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Exercise-induced hypoalgesia after aerobic versus neck-specific exercise in acute/subacute whiplash associated disorders: Protocol for a randomised controlled trial

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Abstract

Introduction: A disturbance in exercise-induced hypoalgesia (EIH) has been observed in patients with chronic whiplash associated disorders (WAD). Yet, no studies have examined whether EIH occurs in people with acute/subacute WAD. This study will determine whether EIH occurs immediately after and 24 hours after aerobic exercise (AE) and neck-specific exercise (NSE) in people with acute/subacute WAD.

Methods and analysis: A randomised controlled trial has been designed and reported in line with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT). EIH will be assessed immediately after and 24 hours after AE, NSE and a control intervention (randomly allocated). As dependent variables of the study, we will measure Pressure Pain Thresholds measured over the region of the spinous process of C2 and C5, the muscle belly of the tibialis anterior and over the three main peripheral nerve trunks, Neck Pain Intensity, Neck-Disability Index, Pain Catastrophizing Scale, Tampa Scale Kinesiophobia-11, Self-Reported Leeds Assessment of Neuropathic Signs and Symptoms and Self-Efficacy.

Ethics approval and dissemination: Ethical approval has been granted by the Ethics Committee from University Rey Juan Carlos (Madrid, Spain; reference number 0707202116721). The results of this study will be disseminated through presentations at scientific conferences and publication in scientific journals.

Trial registration number: RBR-9tqr2jt

Keywords: whiplash associated disorders, exercise-induce hypoalgesia, exercise, neck pain

Strengths and limitations of this study

· This will be the first randomised controlled trial evaluating exercise induced hypoalgesia (EIH) in response to different exercises in patients who have suffered a whiplash injury.

· This study will provide data regarding the influence of psychosocial variables and neuropathic pain features on EIH in people with Whiplash Associated Disorders (WAD).

· Only people classified as WAD grade II will be included in the study, which could become a limitation to extrapolate the results to all patients suffering with WAD

Introduction

Whiplash associated disorders (WAD) is the term given to describe a wide variety of symptoms commonly reported following a whiplash injury [1]. After a whiplash injury, most individuals recover within 2 to 3 weeks, however up to 42% will suffer persistent pain, resulting in the substantial economical and societal costs [2].

It is accepted that an initial peripheral injury could be a source of nociception following a whiplash injury [3], and different structures can be a source of nociceptive pain such as facet joints, intervertebral discs or muscles, among others [4]. However, identifying a specific pathoanatomical cause of a patient's pain following a whiplash injury is often difficult to achieve [5]. In addition to nociceptive pain, people with WAD can present with disturbances in the central processing of pain (i.e., central sensitisation), neuropathic pain features and the presence of psychological factors [6-8].

Exercise-induced hypoalgesia (EIH) refers to a reduction in pain sensitivity following exercise [9] due to the activation of endogenous pain inhibitory processes. There are inconclusive results on which is the most appropriate form of exercise, for example aerobic versus isometric exercise, to reduce pain sensitivity in people with chronic WAD [9,10]. Importantly, previous studies have shown that patients with chronic WAD may present with dysfunctional pain inhibition [11,12,13] and, specifically, impaired EIH. Exercise is used early following a whiplash injury with the aim of providing pain relief [14], yet no study has investigated whether EIH can be achieved in people with acute/subacute WAD and what exercise is best to achieve this.

The purpose of this study is to assess whether EIH occurs immediately after and 24 hours after two different types of exercise performed by people with acute/subacute WAD. EIH will be assessed as the change in pressure pain threshold (PPT) at both local and remote sites as a measure of pain sensitivity [15,16]. Additionally, we will assess

whether the extent of EIH is associated with a reduction in subjective reports of neck pain intensity immediately after and 24 hours after the exercise. As a final aim, we will evaluate whether baseline measures of neck pain intensity, disability and psychosocial factors determine the extent of EIH following exercise in people with acute/subacute WAD. We hypothesise that some patients with acute/subacute WAD will demonstrate impaired EIH following both aerobic exercise (AE) and neck-specific exercises (NSE), both immediately after and 24 hours after exercise; we expect that this impairment will be related to a greater presence of psychological and neuropathic features. Additionally, we predict that the change in pain sensitivity following exercise will be directly related to the extent of reduction in their subjective report of neck pain intensity.

Methods

Trial design

This study is designed a randomised, controlled, parallel, double-blind, three-arm clinical trial; the study protocol has been designed following the standard protocol items for randomised interventional trials (SPIRIT) [17] and is registered in a clinical trial registry (https://ensaiosclinicos.gov.br/rg/RBR-9tqr2jt). Participants will be randomised to receive either AE, NSE or a control intervention of passive therapies. The flow diagram of the selection procedure, interventions and assessments is provided in Figure 1, and a populated SPIRIT checklist is provided in Supplementary File 1.

Setting

The study will be conducted in the Physical Therapy Department of an outpatient Traumatology Clinic in Madrid, Spain. Patients are referred to this clinic after having a car accident and are evaluated by a physician. If physical therapy

treatment is recommended by the physician, then the patient is referred to the Physical Therapy Department, where they are managed by physical therapists with expertise in Orthopaedic Manual Therapy.

Participants

All eligible patients consecutively presenting to the Clinic with a whiplash injury following a car accident will be approached for recruitment until the sample size is achieved. The physician will determine the grade of WAD according to the Quebec Task Force [18] and will determine whether the patient meets the eligibility criteria. If so, the physician will explain the study to the patient and will provide them with the patient information form and if the patient is willing to participate, written informed consent will be obtained.

Eligibility criteria

Inclusion criteria are aged between 18-65 years [11], have sustained a whiplash injury within the last 7-30 days, diagnosis of WAD grade II according to QTF. Exclusion criteria are WAD grade I, III or IV injury (neurological deficit, fracture or dislocation) [11], presence of previous generalized pain or neuropathic pain condition, nerve root compromise (at least 2 of the following signs: weakness/reflex changes/sensory loss associated with the same spinal nerve) [9], loss of consciousness after the accident [16], instability signs [19], psychiatric disorders [20], inflammatory or rheumatic disease, or tumours [21], previous surgery in the cervical or upper limbs region [22], previous whiplash injury [16], unwilling to perform a prescribed exercise intervention [11].

