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DO MEASURES OF PHYSICAL FUNCTION ENHANCE THE PREDICTION OF PERSISTENT PAIN AND DISABILITY FOLLOWING A WHIPLASH INJURY? PROTOCOL FOR A PROSPECTIVE OBSERVATIONAL STUDY

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DO MEASURES OF PHYSICAL FUNCTION ENHANCE THE PREDICTION OF PERSISTENT PAIN AND DISABILITY FOLLOWING A WHIPLASH INJURY? PROTOCOL FOR A PROSPECTIVE OBSERVATIONAL STUDY

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ABSTRACT

Introduction

Not all factors that predict persistent pain and disability following whiplash injury are known. In particular, few physical factors, such as changes in motor function and muscle behaviour have been investigated.

Aims and objectives

The aim of this study is to identify predictive factors that are associated with the development of persistent pain and disability following a whiplash injury by combining contemporary measures of physical function together with established psychological and pain-related predictive factors.

Methods and analysis

A prospective observational study will recruit 150 consecutive eligible patients experiencing whiplash-related symptoms, admitted to a private physiotherapy clinic in Spain within 15 days of their whiplash injury. The absolute risk of poor outcome will be measured using the Neck Disability Index (NDI). Poor outcome is defined as an NDI absolute score of 30% or greater at 6 months post-injury. Candidate predictors, including demographic characteristics, injury characteristics, pain characteristics, self-reported psychosocial factors and physical factors will be collected at baseline (within 15 days of inception). Regression analyses will be performed to identify factors that are associated with persistent neck pain and disability over the study period.

Ethics and dissemination

The project has been approved by the University of Birmingham Research Ethics Committee and the Ethics Committee of the province of Malaga, Spain (#30052019). The results of this study will be published in peer-reviewed journals.

STRENGTHS AND LIMITATIONS OF THIS STUDY

1. This protocol describes, *a priori*, the methods and analysis of identifying predictors of persistent pain and disability following a whiplash injury.
2. Specific physical measures together with established self-reported measures will be captured within 15 days of inception.
3. Candidate predictors are selected using a combination of best available knowledge and theory, and their applicability in clinical practice.
4. Trajectories of self-reported pain and disability will be recorded over the 12 month study period.
5. Physical measures will not be measured throughout the course of the study.

INTRODUCTION

The term 'whiplash' refers to an acceleration-deceleration motion of the neck, most commonly following a motor vehicle collision, that can result in tissue injury (1). Following whiplash, individuals may develop a variety of clinical signs and symptoms, collectively termed whiplash-associated disorders (WAD) (1). Soft tissue damage has been detected in some individuals with WAD; however, this has not been linked to the progression of symptoms (2-4). WAD is associated with a significant socioeconomic burden (5); the cost to the UK economy is ~£3 billion per year (6). This burden is primarily acquired by those developing chronic, long-term symptoms and half of those with WAD continue to report neck pain at least one year after the injury (7). This highlights the importance of early identification of features associated with ongoing pain and disability; this would facilitate personalised treatment approaches to mitigate the risk associated with the development of chronic WAD (8).

High-quality evidence has shown higher pain and disability immediately post-injury to be the most consistent factor predicting longer-term pain and disability (9, 10). Studies have examined other factors that might predict the development of ongoing pain following whiplash covering all three elements of the biopsychosocial model: demographic factors (7, 11-14), pre-existing comorbidities (11, 13, 14), collision factors (7, 11-13, 15-18), physical factors (14, 19-24), radiological changes (2, 25-30), societal factors (31), and psychological factors (7, 32, 33). Yet, there is controversial evidence concerning the predictive ability of other factors including: general psychological distress, depression, previous neck pain, gender, and the use of a seatbelt at the time of the collision (9, 14, 32, 34, 35). This illustrates an incomplete picture regarding the predictive factors for recovery versus ongoing pain in WAD.

There has been little investigation of the predictive utility of physical factors following whiplash injury; of the studies conducted, measures of physical function have been limited to measures such as range of motion (19, 20, 36, 37) and cranio-cervical flexion test performance (38, 39). Yet, physical factors offer potential to improve prediction accuracy. For example, there is a wealth of evidence describing changes in motor function and muscle behaviour (40-42). Decreased maximum angular velocity of neck movements has been observed in individuals with chronic WAD when compared to healthy individuals (40). Such changes in movement behaviour have been confirmed in individuals with WAD and insidious neck pain, where lower peak velocity was observed in both groups (41). In addition, a significantly larger jerk index (measure of the smoothness of neck movement) has been reported in individuals with chronic neck pain of both insidious and traumatic onset, when compared to asymptomatic individuals (41). Another feature reported in those with chronic neck pain is increased co-activation of the neck flexors and extensors (42), which is associated with reduced neck strength (42). These additional features have not been investigated in individuals with acute WAD, but results from experimental pain studies suggest these adaptations occur soon after pain onset and may therefore have relevance for ongoing symptoms in individuals with chronic WAD (43-50).

A number of methodological limitations of previously published studies in the field of WAD prognosis have been identified. For instance, a review conducted by Walton et al. (10) found that many predictors have conflicting results (11, 12, 32). Inconsistent outcome measures have previously been used by to define recovery in WAD (51), with a different definition of recovery used in each study (7, 52). Other reasons for inconsistency can be attributed to poor reporting (11, 53) and the inclusion of subjects from different settings and at different inception points. Another recent review found controversial evidence with

regards to which demographic factors, prior pain, and psychological factors are associated with the transition to chronic WAD. (9).

Collectively, these limitations impact on our understanding of factors associated with the transition to chronic WAD following a whiplash injury and highlight the need for an adequately powered, methodologically robust observational study to provide useful predictive estimates. Such knowledge could lead to the development of a new clinical care pathway that matches early interventions to risk factors for poor recovery.

Aims of study

The aim of the study is to identify factors soon after a whiplash injury that predict the occurrence of persistent pain and disability six months later. We will include a broad range of candidate predictors, including measures of physical function with self-reported measures of pain, disability and established psychological constructs.

METHODS

Study Design

The study will be a prospective observational design. This protocol has been developed in accordance with guidelines from the SPIRIT 2013 Statement (54), the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis Or Diagnosis (TRIPOD) statement (55), the Quality In Prognosis Studies (QUIPS) tool (56), the CHecklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies (CHARMS) (57), and the PROGnosis RESearch Strategy (PROGRESS) framework (58).

Participants

We aim to recruit 150 individuals presenting to a private physiotherapy clinic in Malaga, Spain with symptoms attributed to a recent (within the previous 15 days) whiplash injury. Consecutive eligible individuals will be invited to participate in the study for a follow-up period of 12 months until this target is achieved.

