movements. The diagnosis of pain will be evaluated by

the Visual Analog Scale (VAS) and quality of life will be determined by applying the adapted EuroQol-5D.

Pre-clinical trial

Inclusion Criteria: Young people between 15 and 25 years of age with a diagnosis of TMD in group I (Chronic myofascial pain in accordance with the RDC-TMD) will be included in the study.

Exclusion Criteria: Individuals with dental-facial anomalies who were in orthodontic or orthopedic treatment of the jaws or in psychological or physical therapy will be excluded. Individuals who were taking muscle relaxants or anti-inflammatory medications will also be excluded.

Randomization

Participants will be divided into 3 groups, as shown in Table 3.

Table 3. Distribution of participants into research groups

Control	Participants	Therapeutic Intervention
1	15	Photobiomodulation
2	15	Occlusal Splint
3	15	Placebo

For the random distribution of volunteers with TMD, will be use the randomized computer-generated list. At the beginning of the first evaluation of each patient, will received one number to determine to which group they will be allocated.

Procedures

Treatment with Photobiomodulation

For the Photobiomodulation Therapy, a gallium-aluminum-arsenide (GaAIAs) laser, model Twin Flex Evolution ®, from MM Optics, will be used. The laser therapy sessions will be performed in a reserved room, annexed to the dental clinic offices, free from sound interference. At the time of application, only the volunteer to be treated and the professional responsible will be present, both wearing special glasses for eye

protection. The tip of the laser will be coated with disposable transparent plastic (PVC) (to avoid cross-contamination and for reasons of hygiene) and the facial site to be irradiated will be cleansed with 70% alcohol. During the applications the patient will remain seated, with the Frankfurt plane parallel to the ground.

Twelve laser applications will be applied as initial treatment, with 2 sessions per week. A wave length of 780 nm, with an energy density of 25 J/cm2, a power of 50 mW and power density of 1.25 W/cm2, will be used for a duration of 20 seconds per point, resulting in a total energy of 1J per point. The laser will be applied at each point, using a conventional tip in contact with the skin, thus considering an area of 0.04 cm^2, in accordance with the protocol.[8 16] The laser will be applied to 3 points of the masseter muscle (upper, middle, and lower bundles) and 1 point in the anterior temporalis on each side of the face.[16] The patients were called back for follow-up visits on 1, 3 ,6 and 12 months after the last day of plotobiomodulation therapy.

Placebo group

For the placebo group, all the measures described for the group 1 (photobiomodulation) will be adopted, however the laser equipment will remain switched off. But the same sound of the equipment will be simulated and a guide light will be on.The placebo group will also have the same follow-up of visits that group 1.

Treatment with Occlusal Splints

The type of occlusal splint used in this study is Stabilization splint made in hard acrylic fabricated for the maxillary arch. The group undergoing treatment with occlusal splints will be instructed to use the device during sleep, 8 hours per night, for a period of 06 months. The splints will be made following the principles established by literature.[1] Participants will be molded with alginate to obtain models. In the upper model, a 2 mm acetate splint will be made, to be later replaced with acrylic resin [30], and these splints will be adjusted in centric relation, to promote occlusal stability and disocclusion guide. Weekly follow-up and adjustments will be performed during the evaluation period, until the completion of treatment. [31] The patients were called back for follow-up visits on 1, 3 ,6 and 12 months after start to use the occlusal splint.

Evaluation of pain

Muscle pain will be analyzed by clinical criteria of the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD). The clinical examination will be conducted periodically, and the parameters for analysis will be at intervals of 1, 3, 6 and 12 months. We will use a visual analogue scale (VAS) to assess pain level.

Evaluation of the impact of the treatment on quality of life

To assess the impact of treatment on the quality of life of the participants, the EQ-5D will be used, which is a generic instrument for assessing quality of life related to health, developed in Europe, translated and validated for several languages, including Portuguese. [32] Because it was developed for the purpose of determining a single cardinal indicator of the state of health, it can be used for both clinical evaluation and economic evaluation.

For this type of study, it is important that the instrument is short and simple, and represents dimensions relating to quality of life and health status.[33] Currently, the original version is called EQ-5D-3L, as another version, EQ- 5D-5L, was launched. EQ-5D-3L is composed of two stages, a questionnaire and a Visual Analogue Scale (VAS). The questionnaire contains five questions that evaluate the domains mobility, personal care, usual activities, pain or discomfort and anxiety/depression. For each question, patients are asked to select the option that best reflects their conditions, selecting from three alternatives. The first alternative indicates the absence of problems, the second indicates some problems, and the third, severe problems. The instrument will be applied at intervals of 1, 3, 6 and 12 months, when each group called back for follow-up visits. The responses will be compared intra-groups (same subject in the different intervals) and between groups.

Cost Analysis

This phase of the study will consist in the quantification of resources, i.e. determining the frequency of use of resources and materials during the treatment. It is a preliminary cost-effectiveness study, so we opted to analyze only direct costs. The units used to quantify the direct costs consumed are physical units such as consultation time, number of sessions, equipment used, and materials consumed. These data will be collected using a specific form. In this phase, the prospective method of quantification of resources will be used which, according literature [34], is a method that collects information on resources

according to a prior plan, in conjunction with clinical study. The consumption is recorded as the actions occur. The resources will be assigned a value and the cost of each treatment determined for each participant and in each group studied, from the first visit to the start the treatment until the last follow-up visit.

Organization and statistical treatment of the Data

The numerical data are described by mean and standard deviation or median and interquartile range (IQR) when the distribution is not presented as normal. The categorical variables are described by means of absolute frequencies and percentages. The measure of outcome used in this study will be the cost ratio and the effectiveness evaluated by muscle pain reported by the patient.

Measurement of costs: Monetary Units (C)

Measurement of Effects (effectiveness): PAIN

Treatment groups: G1 (photobiomodulation), G2 (occlusal splint) and G3 (placebo).

Analyses: $(C_{G1}/PAIN_{G1}) - (C_{G2}/PAIN_{G2})$

CE (cost-effectiveness) = $(C_{G1} - C_{G2})/ (PAIN_{G1} - PAIN_{G2})$

The data will be tabulated and processed in SPSS for Windows. Descriptive statistics will be performed, for presentation of the distribution of the variables. To evaluate the association of categorical variables, the Chi-squared and Fisher's exact test will be used; for the comparison of means, the Student t-test and analysis of variance (ANOVA) will be used, and for the correlation analysis between continuous variables, Pearson's correlation test will be applied. A significance level of 95% ($p<0.05$) will be considered. The study will follow the flow chart presented in Figure 1.

Discussion

The TMD is the most common orofacial pain and the Myogenic TMD is the frequent subtype. As TMD can be self-limiting, and the patient's complaints about: pain, loss of function and trismus, the TMD causes a decrease in quality of life. [35-37] Due of this, is very import to know how treatment (Occlusal Splint or Photobiomodulation Therapy) is more cost-effectiveness to TDM pain.

