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TITLE: CRYOTHERAPY ASSOCIATED WITH TAILORED LAND-BASED EXERCISES FOR INDIVIDUALS WITH KNEE OSTEOARTHRITIS: A PROTOCOL FOR A RANDOMIZED TRIAL

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ABSTRACT

Introduction: There is an unmet need to develop new strength therapeutic exercises (STE) protocols using different treatment durations, frequencies, modalities, and intensities for individuals with knee osteoarthritis (KOA). Cryotherapy has been widely used as adjunct treatment for clinical improvement in individuals with KOA due its effects on pain and inflammation process. However, there are still disagreements in its recommendation by some prestigious KOA guidelines. The aim of this study was to verify the complementary effects of cryotherapy when associated with a STE protocol on patients with KOA. **Methods and analysis:** Placebo-controlled randomized trial with concealed allocation and intention-to-treat analysis. A baseline assessment will be performed before the 8-week intervention period, and a post-intervention assessment right after the last session. To check for residual effects of the interventions applied, a three- and a six-month follow-up will be performed. Participants will be people living in the community with KOA. There will be three groups: (1) the experimental group that will receive a tailored STE protocol and after, a cryotherapy session of 20 minutes; (2) the sham control group that will receive the same regimen but with sham packs filled with sand; and (3) the active treatment control group that will receive only the STE protocol. The primary outcome will be pain intensity according to a visual analogue scale. Secondary outcomes will be changes according to the Western Ontario & McMaster Universities Osteoarthritis; the Short-Form 36 questionnaire; the 30-Second Chair Stand Test; the Stair test; and the 40-meter fast paced walk test. **Ethics and dissemination:** The trial was approved by the Institutional Ethics Committee of Federal University of Sao Carlos, São Paulo, Brazil. Registration approval number: CAAE: 65966617.9.0000.5504. The results will be expected to be published in peer-reviewed journals.

Trial registration number: NCT03360500

Strengths and limitations of this study:

- The trial will be conducted following well-established reporting guidelines to improve the evidence synthesis regarding this topic. The methodology is designed to minimise bias by including concealed treatment allocation, and blinding of the outcome assessor and biostatistician.
- Participants will present radiographically confirmed knee osteoarthritis and a sufficient level of pain to ensure ample scope for improvement.
- The therapist who will deliver cryotherapy or the placebo intervention, and the patients will not be blinded. Although this may have resulted in bias, given the study design, a method of blinding patients and therapists to thermal agents has yet to be established.

Knee osteoarthritis (KOA) is a serious disease with a high societal and economic burden,[1] affecting approximately 250 million people worldwide.[2] Current clinical practice guidelines recommend a combination of pharmacological[3] and non-pharmacological[4] treatment strategies to manage KOA symptoms, and to improve patient's quality of life (QoL). However, pharmacological treatment options remain limited, poorly tolerated, with frequent toxicities,[5,6] and misused by patients.[7]

Physical Therapy, specifically the use of strength therapeutic exercises (STE) protocols, is a well-established treatment for KOA, since it can relieve pain, reduce stiffness, improve physical function, and ultimately ameliorate quality of life.[1,8] There is high-quality evidence demonstrating that the benefits of STE protocols for pain and quality of life are sustained for at least two to six months after the end of a treatment for individuals with KOA[8]. Therefore, there is no need for new studies to demonstrate the effectiveness of STE for KOA patients.[9] However, there is a call for further research to develop novel insights within STE protocols regarding different treatment durations, frequencies, modalities (types), and intensities.[10] The majority of the current protocols have low exercise adherence and are substantially under-utilized by KOA patients mainly due to their beliefs, socioeconomical barriers, fear of movement, and early treatment pain aggravation.[11,12] These barriers create an unmet need for science-based STE protocols that are tailored and cost-effective for KOA patients and that can help clinicians to target rehabilitation.

Associated with therapeutic exercises, many physical modalities such as thermal agents, laser therapy, therapeutic ultrasound, and electrical stimulation have been used as adjunct treatments for clinical improvement in individuals with KOA.[4,13] Cryotherapy, a non-pharmacological intervention, has been widely used in some rheumatic joint diseases[14,15] for its effects on pain,

inflammation and oedema.[16,17] It is considered safe, inexpensive, and easy to administer for healthcare professionals and patients. Moreover, it can be prescribed in isolation or as a complementary treatment[15], and seems to be well accepted by KOA individuals.[18,19] However, altough cryotherapy is recommended as a treatment option by some international KOA guidelines,[20,21] others found insufficient evidence to support it.[22–24] Mainly due to methodological limitations, relevant systematic reviews conclude that further trials are needed to evaluate cryotherapy effects on pain, function, and quality of life in individuals with KOA.[17,25,26]

In this study, we aim to design a randomized trial to verify the complementary effects of cryotherapy associated with a tailored STE protocol intervention for pain, function, and quality of life in individuals with KOA. The proposed trial will contribute with new evidence to target KOA rehabilitation, help pain management, and thereby improve physical function and quality of life of these patients. The STE protocol described on this study was developed by our research group and was also used in another randomized trial testing the complementary effects of low-level laser therapy in individuals with KOA (trial registration number: U1111-1215-6510).

METHODS

To report this study protocol, we followed the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT),[27] the Osteoarthritis Research Society International clinical trials recommendations: design, conduct and reporting of clinical trials for knee osteoarthritis,[28] and the Template for Intervention Description and Replication checklist (TIDieR).[29] The randomized trial developed using this protocol, will be reported according to the Consolidated Standards of

Reporting Trials (CONSORT) statement for randomized trials of non-pharmacologic treatments.[30] The trial is registered on clinicaltrials.gov (NCT03360500) platform.

Study design and setting

This will be a placebo-controlled randomized clinical trial. A baseline assessment (A1) will be performed on the weekday before the 8-week intervention period, and a post-intervention assessment (A2) right after the last session. To check for residual effects of the interventions, a three-month (A3) and six-month (A4) follow-up assessment will be performed. Each patient will be assessed in the same period of the day in a physiotherapy research laboratory by the same assessor. To reduce bias, the therapists responsible for applying the intervention and the outcomes assessor will follow standardized scripts to give explanations regarding the general objective of the study.[28] Moreover, prior to the beginning of the study, the therapists responsible for the intervention will participate in a 10-hour training module, which will consist of scientific information and clinical training regarding KOA, the STE protocol, and the use of the cryotherapy. Intervention adherence, medication intake and adverse events will be tracked with an 8-week assessment diary given to the participants at baseline assessment and with a 12-week assessment diary for the three-month follow-up assessment. All the participants will be advised to not practice any other type of regular physical exercises during the study protocol that could interfere with the STE protocol. A verbal and written explanation of the objectives and methodology of the study will be provided to all the participants, and those willing to participate will sign a written informed consent form, approved by the local ethics committee. A detailed timeline of the trial is presented on **Table 1**.

Patient and Public Involvement

The patients and public were not involved in planning and design of this study.

Participants

Participants will be recruited through public announcements on social media, advertisements via local news, University community newsletters, and banners or leaflets posted at strategic locations at the city. People who express interest in participating in the study will undergo first a screening process to check eligibility criteria, and after a lateral, anteroposterior, and axial radiography of both knees to determine KOA severity. All individuals will be classified with KOA based on the clinical and radiographic criteria of the American College of Rheumatology.[31] Participants will be required to have symptoms and a radiographic grade (Kellgren and Lawrence scale) of ≥2 (at least mild radiographic OA) in at least one knee compartment.[28] To be included in the study, participants will also need to: be aged between 40 and 75 years; be engaged in less than 45 minutes/week in accumulated physical activity of at least moderate intensity[32]; have a body mass index <35 kg/m^2; and pain intensity in the prior week of ≥4 cm on a 10-cm visual analogue scale.[28] Exclusion criteria will comprise: physical therapy in the prior 3 months; intra-articular knee injections in the prior 6 months; medical restrictions such as cardiorespiratory, neurological or any other rheumatology conditions; previous hip, knee or ankle surgery; and any other chronic condition that leads to chronic pain or dysfunction. All the participants will be asked to provide a medical certificate stating to be healthily able to perform physical activities.

Interventions

The interventions will be administered by physical therapists in the physiotherapy clinic of the university. The sessions will last 90-minutes and will take place over a period of eight weeks, three times per week in nonconsecutive days, totaling 24 sessions. All the participants will perform the STE protocol and after, according to the random allocation, cryotherapy or sham will be administered in individual rooms for each patient.

STE protocol

The 8-week land-based supervised exercise protocol was designed according to the recommendations and guidelines of evidence-based practices and specific randomized clinical trials of physical exercise intervention for KOA.[33,34] The STE protocol characteristics are described in **Figure 1** and a detailed description of all the exercises is presented in the **Supplementary file** of this protocol. The protocol is divided into two cycles. Each cycle consists of 4 weeks of progressive exercises, with tailored intensity for each participant, that is performed 3 times per week in non-consecutive days, with 24 hours rest between sessions. The first session is used to demonstrate and explain the STE protocol, and to perform an exercise familiarization using no loads by the participants. The second session is destined to estimate the initial resistance of each participant for each exercise. The volitional interruption method is used in order to achieve the benefits of a resistance training and to provide a low risk of musculoskeletal injuries to the participants. [35] The loads are gradually increased until the participant is able to adequately perform 12 repetitions with no voluntarily interruption due to muscle fatigue.

The STE protocol sessions consist of three phases. The first phase is a 10-minute warm-up in which the patients can choose, according to their preferences, to walk in a comfortable intensity in

an outdoor circuit, treadmill or ride in a stationary bicycle. The second phase consists of 40 minutes of strengthening exercises (resistance training), such as lower limb, trunk muscles, and neuromuscular training involving balance exercises. The third phase is a cool-down phase, consisting of static stretching exercises to potentially reduce musculoskeletal injuries and to maximize the benefit of the STE protocol.[36] To ensure patient safeness, cardiac and respiratory frequencies and blood pressure are monitored at the beginning of each session or if the participant presents an intense rate of perceived exertion according to the Borg scale while performing an exercise.[37,38]

Cryotherapy protocol

To apply cryotherapy, the therapist will explain to the patient that the intervention will consist of crushed ice applied to the more-affected knee for 20 minutes. Participants will be positioned in dorsal decubitus with both legs extended and relaxed. To protect the skin from possible frostbite, the entire knee surface will be covered with a moist surgical gauze (45 × 50 × 0.01 cm). Next, two plastic bags (24 × 34 × 0.08 cm), each containing 1 kg of crushed ice, will be placed on the knee, covering the anterior, posterior, medial and lateral surfaces. A comfortable, non-painful compression will be applied over the ice packs by wrapping an elastic bandage around them, and the therapy will be left in situ for 20 uninterrupted minutes. The main purposes of compression is to maintain the ice packs in position on the knee[39] and to enhance cryotherapy effects.[40]

For the cryotherapy sham intervention, the bags will be filled with 1 kg of dry sand instead of ice. The sand bags will be applied according to the same regimen in the same locations. The therapist's explanation about the intervention will be changed to mention 'application of sand packs' instead

of 'cryotherapy application'. The sand packs will be applied with the same gauze underneath and the same bandage for compression.

Outcome measures

All the outcomes will be measured by the same blinded assessor before and after the intervention, and at the 3- and 6-month follow-up periods. **Table 2** describes the main outcome measures that will be included on the trial and the recommended estimate of the minimum clinically important difference (MCID) for each outcome measure. We will measure pain intensity, knee subjective and objective physical function, and quality of life.

Primary outcome

The primary outcome will be pain intensity at rest assessed with a visual analogue scale. This self-reported pain score is a valid and reliable measure for KOA.[41] The visual analogue scale will be administered at baseline, on the final assessment day, and at the 3- and 6-months follow-up periods.

Secondary outcomes

To subjectively assess physical function and associated problems the Western Ontario & McMaster Universities Osteoarthritis (WOMAC) will be used. The Short-Form 36 (SF-36) questionnaire will be used to asses quality of life. Three objective physical function tests will also be used: The 30-Second chair stand test, the stair test, and the 40-meter fast paced walk test.

Randomization

Eligible patients who consent to participate will be randomly allocated into 3 groups of 40: (1) active control group that will receive the STE protocol only, (2) STE + cryotherapy group, and (3) STE + sham cryotherapy group. Random allocations will be determined by a computer-generated random numbers program and matched for gender (20 men and 20 women in each group). Allocation will be concealed, and the random allocations will be placed in opaque sealed envelopes that will be locked in a central location. Each participant's random allocation will be revealed just before the intervention start.[28]

Sample size

We aimed to detect a minimum clinically important differences (MCID) of 1.75 cm units on the visual analogue scale.[42] In addition, we aimed to detect an MCID of 30 points on the WOMAC global score.[43] Calculations were based on an analysis of covariance adjusting for baseline outcome scores, assuming between-patient standard deviations of 2.0 cm for pain and 45 points for WOMAC global score. Based on these criteria, to achieve a significance level of 0.05 and a power of 0.80%, 37 participants with KOA were required in each group. To allow possible dropouts during the intervention period, 40 participants were recruited per group.

Data analysis

The analyses will be performed by a blinded biostatistician using commercial software. The Kolmogorov-Smirnov test will be applied to evaluate the normality of data distribution. If the distribution is not normal, non-parametric tests will be used. For normal distributions, a 2-factor analysis of variance (ANOVA) will be conducted for the primary outcome (visual analogue scale

for pain) and secondary outcomes, with time (baseline, post-intervention, and follow-up) as the within-subject factor and group (STE, STE + cryotherapy, STE + sham cryotherapy) as the between-subject factor. In addition, tukey's test will be used for post-hoc analysis when necessary and an intention-to-treat analysis will be performed for all randomized participants. All the missing data will be replaced using the expectation maximization method. Between-group differences and their 95% confidence intervals will be reported and interpreted against the nominated thresholds for MCID. For outcomes where the MCID are not nominated, Cohen's *d* coefficient will be calculated to aid interpretation. An effect size greater than 0.8 will be considered large, around 0.5 moderate, and less than or equal to 0.2, small[44].