Eligibility criteria

Inclusion criteria: Adults aged 18 years or older, who are experiencing acute neck pain with or without other whiplash-related symptoms such as headache, upper limb symptoms, or dizziness (59) following a whiplash injury, attributed to a recent (previous 15 days) motor vehicle collision or sports injury. An ability to understand written and verbal Spanish language is also necessary.

Exclusion criteria: Individuals who experienced cervical spine fractures or dislocations during or since their whiplash injury (WAD grade IV) (1), loss of consciousness during or since their whiplash injury (60), or have ever received neck surgery (61) will be excluded from participation. Individuals with malignant spinal disorders, mental disorders (62, 63), or regular use of analgesic medication prior to the injury due to chronic pain will also be excluded.

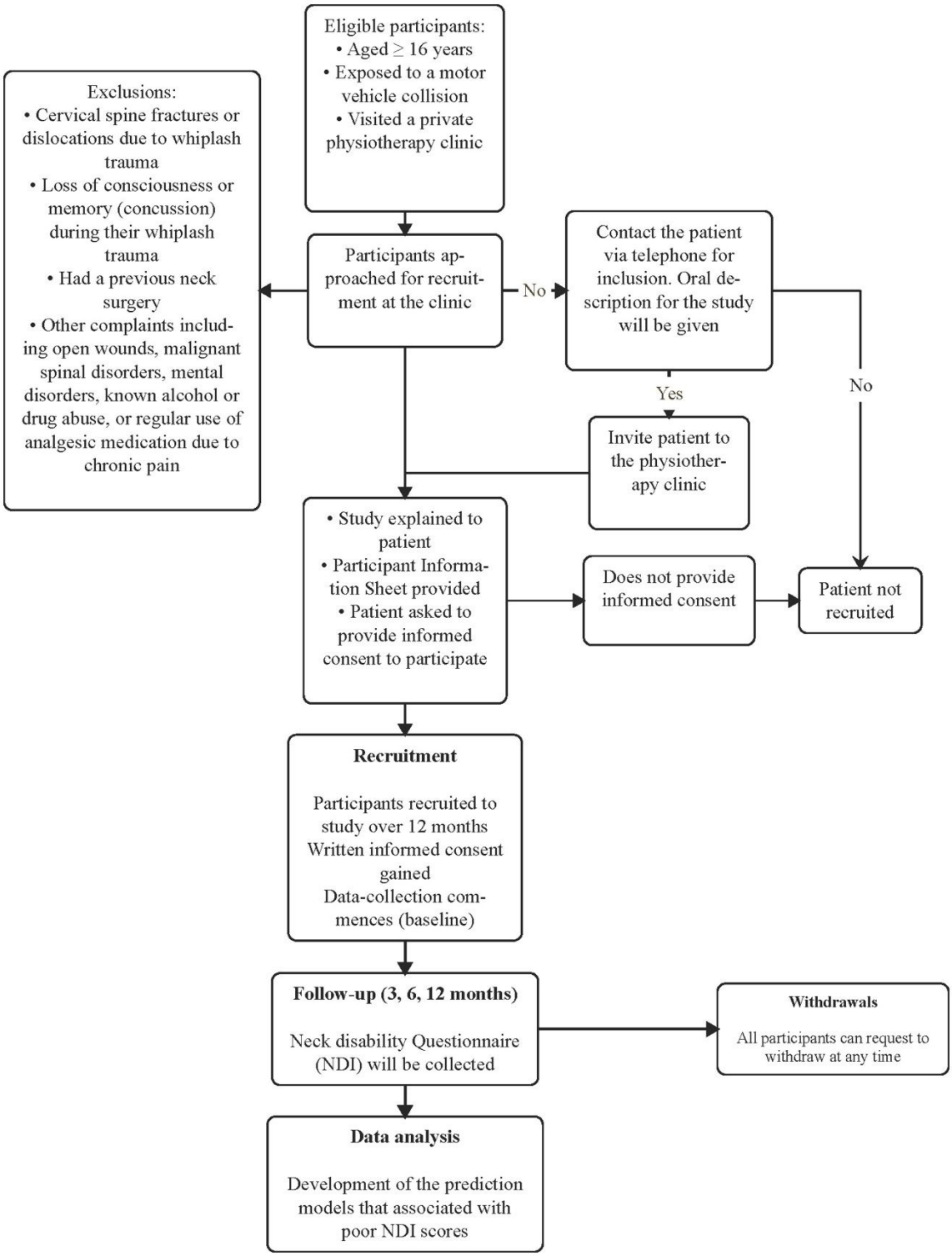
Recruitment

Participants will be recruited from a single private physiotherapy clinic in Malaga, Spain. Based on feasibility data (clinical records), we estimate that at least 300 eligible individuals will be eligible for recruitment over a 12 month period, and that at least 50% can be expected to consent to participation.

We will recruit eligible patients within 15 days of their whiplash injury. One designated physiotherapist working at the physiotherapy clinic will manually check electronic clinical

records of all consecutive patients attending the clinic. Once an eligible patient is identified at the clinic, the designated clinic physiotherapist will contact the patient to invite them to participate in the study; this invitation will be done either in-person at the clinic after the first treatment session or via telephone after patients have returned home from their clinic appointment. A verbal and written description of the study will be provided during the invitation. Those patients interested in participation will be invited to attend an initial study session at the physiotherapy clinic. At this session, the researcher will again explain the study design and context, patients will be given a detailed information sheet, and written informed consent will be sought. Once recruited, participants (Figure 1) will be asked to complete a baseline self-reported questionnaire, after which physical data will be collected (Table 1). Participants will be informed that they can withdraw from the study at any time, without having to provide a reason. They will also be advised to carry on with their daily routines as usual, and that any interventions received during their physiotherapy sessions will be recorded for a descriptive analysis.

Figure 1: Study design



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Outcome

Outcome will be measured using the Neck Disability Index (NDI) (64); a neck-specific self-reported questionnaire used to assess neck pain-related disability. The NDI consists of 10 items of daily activities including personal care, lifting, reading, work, driving, sleeping, and recreation (64). Each item has five ordinal response options from 0 (no disability) to 5 (complete disability), producing a maximum total score of 50 which can be expressed as a percentage (0-100%). The reliability of NDI and validity have been established in individuals with neck pain disorders (65).

The risk of poor outcome will be assessed at six months post-whiplash for the prediction model (66). Using six months as a cut-off for identifying outcome is supported by the finding that most individuals recover within three months of the whiplash injury, with fewer recovering after this (11, 67), and a plateau after six months (68).

