

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<u>http://bmjopen.bmj.com</u>).

If you have any questions on BMJ Open's open peer review process please email <u>info.bmjopen@bmj.com</u>

BMJ Open

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

Journal:	BMJ Open
Manuscript ID	bmjopen-2022-061679
Article Type:	Protocol
Date Submitted by the Author:	02-Feb-2022
Complete List of Authors:	Anarte-Lazo, Ernesto; University of Birmingham, School of Sport, Exercise and Rehabilitation Sciences Bernal-Utrera, Carlos; University of Seville Lopez-Amor , Mario; Clinica San Vicente Porras-Valencia , Eugenia ; Clinica San Vicente Ruy-Diaz-Rojas, Francisco Javier ; Clinica San Vicente Falla, Deborah; University of Birmingham, School of Sport, Exercise and Rehabilitation Sciences Rodriguez-Blanco, Cleofas; Universidad de Sevilla, Physiotherapy
Keywords:	PAIN MANAGEMENT, Rehabilitation medicine < INTERNAL MEDICINE, Musculoskeletal disorders < ORTHOPAEDIC & TRAUMA SURGERY, Spine < ORTHOPAEDIC & TRAUMA SURGERY



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

Anarte-Lazo $E^{1,2,3\dagger}$, Bernal-Utrera $C^{4,5\dagger}$, Lopez-Amor M³, Porras-Valencia E³, Ruy-Diaz-Rojas FJ³, Falla D^{2*}, Rodriguez-Blanco, C^{4,5}

Affiliations

- Doctoral Program in Health Sciences, University of Seville, 41009, Seville, Spain
- Centre of Precision Rehabilitation for Spinal Pain (CPR Spine), School of Sport, Exercise and Rehabilitation Sciences, University of Birmingham, Birmingham, UK
- Clinica San Vicente, Avda Ventisquero de la Condesa, 46, 280235, Madrid, Spain
- Faculty of Nursing, Physiotherapy and Podiatry, Department of Physiotherapy, University of Seville, 41009, Seville, Spain
- 5. Fisiosur I+D Research Institute, 04630 Almeria, Spain

*Corresponding author

Deborah Falla; D.Falla@bham.ac.uk

[†]Contributed equally

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 Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

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

BMJ Open

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, threearm 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

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

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

BMJ Open

(<u>https://www.randomizer.org/</u>). 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 reassessment [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

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

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

BMJ Open

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 midresistance 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, the elastic band 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). Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

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/ cm²using a digital algometer (Force TenTM -Model FDX; Wagner, Greenwich, CT, USA) with a round tip surface area of 1 cm². 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

BMJ Open

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

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

BMJ Open

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 selfefficacy and pain catastrophizing [44]. In the current study, we will examine whether

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

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 codirector 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

BMJ Open

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.

Funding

The are no sources of funding

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

References

- Sterling M. Physiotherapy management of whiplash-associated disorders (WAD). J Physiother. 2014 Mar;60(1):5-12.
- Elliott JM, Noteboom JT, Flynn TW, Sterling M. Characterization of acute and chronic whiplash-associated disorders. J Orthop Sports Phys Ther. 2009 May;39(5):312-23.
- Siegmund GP, Winkelstein BA, Ivancic PC, Svensson MY, Vasavada A. The anatomy and biomechanics of acute and chronic whiplash injury. Traffic Inj Prev. 2009 Apr;10(2):101-12.
- Michele Sterling, Julia Treleaven, Sandra Edwards & Gwendolen Jull (2002) Pressure Pain Thresholds in Chronic Whiplash Associated Disorder: Further Evidence of Altered Central Pain Processing, Journal of Musculoskeletal Pain,10:3, 69-81
- Sterling M. Whiplash-associated disorder: musculoskeletal pain and related clinical findings. *J Man Manip Ther*. 2011;19(4):194-200. doi:10.1179/106698111X13129729551949
- 6. Chien A, Eliav E, Sterling M. Whiplash (grade II) and cervical radiculopathy share a similar sensory presentation: an investigation using quantitative sensory testing. Clin J Pain. 2008 Sep;24(7):595-603.
- Miettinen T, Airaksinen O, Lindgren KA, Leino E. Whiplash injuries in Finland--the possibility of some sociodemographic and psychosocial factors to predict the outcome after one year. Disabil Rehabil. 2004 Dec 2;26(23):1367-72.
- Kasch H, Stengaard-Pedersen K, Arendt-Nielsen L, Staehelin Jensen T. Pain thresholds and tenderness in neck and head following acute whiplash injury: a prospective study. Cephalalgia. 2001 Apr;21(3):189-97.
- 9. Smith A, Ritchie C, Pedler A, McCamley K, Roberts K, Sterling M. Exercise induced hypoalgesia is elicited by isometric, but not aerobic exercise in

BMJ Open

ו ר			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			
17			
18			
19			
20			
21			
22			
23			
24			
25			
26			
27			
28			
29			
30			
31			
32			
33			
34			
35			
36			
3/			
38			
39			
40 1			
41 43			
42			
75 77			
45 45			
46			
47			
48			
49			
50			
51			
52			
53			
54			
55			
56			
57			
58			
59			
60			

individuals with chronic whiplash associated disorders. Scand J Pain. 2017 Apr;15:14-21.

- 10. Van Oosterwijck J, Nijs J, Meeus M, Van Loo M, Paul L. Lack of endogenous pain inhibition during exercise in people with chronic whiplash associated disorders: an experimental study. J Pain. 2012 Mar;13(3):242-54.
- 11. Smith A, Ritchie C, Warren J, Sterling M. Exercise-induced Hypoalgesia Is Impaired in Chronic Whiplash-associated Disorders (WAD) With Both Aerobic and Isometric Exercise. Clin J Pain. 2020 Aug;36(8):601-611.
- 12. Ng TS, Pedler A, Vicenzino B, Sterling M. Less efficacious conditioned pain modulation and sensory hypersensitivity in chronic whiplash-associated disorders in Singapore. Clin J Pain. 2014 May;30(5):436-42.
- 13. Daenen L, Nijs J, Roussel N, Wouters K, Van Loo M, Cras P. Dysfunctional pain inhibition in patients with chronic whiplash-associated disorders: an experimental study. Clin Rheumatol. 2013 Jan;32(1):23-31.
- 14. Teasell RW, McClure JA, Walton D, Pretty J, Salter K, Meyer M, Sequeira K, Death B. A research synthesis of therapeutic interventions for whiplashassociated disorder (WAD): part 2 - interventions for acute WAD. Pain Res Manag. 2010 Sep-Oct;15(5):295-304.
- 15. Sterling M, Jull G, Vicenzino B, Kenardy J. Sensory hypersensitivity occurs soon after whiplash injury and is associated with poor recovery. Pain. 2003 Aug;104(3):509-517.
- 16. Sterling M, Pedler A. A neuropathic pain component is common in acute whiplash and associated with a more complex clinical presentation. Man Ther. 2009 Apr;14(2):173-9.
- 17. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin JA, Doré CJ, Parulekar WR, Summerskill WS, Groves T, Schulz KF, Sox HC, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Ann Intern Med. 2013 Feb 5;158(3):200-7.
- 18. Gurumoorthy D, Twomey L. The Quebec Task Force on Whiplash-Associated Disorders. Spine (Phila Pa 1976). 1996 Apr 1;21(7):897-8.
- 19. Wiangkham T, Duda J, Haque MS, Price J, Rushton A. A cluster randomised, double-blind pilot and feasibility trial of an active behavioural physiotherapy