ETHICS AND DISSEMINATION

All participants will provide written informed consent following verbal and written explanation of the study protocol and the opportunity to ask questions. Participants are free to withdraw from the trial at any time without prejudice to future treatment. Results will be presented at scientific meetings and published in peer-reviewed journals. All publications and presentations related to the study will be authorized and reviewed by the study investigators.

TRIAL STATUS

The trial is currently recruiting and is expected to be completed (including follow-up testing) by June 2020.

AUTHORS CONTRIBUTION

L.O.D., A.E.S.J., P.R.S., F.A.S., and T.F.S. designed the study protocol. L.O.D. wrote the first draft of the manuscript and together with A.E.S.J., P.R.S., F.A.S., and T.F.S. revised and produced the final version. All authors have read and approved the final version of the manuscript. L.O.D. takes responsibility for the integrity of the work as a whole.

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DISCLAIMER

The study funders have had no role in study design; collection, management, analysis and interpretation of data; writing of the report; or the decision to submit the report for publication, and do not own ultimate authority over any of these activities.

COMPETING INTERESTS

All authors have completed a uniform disclosure form and declare no conflicts of interest

ETHICS APPROVAL

The trial was approved by the Institutional Ethics Committee of Federal University of Sao Carlos, São Paulo, Brazil. Registration approval number: CAAE: 65966617.9.0000.5504. All participants will be asked to give written informed consent before data collection began. The trial will be conducted according to the Helsinki Statement.

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Figure 1 Legend: Land Based Exercise Protocol Characteristics

Table 1.
Detailed timeline of the measurements to be taken at each point on the trials

	TIMELINE	Enrolment	STE protocol training	Baseline assessment (A1)	Intervention	Post-intervention assessment (A2)	Follow-up assessment (A3)	Follow-up assessment (A4)
		-2 weeks (-14 to -7 day)	-1 week (-7 to 0 day)	Day 0		8 weeks (±3 days)	20 weeks (±3 days)	32 weeks (±3 days)
Enrolment	Eligibility screen	**X**						
	Informed consent	**X**						
Interventions	Allocation			**X**				
	STE				**X**			
	STE + cryotherapy				**X**			
	STE + sham cryotherapy				**X**			
	X-ray examination of both knees	**X**						
Assessments	VAS			**X**		**X**	**X**	**X**
	WOMAC			**X**		**X**	**X**	**X**
	KOOS			**X**		**X**	**X**	**X**
	SF-36			**X**		**X**	**X**	**X**
	Timed-up and Go Test			**X**		**X**	**X**	**X**
	30-Second Chair to Stand Test			**X**		**X**	**X**	**X**
	Stair Climb Test			**X**		**X**	**X**	**X**
	40m (4x10m) Fast Paced Walk Test			**X**		**X**	**X**	**X**

STE: Strength Therapeutic Exercises; VAS: Visual Analogue Scale, WOMAC: Western Ontario & McMaster Universities Osteoarthritis questionnaire; KOOS: Knee Injury and Osteoarthritis Outcome Score; SF-36: Short Form-36 questionnaire.

A: Assessment

Table 2.

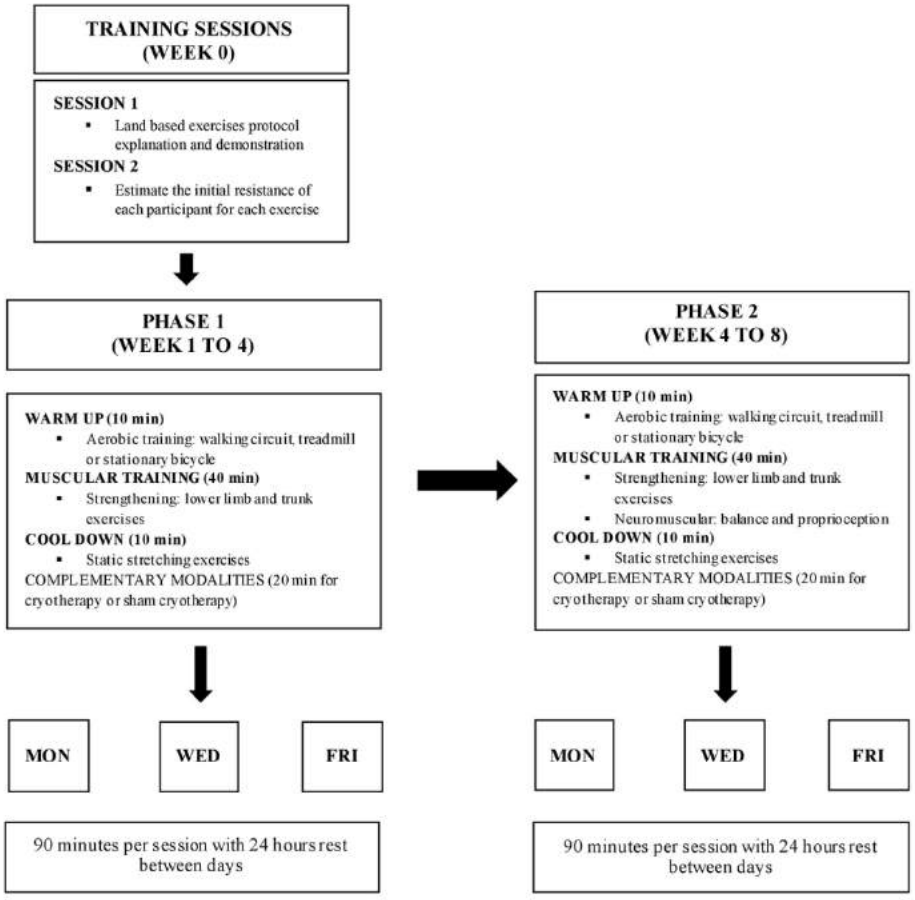
Detailed description of the study's outcome measures.

Outcome measure	Description of the test	Scoring	Minimum clinically important difference
Visual analogue scale	The scale is placed in front of the patient who is asked to rate their pain intensity in the prior week.[41]	The scale ranges from 0 (no pain) to 10 cm (maximum pain intensity).	A pain reduction of 1.75 cm is recommended in OA research.[42]
Western Ontario & McMaster Universities Osteoarthritis questionnaire	This self-report questionnaire assesses the problems experienced by people with lower limb OA in the prior 72 hours. It contains 24 questions in 3 domains: pain, stiffness and physical function.	Each question is scored from 0 to 4. The maximum score is 96. High scores indicate worse status.	An improvement of 12% from baseline is recommended in OA research.[45]
Knee Injury and Osteoarthritis Outcome Score	This self-report questionnaire assesses the problems experienced by people with lower limb OA in the prior week, by measuring quality of life and knee function. It contains 42 questions in 5 domains: pain; other symptoms; function in daily life; sports-related function and recreation; and knee-related quality of life.	The answers are standardised and scored from 0 to 4. The total score is 168. High scores indicate worse status.	A difference of 8 to 10 in the total score is recommended in OA research.[46]
Stair Climb Test	The participant is positioned in front of the stairs and, at the therapist signal, he/she has to climb the indicated steps (we used the 12-step SCT) and descend promptly, being able to use the handrail as a security instrument. We used 20 cm steps height, a handrail stair in an illuminated environment, free of traffic or external distractions. Moreover, a pre-test was conducted to identify the need for safety measures.	The final score was calculated based on the time the participant took to perform the test and compared to the normative values available for the test.	A reduction of 5.5 seconds in the test is the recommended MCID in OA research[47]
40m (4x10m) Fast Paced Walk Test	Administered at a distance of 10 meters (marked by tapes), a cone is placed 2 meters before the start and 2 meters after the end of each marking. The participant is instructed to walk as quickly but as safely as possible the first 10 meters (from the start mark), to turn around in the cone and walk back the 10 meters again, successively until completing the distance of 40 meters.	Speed (m/s)	An increase of 0.2-0.3 meters per second in the test is the recommended MCID in OA research[47]
30-Second Chair to Stand Test	A chair with no arms is placed against a wall to prevent oscillations. Patients sit in the middle of the chair, with their back straight and feet resting on the floor in line with their shoulders. The participant is asked to rise from sitting to standing as many times as possible in 30 seconds.	Total number of repetitions within 30 seconds	An increase of 2 to 3 repetitions is recommended in OA research.[48]

OA: osteoarthritis

Figure 1

Legend: Land Based Exercise Protocol Characteristics



Land Based Exercise Protocol Characteristics

107x139mm (300 x 300 DPI)

SUPPLEMENTARY FILE

Land-Based Exercises Protocol for Patients with Knee Osteoarthritis

Warm-up Phase (10 min)



Description: treadmill, stationary bicycle, or walking.
Performed in a comfortable cardiorespiratory intensity aiming the joints mobility.

Cool-down Phase (10 min)

Description: Quadriceps stretching.
Active stretching performed with maximum tolerable range of motion.

Set: 1 x 30 seconds

Description: Gastrocnemius stretching.
Active stretching performed with maximum tolerable range of motion.

Set: 1 x 30 seconds


Description: Hamstrings stretching.
Active stretching performed with maximum tolerable range of motion.

Set: 1 x 30 seconds

SUPPLEMENTARY FILE

Conditioning PHASE 1

A	B
	
	
	
	
	

Name: Bridge
Type: isometric
Position A: lie down on the mat, knees pointing to the ceiling, knees aligned with hips.
Position B: raise your hips up toward the ceiling and hold for 15 up to 30 s.
Sets: 3 x 15-30 seconds

Name: Straight Leg Raise (SLR) – hip flexion
Type: Isotonic
Position A: lie down, one leg bent and another straight, pull up your foot.
Position B: raise your leg straight up until it is aligned with the other thigh, then slowly lower it down.
Sets: 3
Repetitions: 12

Name: SLR – hip abduction
Type: Isotonic
Position A: side lying position, bend the knee in contact with the floor and straight the other leg.
Position B: raise your leg straight up, kneecap pointing forward, pulling up your foot.
Sets: 3
Repetitions: 12

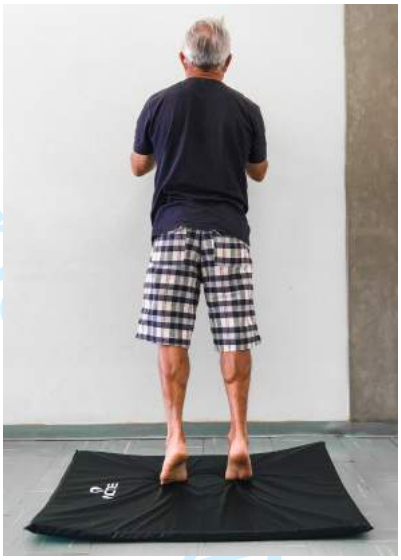
Name: SLR – hip adduction
Type: Isotonic
Position A: side lying position, leg in contact with the floor straight and the other leg bent.
Position B: raise your leg straight up, kneecap pointing forward, pulling up your foot.
Sets: 3
Repetitions: 12

Name: SLR – hip extension
Type: Isotonic
Position A: prone position, both legs straight touching the floor.
Position B: raise one leg up at a time, keeping the totally knee straight.
Sets: 3
Repetitions: 12

SUPPLEMENTARY FILE

A

B



Name: Abdominal curls (crunchs)
Type: Isotonic
Position A: lie down on the mat, place your hands behind your head, bend your knees and keep them aligned with hips.
Position B: as you exhale, slowly lift your chest up; as you inhale, slowly lower your chest down. Avoid bringing your chin to your chest.
Sets: 3
Repetitions: 12

Name: Standing calf raises
Type: Isotonic
Position A: Standing on both legs, hands on the wall for balance (if needed).
Position B: rise up on toes then slowly lower down.
Sets: 3
Repetitions: 12

Conditioning PHASE 2

A

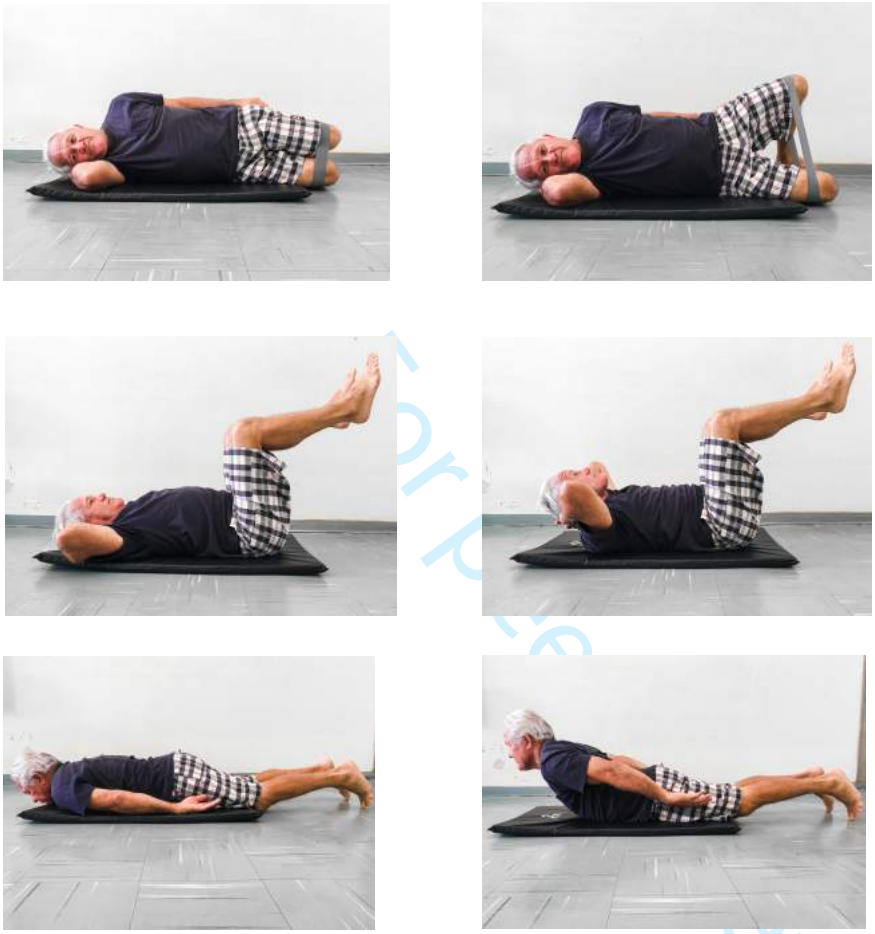
B

Name: Plank
Type: Isometric
Position A: lying on your belly (prone position).
Position B: lift your entire body up with elbow and feet supports. Hold for 15 up to 30 seconds.
Sets: 3 x 15-30 seconds