Randomisation

After providing informed consent, each patient will be randomly assigned to the AE group, NSE group or control group (CG) based on a random sequence

(https://www.randomizer.org/). The randomization sequence will only be known by the principal investigator and auditor.

Blinding

The evaluator and participants in the study will be blinded during the entire process. Participants will not know the description of the other exercise intervention or control intervention. The evaluator will not know which group participants are assigned to.

Sample size calculation

The sample size was calculated using the Grammo calculator v.7.12. Based on the analysis of the variance of means and estimating an alpha risk of 5% (0.05), a beta risk of 20% (0.2), a bilateral contrast, a standard deviation of 15% (0.15), a minimum difference to detect of 15% (0.15) which is based as the minimum clinically important differences on PPT, and a rate of follow-up losses of 10%, 24 participants are required in each group. Thus, we will include 72 patients who will be divided into the three groups.

Intervention

Participants will be asked to only perform the assigned exercise intervention; any interference with the prescribed treatment will lead to exclusion. Participants will be asked to avoid analgesic drug intake 24 hours prior to the intervention and re-assessment [9], caffeine intake 8 hours before the intervention [9] and to avoid physical activity other than daily activities, 24 hours before the intervention and re-assessment [9]. The re-assessment will take place at the same time of day as the first session. The intervention will take place in a Traumatology Clinic; patients will be managed by one of two physical therapists. Both therapists (MLA and EPV) have expertise in

Orthopaedic Manual Therapy with at least two years of experience, and they will be trained to deliver the intervention by EAL.

Aerobic exercise

A submaximal aerobic exercise intervention will be performed using a cycle ergometer (Kardiomed 520 basic cycle, Proxomed, Alzenau, Germany). The seat will be adjusted to suit each participant. The exercise protocol is based on the Aerobic Power Index Test [23], previously used in similar studies [9,24]. The duration of the test will be kept below 20 minutes, thus avoiding early fatigue in the lower extremities [25]. The submaximal level is defined as 75% of the age predicted maximal heart rate [(220-age) x 0.75]. The participant will start at 25 W and approximately at a constant pedalling rate of 60rpm, will maintain this intensity a minute for warm-up. Then the power output will be increased by 25 W every minute until the participant reaches their individual target heart rate, maintaining this power output for 17 minutes; then, power output will be reduced to 25W again for cooling down (2 minutes). Heart rate will be recorded each minute during the increase in power output and then once every 3 minutes until the end of the exercise session. The total exercise time will be 20 minutes.

Neck-specific exercise

Two neck-specific exercises will be implemented which have been selected since they have either resulted in a reduction in pressure pain sensitivity after exercise [26], a decrease in neck pain intensity or disability following the exercise [27], or an improvement in muscle function [28,29,30]. Approximately 5 minutes will be spent firstly teaching the patient how to perform the exercises. Two different exercises will be performed with a short rest in between for a total time of 20 minutes.

· Cranio-Cervical Flexion (CCF) Exercise

Participants will perform CCF exercise in supine, following on an established protocol [31,32]. This task consists of flexion of the cranium over the cervical spine without lifting the head from the supporting surface. The therapist will firstly determine, using a pressure biofeedback device (Stabilizer; Chattanooga Group Inc., Chattanooga, TN), the highest pressure increment (from 22 to 30 mmHg) [33] the participant can correctly sustain for 10 seconds. Once this is determined they will perform 3 sets of 10 repetitions of 10-seconds duration, at this target level with a 10-second rest interval between each contraction and 1 minute rest interval between sets (total contraction time=300 seconds, total time of exercise = 690 seconds).

· Cervical Extension (CE) Exercise

Participants will be asked to position themselves in four-kneeling, and a mid-resistance elastic band (Pilates Band Medium, Decathlon, Villaneuve d'Ascq, France) will be placed over their head, as they hold the elastic band with their hands. The participant will be required to perform CE with the cervical spine in a neutral position against the resistance of the elastic band. During the first 5 minutes of the session, each participant's pain-free 12 repetition maximum (12RM) will be assessed. If the participant can perform 12 repetitions with no pain, this will be the exercise performed. If they are unable to perform 12 repetitions, the elastic band will be changed to one of lower resistance (Pilates Band Light, Decathlon, Villaneuve d'Ascq, France). If the participant is still not able to perform the exercise, it will be performed without an elastic band or they will be moved to a position of prone on elbows. Three sets of 10 repetitions at the predetermined intensity level will be performed with each repetition lasting 3 seconds, with 3 seconds of rest between repetitions, and 30 seconds between sets (total contraction time = 90 seconds, total time of session = 231 seconds).

Control intervention

The control group will receive an intervention considered as a placebo, based on a previous study [27]. Firstly, ultrasound therapy will be applied over the trapezius muscle bilaterally, with the patient in prone. The ultrasound will be applied for four minutes over each side, with 30 seconds rest between sides. Following a further 30 seconds of rest, laser therapy will be applicated over the C2/C3 level, for 5 minutes. Following a further 60 seconds of rest, the patient will be positioned in supine and the therapist will place their hands without therapeutic intention on the patient's neck for 5 minutes. The total duration of the session will be 20 minutes.

Outcome measures

Pressure Pain Threshold

The PPT, which will be the primary outcome measure to quantify EIH and will be recorded in newton/ cm^2using a digital algometer (Force Ten™ -Model FDX; Wagner, Greenwich, CT, USA) with a round tip surface area of 1 cm^2. The measurement will be taken over: a) the spinous process of C2 and C5, providing a measure of local pain sensitivity; b) muscle belly of the left tibialis anterior, providing a measure of remote sensitivity; and c) three bilateral upper limb sites (over the three main peripheral nerve trunks). These sites have already been used in investigations of pain sensitivity in patients with WAD [11,15]. The evaluator will gradually increase the pressure until the patient indicates "Yes" at the first perception of pain. Two measurements will be taken at each site, with 30 seconds between each measurement, obtaining an average of the PPT at each site for the statistical analysis [25]. This measure will be taken at baseline, post-intervention and 24 hours later. EIH will be defined as the difference between the pre and post intervention PPT.