intervention for acute whiplash-associated disorder (WAD)II. PLoS One. 2019 May 9;14(5):e0215803.

20. Chien A, Eliav E, Sterling M. Hypoesthesia occurs in acute whiplash irrespective of pain and disability levels and the presence of sensory hypersensitivity. Clin J Pain. 2008 Nov-Dec;24(9):759-66.

- Tough EA, White AR, Richards SH, Campbell JL. Myofascial trigger point needling for whiplash associated pain--a feasibility study. Man Ther. 2010 Dec;15(6):529-35.
- Crawford JR, Khan RJ, Varley GW. Early management and outcome following soft tissue injuries of the neck-a randomised controlled trial. Injury. 2004 Sep;35(9):891-5.
- 23. Telford, R. D., Minikin, B. R., Hahn, A. G., & Hooper, L. A. (1989). A simple method for the assessment of general fitness: The Tri-level Profile. *Australian Journal of Science and Medicine in Sport*, 21(3), 6-9.
- 24. Wallman KE, Morton AR, Goodman C, Grove R. Physiological responses during a submaximal cycle test in chronic fatigue syndrome. Med Sci Sports Exerc. 2004 Oct;36(10):1682-8.
- 25. Ickmans K, Malfliet A, De Kooning M, Goudman L, Hubloue I, Schmitz T, Goubert D, Aguilar-Ferrandiz ME. Lack of Gender and Age Differences in Pain Measurements Following Exercise in People with Chronic Whiplash-Associated Disorders. Pain Physician. 2017 Sep;20(6):E829-E840.
- 26. O'Leary S, Falla D, Hodges PW, Jull G, Vicenzino B. Specific therapeutic exercise of the neck induces immediate local hypoalgesia. J Pain. 2007 Nov;8(11):832-9.
- 27. Bernal-Utrera, C., Gonzalez-Gerez, J.J., Anarte-Lazo, E. *et al.* Manual therapy versus therapeutic exercise in non-specific chronic neck pain: a randomized controlled trial.*Trials* **21**, 682 (2020).
- Schomacher J, Falla D. Function and structure of the deep cervical extensor muscles in patients with neck pain. Man Ther. 2013 Oct;18(5):360-6.
- 29. Falla D, O'Leary S, Farina D, Jull G. The change in deep cervical flexor activity after training is associated with the degree of pain reduction in patients with chronic neck pain. Clin J Pain. 2012 Sep;28(7):628-34.

BMJ Open

2	
3	
4	
5	
6	
7	
/	
8	
9	
10	
11	
12	
13	
14	
15	
16	
10	
1/	
18	
19	
20	
21	
22	
23	
24	
25	
25	
20	
27	
28	
29	
30	
31	
32	
33	
34	
35	
26	
30	
37	
38	
39	
40	
41	
42	
43	
10	
15	
45 47	
46	
47	
48	
49	
50	
51	
52	
52	
22	
54 5-	
55	
56	
57	
58	
59	

- 30. Jull GA, Falla D, Vicenzino B, Hodges PW. The effect of therapeutic exercise on activation of the deep cervical flexor muscles in people with chronic neck pain. Man Ther. 2009 Dec;14(6):696-701.
- Jull GA, O'Leary SP, Falla DL. Clinical assessment of the deep cervical flexor muscles: the craniocervical flexion test. J Manipulative Physiol Ther. 2008 Sep;31(7):525-33.
- 32. Jull G, Falla D, Treleaven J, O'Leary S "Management of neck pain disorders: a research informed approach". Elsevier, UK 2019
- Jull GA. Deep Cervical Flexor Muscle Dysfunction in Whiplash, Journal of Musculoskeletal Pain, 2000, 8:1-2, 143-154
- 34. Hawker GA, Mian S, Kendzerska T, French M. Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP). Arthritis Care Res (Hoboken). 2011 Nov;63 Suppl 11:S240-52.
- 35. Vernon H.The Neck Disability Index. Journal of Musculoskeletal Pain, 1996 4:4, 95-104,
- 36. Kovacs FM, Bagó J, Royuela A, Seco J, Giménez S, Muriel A, Abraira V, Martín JL, Peña JL, Gestoso M, Mufraggi N, Núñez M, Corcoll J, Gómez-Ochoa I, Ramírez MJ, Calvo E, Castillo MD, Martí D, Fuster S, Fernández C, Gimeno N, Carballo A, Milán A, Vázquez D, Cañellas M, Blanco R, Brieva P, Rueda MT, Alvarez L, Del Real MT, Ayerbe J, González L, Ginel L, Ortega M, Bernal M, Bolado G, Vidal A, Ausín A, Ramón D, Mir MA, Tomás M, Zamora J, Cano A. Psychometric characteristics of the Spanish version of instruments to measure neck pain disability. BMC Musculoskelet Disord. 2008 Apr 9;9:42.
- 37. Sullivan M, Bishop S, Pivik J.The Pain Catastrophizing Scale: Development and validation. Psychological Assessment 1995, 7. 524-532.
- Andersen TE, Karstoft KI, Brink O, Elklit A. Pain-catastrophizing and fearavoidance beliefs as mediators between post-traumatic stress symptoms and pain following whiplash injury - A prospective cohort study. Eur J Pain. 2016 Sep;20(8):1241-52.
- García Campayo J, Rodero B, Alda M, Sobradiel N, Montero J, Moreno S.
 Validación de la versión española de la escala de la catastrofización ante el dolor

(Pain Catastrophizing Scale) en la fibromialgia [Validation of the Spanish version of the Pain Catastrophizing Scale in fibromyalgia]. Med Clin (Barc). 2008 Oct 18;131(13):487-92. Spanish.