Name: Bridge with one leg
Type: Isometric
Position A: lie down on the mat, knees pointing to the ceiling, knees aligned with hips.
Position B: raise your hips up toward the ceiling then carefully take one leg off the floor. Hold for 15 up to 30 s.
Sets: 3 x 15-30 seconds

SUPPLEMENTARY FILE

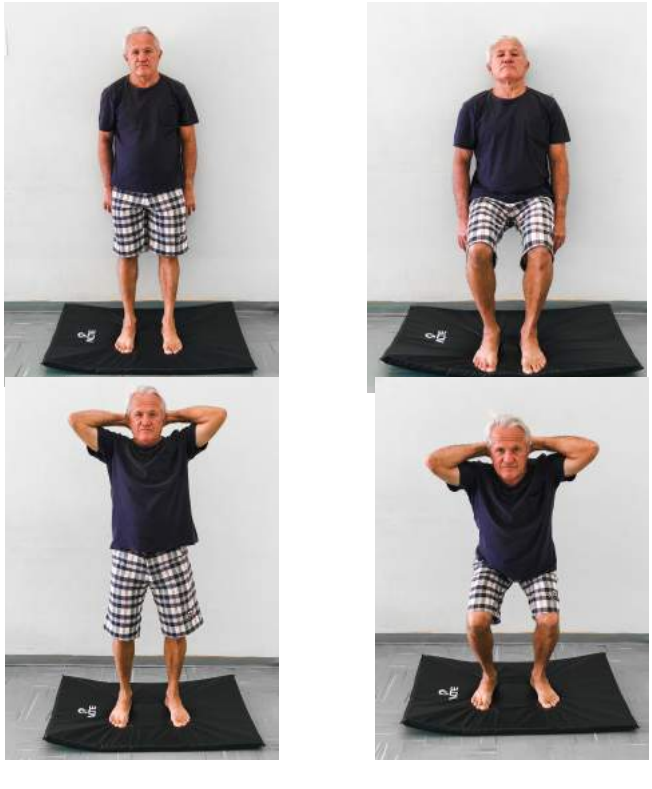
A **B**



Name: Clam shell
Type: Isotonic
Position A: side lying position, elastic band around your thighs, knees bent.
Position B: move your knee away, squeezing your buttocks then slowly return. Repeat with the other side/leg.
Sets: 3
Repetitions: 12

Name: Abdominal curls with lifted legs
Type: Isotonic
Position A: lie down on the mat, place your hands behind your head, bend your knees and keep them aligned with hips. Lift both legs up.
Position B: as you exhale, slowly lift your chest up; as you inhale, slowly lower your chest down. Avoid bringing your chin to your chest.
Sets: 3
Repetitions: 12

Name: Trunk extension
Type: Isometric
Position A: lying on your belly (prone position).
Position B: move your chest away from the floor. Look at the ground. Hold for 30 seconds at least.
Repetitions: 3 x 30 seconds



Name: Wall squat
Type: Isometric contraction
Position A: stand with your trunk to a wall, feet aligned with knees and hips, and away from the wall.
Position B: slide down and keep your trunk towards the wall. Hold for 30 seconds up to one minute.
Repetitions: 3

Name: Partial squat
Type: isotonic contraction
Position A: standing on both legs.
Position B: slowly bend your knees and stand up again. Maintain your knees over your feet.
Repetitions: 3

SUPPLEMENTARY FILE

A	B	
		**Name: Standing hip abduction.** **Type:** static balance **Position A:** standing on both legs with an elastic band around both legs. **Position B:** lift one leg out, maintain the kneecap pointing forward, and hold for 30 seconds or more. **Repetitions:** 3 (each leg)
		**Name: Standing on one leg** **Type:** static balance on stable surface **Position A:** standing on both legs, eyes opened. **Position B:** standing on one leg, knee slightly bent, lift the other leg off the floor and maintain the position up to 1 minute. **Repetitions:** 2 (each leg)
		**Name: Standing on one leg** **Type:** static balance on unstable surface (trampoline, foam etc) **Position A:** standing on both legs, eyes opened. **Position B:** standing on one leg, remove another leg from ground and maintain the position. **Repetitions:** 2 (each leg)
		**Name: Step-up** **Type:** isotonic contraction **Position A:** on leg onto a step. **Position B:** step up onto the next step, use the wall for balance if needed. Step back down carefully to the position A. **Sets:** 2 (each leg) **Repetitions:** 12

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
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym **– PAGE 01**
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry **– PAGE 02**
	2b	All items from the World Health Organization Trial Registration Data Set **- N/A**
Protocol version	3	Date and version identifier **- N/A**
Funding	4	Sources and types of financial, material, and other support - **PAGE 14**
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors **– PAGE 01**
	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 **– PAGE 4-6**
	6b	Explanation for choice of comparators **– PAGE 4-6**
Objectives	7	Specific objectives or hypotheses **– PAGE 4-6**

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) **– PAGE 6**
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 **– PAGE 6**
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) **– PAGE 7**
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered **– PAGE 8-10**
	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) **– PAGE 8-10**
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) **– PAGE 8-10**
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial **– PAGE 8-10**
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 **– PAGE 11**
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) **– PAGE 21**
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 **– PAGE 12**
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size **– PAGE 7**
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 **– PAGE 11,12**
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 **– PAGE 11,12**
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions **– PAGE 11,12**
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how **– PAGE 8, 9, 11, 12**
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial **– PAGE 8, 9, 11, 12**
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 **– PAGE 12, 13**
	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 **– PAGE 12, 13**
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 **– PAGE 12, 13**
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 **– PAGE 12, 13**
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) **– PAGE 12, 13**
	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) **– PAGE 12, 13**

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 **– PAGE 5-7**
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 **– PAGE 5-7**
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor **– PAGE 5-7**

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval **– PAGE 13, 14**
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) **– PAGE 13, 14**
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) **– PAGE 13, 14**
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable **N/A**
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 **– PAGE 06, 07**
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site **– PAGE 14**
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 **N/A**
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 **– PAGE 13, 14**
	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 **– PAGE 13, 14**
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.

BMJ Open

CRYOTHERAPY ASSOCIATED WITH TAILORED LAND-BASED EXERCISES FOR KNEE OSTEOARTHRITIS: A PROTOCOL FOR A RANDOMIZED TRIAL

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Primary Subject Heading:	Rheumatology
Secondary Subject Heading:	Rheumatology, Rehabilitation medicine
Keywords:	PAIN MANAGEMENT, REHABILITATION MEDICINE, PUBLIC HEALTH

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TITLE: CRYOTHERAPY ASSOCIATED WITH TAILORED LAND-BASED EXERCISES FOR KNEE OSTEOARTHRITIS: A PROTOCOL FOR A RANDOMIZED TRIAL

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ABSTRACT

Introduction: There is an unmet need to develop tailored therapeutic exercise protocols applying different treatment parameters and modalities for individuals with knee osteoarthritis (KOA). Cryotherapy is widely used in rehabilitation as an adjunct treatment due to its effects on pain and the inflammatory process. However, disagreement between KOA guidelines remains with respect to its recommendation status. The aim of this study is to verify the complementary effects of cryotherapy when associated with a tailored therapeutic exercise protocol on patients with KOA.

Methods and analysis: This study is a placebo-controlled, randomized trial with concealed allocation and intention-to-treat analysis. Assessments will be performed at baseline and immediately following the intervention period. To check for residual effects of the interventions applied, three- and six-month follow-up assessments will be performed. Participants will be community members living with KOA. There will be three groups: (1) the experimental group that will receive a tailored therapeutic exercise protocol followed by a cryotherapy session of 20 minutes; (2) the sham control group that will receive the same regimen as the first group, but with sham packs filled with dry sand; and (3) the active treatment control group that will receive only the therapeutic exercise protocol. The primary outcome will be pain intensity according to a Visual Analogue Scale. Secondary outcomes will be the Western Ontario & McMaster Universities Osteoarthritis Index; the Medical Outcomes Survey Short-Form 36 questionnaire; the 30-Second Chair Stand Test; the Stair Climb test; and the 40-Meter fast-paced walk test.

Ethics and dissemination: The trial was approved by the Institutional Ethics Committee of Federal University of Sao Carlos, São Paulo, Brazil. Registration approval number: CAAE: 65966617.9.0000.5504. The results will be published in peer-reviewed journals.

Trial registration number: NCT03360500

Strengths and limitations of this study:

- The trial will be conducted according to well-established reporting guidelines.
- Participants will present with radiographically confirmed knee osteoarthritis and a sufficient level of pain to ensure ample scope for improvement.
- The trial will use both subjective and objective outcome measures.
- The therapist who delivers cryotherapy or the placebo intervention and the patients will not be blinded.
- The loss to follow-up after randomization in the placebo group might be higher than those in the other groups.

Knee osteoarthritis (KOA) is a serious disease with a high societal and economic burden,[1] affecting approximately 250 million people worldwide.[2] Current clinical practice guidelines recommend a combination of pharmacological[3] and non-pharmacological[4] treatment strategies to manage KOA symptoms and improve patients' quality of life. However, pharmacological treatment options that have been proven to relieve symptoms remain limited, and some of the most commonly recommended pharmacologic treatments are poorly tolerated, with long-term use resulting in serious systemic adverse events.[5–7]

Physical Therapy, specifically the use of strengthening therapeutic exercise (STE) protocols, have been shown to relieve pain, reduce stiffness, increase physical function, and improve quality of life in patients with KOA.[1,8] High-quality evidence has demonstrated that the benefits of STE protocols on pain and quality of life in individuals with KOA are sustained for at least two to six months after the end of a treatment.[8] There is, however, a call for further research to develop novel insights within STE protocols regarding differences in treatment durations, frequencies, modalities, and intensities.[9] The majority of current protocols have reported low adherence and are substantially under-utilized by KOA patients, mainly due to socioeconomic barriers, personal beliefs, fear of movement, and aggravation of pain in the early phases of treatment.[10,11] Therefore, there is an unmet need for cost-effective, evidence-based STE protocols that are tailored to the needs of KOA patients, and that can aid clinicians in targeting rehabilitation goals.

Physical modalities such as thermal agents, laser therapy, therapeutic ultrasound, and electrical stimulation are often used as adjunct treatments with therapeutic exercises in individuals with KOA.[4,12] Cryotherapy, a non-pharmacological intervention, has been widely used in some

rheumatic joint diseases[13,14] based on its effects on pain, inflammation, and edema.[15,16] The intervention is considered safe, and is inexpensive and easy to administer for healthcare professionals and patients. Moreover, it can be prescribed in isolation or as an adjunct treatment and seems to be well accepted by individuals with KOA.[14,17,18] Although cryotherapy is recommended as a treatment option by some international KOA guidelines,[19,20] others have found insufficient evidence to support it.[21–23] Relevant systematic reviews have likewise concluded that further evidence, produced with greater methodological rigor, is needed to evaluate the effects of cryotherapy on pain, function, and quality of life in individuals with KOA.[16,24]

In this study, we aim to design a randomized trial to verify the complementary effects of cryotherapy in conjunction with a tailored STE protocol on pain, function, and quality of life in individuals with KOA. We hypothesize that cryotherapy combined with the STE protocol will achieve better treatment effects on KOA patients when compared to the other two groups. The proposed trial will contribute new evidence to the Physical Therapy field in KOA by focusing on interventions that target rehabilitation and enhance pain management, thereby improving the physical function and quality of life of these patients. Our research group developed the STE protocol described in this study. The protocol was also used in another randomized trial testing the complementary effects of Photobiomodulation in individuals with KOA (trial registration number at www.ensaiosclinicos.gov.br: U1111-1215-6510). This manuscript has been submitted simultaneously with the manuscript entitled "Photobiomodulation therapy associated with supervised therapeutic exercises for people with knee osteoarthritis: a protocol for randomized trials" (ID bmjopen-2019-035711).

METHODS

To report this study protocol, we followed the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT),[25] the Osteoarthritis Research Society International clinical trials recommendations: design, conduct, and reporting of clinical trials for knee osteoarthritis,[26] and the Template for Intervention Description and Replication checklist (TIDieR).[27] The randomized trial will be reported according to the Consolidated Standards of Reporting Trials (CONSORT) statement for randomized trials of non-pharmacologic treatments.[28] The trial is registered on the clinicaltrials.gov (NCT03360500) platform.