Self-reported Pain Intensity

Self-reported neck pain intensity will be measured using a Visual Analogue Scale (VAS). Participants will be instructed to indicate their current pain intensity by drawing a vertical line on a 0-100 mm horizontal line, with 0 representing no pain and 100 unbearable pain, obtaining a score ranging from 0-100. This outcome has good validity and reliability [34]. This outcome will be measured at baseline, immediately post exercise and 24 hours post exercise.[25]

Additional patient reported outcome measures assessed only at baseline

- Neck Disability Index (NDI)

The NDI is a self-assessment instrument of the specific functional status of subjects with neck pain. It consists of 10 items, each of them rated on a 6-point scale with responses ranging from no disability (0) to complete disability (5). An overall score is generated by summing the score for each item and multiplying by 2. The NDI has been widely applied in patients with WAD with good reliability and validity, and has been validated in Spanish [35,36].

-Pain Catastrophizing Scale (PCS)

PCS is a self-administered scale consisting of 13 items on catastrophic thinking about pain. All items are rated in a 5-point. The total score is generated by summing the ratings of each item [37]. PCS has been used in patients with WAD and is validated in Spanish [38,39].

-Tampa Scale Kinesiophobia-11 (TSK-11)

TSK-11 is a self-administered questionnaire consisting of 11 items designed to assess fear of movement/(re)injury in which patients are instructed to rate each item on a 4-point scale [40]. This scale has been used in patients with WAD and translated to Spanish [41,42].

-Self-reported Leeds Assessment of Neuropathic Signs and Symptoms' Scale (S-LANSS)

This is a self-report version of the Leeds Assessment of Neuropathic Symptoms and Signs scale [43]. It is composed of 7 items and includes two self-examination items. A score of 12 or greater identify patients with pain of a predominantly neuropathic nature. It has been used in patients with WAD [16] and validated to Spanish [44].

-Chronic Disease Self-Efficacy (CDSE)

The Spanish version of this scale will be used [45]. This scale has already been used in patients with acute/subacute WAD and consists of four items whose ranges from 0 "very insecure" to 10 "very safe". The total score ranges from 0 to 40, with higher scores reflecting greater self-efficacy beliefs [46].

Statistical analysis

An intention to treat analysis will be carried out using IBM-SPSS Statistics 24 software. The normality test applied to all the variables will be the Kolmogorov-Smirnov test. For the contrast of intragroup hypotheses, Student's *t* test for paired variables will be applied in the case of parametric distributions and Kruskal-Wallis *H* for non-parametric distributions. Effect Size will be calculated through eta squared; values of r2 will be considered as 0.01 (small), 0.06 (medium) and 0.14 (large). To compare the extent of EIH between groups, one-factor analysis of variance (ANOVA) will be used in the case of parametric distributions and Kruskal-Wallis *H* for non-parametric distributions. Post analysis will be obtained through Bonferroni's contrast for parametric distributions and Mann-Whitney's U for non-parametric ones. Associations between the extent of EIH and pain intensity and psychological factors

will be analyzed via Pearson's *R* or Spearmen's rho. The confidence level used will be 95% (0.05), and the power of the study will be 90% (0.1).

Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting of this study protocol but will be involved in dissemination plans of our research.

Discussion

This protocol paper describes a randomised controlled trial which will determine whether EIH, measured as a change in PPT, occurs in patients with acute/subacute WAD in response to two different exercise modalities and whether EIH is sustained 24 hours later.

Exercise is a fundamental intervention for physical therapists to prescribe for the management of musculoskeletal pain, including for patients with WAD [47]. By examining the effects on pain sensitivity following either AE or NSE, we will be able to determine whether either exercise approach can be used to induce immediate pain relief for patients with acute/subacute WAD. We may find that, comparable to patients with chronic WAD [9,13], some people with acute/subacute pain following a whiplash injury do not respond favourably to the exercises, especially since these patients may have increased pain sensitivity [15,20].

Our results also intend to establish whether the extent of EIH following exercise is determined by other factors including their level of pain and psychological factors. A recent study found that self-efficacy beliefs are an important factor in patients with acute/subacute WAD, and that kinesiophobia mediates the association between self-efficacy and pain catastrophizing [44]. In the current study, we will examine whether

the extent of such features affect the EIH response. Given that a neuropathic component may explain the clinical presentation of some patients with acute pain following a whiplash injury, [16], we will also examine the relationship between neuropathic features and the extent of EIH.

Trial status

This is the first version of the study protocol. Participants will be recruited between February, 2022 and December, 2022. Study completion is expected to be May, 2024.

Abbreviations

SPIRIT: Standard Protocol Items Recommendations for Interventional Trials; WAD: Whiplash Associated Disorders; EIH: Exercise-Induced Hypoalgesia; PPT: Pressure Pain Threshold; AE: Aerobic Exercise; NSE: Neck-Specific Exercise; CCF: Cranio-Cervical Flexion; CF: Cervical Flexion; CE: Cervical Extension; CCE: Cranio-Cervical Extension; PCS: Pain Catastrophizing Scale; TSK-11: Tampa Scale Kinesiophobia-11; NDI: Neck Disability Index; S-LANSS: Self-reported Leeds Assessment of Neuropathic Signs and Symptom's Scale; CDSE: Chronic Diseases Self-Efficacy

Acknowledgments

Not applicable

Authors` contributions

CRB is the director of the project, contributed to the protocol development, provided clinical expertise and is responsible of designing the statistical procedures. DF is the co-director of the project, contributed to protocol development and methodological considerations, and provided clinical expertise. MLA and EPV are the two physical therapists who will perform the interventions for the study. FJRDR will help in the organization of subjects and data extraction. EAL and CBL are the main investigators

who will run the study; they contributed to the concept and study design, provided clinical expertise, and developed the manuscript with feedback from all authors. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets analysed during the current study are available from the corresponding author on reasonable request. The data will be available after the main publication of them; for other circumstances, they should consult the corresponding author. Any data required to support the protocol can be supplied or request.