- 40. Tkachuk GA, Harris CA. Psychometric properties of the Tampa Scale for Kinesiophobia-11 (TSK-11). J Pain. 2012 Oct;13(10):970-7.
- 41. Gómez-Pérez L, López-Martínez AE, Ruiz-Párraga GT. Psychometric Properties of the Spanish Version of the Tampa Scale for Kinesiophobia (TSK). J Pain. 2011 Apr;12(4):425-35.
- Nieto R, Miró J, Huguet A. The fear-avoidance model in whiplash injuries. Eur J Pain. 2009 May;13(5):518-23.
- 43. Bennett MI, Smith BH, Torrance N, Potter J. The S-LANSS score for identifying pain of predominantly neuropathic origin: validation for use in clinical and postal research. J Pain. 2005 Mar;6(3):149-58.
- 44. López-de-Uralde-Villanueva I, Gil-Martínez A, Candelas-Fernández P, de Andrés-Ares J, Beltrán-Alacreu H, La Touche R. Validity and reliability of the Spanish-language version of the self-administered Leeds Assessment of Neuropathic Symptoms and Signs (S-LANSS) pain scale. Neurologia. 2018 Oct;33(8):505-514. English, Spanish.
- 45. Lorig KR, Ritter PL, González VM. Hispanic chronic disease self-management: a randomized community-based outcome trial. Nurs Res. 2003 Nov-Dec;52(6):361-9.
- 46. Pedrero-Martin Y, Falla D, Martinez-Calderon J, Liew BXW, Scutari M, Luque-Suarez A. Self-efficacy beliefs mediate the association between pain intensity and pain interference in acute/subacute whiplash-associated disorders. Eur Spine J. 2021 Jan 27.
- 47. Teasell RW, McClure JA, Walton D, Pretty J, Salter K, Meyer M, Sequeira K, Death B. A research synthesis of therapeutic interventions for whiplash-associated disorder (WAD): part 4 noninvasive interventions for chronic WAD. Pain Res Manag. 2010 Sep-Oct;15(5):313-22.



Section/item	ltem No	Description	Addressed on page number
Administrative inf	ormatior		
Title	1	କୁ ବୁଁ ରୁ Descriptive title identifying the study design, population, interventions, and, if appt କୁଣ୍ଟି, trial acronym	1
Frial 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	5a	Names, affiliations, and roles of protocol contributors	1, 14
responsibilities	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, managemerit, 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

Page	23 of 27		BMJ Open by copy 22	
1 2	Introduction		ight, i	
3 4 5	Background and rationale	6a	Description of research question and justification for undertaking the trial, including symmary of relevant	3,4
6 7		6b	Explanation for choice of comparators	4
8 9	Objectives	7	Specific objectives or hypotheses	4
10 11 12 13	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, face and framework (eg, superiority, equivalence, noninferiority, exploration),	4
14 15	Methods: Participa	nts, inte	erventions, and outcomes	
16 17 18	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of a gradient where data will	5
19 20 21 22 23 24 25 26 27 28 29 30 31	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and	5
	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including hogy and when they will be	6-9
		11b	Criteria for discontinuing or modifying allocated interventions for a given trial part gip and to be	N/A
		11c	Strategies to improve adherence to intervention protocols, and any procedures for monotocols and any procedures for monotocols, and any procedures for monot	N/A
32 33		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial $_$	5
34 35 36 37 38 39 40 41	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variability (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
42 43 44 45 46			For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	2

			BMJ Open	I	Page 24 of 27		
1 2 2	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), بعن المجت المجتي المحتية	4			
4 5 6	Sample size	14	Estimated number of participants needed to achieve study objectives and how it sasdetermined, including clinical and statistical assumptions supporting any sample size calculations of s	6			
7 8	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6			
9 10 11 12	Methods: Assignm	ent of i	nterventions (for controlled trials)				
13 14 15 16 17 18 19 20 21 22 23	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random reference), and list of any	6			
	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequent ally numbered,	6	-		
24 25 26	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to	6			
27 28 29	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care مترة منوفي) who will be blinded after assignment to interventions (eg, trial participants, care مترة منوفي), and how	6			
30 31 32 33		17b	If blinded, circumstances under which unblinding is permissible, and procedure for regealing a participant's allocated intervention during the trial	6			
34 35	Methods: Data collection, management, and analysis						
36 37 38 39 40 41 42 43	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 assessore) 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	3		
44 45 46			$\overline{\mathbf{o}}$				

Page	25 of 27		BMJ Open cop -22	
1 2		18b	Plans to promote participant retention and complete follow-up, including list of any our come data to be collected for participants who discontinue or deviate from intervention protocols 🛓 👌	N/A
3 4 5 6 7	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 bata management procedures can be found, if not in the protocol	14
8 9 10	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to the other details of the statistical analysis plan can be found, if not in the protocol	12
11 12		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12
13 14 15 16		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomed analysis), and any statistical methods to handle missing data (eg, multiple imputation)	12
17 18	Methods: Monitorir	ng	a ABES	
19 20 21 22 23	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 if why a DMC is not needed	N/A
25 26 27		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
28 29 30	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneo	
31 32 33 34	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
35 36	Ethics and dissemi	nation	Agen	
37 38 39 40	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	15
41 42 43 44 45 46			For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	4

			BMJ Open BMJ Open 20	Page 26
1 2 3 4	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility ceteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial egistries, journals, regulators)	Registry would be updated
5 6 7	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	5
8 9 10 11 12 13		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
14 15 16	Confidentiality	27	How personal information about potential and enrolled participants will be collected and maintained in order to protect confidentiality before, during, and after the trial	
17 18 19	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall transford each study site	15
20 21 22	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractional agreements that limit such access for investigators	15
23 24 25 26	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
20 27 28 29 30	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, here althouse professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	14
31 32		31b	Authorship eligibility guidelines and any intended use of professional writers	14
33 34 35		31c	بة بي Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code خ	14
36 37	Appendices		en ce	
38 39 40 41 42	Informed consent materials	32	Model consent form and other related documentation given to participants and autho	15
43 44 45 46			For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	