Study design and setting

This study is a single-center, placebo-controlled randomized clinical trial. A baseline assessment (A1) will be performed on the weekday before the 8-week intervention period, and a post-intervention assessment (A2) will be performed immediately following the last session. To check for residual effects of the interventions, three-month (A3) and six-month (A4) follow-up assessments will be performed. Each patient will be assessed in a physiotherapy research laboratory, during the same period of the day and by the same assessor. To reduce bias, the therapists responsible for applying the intervention and the outcome assessors will follow standardized scripts that describe the general objective of the study.[26]

Intervention adherence, medication intake, and adverse events will be tracked with an 8-week assessment diary that will be given to participants at the baseline assessment and with a 12-week assessment diary for the three-month follow-up assessment. All the participants will be advised not to practice any other type of regular physical exercise during the course of the study that could

interfere with the STE protocol. A verbal and written explanation of the objectives and methodology of the study will be provided to all the participants, and those willing to participate will sign a written informed consent form, approved by the local ethics committee. A detailed timeline of the trial is presented in **Table 1**.

Patient and Public Involvement

The patients and the public were not involved in the planning and design of this study.

Participants

Participants will be recruited through public announcements on social media, advertisements via local news outlets, University community newsletters, and banners or leaflets posted at strategic locations in the city. People who are interested in participating in the study will first be screened to check the eligibility criteria. Eligible participants will then undergo a lateral, anteroposterior, and axial radiography of both knees to determine KOA severity, which will take place at the University Hospital. Participants will be classified with KOA based on the clinical and radiographic criteria of the American College of Rheumatology,[29] and will be required to have symptoms and a radiographic grade (Kellgren and Lawrence scale) of ≥2 (mild radiographic OA) in at least one knee compartment.[26]

To be included in the study, participants will also need to: be between 40 and 75 years old; be engaged in a total of less than 45 minutes/week of physical activity of at least moderate intensity[30]; have a body mass index <35 kg/m^2; and to have reported pain intensity in the prior week of ≥4 cm on a 10-cm visual analogue scale.[26] Exclusion criteria will comprise physical therapy in the prior

three months; intra-articular knee injections in the prior six months; medical restrictions such as cardiorespiratory, neurological, or any other rheumatology conditions; previous hip, knee, or ankle surgery; and any other chronic condition that leads to chronic pain or dysfunction. Additionally, participants presenting with contraindication(s) to cryotherapy application (i.e., those that feel a high level of discomfort or pain during the application) will be excluded.

All the participants will be asked to provide a medical certificate stating that they are healthy enough to perform physical activities before the start of the intervention.

Interventions

Two physical therapists will administer the interventions in the physiotherapy clinic of the University. The study will take place over the course of eight weeks, with three 90-minute sessions per week occurring on non-consecutive days, for a total of 24 sessions. All randomized participants will perform the STE protocol and then, according to random allocation, each patient will subsequently receive either cryotherapy or sham interventions in individual rooms.

Prior to the beginning of the study, the therapists responsible for the interventions will participate in a 10-hour training module, which will consist of scientific information and clinical training regarding KOA, the STE protocol, and the use of cryotherapy. After the first training module is completed, the therapists will do an eight-week training module, which will consist of practicing the full-length protocol and intervention application(s) three times per week. Both therapists will be responsible for delivering cryotherapy and sham interventions.

STE protocol

We designed the 8-week land-based supervised exercise protocol according to the evidence-based recommendations for physical exercise interventions in KOA.[31,32] The STE protocol characteristics are described in **Figure 1,** and a detailed description of all the exercises is presented in the **Supplementary file** of this protocol. The protocol is divided into two phases. Each phase consists of 4 weeks of progressive exercises, performed three times per week on non-consecutive days (24 hours rest between sessions), with exercise intensity individually tailored for each participant. The first session is used to demonstrate and explain the STE protocol, and to perform an exercise familiarization using no loads by the participants. The second session is designed to estimate the initial resistance of each participant for each exercise. The volitional interruption method is used in order to achieve the benefits of resistance training and to reduce the risk of musculoskeletal injuries to the participants.[33] The loads are gradually increased until the participant can adequately perform 12 repetitions with no voluntary interruption due to muscle fatigue.

The STE protocol sessions consist of three phases. The first phase is a 10-minute warm-up in which the patients can choose, according to their preferences, to walk in a comfortable intensity in an outdoor circuit, treadmill, or ride in a stationary bicycle. The second phase consists of 40 minutes of strengthening exercises (resistance training), such as a lower limb and trunk muscles, and neuromuscular training involving balance exercises. The third phase is a cool-down phase, consisting of static stretching exercises to reduce the risk of musculoskeletal injuries and to maximize the benefit of the STE protocol.[34] Cardiac and respiratory frequencies and blood pressure are monitored at the beginning of each session or if the participant presents an intense

rate of perceived exertion according to the Borg scale while performing an exercise, to ensure patient safety.[35,36]

Cryotherapy protocol

To apply cryotherapy, the therapist will explain to the patient that the intervention will consist of crushed ice applied to the more-affected knee for 20 minutes. Participants will be positioned in dorsal decubitus with both legs extended and relaxed. The entire knee surface will be covered with a moist surgical gauze (45 × 50 × 0.01 cm) to protect the skin from possible frostbite. Next, two plastic bags (24 × 34 × 0.08 cm), each containing 1 kg of crushed ice, will be placed on the knee, covering the anterior, posterior, medial, and lateral surfaces. A comfortable, non-painful compression will be applied over the ice packs by wrapping an elastic bandage around them, and the therapy will be left in situ, uninterrupted, for 20 minutes. The primary purpose of compression is to maintain the ice packs in position on the knee[37] and to enhance cryotherapy effects.[38]

For the sham cryotherapy intervention, the bags will be filled with 1 kg of dry sand instead of ice. The sandbags will be applied according to the same regimen in the same locations. The therapist's explanation about the intervention will be changed to mention the 'application of sand packs' instead of 'cryotherapy application.' The sandbags will be applied with the same gauze underneath and the same bandage for compression.

Outcome measures

The same blinded assessor will measure all outcomes before and after the intervention, and at the 3- and 6-month follow-up periods. Before the study begins, the two outcome assessors will be

trained to conduct interviews and perform data collection following a standard protocol. **Table 2** describes the outcome measures that will be included in the trial and the recommended estimate of the minimum clinically important difference (MCID) for each outcome measure. We will measure pain intensity, subjective and objective physical function, and quality of life.

Primary outcome

The primary outcome will be pain intensity at rest, assessed with a Visual Analogue Scale (VAS). This self-reported pain score is a valid and reliable measure for KOA.[39] The VAS will be administered at rest and after each physical function test, occurring at baseline, on the final assessment day, and at the 3- and 6-month follow-up periods.

Secondary outcomes

To subjectively assess physical function and associated problems, the Western Ontario & McMaster Universities Osteoarthritis Index (WOMAC) will be used. WOMAC is a frequently used questionnaire in KOA and is translated, reproducible, and valid to Brazilian Portuguese.[40] The Medical Outcomes Survey Short-Form 36 (SF-36) questionnaire will be used to asses quality of life. The questionnaire is translated, reproducible, and valid to use in Brazilian Portuguese.[41] Three objective physical function tests will also be used: The 30-Second Chair Stand test, the Stair Climb test, and the 40-Meter fast-paced walk test. The questionnaires and physical function tests described are well-established core assessment measures of pain and physical function in patients with KOA, and presenting good scores for reliability, validity, and ability to detect change.[42–46]

Randomization

Eligible patients who consent to participate will be randomly allocated into three groups of 40: (1) active control group that will receive the STE protocol only, (2) STE + cryotherapy group, and (3) STE + sham cryotherapy group. The allocation of patients will be performed using permuted block randomization stratified by gender (20 men and 20 women in each group); randomization sequences will be determined by a computer-generated random numbers program (www.randomization.com). Allocation will be concealed by placing randomization assignments in opaque sealed envelopes that will be locked in a central location. A biostatistician will be responsible for generating the random numbers and each participant's random allocation will be revealed to the therapist administering the intervention just before study onset.[26]

Sample size

We aim to detect a minimum clinically important difference (MCID) of 1.75 cm units on the VAS for pain intensity at rest.[47] Also, we aim to detect an MCID of 30 points on the WOMAC global score.[48] Calculations were based on an analysis of covariance adjusting for baseline outcome scores, assuming between-patient standard deviations of 2.0 cm for pain and 45 points for WOMAC global score. Based on these criteria, to achieve a significance level of 0.05 and a power of 0.80%, 37 participants with KOA will be required in each group. We will recruit 40 participants per group to allow possible dropouts during the intervention period.

Data analysis

The analyses will be performed by a blinded biostatistician using commercial software. The Kolmogorov-Smirnov test will be applied to evaluate the normality of data distribution. If the

distribution is not normal, non-parametric tests will be used. For normal distributions, a 2-factor analysis of variance (ANOVA) will be conducted for the primary outcome (visual analogue scale for pain) and secondary outcomes, with time (baseline, post-intervention, and follow-up) as the within-subject factor and group (STE, STE + cryotherapy, STE + sham cryotherapy) as the between-subject factor. In addition, Tukey's test will be used for post-hoc analysis when necessary, and an intention-to-treat analysis will be performed for all randomized participants. All the missing data will be replaced using the expectation-maximization method. Between-group differences and their 95% confidence intervals will be reported and interpreted against the nominated thresholds for MCID. For the outcomes where the MCID is not nominated, Cohen's *d* coefficient will be calculated to aid interpretation. An effect size greater than 0.8 will be considered large, around 0.5 moderate, and less than or equal to 0.2, small[49].

ETHICS AND DISSEMINATION

The Institutional Ethics Committee of the Federal University of Sao Carlos, São Paulo, Brazil, approved the under the registration approval number: CAAE: 65966617.9.0000.5504. The trial will be conducted according to the Helsinki Statement. All participants will provide written informed consent following a verbal and written explanation of the study protocol. Participants will be free to withdraw from the trial at any time without prejudice to future treatment. Results will be presented at scientific meetings and published in peer-reviewed journals. All publications and presentations related to the study will be authorized and reviewed by the study investigators.

TRIAL STATUS

The trial is currently recruiting and is expected to be completed (including follow-up testing) by December 2020.

AUTHORS CONTRIBUTION

L.O.D., A.E.S.J., P.R.S., F.A.S., and T.F.S. designed the study protocol. L.O.D. wrote the first draft of the manuscript, and together with A.E.S.J., P.R.S., F.A.S., and T.F.S. revised and produced the final version. All authors have read and approved the final version of the manuscript. L.O.D. takes responsibility for the integrity of the work as a whole.

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DISCLAIMER

The study funders have had no role in study design; collection, management, analysis and interpretation of data; writing of the report; or the decision to submit the report for publication, and do not own ultimate authority over any of these activities.

COMPETING INTERESTS

All authors have completed a uniform disclosure form and declare no conflicts of interest

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Figure 1

Legend: Land Based Exercise Protocol Characteristics

Table 1. Timeline of the measurements to be taken at each point on the trials

	TIMELINE	Enrolment	STE protocol training	Baseline assessment (A1)	Intervention	Post-intervention assessment (A2)	Follow-up assessment (A3)	Follow-up assessment (A4)
		-2 weeks (-14 to -7 day)	-1 week (-7 to 0 day)	Day 0		8 weeks (±3 days)	20 weeks (±3 days)	32 weeks (±3 days)
Enrolment	Eligibility screen	**X**						
	Informed consent	**X**						
Interventions	Allocation			**X**				
	STE				**X**			
	STE + cryotherapy				**X**			
	STE + sham cryotherapy				**X**			
	X-ray examination of both knees	**X**						
Assessments	VAS			**X**		**X**	**X**	**X**
	WOMAC			**X**		**X**	**X**	**X**
	SF-36			**X**		**X**	**X**	**X**
	Timed-up and Go Test			**X**		**X**	**X**	**X**
	30-Second Chair to Stand Test			**X**		**X**	**X**	**X**
	Stair Climb Test			**X**		**X**	**X**	**X**
	40m (4x10m) Fast Paced Walk Test			**X**		**X**	**X**	**X**

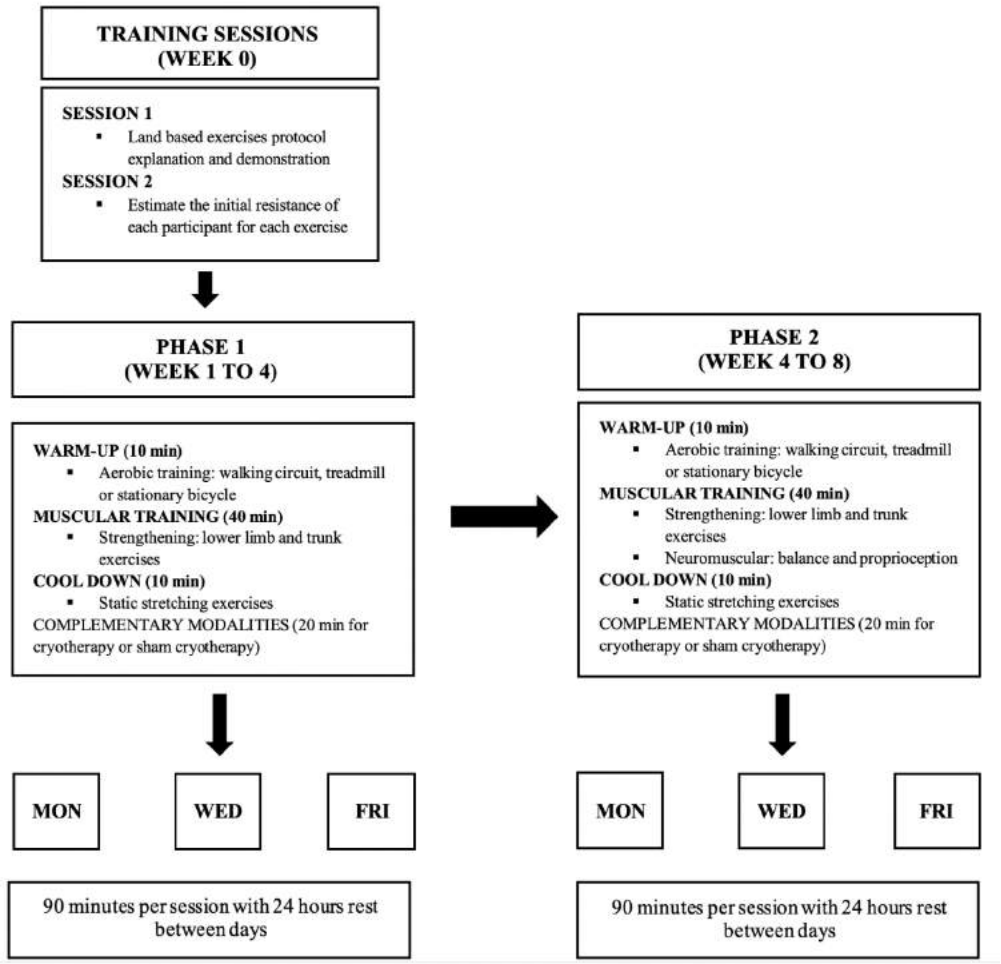
STE: Strength Therapeutic Exercises; VAS: Visual Analogue Scale, WOMAC: Western Ontario & McMaster Universities Osteoarthritis questionnaire; KOOS: Knee Injury and Osteoarthritis Outcome Score; SF-36: Short Form-36 questionnaire.