Ethics approval and consent to participate

This study complies with the Helsinki guidelines for human research, and it has been approved by the Ethics Committee from Universidad Rey Juan Carlos, Madrid, Spain. All study participants will sign an informed consent approved by the ethics committee. The identification of each individual will remain concealed based on the ethical principles of confidentiality and privacy. Any reason for compensation will be covered by professional liability insurance. Informed consent is available in the Spanish language from the corresponding author on request. There is no anticipated harm and compensation for trial participation.

Consent for publication

Not applicable

Competing interests

The authors declare they have no competing interests.

Figure Legends

Figure 1: Participant recruitment and flow through the study

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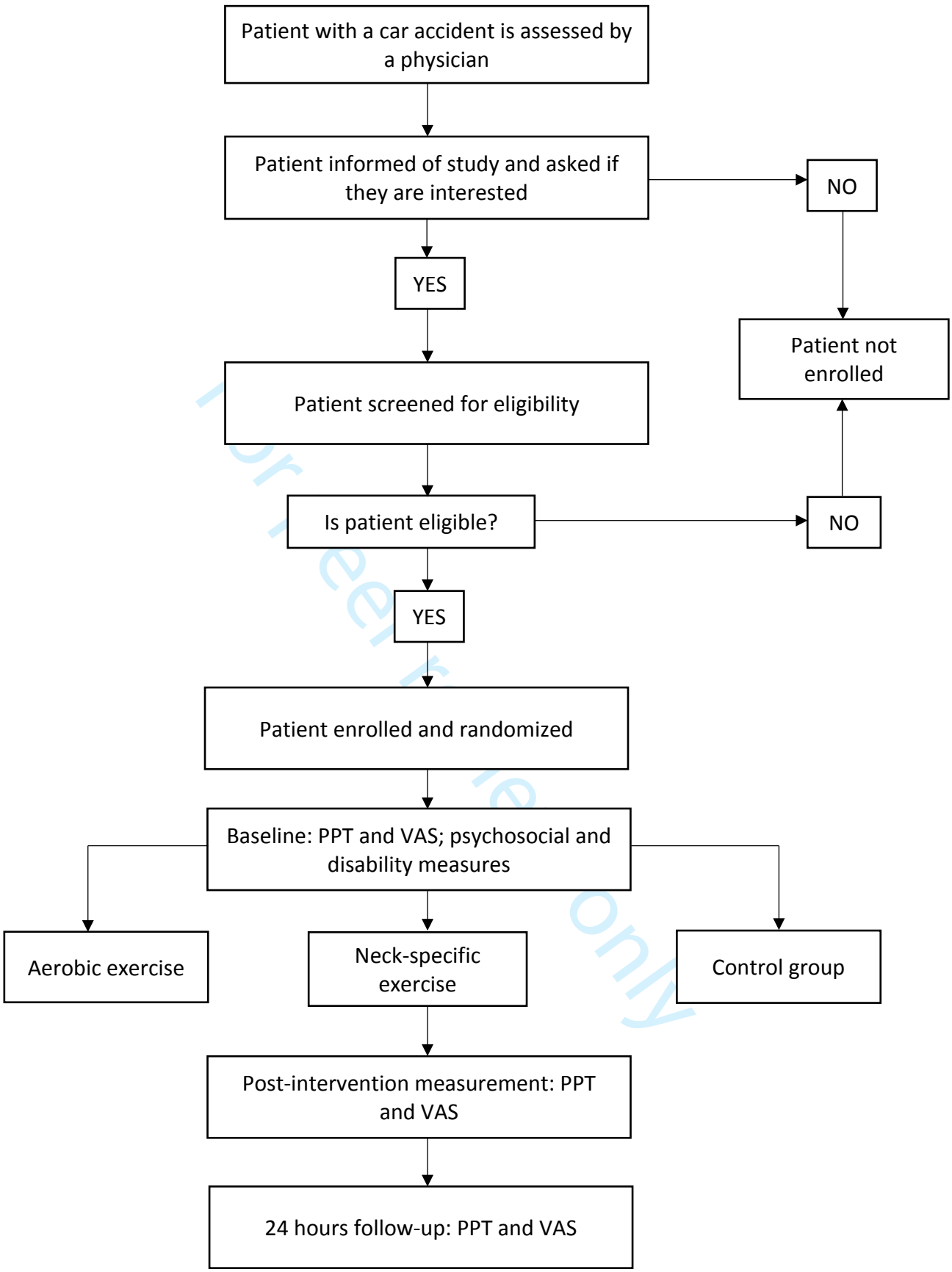

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
	2b	All items from the World Health Organization Trial Registration Data Set	1
Protocol version	3	Date and version identifier	13
Funding	4	Sources and types of financial, material, and other support	14
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 14
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	14
	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)	6

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	3,4
	6b	Explanation for choice of comparators	4
Objectives	7	Specific objectives or hypotheses	4
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)	4

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6-9
	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)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	N/A
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	5
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9-12

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)	4
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	6
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	6
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	6
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9-12

	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	N/A
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	14
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	12
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	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	-
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 No external auditing
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	15

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)	Registry would be updated
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	5
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A no biological specimen were collected as part of this trial
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	
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	15
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	15
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	14
	31b	Authorship eligibility guidelines and any intended use of professional writers	14
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	14
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	15

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 no biological specimen were collected as part of this trial

*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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Exercise-induced hypoalgesia after aerobic versus neck-specific exercise in acute/subacute whiplash associated disorders: Protocol for a randomised controlled trial

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Exercise-induced hypoalgesia after aerobic versus neck-specific exercise in acute/subacute whiplash associated disorders: Protocol for a randomised controlled trial

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Abstract

Introduction: A disturbance in exercise-induced hypoalgesia (EIH) has been observed in patients with chronic whiplash associated disorders (WAD). Yet, no studies have examined whether EIH occurs in people with acute/subacute WAD. This study will determine whether EIH occurs immediately after and 24 hours after aerobic exercise (AE) and neck-specific exercise (NSE) in people with acute/subacute WAD.