Page	27 of 27		BMJ Open BMJ Open	
1 2 3 4 5	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular N/A no biological specimens for genetic or molecular Specimen wer specimen wer collected as p of this trial	ical re part
6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38	*It is strongly reco Amendments to t " <u>Attribution-NonC</u>	ommended he protocol	that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Clarific the Creative Commons NoDerivs 3.0 Unported" license.	S.
 40 41 42 43 44 45 46 			For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	6

BMJ Open

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

Journal:	BMJ Open
Manuscript ID	bmjopen-2022-061679.R1
Article Type:	Protocol
Date Submitted by the Author:	30-Jun-2022
Complete List of Authors:	Anarte-Lazo, Ernesto; University of Birmingham, School of Sport, Exercise and Rehabilitation Sciences Bernal-Utrera, Carlos; University of Seville Lopez-Amor , Mario; Clinica San Vicente Porras-Valencia , Eugenia ; Clinica San Vicente Ruy-Diaz-Rojas, Francisco Javier ; Clinica San Vicente Falla, Deborah; University of Birmingham, School of Sport, Exercise and Rehabilitation Sciences Rodriguez-Blanco, Cleofas; Universidad de Sevilla, Physiotherapy
Primary Subject Heading :	Rehabilitation medicine
Secondary Subject Heading:	Medical management
Keywords:	PAIN MANAGEMENT, Rehabilitation medicine < INTERNAL MEDICINE, Musculoskeletal disorders < ORTHOPAEDIC & TRAUMA SURGERY, Spine < ORTHOPAEDIC & TRAUMA SURGERY

SCHOLARONE[™] Manuscripts

1		
2		
3	1	Exercise-induced hypoalgesia after aerobic versus neck-specific
4		
5 6 7	2	exercise in acute/subacute whiplash associated disorders: Protocol for
8 9	3	a randomised controlled trial
10		
11	4	Anarte-Lazo E ^{1,2,3†} , Bernal-Utrera C ^{4,5†} , Lopez-Amor M ³ , Porras-Valencia E, Ruy-Diaz-
12	5	Rojas FJ ³ , Falla D ^{2*} , Rodriguez-Blanco, C ^{4,5}
14	6	
15 16	7	Affiliations
17 18 19	8	1. Doctoral Program in Health Sciences, University of Seville, 41009, Seville,
20 21	9	Spain
22 23 24	10	2. Centre of Precision Rehabilitation for Spinal Pain (CPR Spine), School of Sport,
24 25 26	11	Exercise and Rehabilitation Sciences, University of Birmingham, Birmingham,
27 28	12	UK
29 30 31	13	3. Clinica San Vicente, Avda Ventisquero de la Condesa, 46, 280235, Madrid,
32 33	14	Spain
34 35	15	4. Faculty of Nursing, Physiotherapy and Podiatry, Department of Physiotherapy,
37 38	16	University of Seville, 41009, Seville, Spain
39 40	17	5. Fisiosur I+D Research Institute, 04630 Almeria, Spain
41 42	18	*Corresponding author
43	10	
44	19	Deboran Falla; <u>D.Falla(a)bnam.ac.uk</u>
45 46 47	20	[†] Contributed equally
48	21	
49	$\frac{21}{22}$	
50	22	
51	23	
52	24	
53	∠4	
54 55	25	
55 56	23	
57	26	
58	20	
59 60	27	

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

28	Abstract
29	Introduction: A disturbance in exercise-induced hypoalgesia (EIH) has been observed
30	in patients with chronic whiplash associated disorders (WAD). Yet, no studies have
31	examined whether EIH occurs in people with acute/subacute WAD. This study will
32	determine whether EIH occurs immediately after and 24 hours after aerobic exercise
33	(AE) and neck-specific exercise (NSE) in people with acute/subacute WAD.
34	Methods and analysis: A randomised controlled trial has been designed and is reported
35	in line with the Standard Protocol Items: Recommendations for Interventional Trials
36	(SPIRIT). EIH will be assessed immediately after and 24 hours after AE, NSE and a
37	control intervention (randomly allocated). As dependent variables of the study, we will
38	measure Pressure Pain Thresholds measured over the region of the spinous process of
39	C2 and C5, the muscle belly of the tibialis anterior and over the three main peripheral
40	nerve trunks, Neck Pain Intensity, Neck-Disability Index, Pain Catastrophizing Scale,
41	Tampa Scale Kinesiophobia-11, Self-Reported Leeds Assessment of Neuropathic Signs
42	and Symptoms and Self-Efficacy.
43	Ethics approval and dissemination: Ethical approval has been granted by the Ethics
44	Committee from University Rey Juan Carlos (Madrid, Spain; reference number
45	0707202116721). The results of this study will be disseminated through presentations at
46	scientific conferences and publication in scientific journals.
47	Trial registration number: RBR-9tqr2jt
48	Keywords: whiplash associated disorders, exercise-induce hypoalgesia, exercise, neck
49	pain
50	
51	
52	
53	
54	
55	
56	
57	
58	
59	
60	

2		
3	61	Strengths and limitations of this study
4 5 6	62	· This trial will evaluate exercise induced hypoalgesia (EIH) in response to different
7 8	63	exercises in patients who have suffered a whiplash injury.
9 10 11	64	\cdot EIH will be assessed as a change in pressure pain thresholds (PPT)
12 13	65	· This study will assess EIH immediately and 24 hours after the intervention in people
14 15 16	66	with whiplash associated disorders (WAD)
17 18	67	\cdot The influence of psychological variables and neuropathic pain features on EIH will be
19 20	68	assessed
21 22 23	69	· Only people classified as WAD grade II will be included in the study, which could
24 25	70	become a limitation to extrapolate the results to all patients suffering with WAD
26 27 28	71	
20 29 30	72	
31 32	73	
33 34 35	74	
36 37	75	
38 39 40	76	
41 42	77	
43 44 45	70	
46 47	70	
48 49 50	79	
50 51 52	80	
53 54	81	
55 56 57	82	
58 59	83	
60		

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

BMJ Open

84 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

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open

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.

120 Methods

121 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.

132 Setting

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

BMJ Open

133The study will be conducted in the Physical Therapy Department of an134outpatient Traumatology Clinic in Madrid, Spain. Patients are referred to this clinic135after having a car accident and are evaluated by a physician. If physical therapy136treatment is recommended by the physician, then the patient is referred to the Physical137Therapy Department, where they are managed by physical therapists with expertise in138Orthopaedic Manual Therapy. Before starting the study, the evaluator will be trained in139the different assessment procedures to standardise the evaluation.