A: Assessment

Table 2. Description of the outcome measures.

Outcome measure	Description of the test	Scoring	Minimum clinically important difference
Visual analogue scale	The scale is positioned in front of the patient who is asked to evaluate pain intensity in the prior week.[39]	The scale ranges from 0 (no pain) to 10 cm (maximum pain intensity).	A pain reduction of 1.75 cm is recommended in OA research.[47]
Western Ontario & McMaster Universities Osteoarthritis questionnaire	This self-report questionnaire evaluates the difficulties experienced by individuals with lower limb OA in the prior 72 hours. It contains 24 questions in 3 domains: pain, stiffness, and physical function.	Each question is scored from 0 to 4, and the maximum score possible is 96. The higher the scores, the worse the status of a patient.	An improvement of 12% from baseline is recommended in OA research.[50]
Stair Climb Test	The participant is positioned in front of the stairs. At the therapist's signal, he/she has to climb the indicated steps (we used the 12-step SCT) and descend promptly, being able to use the handrail as a security instrument. We used 20 cm steps height, a handrail stair in an lighted environment, free of traffic, or external distractions. Moreover, a pre-test was conducted to identify the need for safety measures.	The final score is calculated based on the time the participant took to perform the test and compared it to the literature normative values of the test.	A reduction of 5.5 seconds in the test is the recommended MCID in OA research[42]
40m (4x10m) Fast Paced Walk Test	Administered at a distance of 10 meters (marked by tapes), a cone is placed 2 meters before the start and 2 meters after the end of each marking. The participant is instructed to walk as quickly but as safely as possible the first 10 meters (from the start mark), to turn around in the cone and walk back the 10 meters again, successively until completing the distance of 40 meters.	Speed (m/s)	An increase of 0.2-0.3 meters per second in the test is the recommended MCID in OA research[42]
30-Second Chair to Stand Test	A chair with no arms is placed against a wall to prevent oscillations. Patients sit in the middle of the chair, with their back straight and feet resting on the floor in line with their shoulders. The participant is asked to rise from sitting to standing as many times as possible in 30 seconds.	Total number of repetitions within 30 seconds	An increase of 2 to 3 repetitions is recommended in OA research.[51]

OA: Osteoarthritis


TRAINING SESSIONS
(WEEK 0)
SESSION 1
Land based exercises protocol explanation and demonstration
SESSION 2
Estimate the initial resistance of each participant for each exercise
PHASE 1
(WEEK 1 TO 4)
WARM-UP (10 min)
Aerobic training: walking circuit, treadmill or stationary bicycle
MUSCULAR TRAINING (40 min)
Strengthening: lower limb and trunk exercises
COOL DOWN (10 min)
Static stretching exercises
COMPLEMENTARY MODALITIES (20 min for cryotherapy or sham cryotherapy)
MON
WED
FRI
90 minutes per session with 24 hours rest between days
PHASE 2
(WEEK 4 TO 8)
WARM-UP (10 min)
Aerobic training: walking circuit, treadmill or stationary bicycle
MUSCULAR TRAINING (40 min)
Strengthening: lower limb and trunk exercises
Neuromuscular: balance and proprioception
COOL DOWN (10 min)
Static stretching exercises
COMPLEMENTARY MODALITIES (20 min for cryotherapy or sham cryotherapy)
MON
WED
FRI
90 minutes per session with 24 hours rest between days

SUPPLEMENTARY FILE

Land-Based Exercises Protocol for Patients with Knee Osteoarthritis

Warm-up Phase (10 min)



Description: treadmill, stationary bicycle, or walking.
Performed in a comfortable cardiorespiratory intensity aiming the joints mobility.

Cool-down Phase (10 min)

Description: Quadriceps stretching.
Active stretching performed with maximum tolerable range of motion.

Set: 1 x 30 seconds

Description: Gastrocnemius stretching.
Active stretching performed with maximum tolerable range of motion.

Set: 1 x 30 seconds


Description: Hamstrings stretching.
Active stretching performed with maximum tolerable range of motion.

Set: 1 x 30 seconds

SUPPLEMENTARY FILE

Conditioning PHASE 1

A	B
	
	
	
	
	

Name: Bridge
Type: isometric
Position A: lie down on the mat, knees pointing to the ceiling, knees aligned with hips.
Position B: raise your hips up toward the ceiling and hold for 15 up to 30 s.
Sets: 3 x 15-30 seconds

Name: Straight Leg Raise (SLR) – hip flexion
Type: Isotonic
Position A: lie down, one leg bent and another straight, pull up your foot.
Position B: raise your leg straight up until it is aligned with the other thigh, then slowly lower it down.
Sets: 3
Repetitions: 12

Name: SLR – hip abduction
Type: Isotonic
Position A: side lying position, bend the knee in contact with the floor and straight the other leg.
Position B: raise your leg straight up, kneecap pointing forward, pulling up your foot.
Sets: 3
Repetitions: 12

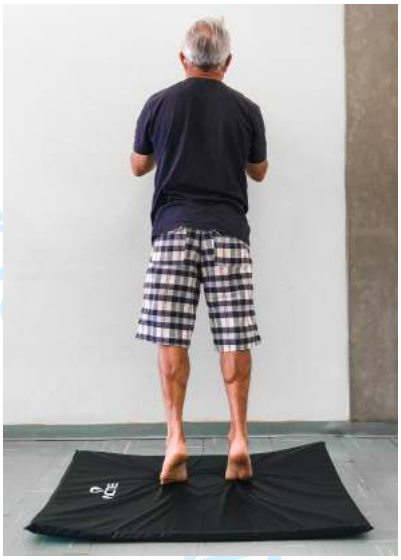
Name: SLR – hip adduction
Type: Isotonic
Position A: side lying position, leg in contact with the floor straight and the other leg bent.
Position B: raise your leg straight up, kneecap pointing forward, pulling up your foot.
Sets: 3
Repetitions: 12

Name: SLR – hip extension
Type: Isotonic
Position A: prone position, both legs straight touching the floor.
Position B: raise one leg up at a time, keeping the totally knee straight.
Sets: 3
Repetitions: 12

SUPPLEMENTARY FILE

A **B**



Name: Abdominal curls (crunchs)
Type: Isotonic
Position A: lie down on the mat, place your hands behind your head, bend your knees and keep them aligned with hips.
Position B: as you exhale, slowly lift your chest up; as you inhale, slowly lower your chest down. Avoid bringing your chin to your chest.
Sets: 3
Repetitions: 12

Name: Standing calf raises
Type: Isotonic
Position A: Standing on both legs, hands on the wall for balance (if needed).
Position B: rise up on toes then slowly lower down.
Sets: 3
Repetitions: 12

Conditioning PHASE 2

A **B**

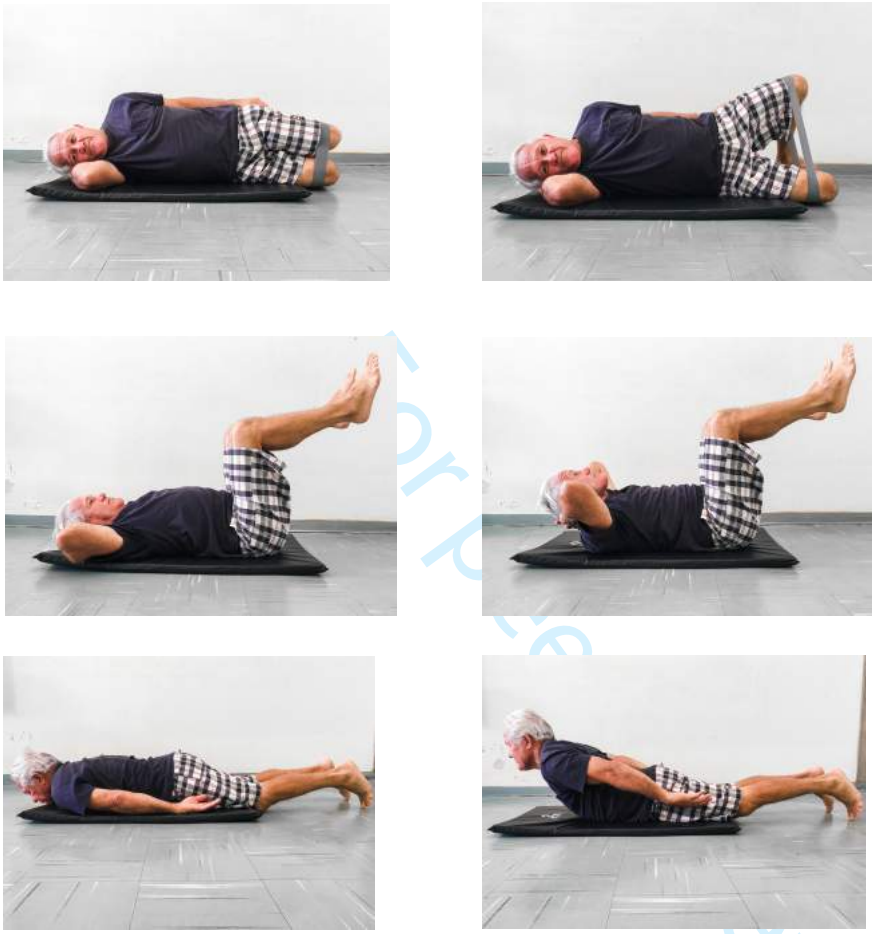



Name: Plank
Type: Isometric
Position A: lying on your belly (prone position).
Position B: lift your entire body up with elbow and feet supports. Hold for 15 up to 30 seconds.
Sets: 3 x 15-30 seconds

Name: Bridge with one leg
Type: Isometric
Position A: lie down on the mat, knees pointing to the ceiling, knees aligned with hips.
Position B: raise your hips up toward the ceiling then carefully take one leg off the floor. Hold for 15 up to 30 s.
Sets: 3 x 15-30 seconds

SUPPLEMENTARY FILE

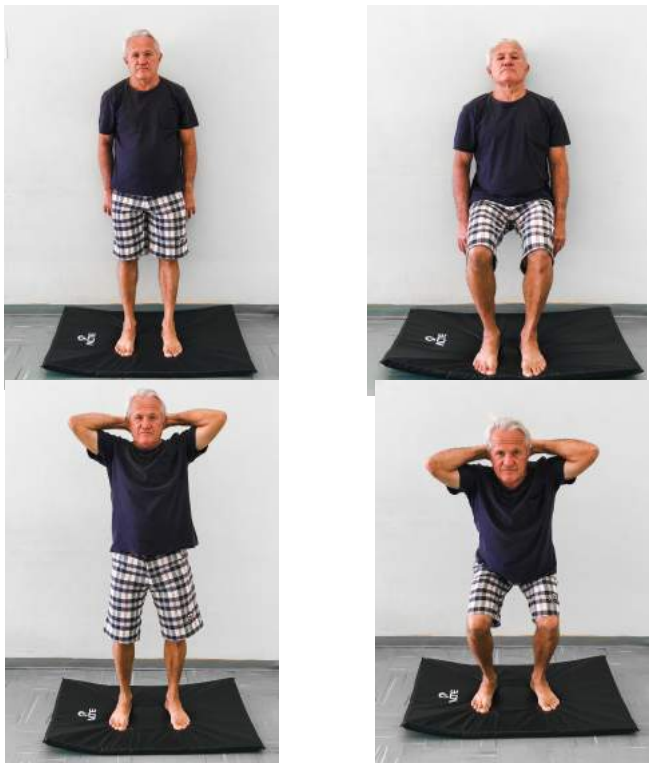
A **B**



Name: Clam shell
Type: Isotonic
Position A: side lying position, elastic band around your thighs, knees bent.
Position B: move your knee away, squeezing your buttocks then slowly return. Repeat with the other side/leg.
Sets: 3
Repetitions: 12

Name: Abdominal curls with lifted legs
Type: Isotonic
Position A: lie down on the mat, place your hands behind your head, bend your knees and keep them aligned with hips. Lift both legs up.
Position B: as you exhale, slowly lift your chest up; as you inhale, slowly lower your chest down. Avoid bringing your chin to your chest.
Sets: 3
Repetitions: 12