Candidate predictors

Due to the current lack of consensus on predictive factors of poor outcome, several self-reported and physical measures will be collected (9). Factors have been selected based on current knowledge of prognosis in whiplash (2, 7, 9, 11-13, 24, 31-34, 69) and a theoretical association with prognosis in individuals with neck pain, as informed by the biopsychosocial model of pain (70). These factors are also chosen due to being feasible to measure in clinical practice. Candidate predictors are summarised in Table 1 with further information available in the supplementary file S1. All data collection will be standardised through protocols and clinical report forms

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Table 1: Summary of self-reported and physical measures that will be collected			
Domain/Candidate predictor	Data collection instrument	Baseline commencing ≤ 15 days post-injury	3, 12 months, clinical course; 6 months, outcome assessment point
General patient characteristics including previous musculoskeletal pain			
Gender at birth	Male/Female	✓	
Education	Highest educational level attained	✓	
Psychosocial features			
Catastrophizing	Pain Catastrophizing Scale (PCS)	✓	
Kinesiophobia	Tampa Scale of Kinesiophobia [TSK-11]	✓	
Recovery Expectation	Numeric Rating scales (NRS)	✓	
Injury characteristics			
Disability	Neck Disability Index (NDI)	✓	✓
Pain characteristics			
Current neck pain intensity	Numeric Rating scales (NRS)	✓	
Neck pain intensity at the end of neck range of motion tasks.	Numeric Rating scales (NRS)	✓	
Neck pain intensity at the end of maximum contraction tasks of cranio-cervical flexion, neck flexion, and neck extension.	Numeric Rating scales (NRS)	✓	
Neck pain intensity at the end of submaximum contraction tasks of cranio-cervical flexion, neck flexion, and neck extension.	Numeric Rating scales (NRS)	✓	
Physical measures			
Neck range of motion	G-Walk (Flexion, extension, rotation, & side flexion)	✓	
Neck angular velocity	G-Walk (Flexion, extension, rotation, & side flexion)	✓	
Smoothness of Neck movement	G-Walk (Flexion, extension, rotation, & side flexion)	✓	
Neck proprioception	G-Walk (Rotation with eyes closed)	✓	
Maximal and sub-maximal isometric contractions	Dynamometer – evaluation of cranio-cervical flexion, flexion, and extension maximum voluntary contraction and control of sub-maximal force	✓	
Co-activation of the sternocleidomastoid and splenius capitis	Surface electromyography (EMG) during physical tests described above	✓	

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Data collection

Baseline and follow-up

Baseline data including self-reported questionnaires and physical assessments will be collected immediately following recruitment, at the physiotherapy clinic, by a trained assessor (MFS) within 15 days of injury. Participants will be contacted by the same assessor by telephone (MFS) at the University of Malaga (UoM) at three, six and twelve months follow-up, in order to complete the NDI, as used previously (71).

Data management

Participant data privacy will be maintained throughout data handling (collection transfer, storage, and processing) and will comply with data protection requirements as set out by the General Data Protection Regulation (GDPR) of the European Union, and UK Data Protection Act 2018 (Figure 2). Participant data will be tracked using only study identification (ID) numbers. Study ID numbers will be kept separate from study research data, which will be accessible only by members of the UoM research team.

Sensitive data management:

Some participant data will be sensitive in nature; in particular consent forms which contain identifiable data, name, phone, contact address and study ID numbers. Once each participant has completed a consent form in the clinic, it will then be sealed in an envelope and temporarily locked in a secure drawer at the physiotherapy clinic, with access only available to members of the UoM research team. Once daily data collection has ended, all sealed envelopes containing consent forms collected on that day will be physically transferred to the UoM by one of the research team and locked in a secure filing cabinet there. Identifiable data

will be securely stored at UoM for a period of 10 years, after which they will be destroyed. No identifiable data will be transferred outside of the UoM.

Self-reported questionnaires management:

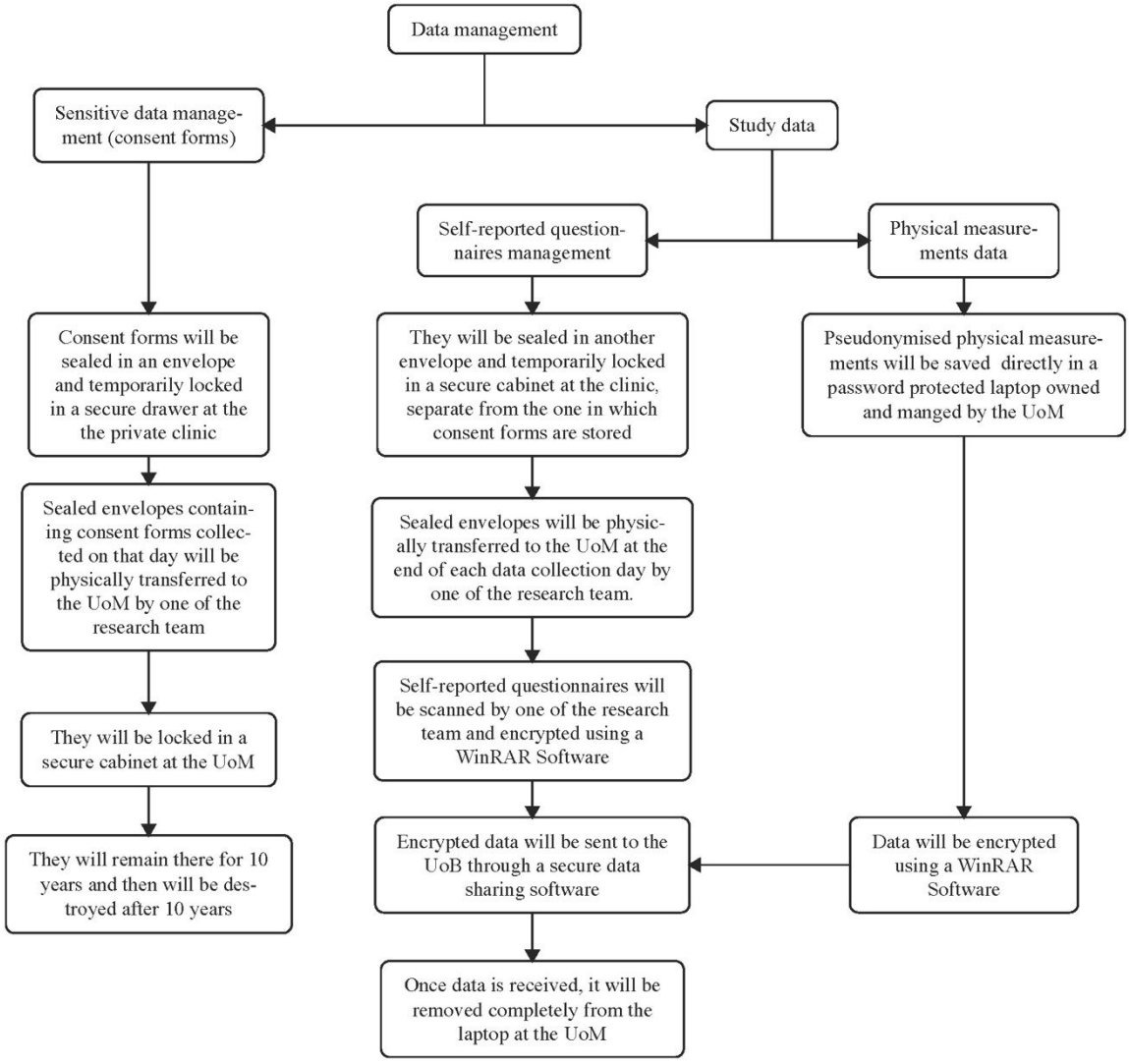
Self-reported paper questionnaires, identifiable only by study ID number for each participant, will be sealed in another envelope and temporarily locked in a secure cabinet at the clinic, separate from the one in which consent forms are stored. Sealed envelopes containing the pseudonymised self-reported questionnaires will be physically transferred to the UoM at the end of each data collection day by one of the research team. Once transferred, self-reported questionnaires will be scanned by one of the research team and saved in a password protected laptop computer, owned and managed by UoM. Scanned self-reported electronic data will be encrypted using a WinRAR Software before transit to the University of Birmingham (UoB) (via Power Folder data sharing software, hosted locally at the University). Once received, this pseudonymised data will be uploaded directly to physically secure servers at the UoB, where they will remain indefinitely on secure UoB servers with access restricted to members of the study team. Once uploaded to UoB servers, data will be removed completely from the laptop at UoM. The same procedures will be followed for follow-up NDI data at 3, 6, and 12 months.