The Therapy with an occlusal splint is commonly used as a basic TMD treatment in the dental practice, because their manufacturing making is simple, have a low cost, are

reversible and have obtain a high prevalence of outcome in the treatment of the most painfull symptoms of TDM. [38 39]

Photobiomodulation therapy has been used to control pain in TMD and clinical studies have reported favorable results. [4-7 16-24 26] However, the relationship between the cost of treatment and its effectiveness has not been established in the literature. Clinical and economic data evaluated together can serve as a support for decision making in choosing a treatment or a new protocol to provide optimum conditions for affected patients.

TMD has a multifactorial etiology and is complex dysfunction, so, the goal of this study is to evaluate the control of chronic pain of myofascial muscle in each group analyzed and not to treat TMD.

Cost-effectiveness analysis has been used when costs are a crucial factor to choose certain product or technology. It has been considered the most suitable method to compare two or more alternatives regarding a new technology in health. Thus, in health, the economic analysis represents the evaluation of choice alternatives for allocation of resources. It has great importance, since it evaluates and compares alternatives and facilitates the use and a proper allocation of resources for spheres that may have greater benefits regarding reduction of morbidity costs or greater clinical effect. [40]

The development of a clinical and economic trial of treatments for control of muscle pain in patients with TMD provides relevant information for clinical decision making and choosing new care protocols for inclusion. Through this study, we hope to: Obtain data related to the direct costs of treatments with photobiomodulation therapy and occlusal splints in the treatment of muscle pain in patients with TMD. Determine the ratio between the cost and effectiveness of treatments, considering pain as the endpoint for measuring effectiveness, and define the impact of the treatments evaluated to the quality of life of patients with TMD.

Contributors: Substantial contributions to the conception: APTS and LJM. Design of the work: CLHG, APTS and LJM. Drafting the work: APTS and LJM. Revising the work: APTS, CLHG, KPSF, SKB, RAMF, ACRTH, SFM and LJM. Final approval of the work: SKB, KPSF, APTS and LJM.

Ethics approval and consent to participate: This study was approved the Nove de Julho University Ethics Committee - Protocol Number: 2.014.339. All participants will provide informed consent before participating in this study.

Availability of data and materials: Not appropriate. This paper is a protocol description and does not contain any data.

Competing interest: None declared. The authors have no conflict of interest, financial or otherwise to declare.

Data sharing statement: The original protocol and substantive amendments are available. These were available for the included authors and the local medical ethical committee.

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Figure 1 Flowchart of search strategy

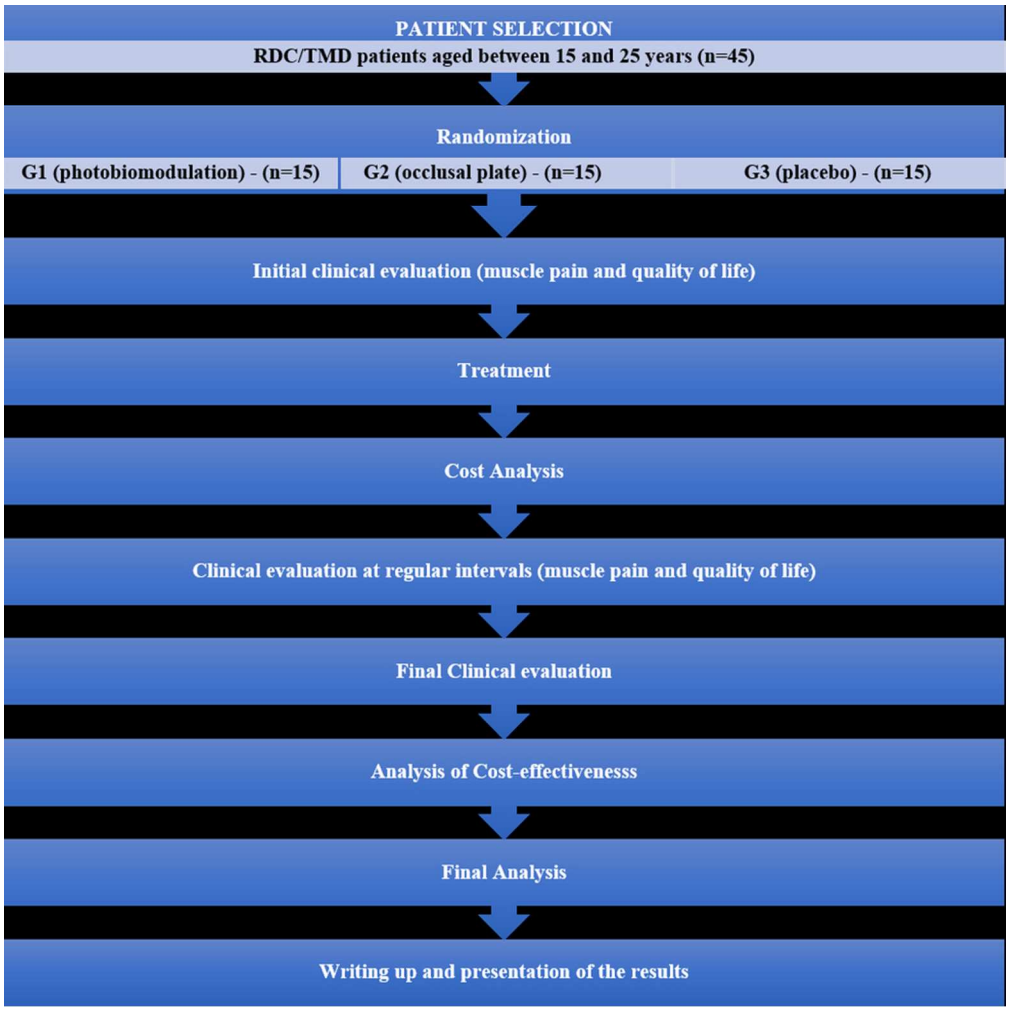

Figure 1 Flowchart of search strategy

82x82mm (300 x 300 DPI)

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description	Addressed on 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	2
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	N/A
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	N/A
	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	N/A
	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)	N/A

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	2-3
	6b	Explanation for choice of comparators	2-3
Objectives	7	Specific objectives or hypotheses	2-3
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)	3-4
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	3-5
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)	8-9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	N/A
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
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	8-9
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)	6, Table 3

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	5, Table 2
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6, table 3
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	6
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	6
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	6
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	N/A
	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	N/A

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	N/A
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	9
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9
	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)	N/A
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	N/A
	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	N/A
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	N/A
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	11
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)	N/A

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	4
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	4
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	4
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	11
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	11
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	N/A
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	N/A
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
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	N/A

*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.

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PHOTOMODULATION IN THE TREATMENT OF CHRONIC PAIN IN PATIENTS WITH TEMPOROMANDIBULAR DISORDER: PROTOCOL FOR COST-EFFECTIVENESS ANALYSIS

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PHOTOMODULATION IN THE TREATMENT OF CHRONIC PAIN IN PATIENTS WITH TEMPOROMANDIBULAR DISORDER: PROTOCOL FOR COST-EFFECTIVENESS ANALYSIS

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ABSTRACT

Introduction Epidemiological data show that the signs and symptoms of Temporomandibular disorder (TMD) start to become apparent from six years of age, and in adolescence these signs and symptoms are similar to those of adults. The present study aims: to estimate the direct costs in the treatment of chronic muscle full in patients with TMD with photobiomodulation therapy and with occlusal splint and a placebo group; to evaluate the effectiveness of the treatments with photobiomodulation therapy and occlusal splint for muscle pain in patients with TMD; to analyze the cost-effectiveness of the two proposed treatments for pain; and to describe and compare the results of analyses of treatments for pain in patients with TMD.