140 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],

BMJ Open

2	
3	
Δ	
5	
5	
6	
7	
8	
9	
10	
11	
17	
12	
13	
14	
15	
16	
17	
18	
10	
19	
20	
21	
22	
23	
24	
25	
26	
20	
27	
28	
29	
30	
31	
32	
33	
37	
25	
22	
36	
37	
38	
39	
40	
41	
12	
72 12	
43 44	
44	
45	
46	
47	
48	
49	
50	
51	
51	
52	
53	
54	
55	
56	
57	
58	
50	
23	
nυ	

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

159 **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
(<u>https://www.randomizer.org/</u>). The randomization sequence will only be known by the
principal investigator and auditor.

164 Blinding

165 The evaluator and participants in the study will be blinded during the entire 166 process. Participants will not know the description of the other exercise intervention or 167 control intervention. The evaluator will not know which group participants are assigned 168 to. To achieve this, the evaluator will assess the participant, and then leave the room as 169 the participant performs the intervention with another investigator and, when finished, 170 the evaluator will re-enter the room to re-evaluate the participant, approximately two 171 minutes after completion of the intervention. Blinding will be maintained during the 24 172 hour post-intervention assessment.

173 Sample size calculation

181

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.

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

182 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.

194 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

BMJ Open

2 3 4	206	minute during the increase in power output and then once every 3 minutes until the end
5 6	207	of the exercise session. The total exercise time will be 20 minutes.
7 8	208	
9 10 11	209	Neck-specific exercise
12 13	210	Two neck-specific exercises will be implemented which have been selected
14 15	211	since they have either resulted in a reduction in pressure pain sensitivity after exercise
16 17 18	212	[26], a decrease in neck pain intensity or disability following the exercise [27], or an
19 20	213	improvement in muscle function [28,29,30]. Approximately 5 minutes will be spent
21 22	214	firstly teaching the patient how to perform the exercises. Two different exercises will be
23 24 25	215	performed with a short rest in between for a total time of 20 minutes.
26 27	216	· Cranio-Cervical Flexion (CCF) Exercise
28 29	217	Participants will perform CCF exercise in supine, following on an established
30 31 32	218	protocol [31,32]. This task consists of flexion of the cranium over the cervical spine
33 34	219	without lifting the head from the supporting surface. The therapist will firstly determine,
35 36	220	using a pressure biofeedback device (Stabilizer; Chattanooga Group Inc., Chattanooga,
37 38 39	221	TN), the highest pressure increment (from 22 to 30 mmHg) [33] the participant can
40 41	222	correctly sustain for 10 seconds. Once this is determined they will perform 3 sets of 10
42 43	223	repetitions of 10-seconds duration, at this target level with a 10-second rest interval
44 45	224	between each contraction and 1 minute rest interval between sets (total contraction
40 47 48	225	time=300 seconds, total time of exercise = 690 seconds).
49 50	226	· Cervical Extension (CE) Exercise
51 52	227	Participants will be asked to position themselves in four-kneeling, and a mid-
53 54 55	228	resistance elastic band (Pilates Band Medium, Decathlon, Villaneuve d'Ascq, France)
56 57	229	will be placed over their head, as they hold the elastic band with their hands. The
58 59 60	230	participant will be required to perform CE with the cervical spine in a neutral position

Page 10 of 28

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

> 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).

241 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**
- 251 Pressure Pain Threshold

The PPT, which will be the primary outcome measure to quantify EIH and will
be recorded in newton/ cm²using a digital algometer (Force TenTM -Model FDX;
Wagner, Greenwich, CT, USA) with a round tip surface area of 1 cm². The
measurements will be taken over several sites in the following order: 1) the spinous

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open

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

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

> 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].

BMJ Open

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.

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

BMJ Open

> 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.

347 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

351 SPIRIT: Standard Protocol Items Recommendations for Interventional Trials; WAD:
352 Whiplash Associated Disorders; EIH: Exercise-Induced Hypoalgesia; PPT: Pressure
353 Pain Threshold; AE: Aerobic Exercise; NSE: Neck-Specific Exercise; CCF: Cranio354 Cervical Flexion; CF: Cervical Flexion; CE: Cervical Extension; CCE: Cranio-Cervical

BMJ Open

1 ว		
2 3 4	355	Extension; PCS: Pain Catastrophizing Scale; TSK-11: Tampa Scale Kinesiophobia-11;
5 6	356	NDI: Neck Disability Index; S-LANSS: Self-reported Leeds Assessment of
/ 8 9	357	Neuropathic Signs and Symptom's Scale; CDSE: Chronic Diseases Self-Efficacy
10 11	358	Acknowledgments
12 13	359	Not applicable
14 15 16	360	Authors' contributions
17 18	361	CRB is the director of the project, contributed to the protocol development, provided
19 20	362	clinical expertise and is responsible of designing the statistical procedures. DF is the co-
21 22	363	director of the project, contributed to protocol development and methodological
23 24 25	364	considerations, and provided clinical expertise. MLA and EPV are the two physical
26 27	365	therapists who will perform the interventions for the study. FJRDR will help in the
28 29	366	organization of subjects and data extraction. EAL and CBL are the main investigators
30 31 22	367	who will run the study; they contributed to the concept and study design, provided
32 33 34	368	clinical expertise, and developed the manuscript with feedback from all authors. All
35 36	369	authors read and approved the final manuscript.
37 38	370	Funding
39 40 41	371	The are no sources of funding
42 43	372	Data availability statement
44 45	373	The datasets analysed during the current study are available from the corresponding
46 47 48	374	author on reasonable request. The data will be available after the main publication of
49 50	375	them; for other circumstances, they should consult the corresponding author. Any data
51 52	376	required to support the protocol can be supplied or request.
53 54	377	Ethics approval and dissemination
55 56 57	378	This study complies with the Helsinki guidelines for human research, and it has been
58 59 60	379	approved by the Ethics Committee from Universidad Rey Juan Carlos, Madrid, Spain.