Name: Trunk extension
Type: Isometric
Position A: lying on your belly (prone position).
Position B: move your chest away from the floor. Look at the ground. Hold for 30 seconds at least.
Repetitions: 3 x 30 seconds



Name: Wall squat
Type: Isometric contraction
Position A: stand with your trunk to a wall, feet aligned with knees and hips, and away from the wall.
Position B: slide down and keep your trunk towards the wall. Hold for 30 seconds up to one minute.
Repetitions: 3

Name: Partial squat
Type: isotonic contraction
Position A: standing on both legs.
Position B: slowly bend your knees and stand up again. Maintain your knees over your feet.
Repetitions: 3

SUPPLEMENTARY FILE

A	B	
		**Name: Standing hip abduction.** **Type:** static balance **Position A:** standing on both legs with an elastic band around both legs. **Position B:** lift one leg out, maintain the kneecap pointing forward, and hold for 30 seconds or more. **Repetitions:** 3 (each leg)
		**Name: Standing on one leg** **Type:** static balance on stable surface **Position A:** standing on both legs, eyes opened. **Position B:** standing on one leg, knee slightly bent, lift the other leg off the floor and maintain the position up to 1 minute. **Repetitions:** 2 (each leg)
		**Name: Standing on one leg** **Type:** static balance on unstable surface (trampoline, foam etc) **Position A:** standing on both legs, eyes opened. **Position B:** standing on one leg, remove another leg from ground and maintain the position. **Repetitions:** 2 (each leg)
		**Name: Step-up** **Type:** isotonic contraction **Position A:** on leg onto a step. **Position B:** step up onto the next step, use the wall for balance if needed. Step back down carefully to the position A. **Sets:** 2 (each leg) **Repetitions:** 12

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
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym **– PAGE 01**
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry **– PAGE 02**
	2b	All items from the World Health Organization Trial Registration Data Set **- N/A**
Protocol version	3	Date and version identifier **- N/A**
Funding	4	Sources and types of financial, material, and other support - **PAGE 14**
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors **– PAGE 01**
	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 **– PAGES 4-5**
	6b	Explanation for choice of comparators **– PAGES 4-5**
Objectives	7	Specific objectives or hypotheses **– PAGES 4-5**

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) **– PAGE 6**

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 **– PAGE 6**
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) **– PAGE 7**
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered **– PAGES 8-10**
	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) **– PAGES 8-10**
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) **– PAGES 8-10**
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial **– PAGES 8-10**
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 **– PAGES 10-11**
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) **– PAGE 22**
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 **– PAGE 12**
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size **– PAGE 7**

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 **– PAGE 12**
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 **– PAGE 12**
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions **– PAGE 12**
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how **– PAGES 8, 10**
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial **– N/A**
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 **– PAGES 12-13**
	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 **– PAGES 12-13**
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 **– PAGE 12-13**
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 **– PAGES 12-13**
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) **– PAGES 12-13**
	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) **– PAGES 12-13**

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 **– PAGES 6-8**
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 **– PAGES 13, 14**
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) **– PAGE 13**
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) **– PAGE 13**
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable **N/A**
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 **– PAGES 06, 07**
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site **– PAGE 14**
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 **N/A**
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 **– PAGES 13, 14**
	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 **– PAGE S13, 14**
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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CRYOTHERAPY ASSOCIATED WITH TAILORED LAND-BASED EXERCISES FOR KNEE OSTEOARTHRITIS: A PROTOCOL FOR A DOUBLE-BLIND SHAM CONTROLLED RANDOMIZED TRIAL

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Primary Subject Heading:	Rheumatology
Secondary Subject Heading:	Rheumatology, Rehabilitation medicine
Keywords:	PAIN MANAGEMENT, REHABILITATION MEDICINE, PUBLIC HEALTH

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TITLE: CRYOTHERAPY ASSOCIATED WITH TAILORED LAND-BASED EXERCISES FOR KNEE OSTEOARTHRITIS: A PROTOCOL FOR A DOUBLE-BLIND SHAM CONTROLLED RANDOMIZED TRIAL

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ABSTRACT

Introduction: There is an unmet need to develop tailored therapeutic exercise protocols applying different treatment parameters and modalities for individuals with knee osteoarthritis (KOA). Cryotherapy is widely used in rehabilitation as an adjunct treatment due to its effects on pain and the inflammatory process. However, disagreement between KOA guidelines remains with respect to its recommendation status. The aim of this study is to verify the complementary effects of cryotherapy when associated with a tailored therapeutic exercise protocol on patients with KOA.

Methods and analysis: This study is a sham-controlled, randomized trial with concealed allocation and intention-to-treat analysis. Assessments will be performed at baseline and immediately following the intervention period. To check for residual effects of the interventions applied, three- and six-month follow-up assessments will be performed. Participants will be community members living with KOA. There will be three groups: (1) the experimental group that will receive a tailored therapeutic exercise protocol followed by a cryotherapy session of 20 minutes; (2) the sham control group that will receive the same regimen as the first group, but with sham packs filled with dry sand; and (3) the active treatment control group that will receive only the therapeutic exercise protocol. The primary outcome will be pain intensity according to a Visual Analogue Scale. Secondary outcomes will be the Western Ontario & McMaster Universities Osteoarthritis Index; the Medical Outcomes Survey Short-Form 36 questionnaire; the 30-Second Chair Stand Test; the Stair Climb test; and the 40-Meter fast-paced walk test.

Ethics and dissemination: The trial was approved by the Institutional Ethics Committee of Federal University of Sao Carlos, São Paulo, Brazil. Registration approval number: CAAE: 65966617.9.0000.5504. The results will be published in peer-reviewed journals.

Trial registration number: NCT03360500

Strengths and limitations of this study:

- The trial will be conducted according to well-established reporting guidelines.
- Participants will present with radiographically confirmed knee osteoarthritis and a sufficient level of pain to ensure ample scope for improvement.
- The trial will use both subjective and objective outcome measures.
- The therapist who delivers cryotherapy or the sham intervention and the patients will not be blinded.
- The loss to follow-up after randomization in the sham group might be higher than those in the other groups.

Knee osteoarthritis (KOA) is a serious disease with a high societal and economic burden,[1] affecting approximately 250 million people worldwide.[2] Current clinical practice guidelines recommend a combination of pharmacological[3] and non-pharmacological[4] treatment strategies to manage KOA symptoms and improve patients' quality of life. However, pharmacological treatment options that have been proven to relieve symptoms remain limited, and some of the most commonly recommended pharmacologic treatments are poorly tolerated, with long-term use resulting in serious systemic adverse events.[5–7]

Physical Therapy, specifically the use of strengthening therapeutic exercise (STE) protocols, have been shown to relieve pain, reduce stiffness, increase physical function, and improve quality of life in patients with KOA.[1,8] High-quality evidence has demonstrated that the benefits of STE protocols on pain and quality of life in individuals with KOA are sustained for at least two to six months after the end of a treatment.[8] There is, however, a call for further research to develop novel insights within STE protocols regarding differences in treatment durations, frequencies, modalities, and intensities.[9] The majority of current protocols have reported low adherence and are substantially under-utilized by KOA patients, mainly due to socioeconomic barriers, personal beliefs, fear of movement, and aggravation of pain in the early phases of treatment.[10,11] Therefore, there is an unmet need for cost-effective, evidence-based STE protocols that are tailored to the needs of KOA patients, and that can aid clinicians in targeting rehabilitation goals.

Physical modalities such as thermal agents, laser therapy, therapeutic ultrasound, and electrical stimulation are often used as adjunct treatments with therapeutic exercises in individuals with KOA.[4,12] Cryotherapy, a non-pharmacological intervention, has been widely used in some

rheumatic joint diseases[13,14] based on its effects on pain, inflammation, and edema.[15,16] The intervention is considered safe, and is inexpensive and easy to administer for healthcare professionals and patients. Moreover, it can be prescribed in isolation or as an adjunct treatment and seems to be well accepted by individuals with KOA.[14,17,18] Although cryotherapy is recommended as a treatment option by some international KOA guidelines,[19,20] others have found insufficient evidence to support it.[21–23] Relevant systematic reviews have likewise concluded that further evidence, produced with greater methodological rigor, is needed to evaluate the effects of cryotherapy on pain, function, and quality of life in individuals with KOA.[16,24]

In this study, we aim to design a randomized trial to verify the complementary effects of cryotherapy in conjunction with a tailored STE protocol on pain, function, and quality of life in individuals with KOA. We hypothesize that cryotherapy combined with the STE protocol will achieve better treatment effects on KOA patients when compared to the other two groups. The proposed trial will contribute new evidence to the Physical Therapy field in KOA by focusing on interventions that target rehabilitation and enhance pain management, thereby improving the physical function and quality of life of these patients. Our research group developed the STE protocol described in this study. The protocol was also used in another randomized trial testing the complementary effects of Photobiomodulation in individuals with KOA (trial registration number at www.ensaiosclinicos.gov.br: U1111-1215-6510). This manuscript has been submitted simultaneously with the manuscript entitled "Photobiomodulation therapy associated with supervised therapeutic exercises for people with knee osteoarthritis: a protocol for randomized trials" (ID bmjopen-2019-035711).

METHODS

To report this study protocol, we followed the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT),[25] the Osteoarthritis Research Society International clinical trials recommendations: design, conduct, and reporting of clinical trials for knee osteoarthritis,[26] and the Template for Intervention Description and Replication checklist (TIDieR).[27] The randomized trial will be reported according to the Consolidated Standards of Reporting Trials (CONSORT) statement for randomized trials of non-pharmacologic treatments.[28] The trial is registered on the clinicaltrials.gov (NCT03360500) platform.

Study design and setting

This study is a single-center, sham-controlled randomized clinical trial. A baseline assessment (A1) will be performed on the weekday before the 8-week intervention period, and a post-intervention assessment (A2) will be performed immediately following the last session. To check for residual effects of the interventions, three-month (A3) and six-month (A4) follow-up assessments will be performed. Each patient will be assessed in a physiotherapy research laboratory, during the same period of the day and by the same assessor. To reduce bias, the therapists responsible for applying the intervention and the outcome assessors will follow standardized scripts that describe the general objective of the study.[26]

Intervention adherence, medication intake, and adverse events will be tracked with an 8-week assessment diary that will be given to participants at the baseline assessment and with a 12-week assessment diary for the three-month follow-up assessment. All the participants will be advised not to practice any other type of regular physical exercise during the course of the study that could

interfere with the STE protocol. A verbal and written explanation of the objectives and methodology of the study will be provided to all the participants, and those willing to participate will sign a written informed consent form, approved by the local ethics committee. A detailed timeline of the trial is presented in **Table 1**.

Patient and Public Involvement

The patients and the public were not involved in the planning and design of this study.

Participants

Participants will be recruited through public announcements on social media, advertisements via local news outlets, University community newsletters, and banners or leaflets posted at strategic locations in the city. People who are interested in participating in the study will first be screened to check the eligibility criteria. Eligible participants will then undergo a lateral, anteroposterior, and axial radiography of both knees to determine KOA severity, which will take place at the University Hospital. Participants will be classified with KOA based on the clinical and radiographic criteria of the American College of Rheumatology,[29] and will be required to have symptoms and a radiographic grade (Kellgren and Lawrence scale) of ≥2 (mild radiographic OA) in at least one knee compartment.[26]

To be included in the study, participants will also need to: be between 40 and 75 years old; be engaged in a total of less than 45 minutes/week of physical activity of at least moderate intensity[30]; have a body mass index <35 kg/m^2; and to have reported pain intensity in the prior week of ≥4 cm on a 10-cm visual analogue scale.[26] Exclusion criteria will comprise physical therapy in the prior

three months; intra-articular knee injections in the prior six months; medical restrictions such as cardiorespiratory, neurological, or any other rheumatology conditions; previous hip, knee, or ankle surgery; and any other chronic condition that leads to chronic pain or dysfunction. Additionally, participants presenting with contraindication(s) to cryotherapy application (i.e., those that feel a high level of discomfort or pain during the application) will be excluded.

All the participants will be asked to provide a medical certificate stating that they are healthy enough to perform physical activities before the start of the intervention.

Interventions

The intervention protocol is based on a previously accepted methodology developed in our research laboratory.[31] Two physical therapists will administer the interventions in the physiotherapy clinic of the University. The study will take place over the course of eight weeks, with three 90-minute sessions per week occurring on non-consecutive days, for a total of 24 sessions. All randomized participants will perform the STE protocol and then, according to random allocation, each patient will subsequently receive either cryotherapy or sham interventions in individual rooms.

Prior to the beginning of the study, the therapists responsible for the interventions will participate in a 10-hour training module, which will consist of scientific information and clinical training regarding KOA, the STE protocol, and the use of cryotherapy. After the first training module is completed, the therapists will do an eight-week training module, which will consist of practicing the full-length protocol and intervention application(s) three times per week. Both therapists will be responsible for delivering cryotherapy and sham interventions.

STE protocol

We designed the 8-week land-based supervised exercise protocol according to the evidence-based recommendations for physical exercise interventions in KOA.[32,33] The STE protocol characteristics are described in **Figure 1,** and a detailed description of all the exercises is presented in the **Supplementary file** of this protocol. The protocol is divided into two phases. Each phase consists of 4 weeks of progressive exercises, performed three times per week on non-consecutive days (24 hours rest between sessions), with exercise intensity individually tailored for each participant. The first session is used to demonstrate and explain the STE protocol, and to perform an exercise familiarization using no loads by the participants. The second session is designed to estimate the initial resistance of each participant for each exercise. The volitional interruption method is used in order to achieve the benefits of resistance training and to reduce the risk of musculoskeletal injuries to the participants.[34] The loads are gradually increased until the participant can adequately perform 12 repetitions with no voluntary interruption due to muscle fatigue.