Methods and analysis It is a prospective trial of clinical and economic analysis.

It will include 45 patients aged between 15 and 25 years with TMD, randomly assigned to a treatment group: G1 (photobiomodulation), G2 (occlusal splint) and G3 (placebo). The analysis will be based on the costs of each treatment during the 12-month period. The outcome for the analysis of the effectiveness will be the pain, measured periodically by means of the clinical examination of the Research Diagnostic Criteria

for Temporomandibular Disorders (RDC/TMD). The cost-effectiveness ratio will be calculated using, as endpoints, pain and the calculation of the ratio between the difference in costs between the groups studied. The evaluation of the impact of the treatment on quality of life will be determined by applying the adapted EuroQol-5D.

Ethics and dissemination Ethics and dissemination This protocol has been ethically approved by the local medical ethical committee Protocol Number: 2.014.339. Results will be submitted to international peer-reviewed journals and presented at international conferences.

Trial registration: NCT03096301

Keywords: Temporomandibular Disorder, Temporomandibular Joint Dysfunction Syndrome, Cost Effectiveness Analysis, Photobiomodulation Therapy, Pain.

Introduction

Temporomandibular disorder (TMD) is a term used to define a number of clinical signs and symptoms that affect the masticatory muscles, the temporomandibular joint (TMJ), and associated structures. [1-6] The most common signs and symptoms are sensitivity of the masticatory muscles, pain in one or both of TMJs, limited mandibular movement, articular noises [6-8] headache [6 9 10], associated dizziness, hearing loss, and tinnitus may also occur. [1 11] Signs and symptoms of TMD are found in all ages; however, the prevalence of this disorder, considered low in children, increases with age in adolescents and young adults. [12 13] The changes caused by the TMD, especially pain, can interfere in the quality of life of these patients. [14]

Various treatment features have been proposed, mainly for pain control, such as occlusal splints, acupuncture, kinesiotherapy, massage therapy, postural training, psychotherapy, joint mobilizations, drug therapy, and laser therapy. [15 16] Photobiomodulation therapy is a non-invasive, non-pharmacological treatment that, according to various studies, has shown beneficial results in the treatment of pain associated with TMD. [4-7 16-24] Photobiomodulation is a radiation located between the visible and infrared portions of the spectrum of electromagnetic waves, with characteristics of monochromaticity, coherence, one-directionality, and variable wave length. [6] Inflammation modulation and analgesic effects are cited among the therapeutic results of Photobiomodulation treatment on TMD.[5 6 22 25 26]

therapy has demonstrated a capacity to assist in the symptomatic treatment of pain, promoting a considerable degree of comfort for the patient immediately after its application. The main advantage of laser applications in the treatment of TMD is that this type of therapy is non-invasive and low cost, and is currently widely used in dental clinics, reducing the demand for surgery or drugs in the treatment of pain relief and tissue regeneration. The application of laser therapy in patients with TMD has demonstrated the ability to relieve pain within minutes of its application, promoting significant well-being. Moreover, it is an adjuvant pain-relief treatment in which the analgesic action of the laser enables the patient to return to their duties, providing more comfort and a better quality of life. [5 6 22 25]

The occlusal splint is a device that is widely used in the treatment of TMD and pain control. The use of an occlusal splint led to improvement after one month and even decreased pain symptoms after one week of use. [27] Therapy with occlusal splints is the most widely used technique in dentistry for the treatment and control of pain in TMDs because it is considered to be a conservative and non-invasive treatment option.

Although clinical studies have been published that demonstrate the benefits of both Photobiomodulation treatment and occlusal splints for pain control, neither the cost of TMD in young patients nor the cost-utility of these two treatments has been established. Cost-utility analysis is a method used to compare the benefits and costs of a technology used in healthcare and the benefits are measured in life utility. [28]

Methods

Overview

The general purpose of this study is to evaluate the cost-effectiveness of Photobiomodulation therapy and occlusal splints in the treatment of pain in patients between 15 and 25 years of age with TMD. This is a controlled clinical study, and in search of greater transparency and quality of this research and Table 1 provides the enrollment, intervention and assessment schedule following SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) recommendations.

Table 1
Schedule of enrolment, interventions, and assessments of TMD Treatment

	STUDY PERIOD						
	Enrolment	Allocation	Post-allocation				Close-out
			0 Baseline	01 month	03 months	06 months	12 months
ENROLMENT:							
Eligibility screen	X						
Informed consent	X						
Allocation		X					
INTERVENTIONS:							
Photobiomodulation Therapy			x	x	x	x	x
Occlusal Splint			x	x	x	x	x
Placebo			x	x	x	x	x
ASSESSMENTS:							
Pain			x	x	x	x	x
Quality of life			x	x	x	x	x
Cost							x

* 0 = Baseline, t_1 = 01 month after the treatment, t_2 = 03 months after the treatment, t_3 = 06 months after the treatment, t_4 = 12 months after the treatment

This is a prospective study of clinical and cost approach. Activities will be conducted at the premises at the Clinic of the School of Dentistry of Universidade Nove de Julho (UNINOVE). The project will follow the regulatory standards for ethics research with humans and will be submitted to the Institutional Review Board of the university. Data collection will begin upon receipt of a favorable opinion and the signing of the informed consent form by the participants and/or their guardians.

Participants

Patients between 15 and 25 years of age selected at the Clinic of the School of Dentistry of Universidade Nove de Julho (UNINOVE) will participate in the study. Forty-five patients will be selected, following the sample calculation based on studies with

photobiomodulation treatment and occlusal splints, using the DINAM 1.0 program (Table 2).

The sample size calculation was based on a previous literature review[16 29 30] and will only be included in the sample, patients with a diagnosis of TMD in group Ia and Ib.

Table 2: Sample calculation

DIMAM 1.0 Sample Sizing
CRITERIA AND PRELIMINARY ESTIMATES:
Level of significance: 5 [%]
Power of the Test: 80 [%]
Standard Deviation (1): 1.9
Standard Deviation (2): 2.8
Experimental Mean (1): 11.9
Experimental Mean (2): 13.4
RESULTS:
Sample size: 15 (each group)

Screening procedures

For a diagnosis of the TMD, the Research Diagnostic Criteria for Temporomandibular Disorders questionnaire (RDC/TMD) [31] will be applied before any intervention. In addition to the questionnaire, a specific clinical examination will be conducted, always by the same previously-trained evaluator, in which the patient will be positioned sitting in a chair, with their feet flat on the floor and the Camper plane parallel to the ground. The exam will consist of palpation of the temporalis, masseter, digastric, and medial pterygoid muscles, palpation of the TMJs, and analysis of mandibular movement, with use of a Digimess® digital pachymeter to measure the vertical and horizontal movements and a stethoscope to check for noises, as well as an investigation of frequent headaches, facial pain, tiredness and difficulty while chewing, bruxism, psychological aspects of adolescence, and para-functional habits. The RDC/TMD questionnaire will be responsible to indicate the diagnosis for myofascial TMD and clinical examination form analyzes the mandibular movements. The diagnosis of pain will be evaluated by

the Visual Analog Scale (VAS) and quality of life will be determined by applying the adapted EuroQol-5D.