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

BMJ Open

2		
- 3 4	380	All study participants will sign an informed consent approved by the ethics committee.
5 6	381	The identification of each individual will remain concealed based on the ethical
7 8	382	principles of confidentiality and privacy. Any reason for compensation will be covered
9 10 11	383	by professional liability insurance. Informed consent is available in the Spanish
12 13	384	language from the corresponding author on request. There is no anticipated harm and
14 15	385	compensation for trial participation. The results of this trial will be published in peer-
16 17	386	reviewed scientific journals and presented at relevant academic conferences.
18 19 20	387	Consent for publication
21 22	388	Not applicable
23 24	389	Competing interests
25 26 27	390	The authors declare they have no competing interests.
28 29	391	
30 31	392	Figure legend
32 33	393	Figure 1. Subject recruitment and flow through the study
34 35 26	394	
36 37 38	395	
39 40	396	
41 42	397	
43 44	200	
45 46	398	
47 48	399	
49 50	400	
51 52	401	
53 54	402	
55 56 57	403	
58 59 60	404	

BMJ Open

1 2		
2 3 4	405	References
5 6	406	1. Sterling M. Physiotherapy management of whiplash-associated disorders
7 8	407	(WAD). J Physiother. 2014 Mar;60(1):5-12.
9	408	2. Elliott JM, Noteboom JT, Flynn TW, Sterling M. Characterization of acute and
10 11	409	chronic whiplash-associated disorders. J Orthop Sports Phys Ther. 2009
12 13	410	May;39(5):312-23.
14	411	3. Siegmund GP, Winkelstein BA, Ivancic PC, Svensson MY, Vasavada A. The
15 16	412	anatomy and biomechanics of acute and chronic whiplash injury. Traffic Inj
17 18	413	Prev. 2009 Apr;10(2):101-12.
19 20	414	4. Michele Sterling, Julia Treleaven, Sandra Edwards & Gwendolen
21	415	Jull (2002) Pressure Pain Thresholds in Chronic Whiplash Associated Disorder:
22 23	416	Further Evidence of Altered Central Pain Processing, Journal of Musculoskeletal
24 25	417	Pain,10:3, 69-81
26	418	5. Sterling M. Whiplash-associated disorder: musculoskeletal pain and related
27 28	419	clinical findings. J Man Manip Ther. 2011;19(4):194-200.
29 30	420	doi:10.1179/106698111X13129729551949
31 32	421	6. Chien A, Eliav E, Sterling M. Whiplash (grade II) and cervical radiculopathy
33 34	422	share a similar sensory presentation: an investigation using quantitative sensory
35	423	testing. Clin J Pain. 2008 Sep;24(7):595-603.
36 37	424	7. Miettinen T, Airaksinen O, Lindgren KA, Leino E. Whiplash injuries in
38 39	425	Finlandthe possibility of some sociodemographic and psychosocial factors to
40	426	predict the outcome after one year. Disabil Rehabil. 2004 Dec 2;26(23):1367-
41 42	427	72.
43 44	428	8. Kasch H, Stengaard-Pedersen K, Arendt-Nielsen L, Staehelin Jensen T. Pain
45 46	429	thresholds and tenderness in neck and head following acute whiplash injury: a
47	430	prospective study. Cephalalgia. 2001 Apr;21(3):189-97.
48 49	431	9. Smith A, Ritchie C, Pedler A, McCamley K, Roberts K, Sterling M. Exercise
50 51	432	induced hypoalgesia is elicited by isometric, but not aerobic exercise in
52 53	433	individuals with chronic whiplash associated disorders. Scand J Pain. 2017
53 54	434	Apr;15:14-21.
55 56	435	10. Van Oosterwijck J, Nijs J, Meeus M, Van Loo M, Paul L. Lack of endogenous
57 58	436	pain inhibition during exercise in people with chronic whiplash associated
59 60	437	disorders: an experimental study. J Pain. 2012 Mar;13(3):242-54.

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

BMJ Open

2		
3 4	438	11. Smith A, Ritchie C, Warren J, Sterling M. Exercise-induced Hypoalgesia Is
5	439	Impaired in Chronic Whiplash-associated Disorders (WAD) With Both Aerobic
6 7	440	and Isometric Exercise. Clin J Pain. 2020 Aug;36(8):601-611.
8 9	441	12. Ng TS, Pedler A, Vicenzino B, Sterling M. Less efficacious conditioned pain
10	442	modulation and sensory hypersensitivity in chronic whiplash-associated
11	443	disorders in Singapore. Clin J Pain. 2014 May;30(5):436-42.
13 14	444	13. Daenen L, Nijs J, Roussel N, Wouters K, Van Loo M, Cras P. Dysfunctional
15	445	pain inhibition in patients with chronic whiplash-associated disorders: an
17	446	experimental study. Clin Rheumatol. 2013 Jan;32(1):23-31.
18 19	447	14. Teasell RW, McClure JA, Walton D, Pretty J, Salter K, Meyer M, Sequeira K,
20 21	448	Death B. A research synthesis of therapeutic interventions for whiplash-
22	449	associated disorder (WAD): part 2 - interventions for acute WAD. Pain Res
23 24	450	Manag. 2010 Sep-Oct;15(5):295-304.
25 26	451	15. Sterling M, Jull G, Vicenzino B, Kenardy J. Sensory hypersensitivity occurs
27	452	soon after whiplash injury and is associated with poor recovery. Pain. 2003
28 29	453	Aug;104(3):509-517.
30 31	454	16. Sterling M, Pedler A. A neuropathic pain component is common in acute
32 33	455	whiplash and associated with a more complex clinical presentation. Man Ther.
34	456	2009 Apr;14(2):173-9.
35 36	457	17. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K,
37 38	458	Hróbjartsson A, Mann H, Dickersin K, Berlin JA, Doré CJ, Parulekar WR,
39 40	459	Summerskill WS, Groves T, Schulz KF, Sox HC, Rockhold FW, Rennie D,
40 41	460	Moher D. SPIRIT 2013 statement: defining standard protocol items for clinical
42 43	461	trials. Ann Intern Med. 2013 Feb 5;158(3):200-7.
44 45	462	18. Gurumoorthy D, Twomey L. The Quebec Task Force on Whiplash-Associated
46	463	Disorders. Spine (Phila Pa 1976). 1996 Apr 1;21(7):897-8.
47 48	464	19. Wiangkham T, Duda J, Haque MS, Price J, Rushton A. A cluster randomised,
49 50	465	double-blind pilot and feasibility trial of an active behavioural physiotherapy
51 52	466	intervention for acute whiplash-associated disorder (WAD)II. PLoS One. 2019
52	467	May 9;14(5):e0215803.
54 55	468	20. Chien A, Eliav E, Sterling M. Hypoesthesia occurs in acute whiplash
56 57	469	irrespective of pain and disability levels and the presence of sensory
58	470	hypersensitivity. Clin J Pain. 2008 Nov-Dec;24(9):759-66.
59 60		