The STE protocol sessions consist of three phases. The first phase is a 10-minute warm-up in which the patients can choose, according to their preferences, to walk in a comfortable intensity in an outdoor circuit, treadmill, or ride in a stationary bicycle. The second phase consists of 40 minutes of strengthening exercises (resistance training), such as a lower limb and trunk muscles, and neuromuscular training involving balance exercises. The third phase is a cool-down phase, consisting of static stretching exercises to reduce the risk of musculoskeletal injuries and to maximize the benefit of the STE protocol.[35] Cardiac and respiratory frequencies and blood pressure are monitored at the beginning of each session or if the participant presents an intense

rate of perceived exertion according to the Borg scale while performing an exercise, to ensure patient safety.[36,37]

Cryotherapy protocol

To apply cryotherapy, the therapist will explain to the patient that the intervention will consist of crushed ice applied to the more-affected knee for 20 minutes. Participants will be positioned in dorsal decubitus with both legs extended and relaxed. The entire knee surface will be covered with a moist surgical gauze (45 × 50 × 0.01 cm) to protect the skin from possible frostbite. Next, two plastic bags (24 × 34 × 0.08 cm), each containing 1 kg of crushed ice, will be placed on the knee, covering the anterior, posterior, medial, and lateral surfaces. A comfortable, non-painful compression will be applied over the ice packs by wrapping an elastic bandage around them, and the therapy will be left in situ, uninterrupted, for 20 minutes. The primary purpose of compression is to maintain the ice packs in position on the knee[38] and to enhance cryotherapy effects.[39]

For the sham cryotherapy intervention, the bags will be filled with 1 kg of dry sand instead of ice. The sandbags will be applied according to the same regimen in the same locations. The therapist's explanation about the intervention will be changed to mention the 'application of sand packs' instead of 'cryotherapy application.' The sandbags will be applied with the same gauze underneath and the same bandage for compression.

Outcome measures

The same blinded assessor will measure all outcomes before and after the intervention, and at the 3- and 6-month follow-up periods. Before the study begins, the two outcome assessors will be

trained to conduct interviews and perform data collection following a standard protocol. **Table 2** describes the outcome measures that will be included in the trial and the recommended estimate of the minimum clinically important difference (MCID) for each outcome measure. We will measure pain intensity, subjective and objective physical function, and quality of life.

Primary outcome

The primary outcome will be pain intensity at rest, assessed with a Visual Analogue Scale (VAS). This self-reported pain score is a valid and reliable measure for KOA.[40] The VAS will be administered at rest and after each physical function test, occurring at baseline, on the final assessment day, and at the 3- and 6-month follow-up periods.

Secondary outcomes

To subjectively assess physical function and associated problems, the Western Ontario & McMaster Universities Osteoarthritis Index (WOMAC) will be used. WOMAC is a frequently used questionnaire in KOA and is translated, reproducible, and valid to Brazilian Portuguese.[41] The Medical Outcomes Survey Short-Form 36 (SF-36) questionnaire will be used to asses quality of life. The questionnaire is translated, reproducible, and valid to use in Brazilian Portuguese.[42] Three objective physical function tests will also be used: The 30-Second Chair Stand test, the Stair Climb test, and the 40-Meter fast-paced walk test. The questionnaires and physical function tests described are well-established core assessment measures of pain and physical function in patients with KOA, and presenting good scores for reliability, validity, and ability to detect change.[43–47]

Randomization

Eligible patients who consent to participate will be randomly allocated into three groups of 40: (1) active control group that will receive the STE protocol only, (2) STE + cryotherapy group, and (3) STE + sham cryotherapy group. The allocation of patients will be performed using permuted block randomization stratified by gender (20 men and 20 women in each group); randomization sequences will be determined by a computer-generated random numbers program (www.randomization.com). Allocation will be concealed by placing randomization assignments in opaque sealed envelopes that will be locked in a central location. A biostatistician will be responsible for generating the random numbers and each participant's random allocation will be revealed to the therapist administering the intervention just before study onset.[26]

Sample size

We aim to detect a minimum clinically important difference (MCID) of 1.75 cm units on the VAS for pain intensity at rest.[48] Also, we aim to detect an MCID of 30 points on the WOMAC global score.[49] Calculations were based on an analysis of covariance adjusting for baseline outcome scores, assuming between-patient standard deviations of 2.0 cm for pain and 45 points for WOMAC global score. Based on these criteria, to achieve a significance level of 0.05 and a power of 0.80%, 37 participants with KOA will be required in each group. We will recruit 40 participants per group to allow possible dropouts during the intervention period.

Data analysis

The analyses will be performed by a blinded biostatistician using commercial software. The Kolmogorov-Smirnov test will be applied to evaluate the normality of data distribution. If the

distribution is not normal, non-parametric tests will be used. For normal distributions, a 2-factor analysis of variance (ANOVA) will be conducted for the primary outcome (visual analogue scale for pain) and secondary outcomes, with time (baseline, post-intervention, and follow-up) as the within-subject factor and group (STE, STE + cryotherapy, STE + sham cryotherapy) as the between-subject factor. In addition, Tukey's test will be used for post-hoc analysis when necessary, and an intention-to-treat analysis will be performed for all randomized participants. All the missing data will be replaced using the expectation-maximization method. Between-group differences and their 95% confidence intervals will be reported and interpreted against the nominated thresholds for MCID. For the outcomes where the MCID is not nominated, Cohen's *d* coefficient will be calculated to aid interpretation. An effect size greater than 0.8 will be considered large, around 0.5 moderate, and less than or equal to 0.2, small[50].

ETHICS AND DISSEMINATION

The Institutional Ethics Committee of the Federal University of Sao Carlos, São Paulo, Brazil, approved the under the registration approval number: CAAE: 65966617.9.0000.5504. The trial will be conducted according to the Helsinki Statement. All participants will provide written informed consent following a verbal and written explanation of the study protocol. Participants will be free to withdraw from the trial at any time without prejudice to future treatment. Results will be presented at scientific meetings and published in peer-reviewed journals. All publications and presentations related to the study will be authorized and reviewed by the study investigators.

TRIAL STATUS

The trial is currently recruiting and is expected to be completed (including follow-up testing) by December 2020.

AUTHORS CONTRIBUTION

L.O.D., A.E.S.J., P.R.S., F.A.S., and T.F.S. designed the study protocol. L.O.D. wrote the first draft of the manuscript, and together with A.E.S.J., P.R.S., F.A.S., and T.F.S. revised and produced the final version. All authors have read and approved the final version of the manuscript. L.O.D. takes responsibility for the integrity of the work as a whole.

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DISCLAIMER

The study funders have had no role in study design; collection, management, analysis and interpretation of data; writing of the report; or the decision to submit the report for publication, and do not own ultimate authority over any of these activities.

COMPETING INTERESTS

All authors have completed a uniform disclosure form and declare no conflicts of interest

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Figure 1

Legend: Land Based Exercise Protocol Characteristics

Table 1. Timeline of the measurements to be taken at each point on the trials

	TIMELINE	Enrolment	STE protocol training	Baseline assessment (A1)	Intervention	Post-intervention assessment (A2)	Follow-up assessment (A3)	Follow-up assessment (A4)
		-2 weeks (-14 to -7 day)	-1 week (-7 to 0 day)	Day 0		8 weeks (±3 days)	20 weeks (±3 days)	32 weeks (±3 days)
Enrolment	Eligibility screen	**X**						
	Informed consent	**X**						
Interventions	Allocation			**X**				
	STE				**X**			
	STE + cryotherapy				**X**			
	STE + sham cryotherapy				**X**			
	X-ray examination of both knees	**X**						
Assessments	VAS			**X**		**X**	**X**	**X**
	WOMAC			**X**		**X**	**X**	**X**
	SF-36			**X**		**X**	**X**	**X**
	Timed-up and Go Test			**X**		**X**	**X**	**X**
	30-Second Chair to Stand Test			**X**		**X**	**X**	**X**
	Stair Climb Test			**X**		**X**	**X**	**X**
	40m (4x10m) Fast Paced Walk Test			**X**		**X**	**X**	**X**

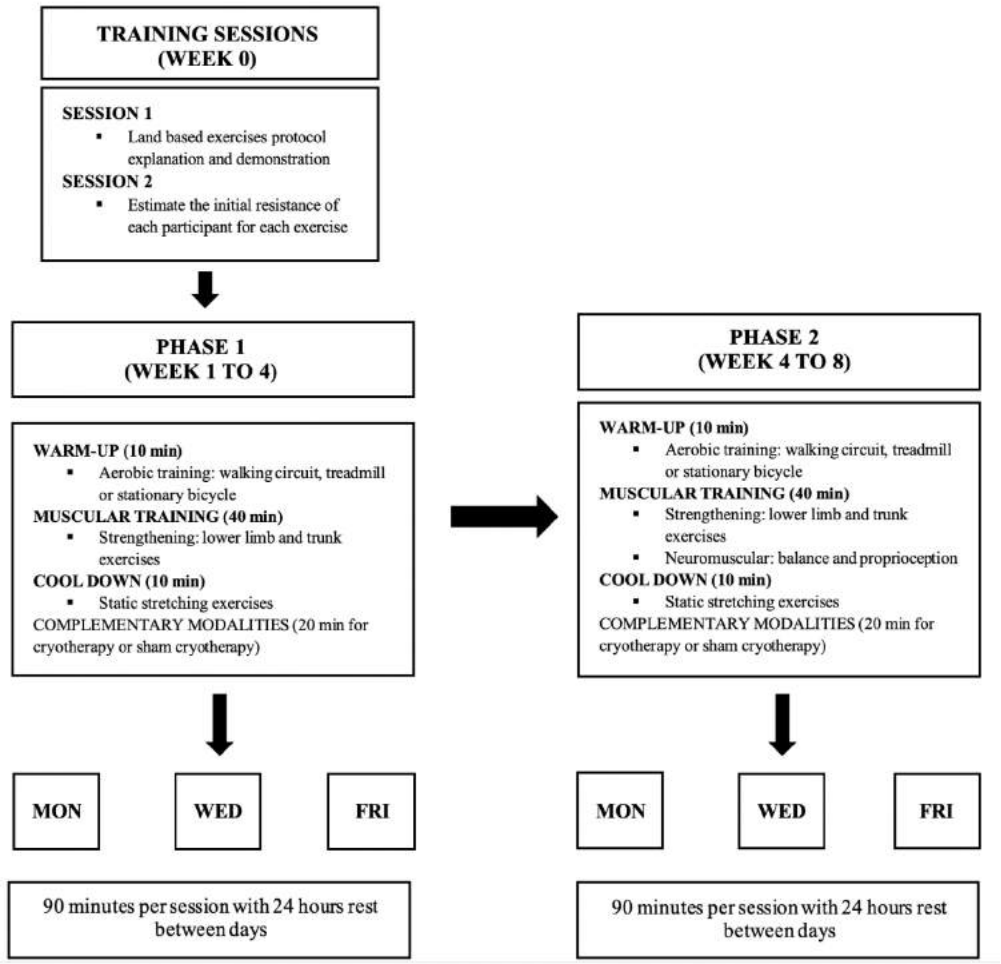
STE: Strength Therapeutic Exercises; VAS: Visual Analogue Scale, WOMAC: Western Ontario & McMaster Universities Osteoarthritis questionnaire; KOOS: Knee Injury and Osteoarthritis Outcome Score; SF-36: Short Form-36 questionnaire.

A: Assessment

Table 2. Description of the outcome measures.

Outcome measure	Description of the test	Scoring	Minimum clinically important difference
Visual analogue scale	The scale is positioned in front of the patient who is asked to evaluate pain intensity in the prior week.[40]	The scale ranges from 0 (no pain) to 10 cm (maximum pain intensity).	A pain reduction of 1.75 cm is recommended in OA research.[48]
Western Ontario & McMaster Universities Osteoarthritis questionnaire	This self-report questionnaire evaluates the difficulties experienced by individuals with lower limb OA in the prior 72 hours. It contains 24 questions in 3 domains: pain, stiffness, and physical function.	Each question is scored from 0 to 4, and the maximum score possible is 96. The higher the scores, the worse the status of a patient.	An improvement of 12% from baseline is recommended in OA research.[51]
Short Form-36 questionnaire (SF-36)	The short form questionnaire is intended to measure the patient's quality of life with 36 items referring to the past four weeks. It presents a multiple-choice scale that evaluates eight domains of life: Physical Functioning, Role Limitations due to Physical Problems, General Health Perceptions, Vitality, Social Functioning, Role Limitations due to Emotional Problems, General Mental Health and Health Transition.	The sum of the total value varies from 0 to 100, with higher indexes indicating a better quality of life. Each of the eight summed scores was linearly transformed into a scale from 0 (negative health) to 100 (positive health) to provide a score for each subscale. Each subscale was used independently.	A difference of 10 points is recommended as an MCID in OA research.[52]
Stair Climb Test	The participant is positioned in front of the stairs. At the therapist's signal, he/she has to climb the indicated steps (we used the 12-step SCT) and descend promptly, being able to use the handrail as a security instrument. We used 20 cm steps height, a handrail stair in an lighted environment, free of traffic, or external distractions. Moreover, a pre-test was conducted to identify the need for safety measures.	The final score is calculated based on the time the participant took to perform the test and compared it to the literature normative values of the test.	A reduction of 5.5 seconds in the test is the recommended MCID in OA research[43]
40m (4x10m) Fast Paced Walk Test	Administered at a distance of 10 meters (marked by tapes), a cone is placed 2 meters before the start and 2 meters after the end of each marking. The participant is instructed to walk as quickly but as safely as possible the first 10 meters (from the start mark), to turn around in the cone and walk back the 10 meters again, successively until completing the distance of 40 meters.	Speed (m/s)	An increase of 0.2-0.3 meters per second in the test is the recommended MCID in OA research[43]
30-Second Chair to Stand Test	A chair with no arms is placed against a wall to prevent oscillations. Patients sit in the middle of the chair, with their back straight and feet resting on the floor in line with their shoulders. The participant is asked to rise from sitting to standing as many times as possible in 30 seconds.	Total number of repetitions within 30 seconds	An increase of 2 to 3 repetitions is recommended in OA research.[53]

OA: Osteoarthritis


TRAINING SESSIONS
(WEEK 0)
SESSION 1
Land based exercises protocol explanation and demonstration
SESSION 2
Estimate the initial resistance of each participant for each exercise
PHASE 1
(WEEK 1 TO 4)
WARM-UP (10 min)
Aerobic training: walking circuit, treadmill or stationary bicycle
MUSCULAR TRAINING (40 min)
Strengthening: lower limb and trunk exercises
COOL DOWN (10 min)
Static stretching exercises
COMPLEMENTARY MODALITIES (20 min for cryotherapy or sham cryotherapy)
MON
WED
FRI
90 minutes per session with 24 hours rest between days
PHASE 2
(WEEK 4 TO 8)
WARM-UP (10 min)
Aerobic training: walking circuit, treadmill or stationary bicycle
MUSCULAR TRAINING (40 min)
Strengthening: lower limb and trunk exercises
Neuromuscular: balance and proprioception
COOL DOWN (10 min)
Static stretching exercises
COMPLEMENTARY MODALITIES (20 min for cryotherapy or sham cryotherapy)
MON
WED
FRI
90 minutes per session with 24 hours rest between days

SUPPLEMENTARY FILE

Land-Based Exercises Protocol for Patients with Knee Osteoarthritis

Warm-up Phase (10 min)



Description: treadmill, stationary bicycle, or walking.
Performed in a comfortable cardiorespiratory intensity aiming the joints mobility.