Pre-clinical trial

Inclusion Criteria: Young people between 15 and 25 years of age with a diagnosis of TMD in group Ia and Ib (Chronic myofascial pain in accordance with the RDC-TMD) will be included in the study.

Exclusion Criteria: Group II (disk displacement of the Temporomandibular joint) and group III (arthralgia, arthritis, arthrosis). Individuals with dental-facial anomalies who were in orthodontic or orthopedic treatment of the jaws or in psychological or physical therapy will be excluded. Individuals who were taking muscle relaxants or anti-inflammatory medications will also be excluded. These patients will be advised and referred for treatment, but will not participate in this study.

Randomization

Participants will be divided into 3 groups, as shown in Table 3.

Table 3. Distribution of participants into research groups

Control	Participants	Therapeutic Intervention
1	15	Photobiomodulation
2	15	Occlusal Splint
3	15	Placebo

For the random distribution of volunteers with TMD, will be use the randomized computer-generated list. At the beginning of the first evaluation of each patient, will received one number to determine to which group they will be allocated.

Procedures

The treatments' protocols of photobiomodulation and occlusal splint presented in this study are based on clinical trials [8 16 29 32].

The participants of three groups will be received standard information about TDM, the complex cause of the pain and the possible contributing factors. The patients will be

counselling on avoid possibly stress-induced habits of grinding, clenching, nail biting or biting on objects like pencils, excessive gum chewing, biting and/or sucking on the lip or cheek, and pressing and/or sucking on the tongue [33].

The baseline of this study will be 02 weeks after the patients received standard information. After 2 weeks each treatment(G1, G2, G3) will be start; if the patient does not respond to treatment (nonresponder), this patients will be excluded from the research sample, but the researchers will be offered the alternative treatment method. The patients who do not respond will be treated according their needs with integral treatment (with psychologists, physiotherapists, and so on). As these data are very important, the number of patients withdrawn from the study will be computed and included in the intention to treat analysis (ITT). At the end of the research, all patients will be treated integrally to resolve the major cause that causes this disorder.

Treatment with Photobiomodulation

For the Photobiomodulation Therapy, a gallium-aluminum-arsenide (GaAIAs) laser, model Twin Flex Evolution ®, from MM Optics, will be used. The laser therapy sessions will be performed in a reserved room, annexed to the dental clinic offices, free from sound interference. At the time of application, only the volunteer to be treated and the professional responsible will be present, both wearing special glasses for eye protection. The tip of the laser will be coated with disposable transparent plastic (PVC) (to avoid cross-contamination and for reasons of hygiene) and the facial site to be irradiated will be cleansed with 70% alcohol. During the applications the patient will remain seated, with the Frankfurt plane parallel to the ground.

Twelve laser applications will be applied, with 2 sessions per week. A wave length of 780 nm, with an energy density of 25 J/cm2, a power of 50 mW and power density of 1.25 W/cm2, will be used for a duration of 20 seconds per point, resulting in a total energy of 1J per point. The laser will be applied at each point, using a conventional tip in contact with the skin, thus considering an area of 0.04 cm^2, in accordance with the protocol.[8 16 29] The laser will be applied to 3 points of the masseter muscle (upper, middle, and lower bundles) and 1 point in the anterior temporalis on each side of the face.[16 29]

The patients were called back for follow-up visits on 1, 3 ,6 and 12 months after the last day of photobiomodulation therapy.

Placebo group

For the placebo group, all the measures described for the group 1 (photobiomodulation) will be adopted, however the laser equipment will remain switched off. But the same sound of the equipment will be simulated and a guide light will be on. The placebo group will also have the same follow-up of visits that group 1.

Treatment with Occlusal Splints

The type of occlusal splint used in this study is Stabilization splint made in hard acrylic fabricated for the maxillary arch. The splints will be made following the principles established by literature.[1] Participants will be molded with alginate to obtain models. In the upper model, a 2 mm acetate splint will be made, to be later replaced with acrylic resin [34], and these splints will be adjusted in centric relation, to promote occlusal stability and disocclusion guide.[35] The group undergoing treatment with occlusal splints will be instructed to use the device during sleep, 8 hours per night. The splints will be check after 2 weeks of use and adjusted them, if needed. The patients will be asked to use the occlusal splints according mentioned and return 3 months after treatment. If in this return the patient did not respond to treatment (nonresponder), the researchers will be offer the alternate treatment method, but these patients will be excluded of the research sample. The respond patients will be continues to use the occlusal splint and return to the 06 months follow-up visit. [32]

Evaluation of pain

Muscle pain will be analyzed by clinical criteria of the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD). The clinical examination will be conducted periodically, and the parameters for analysis will be at intervals of 1, 3, 6 and 12 months. We will use a visual analogue scale (VAS) to assess pain level.

Evaluation of the impact of the treatment on quality of life

To assess the impact of treatment on the quality of life of the participants, the EQ-5D will be used, which is a generic instrument for assessing quality of life related to health, developed in Europe, translated and validated for several languages, including Portuguese. [36] Because it was developed for the purpose of determining a single

cardinal indicator of the state of health, it can be used for both clinical evaluation and economic evaluation.

For this type of study, it is important that the instrument is short and simple, and represents dimensions relating to quality of life and health status.[37] Currently, the original version is called EQ-5D-3L, as another version, EQ- 5D-5L, was launched. EQ-5D-3L is composed of two stages, a questionnaire and a Visual Analogue Scale (VAS). The questionnaire contains five questions that evaluate the domains mobility, personal care, usual activities, pain or discomfort and anxiety/depression. For each question, patients are asked to select the option that best reflects their conditions, selecting from three alternatives. The first alternative indicates the absence of problems, the second indicates some problems, and the third, severe problems. The instrument will be applied at intervals of 1, 3, 6 and 12 months, when each group called back for follow-up visits. The responses will be compared intra-groups (same subject in the different intervals) and between groups.

Cost Analysis

This phase of the study will consist in the quantification of resources, i.e. determining the frequency of use of resources and materials during the treatment. It is a preliminary cost-effectiveness study, so we opted to analyze only direct costs. The units used to quantify the direct costs consumed are physical units such as consultation time, number of sessions, equipment used, and materials consumed. These data will be collected using a specific form. In this phase, the prospective method of quantification of resources will be used which, according literature [38], is a method that collects information on resources according to a prior plan, in conjunction with clinical study. The consumption is recorded as the actions occur. The resources will be assigned a value and the cost of each treatment determined for each participant and in each group studied, from the first visit to the start the treatment until the last follow-up visit.

Organization and statistical treatment of the Data

The numerical data are described by mean and standard deviation or median and interquartile range (IQR) when the distribution is not presented as normal. The categorical variables are described by means of absolute frequencies and percentages. The measure of outcome used in this study will be the cost ratio and the effectiveness evaluated by muscle pain reported by the patient.