Physical data management:

Pseudonymised physical data will be saved in a password protected laptop owned and manged by UoM, whilst at the clinic study session. Access to the UoM laptop is restricted and only available to the local research team. As with other data, pseudonymised electronic data will be encrypted using a WinRAR Software, transferred to the UoB team, and uploaded to the physically secure servers at UoB, where they will remain indefinitely with access restricted to

study researchers. Again, once data has been received by the team at UoB, they will be removed from UoM computers.

Figure 2: Data management



Data analysis

Numbers of individuals will be recorded that are: potentially eligible, examined for eligibility, confirmed eligible, recruited into the study, completing follow-up, and analysed.

Loss to follow-up and withdrawals will be reported, with reasons where available. Descriptive analyses of participants at baseline will include participant demographics, self-reported questionnaires and physical assessment data.

Linear regression analysis:

Multivariate linear regression models will be developed as a primary analysis to determine the association between candidate predictors and neck pain and disability (measured by NDI) at 6 months post injury. Factors with univariate associations at baseline and the outcome will be established $p<0.20$ (72) and deemed eligible to enter multivariable analysis.

Logistic regression analysis:

Outcome (NDI) scores will be dichotomised into good or poor categories with a NDI score of ≥30% at six months post-injury defined as poor outcome, as described previously. Logistic regression will be used to identify factors that are associated with poor outcomes. To avoid overfitting the regression model, several steps will be taken. Firstly, linear univariate associations between each predictor at baseline and the outcome will be assessed to establish factors that are eligible to enter multivariable analysis. Those predictors with strong correlation to the outcome ($p<0.20$) (72), will be identified for the multivariable analysis. Secondly, a univariate logistic regression model will be constructed for each baseline predictor (Table 1) and its association with NDI to select those entering the final logistic model as described previously (73). Next, multivariable analysis will be conducted using stepwise logistic regression (74), to identify predictors that maintain significance ($p<0.05$) when included in the final model. The final logistic model will be constructed to include predictors that maintain significant relationship with chronic disability at all previous steps. The final model will be

checked for multicollinearity using variance inflation factors (VIF) to ensure no significant correlations between the included candidate predictors (75).

Model Performance:

The predictive performance of the prognostic screening tool will be assessed using the established traditional measures of overall prognosis, discrimination, and calibration (76). Brier score will be used to quantify the overall performance of the screening tool where the score ranges from 0 ('perfect model') to 0.25 ('not informative model') (76). The Receiver Operator Characteristic (ROC) curve will be used to discriminate between those who did or did not develop chronic whiplash. Finally, the calibration will be assessed through plotting the mean predicted against observed chronic whiplash cases.

Sample size

This study will consider the association between 16 candidate predictors (Table 1) and neck pain and disability at 6 months. The authors will ensure that at least ten participants per predictor will be used to develop an adequately powered linear regression analysis (77, 78). It is anticipated that some predictors may be excluded due to multicollinearity between predictors and/or not meeting the conditions of developing a predictive model. For example, only candidate predictors that reached the stated liberal significant level with the outcome ($p<0.20$) (72) will be included. Therefore, a sample size target of 120 participants is required to adequately powered a maximum of 12 candidate predictors into the multiple linear regression, with the addition of 30 participants to allow for possible loss of follow-up (total = 150).

For the logistic regression analysis sample size, a minimum of 5 events per predictor will be considered (78), as used previously (72). Based on the current knowledge about the

transition rate from acute to chronic WAD, it is expected that 50% of patients will report persistent neck pain and disability (11, 79, 80). This leaves 60 out of our potential participants who might develop persistent neck pain and disability 6 months post whiplash injury. Therefore, a sample size of 60 participants is adequate to power a logistic regression analysis of 12 candidate predictors with 5 events per predictor.

Management of missing data

For each variable of interest, numbers of participants with missing data will be reported. Any potential bias due to loss of follow-up will be assessed and compared using baseline data of subjects who withdraw or lost at follow-up (66). Multiple imputation (81) will be used to deal with missing outcome data, if appropriate and necessary. Participants will be excluded from the predictive model and subsequent analyses if they request to withdraw from the study following recruitment (66).

Ethics and dissemination:

The study will be conducted according to the Declaration of Helsinki. The project has been approved by the Ethics Committee of the province of Malaga, Spain (#30052019). The results of the study will be disseminated via reports published in peer-reviewed journals and national and international conferences. Participant burden has been taken into consideration when developing this study. The number of measures has been kept to a minimum. To ensure the privacy of each patient, a unique identification number will be assigned to each participant at the time of recruitment. Only pseudonymised or anonymised data will be used during analyses. Participants will be informed that they can withdraw from the study at any time, without having to provide a reason; however, where a reason is given it will be recorded. If a participant withdraws, no further data will be collected but data already

collected will be retained for analyses. Baseline characteristics of any participants that withdraw will be compared to retained participants to assess for any differences.