Methods and analysis: A randomised controlled trial has been designed and is reported in line with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT). EIH will be assessed immediately after and 24 hours after AE, NSE and a control intervention (randomly allocated). As dependent variables of the study, we will measure Pressure Pain Thresholds measured over the region of the spinous process of C2 and C5, the muscle belly of the tibialis anterior and over the three main peripheral nerve trunks, Neck Pain Intensity, Neck-Disability Index, Pain Catastrophizing Scale, Tampa Scale Kinesiophobia-11, Self-Reported Leeds Assessment of Neuropathic Signs and Symptoms and Self-Efficacy.

Ethics approval and dissemination: Ethical approval has been granted by the Ethics Committee from University Rey Juan Carlos (Madrid, Spain; reference number 0707202116721). The results of this study will be disseminated through presentations at scientific conferences and publication in scientific journals.

Trial registration number: RBR-9tqr2jt

Keywords: whiplash associated disorders, exercise-induce hypoalgesia, exercise, neck pain

Strengths and limitations of this study

· This trial will evaluate exercise induced hypoalgesia (EIH) in response to different exercises in patients who have suffered a whiplash injury.

· EIH will be assessed as a change in pressure pain thresholds (PPT)

· This study will assess EIH immediately and 24 hours after the intervention in people with whiplash associated disorders (WAD)

· The influence of psychological variables and neuropathic pain features on EIH will be assessed

· Only people classified as WAD grade II will be included in the study, which could become a limitation to extrapolate the results to all patients suffering with WAD

Introduction

Whiplash associated disorders (WAD) is the term given to describe a wide variety of symptoms commonly reported following a whiplash injury [1]. After a whiplash injury, most individuals recover within 2 to 3 weeks, however up to 42% will suffer persistent pain, resulting in the substantial economical and societal costs [2].

It is accepted that an initial peripheral injury could be a source of nociception following a whiplash injury [3], and different structures can be a source of nociceptive pain such as facet joints, intervertebral discs or muscles, among others [4]. However, identifying a specific pathoanatomical cause of a patient's pain following a whiplash injury is often difficult to achieve [5]. In addition to nociceptive pain, people with WAD can present with disturbances in the central processing of pain (i.e., central sensitisation), neuropathic pain features and the presence of psychological factors [6-8].

Exercise-induced hypoalgesia (EIH) refers to a reduction in pain sensitivity following exercise [9] due to the activation of endogenous pain inhibitory processes. There are inconclusive results on which is the most appropriate form of exercise, for example aerobic versus isometric exercise, to reduce pain sensitivity in people with chronic WAD [9,10]. Importantly, previous studies have shown that patients with chronic WAD may present with dysfunctional pain inhibition [11,12,13] and, specifically, impaired EIH. Exercise is used early following a whiplash injury with the aim of providing pain relief [14], yet no study has investigated whether EIH can be achieved in people with acute/subacute WAD and what exercise is best to achieve this.

The purpose of this study is to assess whether EIH occurs immediately after and 24 hours after two different types of exercise performed by people with acute/subacute WAD. EIH will be assessed as the change in pressure pain threshold (PPT) at both local and remote sites as a measure of pain sensitivity [15,16]. Additionally, we will assess

whether the extent of EIH is associated with a reduction in subjective reports of neck pain intensity immediately after and 24 hours after the exercise. As a final aim, we will evaluate whether baseline measures of neck pain intensity, disability and psychosocial factors determine the extent of EIH following exercise in people with acute/subacute WAD. We hypothesise that some patients with acute/subacute WAD will demonstrate impaired EIH following both aerobic exercise (AE) and neck-specific exercises (NSE), both immediately after and 24 hours after exercise; we expect that this impairment will be related to a greater presence of psychological and neuropathic features. Additionally, we predict that the change in pain sensitivity following exercise will be directly related to the extent of reduction in their subjective report of neck pain intensity.

Methods

Trial design

This study is designed a randomised, controlled, parallel, double-blind, three-arm clinical trial; the study protocol has been designed following the standard protocol items for randomized interventional trials (SPIRIT) [17] and is registered in a clinical trial registry (https://ensaiosclinicos.gov.br/rg/RBR-9tqr2jt). Participants will be randomized to receive either AE, NSE or a control intervention of passive therapies. The information sheet will not describe the details of the three interventions and therefore the participant will not be aware of the other interventions. The flow diagram of the selection procedure, interventions and assessments is provided in Figure 1, and a populated SPIRIT checklist is provided in Additional file 1.

Setting

The study will be conducted in the Physical Therapy Department of an outpatient Traumatology Clinic in Madrid, Spain. Patients are referred to this clinic after having a car accident and are evaluated by a physician. If physical therapy treatment is recommended by the physician, then the patient is referred to the Physical Therapy Department, where they are managed by physical therapists with expertise in Orthopaedic Manual Therapy. Before starting the study, the evaluator will be trained in the different assessment procedures to standardise the evaluation.

Participants

All eligible patients consecutively presenting to the Clinic with a whiplash injury following a car accident will be approached for recruitment until the sample size is achieved. The physician will determine the grade of WAD according to the Quebec Task Force [18] and will determine whether the patient meets the eligibility criteria. If so, the physician will explain the study to the patient and will provide them with the patient information form and if the patient is willing to participate, written informed consent will be obtained.

Eligibility criteria

Inclusion criteria are aged between 18-65 years [11], have sustained a whiplash injury within the last 7-30 days, diagnosis of WAD grade II according to QTF, and not yet recovered from neck pain at the time of the assessment. Exclusion criteria are WAD grade I, III or IV injury (neurological deficit, fracture or dislocation) [11], presence of previous generalized pain or neuropathic pain condition, nerve root compromise (at least 2 of the following signs: weakness/reflex changes/sensory loss associated with the same spinal nerve) [9], loss of consciousness after the accident [16], instability signs [19], psychiatric disorders [20], inflammatory or rheumatic disease, or tumours [21],

previous surgery in the cervical or upper limbs region [22], previous whiplash injury [16], unwilling to perform a prescribed exercise intervention [11].