Measurement of costs: Monetary Units (C)

Measurement of Effects (effectiveness): PAIN

Treatment groups: G1 (photobiomodulation), G2 (occlusal splint) and G3 (placebo).

Analyses: $(C_{G1}/PAIN_{G1}) - (C_{G2}/PAIN_{G2})$

CE (cost-effectiveness) = $(C_{G1} - C_{G2})/ (PAIN_{G1} - PAIN_{G2})$

The data will be tabulated and processed in SPSS for Windows. Descriptive statistics will be performed, for presentation of the distribution of the variables. To evaluate the association of categorical variables, the Chi-squared and Fisher's exact test will be used; for the comparison of means, the Student t-test and analysis of variance (ANOVA) will be used, and for the correlation analysis between continuous variables, Pearson's correlation test will be applied. If subjects fail to make a follow-up, we will use an intention-to-treat analysis. A t-test will be performed to compare the changes in measures within groups. A significance level of 95% ($p<0.05$) will be considered.

The study will follow the flow chart presented in Figure 1.

Discussion

The TMD is the most common orofacial pain and the Myogenic TMD is the frequent subtype. As TMD can be self-limiting, and the patient's complaints about: pain, loss of function and trismus, the TMD causes a decrease in quality of life. [39-41] Due of this, is very import to know how treatment (Occlusal Splint or Photobiomodulation Therapy) is more cost-effectiveness to TDM pain.

The Therapy with an occlusal splint is commonly used as a basic TMD treatment in the dental practice, because their manufacturing making is simple, have a low cost, are reversible and have obtain a high prevalence of outcome in the treatment of the most painful symptoms of TDM. [33 42]

Photobiomodulation therapy has been used to control pain in TMD and clinical studies have reported favorable results. [4-7 16-24 26] However, the relationship between the cost of treatment and its effectiveness has not been established in the literature. Clinical and economic data evaluated together can serve as a support for decision making in choosing a treatment or a new protocol to provide optimum conditions for affected patients.

TMD has a multifactorial etiology and is complex dysfunction, so, the goal of this study is to evaluate the control of chronic pain of myofascial muscle in each group analyzed and not to treat TMD.

Cost-effectiveness analysis has been used when costs are a crucial factor to choose certain product or technology. It has been considered the most suitable method to compare two or more alternatives regarding a new technology in health. Thus, in health, the economic analysis represents the evaluation of choice alternatives for allocation of resources. It has great importance, since it evaluates and compares alternatives and facilitates the use and a proper allocation of resources for spheres that may have greater benefits regarding reduction of morbidity costs or greater clinical effect. [43]

The development of a clinical and economic trial of treatments for control of muscle pain in patients with TMD provides relevant information for clinical decision making and choosing new care protocols for inclusion. Through this study, we hope to: Obtain data related to the direct costs of treatments with photobiomodulation therapy and occlusal splints in the treatment of muscle pain in patients with TMD. Determine the ratio between the cost and effectiveness of treatments, considering pain as the endpoint for measuring effectiveness, and define the impact of the treatments evaluated to the quality of life of patients with TMD.

Contributors: Substantial contributions to the conception: APTS and LJM. Design of the work: CLHG, APTS and LJM. Drafting the work: APTS and LJM. Revising the work: APTS, CLHG, KPSF, SKB, RAMF, ACRTH, SFM and LJM. Final approval of the work: SKB, KPSF, APTS and LJM.

Ethics approval and consent to participate: This study was approved the Nove de Julho University Ethics Committee - Protocol Number: 2.014.339. All participants will provide informed consent before participating in this study.

Availability of data and materials: Not appropriate. This paper is a protocol description and does not contain any data.

Competing interest: None declared. The authors have no conflict of interest, financial or otherwise to declare.

Data sharing statement: The original protocol and substantive amendments are available. These were available for the included authors and the local medical ethical committee.

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Figure 1 Flowchart of search strategy

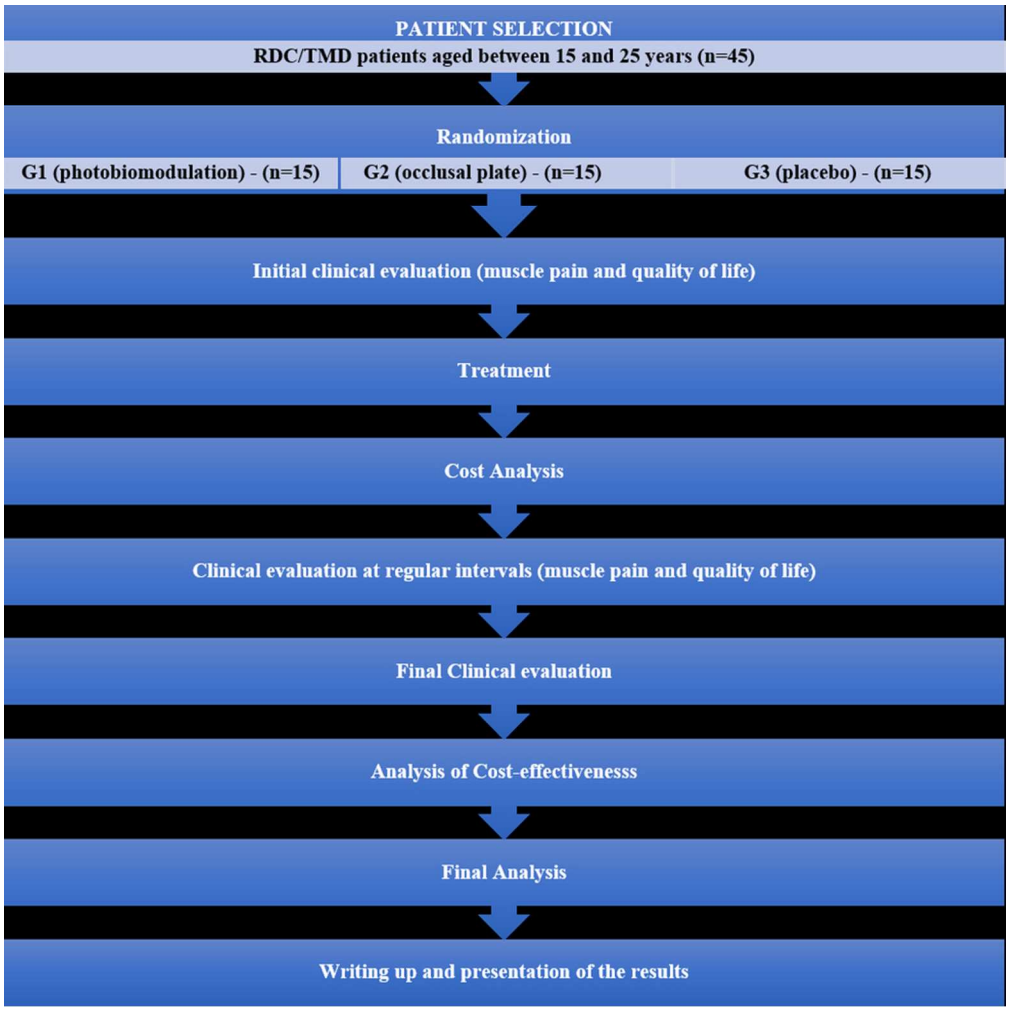

Figure 1 Flowchart of search strategy

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SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description	Addressed on 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	2
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	N/A
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	N/A
	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	N/A
	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)	N/A

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	2-3
	6b	Explanation for choice of comparators	2-3
Objectives	7	Specific objectives or hypotheses	2-3
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)	3-4
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	3-5
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)	8-9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	N/A
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
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	8-9
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)	6, Table 3

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	5, Table 2
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6, table 3
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	6
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	6
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	6
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	N/A
	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	N/A

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	N/A
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	9
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9
	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)	N/A
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	N/A
	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	N/A
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	N/A
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	11
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)	N/A

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	4
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	4
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	4
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	11
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	11
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	N/A
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	N/A
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
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	N/A

*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.