At each data collection session, confirmation to proceed will be gained before any data are collected. Any concerns and/or adverse events will be noted and fed back to clinical staff, according to the Good Clinical Practice principles. For ethical reasons, routine treatment will not be withheld from individuals at any point during the study. The details and frequency of any received treatment will be recorded and reported. The protocol and conduct of this study are strengthened by the inclusion of patient and public involvement, who contributed to the development of study design and documentation. In addition, they will contribute to the processes of performing data analysis, interpretation of results, and producing a lay summary of findings.

DISCUSSION

This is the first protocol to describe, *a priori*, the methods and analysis for identifying predictive factors for ongoing pain and disability following acute whiplash injury. In particular, self-reported measures together with novel physical measure will be incorporated including angular velocity, smoothness of movements, force steadiness, and neck muscle co-activation to predict poor outcome in individuals with WAD recruited within 15 days of the injury. The selected candidate predictors are included based on current knowledge and the possible utilisation in clinical practice. The knowledge gained through this study can assist in the identification of personalised interventions to facilitate recovery and therefore minimise the transition to chronic whiplash.

SPIRIT 2013 Statement, TRIPOD, PROGRESS, QUIPS and CHARMS statements and frameworks have informed design to ensure rigorous conduct of this study (54-58) . The results from this study will provide new insights into who is likely to recover versus who is

likely to develop persistent symptoms following a whiplash injury. Using a novel combination of outcome measures will allow the future development of a tool to predict development of chronic and disabling pain following a whiplash injury providing new opportunities to identify precision intervention.

Author Contributions

All authors contributed to the focus of this study. AA is a PhD student with DF as Lead Supervisor and AG and ALS as Co-Supervisors. AA drafted the initial protocol with guidance from DF at all stages. DE, ALS, MFS and AG provided guidance on topic, methodology and analyses. ALS and MFS will be involved in collecting data from participants. All authors approved the final version for publication. DF is guarantor.

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Competing Interests Statement

The authors have no competing interests to report.

Patient consent

Not required.

Ethics approval

Approved by Ethics Committee of the province of Malaga, Spain (#30052019).

Data sharing statement

No additional data are available.

Amendment Protocol

If changes in the protocol deemed to be necessary during conducting the study, they will be documented on the main report of the study.

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Supplementary file 1. Candidate predictors

General patient characteristics including previous musculoskeletal pain

Participants' demographic data will be recorded at baseline including gender and highest attained education level.

Psychosocial features

Pain Catastrophizing Scale (PCS)

The PCS will be used to evaluate the extent to which patients ruminate, magnify or feel helpless about controlling their pain [1]. It is a 13-item self-reported outcome consisting of three dimensions including rumination, magnification and helplessness to measure pain related catastrophizing. Subjects rate the frequency of experiencing catastrophic thoughts as 0 (not at all) or 4 (all the times) which produces an overall score of from 0-52 with higher scores indicating greater negative pain thoughts. The reliability and validity of the PCS have been established [1], and it has been used in patients with WAD [2, 3]. Moderate evidence of significant association shows that initial catastrophising was a risk factor for developing persistent symptoms in whiplash [4] with pooled odd ratio=3.77 (95% confidence intervals = 1.33 - 10.74) [5].

Tampa Scale of Kinesiophobia [TSK-11]

The TSK-11 is a self-reported outcome used to evaluate fear of movement or injury during activities [6]. It consists of 11-item of which each is scored from 1 ('totally agree') to 4 ('totally disagree') producing a total score from 11 to 44, with higher scores indicating higher fear of movement. The TSK-11 has showed excellent test-retest reliability and good construct validity in detecting changed in pain and disability [7]. Indirect association was found between fear of movement and higher neck pain and disability in patients with acute

WAD [8]; catastrophizing increases fear of movement which leads to decreased functional self-efficacy that results in higher pain and disability [8].

Recovery Expectation (high or low expectation of recovery)

Patients will be asked if they expect to fully recover within the next six months. Recovery expectations will be assessed by the question "In your opinion, how likely is it that you will be fully recovered with no persistent sequelae?" [9]. In response to this question, recovery expectations will be measured using NRS where a patient need to indicate how likely he/she would have completely recovered, by choosing a score from 0 ("not likely") to 10 ("very likely") [10]. Low expectation of making full recovery were found to be an independent predictive factor associated (odds ratio= 4.2 [95% CI = 2.1 - 8.5]) with higher disability in individuals with acute WAD [10].

Pain characteristics

Numeric Rating Scale (NRS)

Current neck pain intensity will be measured using NRS which is a 11-point scale range from 0 (no pain) to 10 (worst possible pain). Also, perceived pain intensity will be measured at the end of each physical measure of neck range of motion tasks, neck maximum contraction tasks, and neck submaximum contraction tasks. The reliability of NRS has been established in patients with neck pain (ICC:0.76) [11]. Also, participants will be asked remotely (through the app) where they have 'experienced pain during the last week' from several body locations [12]. Based on their response of chosen areas, pain intensity will be assessed using NRS. Finally, neck pain intensity following active movements will be measured through NRS. High evidence of significant association shows that initial neck pain

intensity was a consistent risk factor for developing persistent symptoms in whiplash [4] with pooled odd ratio= 5.61 (95% CI = 3.74 - 8.43) [13].

Physical measures

Wearable sensor for motion detection (Neck range of movement, angular velocity, movement smoothness and proprioception)

A wearable BTS G-WALK® sensor system (BTS Bioengineering, Italy) will be utilised to assess neck range of motion, angular velocity, movement smoothness, and neck proprioception. The sensor connects to a computer via Bluetooth; at the end of each analysis an automatic report containing all the parameters recorded during the test, is displayed.

Active neck flexion, side-flexion, extension, and rotation will be measured at baseline. Impaired range of motion has been found in individuals with WAD compared to healthy controls [14, 15] and has also been found to be a factor associated with persistent disability at one year [16, 17], and neck pain and disability at 6 months [18, 19].

Besides range of motion, the angular velocity and movement smoothness will be recorded simultaneously during each neck movement. Each movement direction will be repeated five times and the average taken. These kinematic variables may provide more information about motor control disturbances [20]. A study found maximum angular velocity and acceleration were lower in subjects with chronic WAD when compared to healthy control [20]. The same finding (lower peak velocity) was found in cohorts of both WAD and insidious neck pain [21]. Moreover, significant differences in jerk indices were observed during active neck movements in a study comparing healthy controls to those with chronic neck pain of both insidious onset and traumatic onset [21].

Neck proprioception will be measured by calculating the Joint Position Error (JPE) following active neck rotation. JPE is defined as the ability to relocate the natural head

position without the assistance of vision [22]. To assess this, the same wearable sensor (G-Walk) will be used. Patients will repeat active neck rotation with their eyes closed and will indicate when they think that they have returned to the starting position. JPE will be assessed three times for both right and left rotation and the average taken for each direction. Decreased head repositioning accuracy has been observed in people with idiopathic neck pain [23], but with greater repositioning errors found in individuals with neck pain attributed to a trauma [24], which is even more evident in those with moderate to severe pain and disability [14].