BMJ Open

2		
3 4	471	21. Tough EA, White AR, Richards SH, Campbell JL. Myofascial trigger point
5	472	needling for whiplash associated paina feasibility study. Man Ther. 2010
6 7	473	Dec;15(6):529-35.
8 9	474	22. Crawford JR, Khan RJ, Varley GW. Early management and outcome following
10 11	475	soft tissue injuries of the neck-a randomised controlled trial. Injury. 2004
12	476	Sep;35(9):891-5.
13 14	477	23. Telford, R. D., Minikin, B. R., Hahn, A. G., & Hooper, L. A. (1989). A simple
15 16	478	method for the assessment of general fitness: The Tri-level Profile. Australian
17	479	Journal of Science and Medicine in Sport, 21(3), 6-9.
18 19	480	24. Wallman KE, Morton AR, Goodman C, Grove R. Physiological responses
20 21	481	during a submaximal cycle test in chronic fatigue syndrome. Med Sci Sports
22	482	Exerc. 2004 Oct;36(10):1682-8.
23 24	483	25. Ickmans K, Malfliet A, De Kooning M, Goudman L, Hubloue I, Schmitz T,
25 26	484	Goubert D, Aguilar-Ferrandiz ME. Lack of Gender and Age Differences in Pain
27 28	485	Measurements Following Exercise in People with Chronic Whiplash-Associated
28	486	Disorders. Pain Physician. 2017 Sep;20(6):E829-E840.
30 31	487	26. O'Leary S, Falla D, Hodges PW, Jull G, Vicenzino B. Specific therapeutic
32 33	488	exercise of the neck induces immediate local hypoalgesia. J Pain. 2007
34	489	Nov;8(11):832-9.
35 36	490	27. Bernal-Utrera, C., Gonzalez-Gerez, J.J., Anarte-Lazo, E. et al. Manual therapy
37 38	491	versus therapeutic exercise in non-specific chronic neck pain: a randomized
39 40	492	controlled trial. Trials 21, 682 (2020).
41	493	28. Schomacher J, Falla D. Function and structure of the deep cervical extensor
42 43	494	muscles in patients with neck pain. Man Ther. 2013 Oct;18(5):360-6.
44 45	495	29. Falla D, O'Leary S, Farina D, Jull G. The change in deep cervical flexor activity
46	496	after training is associated with the degree of pain reduction in patients with
47 48	497	chronic neck pain. Clin J Pain. 2012 Sep;28(7):628-34.
49 50	498	30. Jull GA, Falla D, Vicenzino B, Hodges PW. The effect of therapeutic exercise
51 52	499	on activation of the deep cervical flexor muscles in people with chronic neck
53	500	pain. Man Ther. 2009 Dec;14(6):696-701.
54 55	501	31. Jull GA, O'Leary SP, Falla DL. Clinical assessment of the deep cervical flexor
56 57	502	muscles: the craniocervical flexion test. J Manipulative Physiol Ther. 2008
58	503	Sep;31(7):525-33.
60		

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

BMJ Open

3	504	32. Jull G, Falla D, Treleaven J, O'Leary S "Management of neck pain disorders:
4 5	505	a research informed approach". Elsevier, UK 2019
6 7	506	33. Jull GA. Deep Cervical Flexor Muscle Dysfunction in Whiplash, Journal of
8 9	507	Musculoskeletal Pain, 2000, 8:1-2, 143-154
10 11	508	34. Hawker GA, Mian S, Kendzerska T, French M. Measures of adult pain: Visual
12	509	Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain),
13 14	510	McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-
15 16	511	MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale
17 18	512	(SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain
19	513	(ICOAP). Arthritis Care Res (Hoboken). 2011 Nov;63 Suppl 11:S240-52.
20 21	514	35. Vernon H.The Neck Disability Index. Journal of Musculoskeletal Pain, 1996
22 23	515	4:4, 95-104,
24 25	516	36. Kovacs FM, Bagó J, Royuela A, Seco J, Giménez S, Muriel A, Abraira V,
25 26	517	Martín JL, Peña JL, Gestoso M, Mufraggi N, Núñez M, Corcoll J, Gómez-
27 28	518	Ochoa I, Ramírez MJ, Calvo E, Castillo MD, Martí D, Fuster S, Fernández C,
29 30	519	Gimeno N, Carballo A, Milán A, Vázquez D, Cañellas M, Blanco R, Brieva P,
31 22	520	Rueda MT, Alvarez L, Del Real MT, Ayerbe J, González L, Ginel L, Ortega M,
32 33	521	Bernal M, Bolado G, Vidal A, Ausín A, Ramón D, Mir MA, Tomás M, Zamora
34 35	522	J, Cano A. Psychometric characteristics of the Spanish version of instruments to
36 37	523	measure neck pain disability. BMC Musculoskelet Disord. 2008 Apr 9;9:42.
38	524	37. Sullivan M, Bishop S, Pivik J.The Pain Catastrophizing Scale: Development and
39 40	525	validation. Psychological Assessment 1995, 7. 524-532.
41 42	526	38. Andersen TE, Karstoft KI, Brink O, Elklit A. Pain-catastrophizing and fear-
43 44	527	avoidance beliefs as mediators between post-traumatic stress symptoms and pain
45	528	following whiplash injury - A prospective cohort study. Eur J Pain. 2016
46 47	529	Sep;20(8):1241-52.
48 49	530	39. García Campayo J, Rodero B, Alda M, Sobradiel N, Montero J, Moreno S.
50 51	531	Validación de la versión española de la escala de la catastrofización ante el dolor
52	532	(Pain Catastrophizing Scale) en la fibromialgia [Validation of the Spanish
53 54	533	version of the Pain Catastrophizing Scale in fibromyalgia]. Med Clin (Barc).
55 56	534	2008 Oct 18;131(13):487-92. Spanish.
57	535	40. Tkachuk GA, Harris CA. Psychometric properties of the Tampa Scale for
59	536	Kinesiophobia-11 (TSK-11). J Pain. 2012 Oct;13(10):970-7.
60		