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PHOTOMODULATION IN THE TREATMENT OF CHRONIC PAIN IN PATIENTS WITH TEMPOROMANDIBULAR DISORDER: PROTOCOL FOR COST-EFFECTIVENESS ANALYSIS

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PHOTOMODULATION IN THE TREATMENT OF CHRONIC PAIN IN PATIENTS WITH TEMPOROMANDIBULAR DISORDER: PROTOCOL FOR COST-EFFECTIVENESS ANALYSIS

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ABSTRACT

Introduction Epidemiological data show that the signs and symptoms of Temporomandibular disorder (TMD) start to become apparent from six years of age, and in adolescence these signs and symptoms are similar to those of adults. The present study aims: to estimate the direct costs in the treatment of chronic muscle full in patients with TMD with photobiomodulation therapy and with occlusal splint and a placebo group; to evaluate the effectiveness of the treatments with photobiomodulation therapy and occlusal splint for muscle pain in patients with TMD; to analyze the cost-effectiveness of the two proposed treatments for pain; and to describe and compare the results of analyses of treatments for pain in patients with TMD.

Methods and analysis It is a prospective trial of clinical and economic analysis.

It will include 135 patients

aged between 15 and 25 years with TMD, randomly assigned to a treatment group: G1 (photobiomodulation), G2 (occlusal splint) and G3 (placebo). The analysis will be based on the costs of each treatment during the 12-month period. The outcome for the analysis of the effectiveness will be the pain, measured periodically by means of the clinical

examination of the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD). The cost-effectiveness ratio will be calculated using, as endpoints, pain and the calculation of the ratio between the difference in costs between the groups studied. The evaluation of the impact of the treatment on quality of life will be determined by applying the adapted EuroQol-5D.

Ethics and dissemination Ethics and dissemination This protocol has been ethically approved by the local medical ethical committee Protocol Number: 2.014.339. Results will be submitted to international peer-reviewed journals and presented at international conferences.

Trial registration: NCT03096301

Keywords: Temporomandibular Disorder, Temporomandibular Joint Dysfunction Syndrome, Cost Effectiveness Analysis, Photobiomodulation Therapy, Pain.

Introduction

Temporomandibular disorder (TMD) is a term used to define a number of clinical signs and symptoms that affect the masticatory muscles, the temporomandibular joint (TMJ), and associated structures. [1-6] The most common signs and symptoms are sensitivity of the masticatory muscles, pain in one or both of TMJs, limited mandibular movement, articular noises [6-8] headache [6 9 10], associated dizziness, hearing loss, and tinnitus may also occur. [1 11] Signs and symptoms of TMD are found in all ages; however, the prevalence of this disorder, considered low in children, increases with age in adolescents and young adults. [12 13] The changes caused by the TMD, especially pain, can interfere in the quality of life of these patients. [14]

Various treatment features have been proposed, mainly for pain control, such as occlusal splints, acupuncture, kinesiotherapy, massage therapy, postural training, psychotherapy, joint mobilizations, drug therapy, and laser therapy. [15 16] Photobiomodulation therapy is a non-invasive, non-pharmacological treatment that, according to various studies, has shown beneficial results in the treatment of pain associated with TMD. [4-7 16-24] Photobiomodulation is a radiation located between the visible and infrared portions of the spectrum of electromagnetic waves, with characteristics of monochromaticity, coherence, one-directionality, and variable wave length. [6] Inflammation modulation and analgesic effects are cited among the therapeutic results of Photobiomodulation treatment on TMD.[5 6 22 25 26]

therapy has demonstrated a capacity to assist in the symptomatic treatment of pain, promoting a considerable degree of comfort for the patient immediately after its application. The main advantage of laser applications in the treatment of TMD is that this type of therapy is non-invasive and low cost, and is currently widely used in dental clinics, reducing the demand for surgery or drugs in the treatment of pain relief and tissue regeneration. The application of laser therapy in patients with TMD has demonstrated the ability to relieve pain within minutes of its application, promoting significant well-being. Moreover, it is an adjuvant pain-relief treatment in which the analgesic action of the laser enables the patient to return to their duties, providing more comfort and a better quality of life. [5 6 22 25]

The occlusal splint is a device that is widely used in the treatment of TMD and pain control. The use of an occlusal splint led to improvement after one month and even decreased pain symptoms after one week of use. [27] Therapy with occlusal splints is the most widely used technique in dentistry for the treatment and control of pain in TMDs because it is considered to be a conservative and non-invasive treatment option.

Although clinical studies have been published that demonstrate the benefits of both Photobiomodulation treatment and occlusal splints for pain control, neither the cost of TMD in young patients nor the cost-utility of these two treatments has been established. Cost-utility analysis is a method used to compare the benefits and costs of a technology used in healthcare and the benefits are measured in life utility. [28]

Methods

Overview

The general purpose of this study is to evaluate the cost-effectiveness of Photobiomodulation therapy and occlusal splints in the treatment of pain in patients between 15 and 25 years of age with TMD. This is a controlled clinical study, and in search of greater transparency and quality of this research and Table 1 provides the enrollment, intervention and assessment schedule following SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) recommendations.

Table 1
Schedule of enrolment, interventions, and assessments of TMD Treatment

			STUDY PERIOD				
	Enrolment	Allocation	Post-allocation				Close-out
			0 Baseline	01 month	03 months	06 months	12 months
ENROLMENT:							
Eligibility screen	X						
Informed consent	X						
Allocation		X					
INTERVENTIONS:							
Photobiomodulation Therapy			x	x	x	x	x
Occlusal Splint			x	x	x	x	x
Placebo			x	x	x	x	x
ASSESSMENTS:							
Pain			x	x	x	x	x
Quality of life			x	x	x	x	x
Cost							x

* 0 = Baseline, t_1 = 01 month after the treatment, t_2 = 03 months after the treatment, t_3 = 06 months after the treatment, t_4 = 12 months after the treatment

This is a prospective study of clinical and cost approach. Activities will be conducted at the premises at the Clinic of the School of Dentistry of Universidade Nove de Julho (UNINOVE). The project will follow the regulatory standards for ethics research with humans and will be submitted to the Institutional Review Board of the university. Data collection will begin upon receipt of a favorable opinion and the signing of the informed consent form by the participants and/or their guardians.