Randomization

After providing informed consent, each patient will be randomly assigned to the AE group, NSE group or control group (CG) based on a random sequence (https://www.randomizer.org/). The randomization sequence will only be known by the principal investigator and auditor.

Blinding

The evaluator and participants in the study will be blinded during the entire process. Participants will not know the description of the other exercise intervention or control intervention. The evaluator will not know which group participants are assigned to. To achieve this, the evaluator will assess the participant, and then leave the room as the participant performs the intervention with another investigator and, when finished, the evaluator will re-enter the room to re-evaluate the participant, approximately two minutes after completion of the intervention. Blinding will be maintained during the 24 hour post-intervention assessment.

Sample size calculation

The sample size was calculated using the Grammo calculator v.7.12. Based on the analysis of the variance of means and estimating an alpha risk of 5% (0.05), a beta risk of 20% (0.2), a bilateral contrast, a standard deviation of 15% (0.15), a minimum difference to detect of 15% (0.15) which is based as the minimum clinically important differences on PPT, and a rate of follow-up losses of 10%, 24 participants are required in each group. Thus, we will include 72 patients who will be divided into the three groups.

Intervention

Participants will be asked to only perform the assigned exercise intervention; any interference with the prescribed treatment will lead to exclusion. Participants will be asked to avoid analgesic drug intake 24 hours prior to the intervention and re-assessment [9], caffeine intake 8 hours before the intervention [9] and to avoid physical activity other than daily activities, 24 hours before the intervention and re-assessment [9]. The re-assessment will take place at the same time of day as the first session. The intervention will take place in a Traumatology Clinic; patients will be managed by one of two physical therapists. Both therapists (MLA and EPV) have expertise in Orthopaedic Manual Therapy with at least two years of experience, and they will be trained to deliver the intervention by EAL.

Aerobic exercise

A submaximal aerobic exercise intervention will be performed using a cycle ergometer (Kardiomed 520 basic cycle, Proxomed, Alzenau, Germany). The seat will be adjusted to suit each participant. The exercise protocol is based on the Aerobic Power Index Test [23], previously used in similar studies [9,24]. The duration of the test will be kept below 20 minutes, thus avoiding early fatigue in the lower extremities [25]. The submaximal level is defined as 75% of the age predicted maximal heart rate [(220-age) x 0.75]. The participant will start at 25 W and approximately at a constant pedalling rate of 60rpm, will maintain this intensity a minute for warm-up. Then the power output will be increased by 25 W every minute until the participant reaches their individual target heart rate, maintaining this power output for 17 minutes; then, power output will be reduced to 25W again for cooling down (2 minutes). Heart rate will be recorded each

minute during the increase in power output and then once every 3 minutes until the end of the exercise session. The total exercise time will be 20 minutes.

Neck-specific exercise

Two neck-specific exercises will be implemented which have been selected since they have either resulted in a reduction in pressure pain sensitivity after exercise [26], a decrease in neck pain intensity or disability following the exercise [27], or an improvement in muscle function [28,29,30]. Approximately 5 minutes will be spent firstly teaching the patient how to perform the exercises. Two different exercises will be performed with a short rest in between for a total time of 20 minutes.

· Cranio-Cervical Flexion (CCF) Exercise

Participants will perform CCF exercise in supine, following on an established protocol [31,32]. This task consists of flexion of the cranium over the cervical spine without lifting the head from the supporting surface. The therapist will firstly determine, using a pressure biofeedback device (Stabilizer; Chattanooga Group Inc., Chattanooga, TN), the highest pressure increment (from 22 to 30 mmHg) [33] the participant can correctly sustain for 10 seconds. Once this is determined they will perform 3 sets of 10 repetitions of 10-seconds duration, at this target level with a 10-second rest interval between each contraction and 1 minute rest interval between sets (total contraction time=300 seconds, total time of exercise = 690 seconds).

· Cervical Extension (CE) Exercise

Participants will be asked to position themselves in four-kneeling, and a mid-resistance elastic band (Pilates Band Medium, Decathlon, Villaneuve d'Ascq, France) will be placed over their head, as they hold the elastic band with their hands. The participant will be required to perform CE with the cervical spine in a neutral position

against the resistance of the elastic band. During the first 5 minutes of the session, each participant's pain-free 12 repetition maximum (12RM) will be assessed. If the participant can perform 12 repetitions with no pain, this will be the exercise performed. If they are unable to perform 12 repetitions, the elastic band will be changed to one of lower resistance (Pilates Band Light, Decathlon, Villaneuve d'Ascq, France). If the participant is still not able to perform the exercise, it will be performed without an elastic band or they will be moved to a position of prone on elbows. Three sets of 10 repetitions at the predetermined intensity level will be performed with each repetition lasting 3 seconds, with 3 seconds of rest between repetitions, and 30 seconds between sets (total contraction time = 90 seconds, total time of session = 231 seconds).

Control intervention

The control group will receive an intervention considered as a placebo, based on a previous study [27]. Firstly, ultrasound therapy will be applied over the trapezius muscle bilaterally, with the patient in prone. The ultrasound will be applied for four minutes over each side, with 30 seconds rest between sides. Following a further 30 seconds of rest, laser therapy will be applicated over the C2/C3 level, for 5 minutes. Following a further 60 seconds of rest, the patient will be positioned in supine and the therapist will place their hands without therapeutic intention on the patient's neck for 5 minutes. The total duration of the session will be 20 minutes.