Dynamometer (maximal and sub-maximal isometric contractions)

At baseline, the participants will perform maximal and sub-maximal isometric contractions to measure maximum strength and control of sub-maximal forces. Cranio-cervical flexion, neck flexion and extension will be tested using a hand-held dynamometer for neck muscle testing (NOD, OT Bioeletronica, Italy).

1. Maximum voluntary contraction (MVC):

Two MVCs will be performed for cranio-cervical flexion, neck flexion, and extension. Each maximum MVCs will last for 3 seconds, separated by 1 minute rest in between [25]. The mean MVC for each direction will be calculated and used in the analysis [26, 27]. Patients will perform an initial trial to familiarise themselves with each movement under the guidance of a trained examiner with minimal force.

Cranio-cervical flexion strength testing will be performed with the participant in supine lying with the hip and knees flexed to approximately 90 degrees [28]. The head will be placed in neutral position and the dynamometer placed behind the upper cervical spine with the instruction being to nod as if saying yes but as hard as you can. Patients will be seated to measure neck flexion and extension strength with the participant seated comfortably on a chair with hip and knee flexed to 90 degrees with head in neutral position

and feet flat on the ground. To measure neck flexion, the dynamometer will be placed over the forehead and against the resistance of the examiner, the patient will be instructed to "push as hard as you can as you try to bring your chin to your chest" [29]. The dynamometer will then be placed on the back of the head and the patient instructed to "push as hard as you can into the dynamometer as if trying to bring the back of the head to your neck" [29].

Patients with neck pain commonly present with reduced neck strength [29-32], although the extent of impaired strength is highly variable across patients [33]. Significant lower isometric MVC force has been observed in patients with chronic WAD compared to healthy controls [29]. Reduced neck muscle strength has been associated with the extent of disability [25, 34] and pain [34] in people with chronic neck pain..

2. Sub-maximal voluntary contractions:

In the same positions described for the MVC, participants will be instructed to perform a single submaximal contraction at 20% of their maximal force and hold this for 10 seconds for cranio-cervical flexion, flexion and extension. In addition, participants will perform 40%, 60%, 80%, and 100% of their maximal force for the cranio-cervical flexion only. Feedback on force will guide the participant to maintain specific degree of contraction from their MVC over the duration of the contraction.

Surface electromyography (EMG) (co-activation of the sternocleidomastoid and splenius capitis)

The amplitude of sternocleidomastoid (SCM) activity will be measured bilaterally during the isometric maximum and submaximal voluntary contractions of cranio-cervical flexion. In addition, both SCM and splenius capitis (SC) activity will be measured bilaterally during the maximum and submaximal voluntary contractions of neck flexion and extension.

Increased co-activation of the neck flexors and extensors has been observed in patients with chronic neck pain and headache [35], and is associated with reduced neck strength [35]. Changes in neck muscle activation has been observed in people with acute neck pain following a whiplash injury [14, 36].

Following gentle skin preparation, pairs of bipolar surface electrodes will be placed over SCM and SC bilaterally following published guidelines for electrode placement [37]. Signals will be detected using wireless EMG (Ultium® EMG, Noraxon, USA). Co-activation indexes will be calculated as described previously [38].

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	
Funding	4	Sources and types of financial, material, and other support	19
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	
	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)	

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-6
	6b	Explanation for choice of comparators	
Objectives	7	Specific objectives or hypotheses	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
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)	7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	NA
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	NA
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	NA
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure 1)	9

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	16
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7-8
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	10-11

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12-14
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	15-16
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	17
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	_____
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	7
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_____
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	17
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	20

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	12-13
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	19
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	12-13
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	NA
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	17
	31b	Authorship eligibility guidelines and any intended use of professional writers	_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_____
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

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

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DO MEASURES OF PHYSICAL FUNCTION ENHANCE THE PREDICTION OF PERSISTENT PAIN AND DISABILITY FOLLOWING A WHIPLASH INJURY? PROTOCOL FOR A PROSPECTIVE OBSERVATIONAL STUDY IN SPAIN

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Do measures of physical function enhance the prediction of persistent pain and disability following a whiplash injury? Protocol for a prospective observational study in Spain

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ABSTRACT

Introduction

Not all factors that predict persistent pain and disability following whiplash injury are known. In particular, few physical factors, such as changes in motor function and muscle behaviour have been investigated. The aim of this study is to identify predictive factors that are associated with the development of persistent pain and disability following a whiplash injury by combining contemporary measures of physical function together with established psychological and pain-related predictive factors.

Methods and analysis

A prospective observational study will recruit 150 consecutive eligible patients experiencing whiplash-related symptoms, admitted to a private physiotherapy clinic in Spain within 15 days of their whiplash injury. Poor outcome will be measured using the Neck Disability Index (NDI), defined as an NDI score of 30% or greater at 6 months post-injury. Candidate predictors, including demographic characteristics, injury characteristics, pain characteristics, self-reported psychosocial factors and physical factors will be collected at baseline (within 15 days of inception). Regression analyses will be performed to identify factors that are associated with persistent neck pain and disability over the study period.

Ethics and dissemination

The project has been approved by the Ethics Committee of the province of Malaga, Spain (#30052019). The results of this study will be published in peer-reviewed journals.

STRENGTHS AND LIMITATIONS OF THIS STUDY

1. This protocol describes, *a priori*, the methods and analysis of identifying predictors of persistent pain and disability following a whiplash injury.
2. Specific physical measures together with established self-reported measures will be captured within 15 days of inception.
3. Candidate predictors are selected using a combination of best available knowledge and theory, and their applicability in clinical practice.
4. Trajectories of self-reported pain and disability will be recorded over the 12 month study period.
5. Physical measures will not be measured throughout the course of the study.

INTRODUCTION

The term 'whiplash' refers to an acceleration-deceleration motion of the neck, most commonly following a motor vehicle collision, that can result in tissue injury (1). Following whiplash, individuals may develop a variety of clinical signs and symptoms, collectively termed whiplash-associated disorders (WAD) (1). Soft tissue damage has been detected in some individuals with WAD; however, this has not been linked to the progression of symptoms (2-4). WAD is associated with a significant socioeconomic burden (5); the cost to the UK economy is ~£3 billion per year (6). This burden is primarily acquired by those developing chronic, long-term symptoms and half of those with WAD continue to report neck pain at least one year after the injury (7). This highlights the importance of early identification of features associated with ongoing pain and disability; this would facilitate personalised treatment approaches to mitigate the risk associated with the development of chronic WAD (8).