Participants

Patients between 15 and 25 years of age selected at the Clinic of the School of Dentistry of Universidade Nove de Julho (UNINOVE) will participate in the study. One hundred and thirty five patients will be selected, following the sample calculation based on

studies with photobiomodulation treatment and occlusal splints, using the DINAM 1.0 program.

The sample size calculation was based on literature [29] and considering an average of VAS in improving pain, pre and post treatments. Being the level of significance (alpha) 5% with 80% power of the test, it was calculated 42 pacients per group. Thinking in the possibility of lost the pacients, the sample size for this study is 135 patients (45 per group). Only will be included in the sample, patients with a diagnosis of TMD in group Ia and Ib.

Patient and Public Involvement statement

The patients of three groups will be received standard information about the steps of research but they will not be involved in the recruitment and conduct of the study. Data collection will begin upon receipt of a favorable opinion and the signing of the informed consent form by the participants and/or their guardians.

Screening procedures

For a diagnosis of the TMD, the Research Diagnostic Criteria for Temporomandibular Disorders questionnaire (RDC/TMD) [30] will be applied before any intervention. In addition to the questionnaire, a specific clinical examination will be conducted, always by the same previously-trained evaluator, in which the patient will be positioned sitting in a chair, with their feet flat on the floor and the Camper plane parallel to the ground. The exam will consist of palpation of the temporalis, masseter, digastric, and medial pterygoid muscles, palpation of the TMJs, and analysis of mandibular movement, with use of a Digimess® digital pachymeter to measure the vertical and horizontal movements and a stethoscope to check for noises, as well as an investigation of frequent headaches, facial pain, tiredness and difficulty while chewing, bruxism, psychological aspects of adolescence, and para-functional habits. The RDC/TMD questionnaire will be responsible to indicate the diagnosis for myofascial TMD and clinical examination form analyzes the mandibular movements. The diagnosis of pain will be evaluated by the Visual Analog Scale (VAS) and quality of life will be determined by applying the adapted EuroQol-5D.

Pre-clinical trial

Inclusion Criteria: Young people between 15 and 25 years of age with a diagnosis of TMD in group Ia and Ib (Chronic myofascial pain in accordance with the RDC-TMD) will be included in the study.

Exclusion Criteria: Group II (disk displacement of the Temporomandibular joint) and group III (arthralgia, arthritis, arthrosis). Individuals with dental-facial anomalies who were in orthodontic or orthopedic treatment of the jaws or in psychological or physical therapy will be excluded. Individuals who were taking muscle relaxants or anti-inflammatory medications will also be excluded. These patients will be advised and referred for treatment, but will not participate in this study.

Randomization

Participants will be divided into 3 groups, as shown in Table 2.

Table 2. Distribution of participants into research groups

Control	Participants	Therapeutic Intervention
1	45	Photobiomodulation
2	45	Occlusal Splint
3	45	Placebo

For the random distribution of volunteers with TMD, will be use the randomized computer-generated list. At the beginning of the first evaluation of each patient, will received one number to determine to which group they will be allocated.

Procedures

The treatments' protocols of photobiomodulation and occlusal splint presented in this study are based on clinical trials [8 16 29 31].

The participants of three groups will be received standard information about TDM, the complex cause of the pain and the possible contributing factors. The patients will be counselling on avoid possibly stress-induced habits of grinding, clenching, nail biting or biting on objects like pencils, excessive gum chewing, biting and/or sucking on the lip or cheek, and pressing and/or sucking on the tongue [32].

The baseline of this study will be 02 weeks after the patients received standard information. After 2 weeks each treatment (G1, G2, G3) will be start; if the patient does not respond to treatment (nonresponder), this patients will be excluded from the research sample, but the researchers will be offered the alternative treatment method. The patients who do not respond will be treated according their needs with integral treatment (with psychologists, physiotherapists, and so on). As these data are very important, the number of patients withdrawn from the study will be computed and included in the intention to treat analysis (ITT). At the end of the research, all patients will be treated integrally to resolve the major cause that causes this disorder.

Treatment with Photobiomodulation

For the Photobiomodulation Therapy, a gallium-aluminum-arsenide (GaAIAs) laser, model Twin Flex Evolution ®, from MM Optics, will be used. The laser therapy sessions will be performed in a reserved room, annexed to the dental clinic offices, free from sound interference. At the time of application, only the volunteer to be treated and the professional responsible will be present, both wearing special glasses for eye protection. The tip of the laser will be coated with disposable transparent plastic (PVC) (to avoid cross-contamination and for reasons of hygiene) and the facial site to be irradiated will be cleansed with 70% alcohol. During the applications the patient will remain seated, with the Frankfurt plane parallel to the ground.

Twelve laser applications will be applied, with 2 sessions per week. A wave length of 780 nm, with an energy density of 25 J/cm2, a power of 50 mW and power density of 1.25 W/cm2, will be used for a duration of 20 seconds per point, resulting in a total energy of 1J per point. The laser will be applied at each point, using a conventional tip in contact with the skin, thus considering an area of 0.04 cm^2, in accordance with the protocol.[8 16 31] The laser will be applied to 3 points of the masseter muscle (upper, middle, and lower bundles) and 1 point in the anterior temporalis on each side of the face.[16 31]

The patients were called back for follow-up visits on 1, 3 ,6 and 12 months after the last day of photobiomodulation therapy.

Placebo group

For the placebo group, all the measures described for the group 1 (photobiomodulation) will be adopted, however the laser equipment will remain switched off. But the same sound of the equipment will be simulated and a guide light will be on. The placebo group will also have the same follow-up of visits that group 1.

Treatment with Occlusal Splints

The type of occlusal splint used in this study is Stabilization splint made in hard acrylic fabricated for the maxillary arch. The splints will be made following the principles established by literature.[1] Participants will be molded with alginate to obtain models. In the upper model, a 2 mm acetate splint will be made, to be later replaced with acrylic resin [33], and these splints will be adjusted in centric relation, to promote occlusal stability and disocclusion guide. [34] The group undergoing treatment with occlusal splints will be instructed to use the device during sleep, 8 hours per night. The splints will be check after 2 weeks of use and adjusted them, if needed. The patients will be asked to use the occlusal splints according mentioned and return 3 months after treatment. If in this return the patient did not respond to treatment (nonresponder), the researchers will be offer the alternate treatment method, but these patients will be excluded of the research sample. The respond patients will be continues to use the occlusal splint and return to the 06 months follow-up visit. [29]

Evaluation of pain

Muscle pain will be analyzed by clinical criteria of the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD). The clinical examination will be conducted periodically, and the parameters for analysis will be at intervals of 1, 3, 6 and 12 months. We will use a visual analogue scale (VAS) to assess pain level.

Evaluation of the impact of the treatment on quality of life

To assess the impact of treatment on the quality of life of the participants, the EQ-5D will be used, which is a generic instrument for assessing quality of life related to health, developed in Europe, translated and validated for several languages, including Portuguese. [35] Because it was developed for the purpose of determining a single cardinal indicator of the state of health, it can be used for both clinical evaluation and economic evaluation.