Outcome measures

Pressure Pain Threshold

The PPT, which will be the primary outcome measure to quantify EIH and will be recorded in newton/ cm^2using a digital algometer (Force Ten™ -Model FDX; Wagner, Greenwich, CT, USA) with a round tip surface area of 1 cm^2. The measurements will be taken over several sites in the following order: 1) the spinous

process of C2 and C5, providing a measure of local pain sensitivity; 2) muscle belly of the left tibialis anterior, providing a measure of remote sensitivity; and 3) three bilateral upper limb sites (over the three main peripheral nerve trunks). These sites have already been used in investigations of pain sensitivity in patients with WAD [11,15]. The evaluator will gradually increase the pressure until the patient indicates "Yes" at the first perception of pain. Two measurements will be taken at each site, with 30 seconds between each measurement, obtaining an average of the PPT at each site for the statistical analysis [25]. This measure will be taken at baseline, post-intervention and 24 hours later. Relative EIH will be defined as a significant positive change in PPTs, that is, when PPT increases after exercise, according to the following formula: [(PPTPostExercise – PPTPreExercise)/PPTPreExercise)] x 100.

Self-reported Pain Intensity

Self-reported neck pain intensity will be measured using a Visual Analogue Scale (VAS). Participants will be instructed to indicate their current pain intensity by drawing a vertical line on a 0-100 mm horizontal line, with 0 representing no pain and 100 unbearable pain, obtaining a score ranging from 0-100. This outcome has good validity and reliability [34]. This outcome will be measured at baseline, immediately post exercise and 24 hours post exercise.[25] Pain intensity will be evaluated always just before PPT assessment.

Additional patient reported outcome measures assessed only at baseline

- Neck Disability Index (NDI)

The NDI is a self-assessment instrument of the specific functional status of subjects with neck pain. It consists of 10 items, each of them rated on a 6-point scale with responses ranging from no disability (0) to complete disability (5). An overall score is generated by summing the score for each item and multiplying by 2. The NDI

has been widely applied in patients with WAD with good reliability and validity, and has been validated in Spanish [35,36].

-Pain Catastrophizing Scale (PCS)

PCS is a self-administered scale consisting of 13 items on catastrophic thinking about pain. All items are rated in a 5-point. The total score is generated by summing the ratings of each item [37]. PCS has been used in patients with WAD and is validated in Spanish [38,39].

-Tampa Scale Kinesiophobia-11 (TSK-11)

TSK-11 is a self-administered questionnaire consisting of 11 items designed to assess fear of movement/(re)injury in which patients are instructed to rate each item on a 4-point scale [40]. This scale has been used in patients with WAD and translated to Spanish [41,42].

-Self-reported Leeds Assessment of Neuropathic Signs and Symptoms' Scale (S-LANSS)

This is a self-report version of the Leeds Assessment of Neuropathic Symptoms and Signs scale [43]. It is composed of 7 items and includes two self-examination items. A score of 12 or greater identify patients with pain of a predominantly neuropathic nature. It has been used in patients with WAD [16] and validated to Spanish [44].

-Chronic Disease Self-Efficacy (CDSE)

The Spanish version of this scale will be used [45]. This scale has already been used in patients with acute/subacute WAD and consists of four items whose ranges from 0 "very insecure" to 10 "very safe". The total score ranges from 0 to 40, with higher scores reflecting greater self-efficacy beliefs [46].

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Statistical analysis

An intention to treat analysis will be carried out using IBM-SPSS Statistics 24 software. The normality test applied to all the variables will be the Kolmogorov-Smirnov test. For the contrast of intragroup hypotheses, both in the short term and 24 hours after the intervention, Student's *t* test for paired variables will be applied in the case of parametric distributions and Kruskal-Wallis *H* for non-parametric distributions. Effect Size will be calculated through eta squared; values of r2 will be considered as 0.01 (small), 0.06 (medium) and 0.14 (large). To compare the extent of EIH between groups, both in the short term and 24 hours after the intervention, one-factor analysis of variance (ANOVA) will be used in the case of parametric distributions and Kruskal-Wallis *H* for non-parametric distributions. Post analysis will be obtained through Bonferroni's contrast for parametric distributions and Mann-Whitney's U for non-parametric ones. Associations between the extent of EIH and other variables will be analysed via regression analysis. The confidence level used will be 95% (0.05), and the power of the study will be 90% (0.1).

Discussion

This protocol paper describes a randomized controlled trial which will determine whether EIH, measured as a change in PPT, occurs in patients with acute/subacute WAD in response to two different exercise modalities and whether EIH is sustained 24 hours later.

Exercise is a fundamental intervention for physical therapists to prescribe for the management of musculoskeletal pain, including for patients with WAD [47]. By examining the effects on pain sensitivity following either AE or NSE, we will be able to determine whether either exercise approach can be used to induce immediate pain relief for patients with acute/subacute WAD. We may find that, comparable to patients with chronic WAD [9,13], some people with acute/subacute pain following a whiplash injury do not respond favourably to the exercises, especially since these patients may have increased pain sensitivity [15,20].

Our results also intend to establish whether the extent of EIH following exercise is determined by other factors including their level of pain and psychological factors. A recent study found that self-efficacy beliefs are an important factor in patients with acute/subacute WAD, and that kinesiophobia mediates the association between self-efficacy and pain catastrophizing [44]. In the current study, we will examine whether the extent of such features affect the EIH response. Given that a neuropathic component may explain the clinical presentation of some patients with acute pain following a whiplash injury, [16], we will also examine the relationship between neuropathic features and the extent of EIH.

Trial status

This is the first version of the study protocol. Participants will be recruited between February, 2022 and December, 2022. Study completion is expected to be May, 2024.

Abbreviations

SPIRIT: Standard Protocol Items Recommendations for Interventional Trials; WAD: Whiplash Associated Disorders; EIH: Exercise-Induced Hypoalgesia; PPT: Pressure Pain Threshold; AE: Aerobic Exercise; NSE: Neck-Specific Exercise; CCF: Cranio-Cervical Flexion; CF: Cervical Flexion; CE: Cervical Extension; CCE: Cranio-Cervical

Extension; PCS: Pain Catastrophizing Scale; TSK-11: Tampa Scale Kinesiophobia-11; NDI: Neck Disability Index; S-LANSS: Self-reported Leeds Assessment of Neuropathic Signs and Symptom's Scale; CDSE: Chronic Diseases Self-Efficacy

Acknowledgments

Not applicable

Authors` contributions

CRB is the director of the project, contributed to the protocol development, provided clinical expertise and is responsible of designing the statistical procedures. DF is the co-director of the project, contributed to protocol development and methodological considerations, and provided clinical expertise. MLA and EPV are the two physical therapists who will perform the interventions for the study. FJRDR will help in the organization of subjects and data extraction. EAL and CBL are the main investigators who will run the study; they contributed to the concept and study design, provided clinical expertise, and developed the manuscript with feedback from all authors. All authors read and approved the final manuscript.