High-quality evidence has shown higher pain and disability immediately post-injury to be the most consistent factor predicting longer-term pain and disability (9, 10). Studies have examined other factors that might predict the development of ongoing pain following whiplash covering all three elements of the biopsychosocial model: demographic factors (7, 11-14), pre-existing comorbidities (11, 13, 14), collision factors (7, 11-13, 15-18), physical factors (14, 19-24), radiological changes (2, 25-30), societal factors (31), and psychological factors (7, 32, 33). Yet, there is controversial evidence concerning the predictive ability of other factors including: general psychological distress, depression, previous neck pain, gender, and the use of a seatbelt at the time of the collision (9, 14, 32, 34, 35). This illustrates an incomplete picture regarding the predictive factors for recovery versus ongoing pain in WAD.

There has been little investigation of the predictive utility of physical factors following whiplash injury; of the studies conducted, measures of physical function have been limited to measures such as range of motion (19, 20, 36, 37) and cranio-cervical flexion test performance (38, 39). Yet, physical factors offer potential to improve prediction accuracy (REFS). For example, there is a wealth of evidence describing changes in motor function and muscle behaviour (40-42). Decreased maximum angular velocity of neck movements has been observed in individuals with chronic WAD when compared to healthy individuals (40). Such changes in movement behaviour have been confirmed in individuals with WAD and insidious neck pain, where lower peak velocity was observed in both groups (41). In addition, a significantly larger jerk index (measure of the smoothness of neck movement) has been reported in individuals with chronic neck pain of both insidious and traumatic onset, when compared to asymptomatic individuals (41). Another feature reported in those with chronic neck pain is increased co-activation of the neck flexors and extensors (42), which is associated with reduced neck strength (42). These additional features have not been investigated in individuals with acute WAD, but results from experimental pain studies suggest these adaptations occur soon after pain onset and may therefore have relevance for ongoing symptoms in individuals with chronic WAD (43-50).

A number of methodological limitations of previously published studies in the field of WAD prognosis have been identified. For instance, a review conducted by Walton et al. (10) found that many predictors have conflicting results (11, 12, 32). Inconsistent outcome measures have previously been used by to define recovery in WAD (51), with a different definition of recovery used in each study (7, 52). Other reasons for inconsistency can be attributed to poor reporting (11, 53) and the inclusion of subjects from different settings and at different inception points. Another recent review found controversial evidence with

regards to which demographic factors, prior pain, and psychological factors are associated with the transition to chronic WAD. (9).

Collectively, these limitations impact on our understanding of factors associated with the transition to chronic WAD following a whiplash injury and highlight the need for an adequately powered, methodologically robust observational study to provide useful predictive estimates. Such knowledge could lead to the development of a new clinical care pathway that matches early interventions to risk factors for poor recovery.

Aims of study

The aim of the study is to identify factors soon after a whiplash injury that predict the occurrence of persistent pain and disability six months later. We will include a broad range of candidate predictors, including measures of physical function with self-reported measures of pain, disability and established psychological constructs.

METHODS

Study Design

The study will be a prospective observational design. This protocol has been developed in accordance with guidelines from the SPIRIT 2013 Statement (54), the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis Or Diagnosis (TRIPOD) statement (55), the Quality In Prognosis Studies (QUIPS) tool (56), the CHecklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies (CHARMS) (57), and the PROGnosis RESearch Strategy (PROGRESS) framework (58).

Participants

We aim to recruit 150 individuals presenting to a private physiotherapy clinic in Malaga, Spain with symptoms attributed to a recent (within the previous 15 days) whiplash injury. Consecutive eligible individuals will be invited to participate in the study for a follow-up period of 12 months until this target is achieved. Study recruitment will commence November 2019 and will be completed by November 2020.

Eligibility criteria

Inclusion criteria: Adults aged 18 years or older, who are experiencing acute neck pain with or without other whiplash-related symptoms such as headache, upper limb symptoms, or dizziness (59) following a whiplash injury, attributed to a recent (previous 15 days) motor vehicle collision or sports injury. An ability to understand written and verbal Spanish language is also necessary.

Exclusion criteria: Individuals who experienced cervical spine fractures or dislocations during or since their whiplash injury (WAD grade IV) (1), loss of consciousness during or since their whiplash injury (60), or have ever received neck surgery (61) will be excluded from participation. Individuals with malignant spinal disorders, mental disorders (62, 63), or regular use of analgesic medication prior to the injury due to chronic pain will also be excluded.

Recruitment

Participants will be recruited from a single private physiotherapy clinic in Malaga, Spain. Based on feasibility data (clinical records), we estimate that at least 300 eligible individuals will be eligible for recruitment over a 12 month period, and that at least 50% can be expected to consent to participation.

We will recruit eligible patients within 15 days of their whiplash injury. One designated physiotherapist working at the physiotherapy clinic will manually check electronic clinical records of all consecutive patients attending the clinic. Once an eligible patient is identified at the clinic, the designated clinic physiotherapist will contact the patient to invite them to participate in the study; this invitation will be done either in-person at the clinic after the first treatment session or via telephone after patients have returned home from their clinic appointment. A verbal and written description of the study will be provided during the invitation. Those patients interested in participation will be invited to attend an initial study session at the physiotherapy clinic. At this session, the researcher will again explain the study design and context, patients will be given a detailed information sheet, and written informed consent will be sought. The English version of the consent form is provided in the supplementary file. Once recruited, participants (Figure 1) will be asked to complete a baseline self-reported questionnaire, after which physical data will be collected (Table 1). Participants will be informed that they can withdraw from the study at any time, without having to provide a reason. They will also be advised to carry on with their daily routines as usual, and that any interventions received during their physiotherapy sessions will be recorded for a descriptive analysis.

Outcome

Outcome will be measured using the Neck Disability Index (NDI) (64); a neck-specific self-reported questionnaire used to assess neck pain-related disability. The NDI consists of 10 items of daily activities including personal care, lifting, reading, work, driving, sleeping, and recreation (64). Each item has five ordinal response options from 0 (no disability) to 5 (complete disability), producing a maximum total score of 50 which can be

expressed as a percentage (0-100%). The reliability of NDI and validity have been established in individuals with neck pain disorders (65).

Outcome will be assessed at six months for the prediction model (66). Using six months as a cut-off for identifying outcome is supported by the finding that most individuals recover within three months of the whiplash injury, with fewer recovering after this (11, 67), and a plateau after six months (68). To investigate the course of neck pain and disability, the NDI scores will additionally be collected at 3 and 6 months.