Cool-down Phase (10 min)

Description: Quadriceps stretching.
Active stretching performed with maximum tolerable range of motion.

Set: 1 x 30 seconds

Description: Gastrocnemius stretching.
Active stretching performed with maximum tolerable range of motion.

Set: 1 x 30 seconds


Description: Hamstrings stretching.
Active stretching performed with maximum tolerable range of motion.

Set: 1 x 30 seconds

SUPPLEMENTARY FILE

Conditioning PHASE 1

A	B
	
	
	
	
	

Name: Bridge
Type: isometric
Position A: lie down on the mat, knees pointing to the ceiling, knees aligned with hips.
Position B: raise your hips up toward the ceiling and hold for 15 up to 30 s.
Sets: 3 x 15-30 seconds

Name: Straight Leg Raise (SLR) – hip flexion
Type: Isotonic
Position A: lie down, one leg bent and another straight, pull up your foot.
Position B: raise your leg straight up until it is aligned with the other thigh, then slowly lower it down.
Sets: 3
Repetitions: 12

Name: SLR – hip abduction
Type: Isotonic
Position A: side lying position, bend the knee in contact with the floor and straight the other leg.
Position B: raise your leg straight up, kneecap pointing forward, pulling up your foot.
Sets: 3
Repetitions: 12

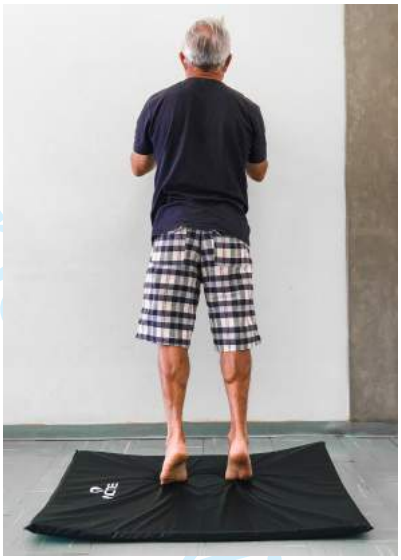
Name: SLR – hip adduction
Type: Isotonic
Position A: side lying position, leg in contact with the floor straight and the other leg bent.
Position B: raise your leg straight up, kneecap pointing forward, pulling up your foot.
Sets: 3
Repetitions: 12

Name: SLR – hip extension
Type: Isotonic
Position A: prone position, both legs straight touching the floor.
Position B: raise one leg up at a time, keeping the totally knee straight.
Sets: 3
Repetitions: 12

SUPPLEMENTARY FILE

A **B**



Name: Abdominal curls (crunchs)
Type: Isotonic
Position A: lie down on the mat, place your hands behind your head, bend your knees and keep them aligned with hips.
Position B: as you exhale, slowly lift your chest up; as you inhale, slowly lower your chest down. Avoid bringing your chin to your chest.
Sets: 3
Repetitions: 12

Name: Standing calf raises
Type: Isotonic
Position A: Standing on both legs, hands on the wall for balance (if needed).
Position B: rise up on toes then slowly lower down.
Sets: 3
Repetitions: 12

Conditioning PHASE 2

A **B**

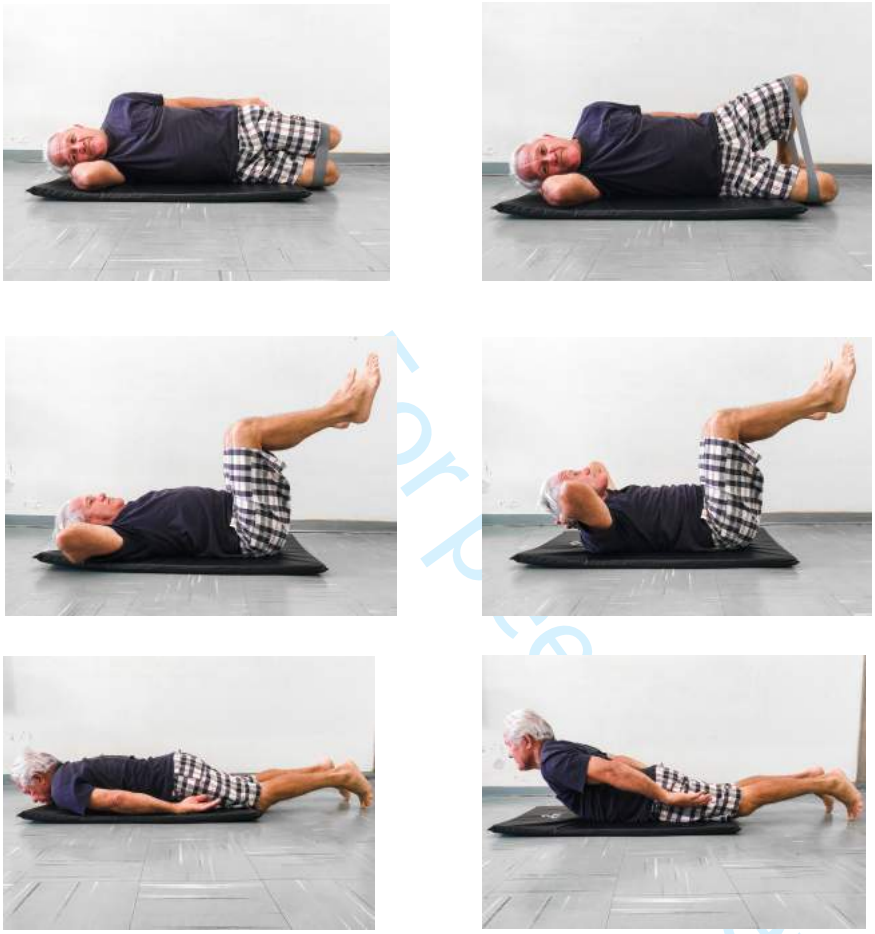



Name: Plank
Type: Isometric
Position A: lying on your belly (prone position).
Position B: lift your entire body up with elbow and feet supports. Hold for 15 up to 30 seconds.
Sets: 3 x 15-30 seconds

Name: Bridge with one leg
Type: Isometric
Position A: lie down on the mat, knees pointing to the ceiling, knees aligned with hips.
Position B: raise your hips up toward the ceiling then carefully take one leg off the floor. Hold for 15 up to 30 s.
Sets: 3 x 15-30 seconds

SUPPLEMENTARY FILE

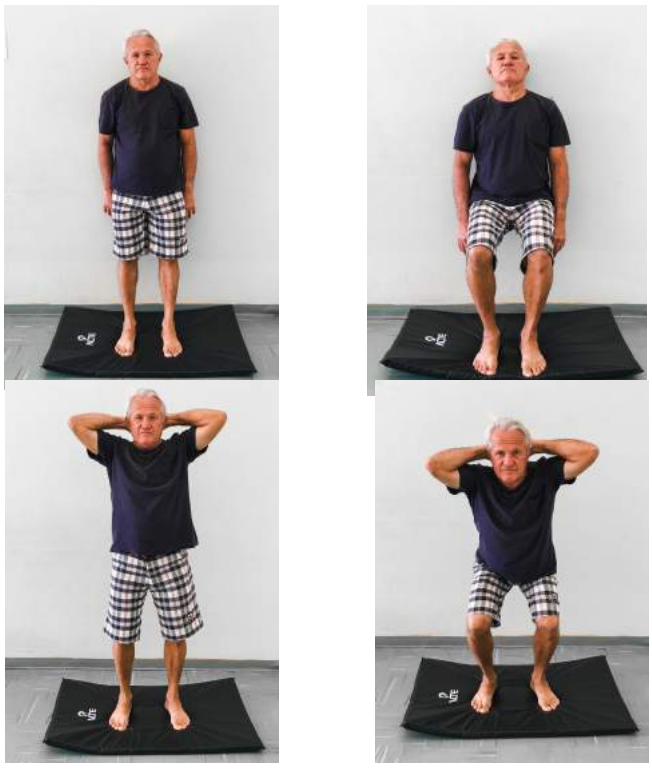
A **B**



Name: Clam shell
Type: Isotonic
Position A: side lying position, elastic band around your thighs, knees bent.
Position B: move your knee away, squeezing your buttocks then slowly return. Repeat with the other side/leg.
Sets: 3
Repetitions: 12

Name: Abdominal curls with lifted legs
Type: Isotonic
Position A: lie down on the mat, place your hands behind your head, bend your knees and keep them aligned with hips. Lift both legs up.
Position B: as you exhale, slowly lift your chest up; as you inhale, slowly lower your chest down. Avoid bringing your chin to your chest.
Sets: 3
Repetitions: 12

Name: Trunk extension
Type: Isometric
Position A: lying on your belly (prone position).
Position B: move your chest away from the floor. Look at the ground. Hold for 30 seconds at least.
Repetitions: 3 x 30 seconds



Name: Wall squat
Type: Isometric contraction
Position A: stand with your trunk to a wall, feet aligned with knees and hips, and away from the wall.
Position B: slide down and keep your trunk towards the wall. Hold for 30 seconds up to one minute.
Repetitions: 3

Name: Partial squat
Type: isotonic contraction
Position A: standing on both legs.
Position B: slowly bend your knees and stand up again. Maintain your knees over your feet.
Repetitions: 3

SUPPLEMENTARY FILE

A	B	
		**Name: Standing hip abduction.** **Type:** static balance **Position A:** standing on both legs with an elastic band around both legs. **Position B:** lift one leg out, maintain the kneecap pointing forward, and hold for 30 seconds or more. **Repetitions:** 3 (each leg)
		**Name: Standing on one leg** **Type:** static balance on stable surface **Position A:** standing on both legs, eyes opened. **Position B:** standing on one leg, knee slightly bent, lift the other leg off the floor and maintain the position up to 1 minute. **Repetitions:** 2 (each leg)
		**Name: Standing on one leg** **Type:** static balance on unstable surface (trampoline, foam etc) **Position A:** standing on both legs, eyes opened. **Position B:** standing on one leg, remove another leg from ground and maintain the position. **Repetitions:** 2 (each leg)
		**Name: Step-up** **Type:** isotonic contraction **Position A:** on leg onto a step. **Position B:** step up onto the next step, use the wall for balance if needed. Step back down carefully to the position A. **Sets:** 2 (each leg) **Repetitions:** 12

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
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym **– PAGE 01**
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry **– PAGE 02**
	2b	All items from the World Health Organization Trial Registration Data Set **- N/A**
Protocol version	3	Date and version identifier **- N/A**
Funding	4	Sources and types of financial, material, and other support - **PAGE 14**
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors **– PAGE 01**
	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 **– PAGES 4-5**
	6b	Explanation for choice of comparators **– PAGES 4-5**
Objectives	7	Specific objectives or hypotheses **– PAGES 4-5**

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) **– PAGE 6**

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 **– PAGE 6**
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) **– PAGE 7**
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered **– PAGES 8-10**
	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) **– PAGES 8-10**
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) **– PAGES 8-10**
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial **– PAGES 8-10**
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 **– PAGES 10-11**
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) **– PAGE 22**
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 **– PAGE 12**
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size **– PAGE 7**

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 **– PAGE 12**
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 **– PAGE 12**
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions **– PAGE 12**
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how **– PAGES 8, 10**
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial **– N/A**
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 **– PAGES 12-13**
	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 **– PAGES 12-13**
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 **– PAGE 12-13**
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 **– PAGES 12-13**
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) **– PAGES 12-13**
	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) **– PAGES 12-13**

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 **– PAGES 6-8**
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 **– PAGES 13, 14**
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) **– PAGE 13**
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) **– PAGE 13**
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable **N/A**
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 **– PAGES 06, 07**
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site **– PAGE 14**
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 **N/A**
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 **– PAGES 13, 14**
	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 **– PAGE S13, 14**
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.