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Data availability statement

The datasets analysed during the current study are available from the corresponding author on reasonable request. The data will be available after the main publication of them; for other circumstances, they should consult the corresponding author. Any data required to support the protocol can be supplied or request.

Ethics approval and dissemination

This study complies with the Helsinki guidelines for human research, and it has been approved by the Ethics Committee from Universidad Rey Juan Carlos, Madrid, Spain.

All study participants will sign an informed consent approved by the ethics committee. The identification of each individual will remain concealed based on the ethical principles of confidentiality and privacy. Any reason for compensation will be covered by professional liability insurance. Informed consent is available in the Spanish language from the corresponding author on request. There is no anticipated harm and compensation for trial participation. The results of this trial will be published in peer-reviewed scientific journals and presented at relevant academic conferences.

Consent for publication

Not applicable

Competing interests

The authors declare they have no competing interests.

Figure legend

Figure 1. Subject recruitment and flow through the study

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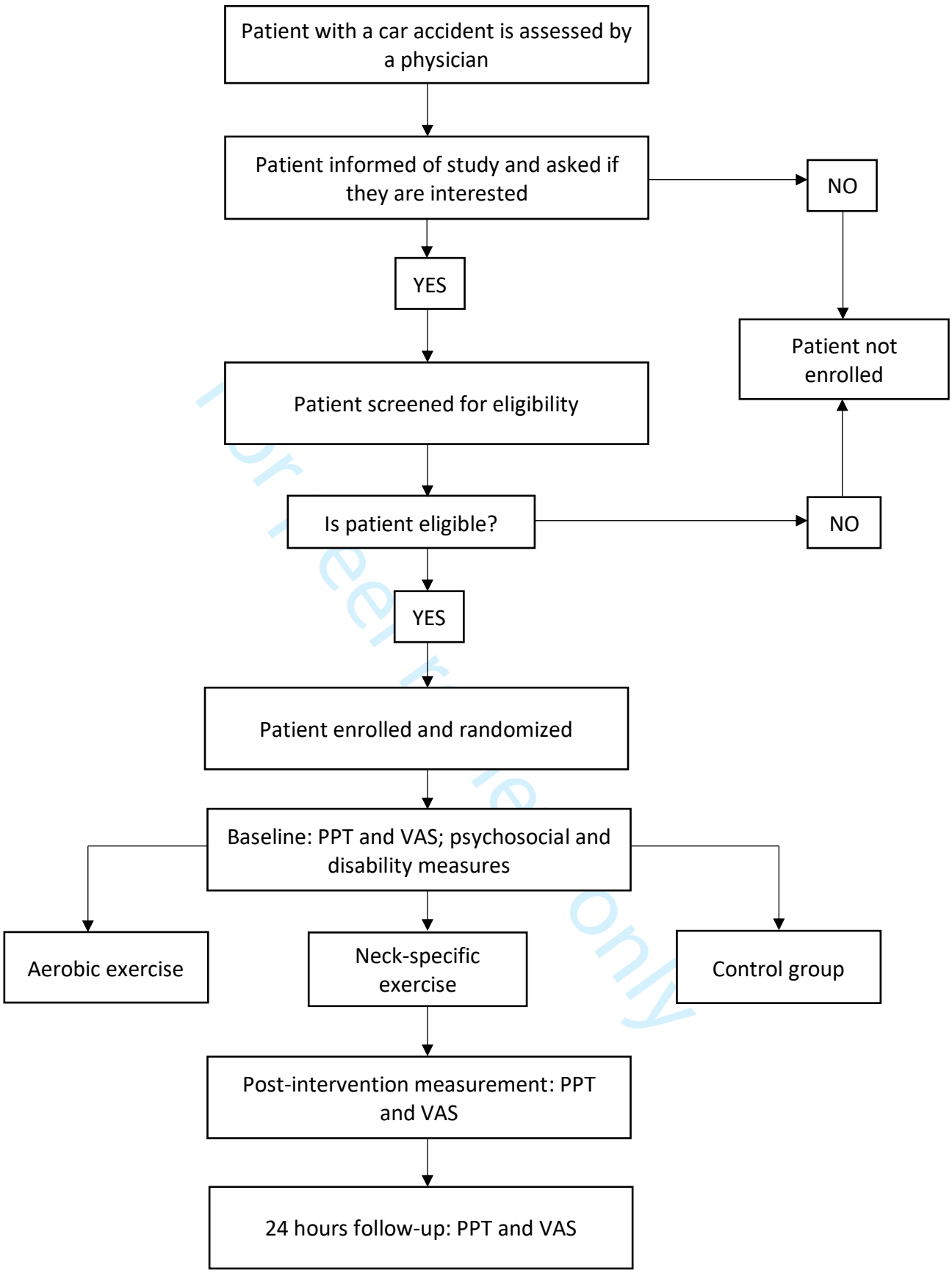

Figure 1. Subject recruitment and flow through the study

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
	2b	All items from the World Health Organization Trial Registration Data Set	1
Protocol version	3	Date and version identifier	13
Funding	4	Sources and types of financial, material, and other support	14
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 14
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	14
	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)	6

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	3,4
	6b	Explanation for choice of comparators	4
Objectives	7	Specific objectives or hypotheses	4
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)	4

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6-9
	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)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	N/A
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	5
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9-12

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)	4
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	6
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	6
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	6
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9-12

	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	N/A
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	14
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	12
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	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	-
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 No external auditing
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	15

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)	Registry would be updated
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	5
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A no biological specimen were collected as part of this trial
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	
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	15
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	15
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	14
	31b	Authorship eligibility guidelines and any intended use of professional writers	14
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	14
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	15

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 no biological specimen were collected as part of this trial

*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.