BMJ Open

2		
3 4	537	41. Gómez-Pérez L, López-Martínez AE, Ruiz-Párraga GT. Psychometric
5	538	Properties of the Spanish Version of the Tampa Scale for Kinesiophobia (TSK).
6 7	539	J Pain. 2011 Apr;12(4):425-35.
8 9	540	42. Nieto R, Miró J, Huguet A. The fear-avoidance model in whiplash injuries. Eur
10	541	J Pain. 2009 May;13(5):518-23.
12	542	43. Bennett MI, Smith BH, Torrance N, Potter J. The S-LANSS score for
13 14	543	identifying pain of predominantly neuropathic origin: validation for use in
15 16	544	clinical and postal research. J Pain. 2005 Mar;6(3):149-58.
17	545	44. López-de-Uralde-Villanueva I, Gil-Martínez A, Candelas-Fernández P, de
18 19	546	Andrés-Ares J, Beltrán-Alacreu H, La Touche R. Validity and reliability of the
20 21	547	Spanish-language version of the self-administered Leeds Assessment of
22	548	Neuropathic Symptoms and Signs (S-LANSS) pain scale. Neurologia. 2018
23	549	Oct;33(8):505-514. English, Spanish.
25 26	550	45. Lorig KR, Ritter PL, González VM. Hispanic chronic disease self-management:
27 28	551	a randomized community-based outcome trial. Nurs Res. 2003 Nov-
29 30	552	Dec;52(6):361-9.
31	553	46. Pedrero-Martin Y, Falla D, Martinez-Calderon J, Liew BXW, Scutari M, Luque-
32 33	554	Suarez A. Self-efficacy beliefs mediate the association between pain intensity
34 35	555	and pain interference in acute/subacute whiplash-associated disorders. Eur Spine
36	556	J. 2021 Jan 27.
37 38	557	47. Teasell RW, McClure JA, Walton D, Pretty J, Salter K, Meyer M, Sequeira K,
39 40	558	Death B. A research synthesis of therapeutic interventions for whiplash-
41 42	559	associated disorder (WAD): part 4 - noninvasive interventions for chronic
43	560	WAD. Pain Res Manag. 2010 Sep-Oct;15(5):313-22.
44 45	561	
46 47	562	
48 49		
50		
51 52		
53		
54 55		
56		
57 58		
50 59		
60		



		STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL IRIALS	
SPIRIT 2013 Check	dist: Reco	mmended items to address in a clinical trial protocol and related documents* ي المع والمعالية mmended items to address in a clinical trial protocol and related documents	
Section/item	ltem No	Description	Addressed or page number
Administrative inf	ormation	to text a	
Title	1	Descriptive title identifying the study design, population, interventions, and, if approved the study design, population, interventions, and, if approved the study design population is the study design of the study design population is the study design of the study design population is the study design of the study design population is the study design of the study design population is the study design population is the study design of the study design population is the study design of the study design population is the study design of the study design population is the study design of the study design population is the study design of the study design population is the study design of the study design population is the study design of	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	5a	Names, affiliations, and roles of protocol contributors	1, 14
responsibilities	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, 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 over seeing the trial, if applicable (see Item 21a for data monitoring committee)	6
		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	

			BMJ Open by copy 202	Page 24 of 28
1 2	Introduction		right, i	
3 4 5	Background and rationale	6a	Description of research question and justification for undertaking the trial, includine some and justification for undertaking the trial, includine some studies (published and unpublished) examining benefits and harms for each interesting on	3,4
6 7		6b	Explanation for choice of comparators	4
8 9	Objectives	7	Specific objectives or hypotheses	4
10 11 12 13	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, face ويتعيق , single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, explore). ي ي ي ي ي ي ي ي ي ي ي	4
14 15	Methods: Participa	nts, int	erventions, and outcomes	
16 17 18	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of study settings where data will be collected. Reference to where list of study sites can be obtained	5
19 20 21	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
22 23 24 25	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be	6-9
26 27 28		11b	Criteria for discontinuing or modifying allocated interventions for a given trial part gip ant (eg, drug dose	N/A
29 30 31		11c	Strategies to improve adherence to intervention protocols, and any procedures for mention adherence	N/A
32 33		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	5
34 35 36 37 38 39	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variability (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
40 41 42 43 44 45 46			For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	2

Page 2	25 of 28		BMJ Open Spen			
1 2	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	_	
3 4 5 6	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		
7 8	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample sign a	6	_	
9 10 11 12	Methods: Assignme	ent of ir	nterventions (for controlled trials)			
13 14 15 16 17 18	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random and the provided in a separate document that is unavailable to the provided in a separate document that the provided in a separate document that is unavailable to the provided in a separate document that is unavailable to the provided in a separate document that is unavailable to the provided in a separate document t	6		
19 20 21 22 23	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequent filly numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	6		
23 24 25 26	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to	6		
27 28 29	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6	_	
30 31 32 33		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	6		
34 35	Methods: Data collection, management, and analysis					
36 37 38 39 40 41 42	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 assessone) 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	3	
43 44 45 46			For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml			

		BMJ Open BMJ Open	Page 26 of 28
	18b	Plans to promote participant retention and complete follow-up, including list of ang out come 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 process to be the promote data quality (eg, double data entry; range checks for data values). Reference to where details of the 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 randomesed analysis), and any statistical methods to handle missing data (eg, multiple imputation)	12
Methods: Monitorir	ng	ABES)	
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 spontaneous ly 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 dissemi	nation	Agen	
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	15
		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	4

Page 2	27 of 28		BMJ Open BMJ Open 20	
1 2 3 4	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility cuteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Registry would be updated
5 6 7	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	5
8 9 10 11 12 13		26b	Additional consent provisions for collection and use of participant data and biological pecimens in ancillary studies, if applicable	N/A no biological specimen were collected as part of this trial
14 15 16	Confidentiality	27	How personal information about potential and enrolled participants will be collected and maintained in order to protect confidentiality before, during, and after the trial	
17 18 19	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall tight and each study site	15
20 21 22	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractinal agreements that limit such access for investigators	15
23 24 25	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
26 27 28 29 30	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
31 32		31b	Authorship eligibility guidelines and any intended use of professional writers	14
33 34 35		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	14
35 36	Appendices		genco	
37 38 39 40 41	Informed consent materials	32	Model consent form and other related documentation given to participants and authors sed surrogates	15
42 43 44 45 46			For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	5

		BMJ Open by open co	Page 2
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for geoetic or mole analysis in the current trial and for future use in ancillary studies, if applicable	ecular N/A no biological specimen were collected as part of this trial
*It is strongly reconnected as a strongly reconnected at a strong to the	ommendec the protoco Commercial	that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for import should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT C	ant clarification on the items. Creative Commons
		2022. Dow lated to tex	
		t and data	
		om http:// BES) · Al	
		training, a	
		nd similar	
		June 10, 2 technolog	
		ies. Age	
		ince Biblio	
		ographique	6
		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	