For this type of study, it is important that the instrument is short and simple, and represents dimensions relating to quality of life and health status.[36] Currently, the original version is called EQ-5D-3L, as another version, EQ- 5D-5L, was launched. EQ-5D-3L is composed of two stages, a questionnaire and a Visual Analogue Scale (VAS). The questionnaire contains five questions that evaluate the domains mobility, personal care, usual activities, pain or discomfort and anxiety/depression. For each question, patients are asked to select the option that best reflects their conditions, selecting from three alternatives. The first alternative indicates the absence of problems, the second indicates some problems, and the third, severe problems. The instrument will be applied at intervals of 1, 3, 6 and 12 months, when each group called back for follow-up visits. The responses will be compared intra-groups (same subject in the different intervals) and between groups.

Cost Analysis

This phase of the study will consist in the quantification of resources, i.e. determining the frequency of use of resources and materials during the treatment. It is a preliminary cost-effectiveness study, so we opted to analyze only direct costs. The units used to quantify the direct costs consumed are physical units such as consultation time, number of sessions, equipment used, and materials consumed. These data will be collected using a specific form. In this phase, the prospective method of quantification of resources will be used which, according literature [37], is a method that collects information on resources according to a prior plan, in conjunction with clinical study. The consumption is recorded as the actions occur. The resources will be assigned a value and the cost of each treatment determined for each participant and in each group studied, from the first visit to the start the treatment until the last follow-up visit.

Organization and statistical treatment of the Data

The numerical data are described by mean and standard deviation or median and interquartile range (IQR) when the distribution is not presented as normal. The categorical variables are described by means of absolute frequencies and percentages. The measure of outcome used in this study will be the cost ratio and the effectiveness evaluated by muscle pain reported by the patient.

Measurement of costs: Monetary Units (C)

Measurement of Effects (effectiveness): PAIN

Treatment groups: G1 (photobiomodulation), G2 (occlusal splint) and G3 (placebo).

Analyses: $(C_{G1}/PAIN_{G1}) - (C_{G2}/PAIN_{G2})$

CE (cost-effectiveness) = $(C_{G1} - C_{G2})/ (PAIN_{G1} - PAIN_{G2})$

The data will be tabulated and processed in SPSS for Windows. Descriptive statistics will be performed, for presentation of the distribution of the variables. To evaluate the association of categorical variables, the Chi-squared and Fisher's exact test will be used; for the comparison of means, the Student t-test and analysis of variance (ANOVA) will be used, and for the correlation analysis between continuous variables, Pearson's correlation test will be applied. If subjects fail to make a follow-up, we will use an intention-to-treat analysis. A t-test will be performed to compare the changes in measures within groups. A significance level of 95% ($p<0.05$) will be considered.

The study will follow the flow chart presented in Figure 1.

Discussion

The TMD is the most common orofacial pain and the Myogenic TMD is the frequent subtype. As TMD can be self-limiting, and the patient's complaints about: pain, loss of function and trismus, the TMD causes a decrease in quality of life. [38-40] Due of this, is very import to know how treatment (Occlusal Splint or Photobiomodulation Therapy) is more cost-effectiveness to TDM pain.

The Therapy with an occlusal splint is commonly used as a basic TMD treatment in the dental practice, because their manufacturing making is simple, have a low cost, are reversible and have obtain a high prevalence of outcome in the treatment of the most painful symptoms of TDM. [32 41]

Photobiomodulation therapy has been used to control pain in TMD and clinical studies have reported favorable results. [4-7 16-24 26] However, the relationship between the cost of treatment and its effectiveness has not been established in the literature. Clinical and economic data evaluated together can serve as a support for decision making in choosing a treatment or a new protocol to provide optimum conditions for affected patients.

TMD has a multifactorial etiology and is complex dysfunction, so, the goal of this study is to evaluate the control of chronic pain of myofascial muscle in each group analyzed and not to treat TMD.

Cost-effectiveness analysis has been used when costs are a crucial factor to choose certain product or technology. It has been considered the most suitable method to compare two or more alternatives regarding a new technology in health. Thus, in health, the economic analysis represents the evaluation of choice alternatives for allocation of resources. It has great importance, since it evaluates and compares alternatives and facilitates the use and a proper allocation of resources for spheres that may have greater benefits regarding reduction of morbidity costs or greater clinical effect. [42]

The development of a clinical and economic trial of treatments for control of muscle pain in patients with TMD provides relevant information for clinical decision making and choosing new care protocols for inclusion. Through this study, we hope to: Obtain data related to the direct costs of treatments with photobiomodulation therapy and occlusal splints in the treatment of muscle pain in patients with TMD. Determine the ratio between the cost and effectiveness of treatments, considering pain as the endpoint for measuring effectiveness, and define the impact of the treatments evaluated to the quality of life of patients with TMD.

Contributors:

Substantial contributions to the conception: A P T Sobral and L J Motta. Design of the work: C L H Godoy, A P T Sobral and L J Motta. Drafting the work: A P T Sobral and L J Motta. Revising the work: A P T Sobral, C L H Godoy, K P S Fernandes, S K Bussadori, R A M Ferrari, A C R T Horliana, S F Monken and L J Motta. Final approval of the work: S K Bussadori, K P S Fernandes, A P T Sobral and L J Motta.

Ethics approval and consent to participate: This study was approved the Nove de Julho University Ethics Committee - Protocol Number: 2.014.339. All participants will provide informed consent before participating in this study.

Availability of data and materials: Not appropriate. This paper is a protocol description and does not contain any data.

Competing interest: None declared. The authors have no conflict of interest, financial or otherwise to declare.

Data sharing statement: The original protocol and substantive amendments are available. These were available for the included authors and the local medical ethical committee.

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Figure 1 Flowchart of search strategy

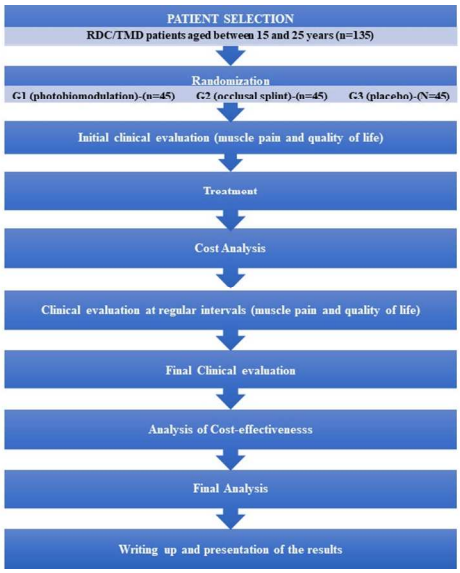

Figure 1 Flowchart of search strategy

108x60mm (300 x 300 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description	Addressed on 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	2
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	N/A
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	N/A
	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	N/A
	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)	N/A

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	2-3
	6b	Explanation for choice of comparators	2-3
Objectives	7	Specific objectives or hypotheses	2-3
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)	3-4
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	3-5
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)	8-9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	N/A
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
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	8-9
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)	6, Table 3

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	5, Table 2
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6, table 3
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	6
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	6
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	6
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	N/A
	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	N/A

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	N/A
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	9
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9
	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)	N/A
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	N/A
	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	N/A
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	N/A
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	11
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)	N/A

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	4
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	4
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	4
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	11
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	11
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	N/A
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	N/A
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
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	N/A

*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.