Candidate predictors

Due to the current lack of consensus on predictive factors of poor outcome, several self-reported and physical measures will be collected (9). Factors have been selected based on current knowledge of prognosis in whiplash (2, 7, 9, 11-13, 24, 31-34, 69) and a theoretical association with prognosis in individuals with neck pain, as informed by the biopsychosocial model of pain (70). These factors are also chosen due to being feasible to measure in clinical practice. Candidate predictors are summarised in Table 1 with further information available in the supplementary file S1. All data collection will be standardised through protocols and clinical report forms

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Table 1: Summary of self-reported and physical measures that will be collected			
Domain/Candidate predictor	Data collection instrument	Baseline commencing ≤ 15 days post-injury	3, 12 months, clinical course; 6 months, outcome assessment point
General patient characteristics including previous musculoskeletal pain			
Gender at birth	Male/Female	✓	
Education	Highest educational level attained	✓	
Psychosocial features			
Catastrophizing	Pain Catastrophizing Scale (PCS)	✓	
Kinesiophobia	Tampa Scale of Kinesiophobia [TSK-11]	✓	
Recovery Expectation	Numeric Rating scales (NRS)	✓	
Injury characteristics			
Disability	Neck Disability Index (NDI)	✓	✓
Pain characteristics			
Current neck pain intensity	Numeric Rating scales (NRS)	✓	
Neck pain intensity at the end of neck range of motion tasks.	Numeric Rating scales (NRS)	✓	
Neck pain intensity at the end of maximum contraction tasks of cranio-cervical flexion, neck flexion, and neck extension.	Numeric Rating scales (NRS)	✓	
Neck pain intensity at the end of submaximum contraction tasks of cranio-cervical flexion, neck flexion, and neck extension.	Numeric Rating scales (NRS)	✓	
Physical measures			
Neck range of motion	G-Walk (Flexion, extension, rotation, & side flexion)	✓	
Neck angular velocity	G-Walk (Flexion, extension, rotation, & side flexion)	✓	
Smoothness of Neck movement	G-Walk (Flexion, extension, rotation, & side flexion)	✓	
Neck proprioception	G-Walk (Rotation with eyes closed)	✓	
Maximal and sub-maximal isometric contractions	Dynamometer – evaluation of cranio-cervical flexion, flexion, and extension maximum voluntary contraction and control of sub-maximal force	✓	
Co-activation of the sternocleidomastoid and splenius capitis	Surface electromyography (EMG) during physical tests described above	✓	

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Data collection

Baseline and follow-up

Baseline data including self-reported questionnaires and physical assessments will be collected immediately following recruitment, at the physiotherapy clinic, by a trained assessor (MFS) within 15 days of injury. Participants will be contacted by the same assessor by telephone (MFS) at the University of Malaga (UoM) at three, six and twelve months follow-up, in order to complete the NDI, as used previously (71).

Data management

Participant data privacy will be maintained throughout data handling (collection transfer, storage, and processing) and will comply with data protection requirements as set out by the General Data Protection Regulation (GDPR) of the European Union, and UK Data Protection Act 2018 (Figure 2). Participant data will be tracked using only study identification (ID) numbers. Study ID numbers will be kept separate from study research data, which will be accessible only by members of the UoM research team.

Sensitive data management:

Some participant data will be sensitive in nature; in particular consent forms which contain identifiable data, name, phone, contact address and study ID numbers. Once each participant has completed a consent form in the clinic, it will then be sealed in an envelope and temporarily locked in a secure drawer at the physiotherapy clinic, with access only available to members of the UoM research team. Once daily data collection has ended, all sealed envelopes containing consent forms collected on that day will be physically transferred to the UoM by one of the research team and locked in a secure filing cabinet there. Identifiable data

will be securely stored at UoM for a period of 10 years, after which they will be destroyed. No identifiable data will be transferred outside of the UoM.

Self-reported questionnaires management:

Self-reported paper questionnaires, identifiable only by study ID number for each participant, will be sealed in another envelope and temporarily locked in a secure cabinet at the clinic, separate from the one in which consent forms are stored. Sealed envelopes containing the pseudonymised self-reported questionnaires will be physically transferred to the UoM at the end of each data collection day by one of the research team. Once transferred, self-reported questionnaires will be scanned by one of the research team and saved in a password protected laptop computer, owned and managed by UoM. Scanned self-reported electronic data will be encrypted using a WinRAR Software before transit to the University of Birmingham (UoB) (via Power Folder data sharing software, hosted locally at the University). Once received, this pseudonymised data will be uploaded directly to physically secure servers at the UoB, where they will remain indefinitely on secure UoB servers with access restricted to members of the study team. Once uploaded to UoB servers, data will be removed completely from the laptop at UoM. The same procedures will be followed for follow-up NDI data at 3, 6, and 12 months.

Physical data management:

Pseudonymised physical data will be saved in a password protected laptop owned and manged by UoM, whilst at the clinic study session. Access to the UoM laptop is restricted and only available to the local research team. As with other data, pseudonymised electronic data will be encrypted using a WinRAR Software, transferred to the UoB team, and uploaded to the physically secure servers at UoB, where they will remain indefinitely with access restricted to

study researchers. Again, once data has been received by the team at UoB, they will be removed from UoM computers.

Data analysis

Numbers of individuals will be recorded that are: potentially eligible, examined for eligibility, confirmed eligible, recruited into the study, completing follow-up, and analysed. Loss to follow-up and withdrawals will be reported, with reasons where available. Descriptive analyses of participants at baseline will include participant demographics, self-reported questionnaires and physical assessment data.

Linear and logistic regression analysis:

Linear regression analysis will be used as the primary analysis to develop a linear model to determine the association between candidate predictors and neck pain and disability (measured by NDI) at 6 months post injury. Linear regression analysis was included as a primary analysis to allow for the inclusion of the outcome (NDI) without dichotomisation. This approach follows the recommendations by PROGRESS series recommending of analysing continuous variables on their continuous scale (72), as well as to the fact that this approach method increases the statistical power and reduces information loss.

In addition to the linear regression analysis, Logistic regression will be included as a secondary analysis to identify factors that are associated with poor outcomes. Outcome (NDI) scores will be dichotomised into good or poor categories with a NDI score of ≥30% at six months post-injury defined as poor outcome, as described previously.

Variable selection:

Penalization (shrinkage) approach will be used to avoid overfitting the final prognostic model, given the minimum number of events (10) per variable will be adopted in this study to develop prognostic modes (73).

Firstly a full model will be constructed including all baseline candidate predictors (Table1) with their estimated adjusted regression coefficients calculated by standard methods. Next, a shrinkage method, a least absolute shrinkage and selection operator (LASSO) regression, will be used to effectively exclude candidate predictors from the final model by shrinking their coefficients to exactly zero (74). Candidate predictors with zero coefficients will be excluded from the model, leaving the remaining candidate predictors with regression confidents of more than zero. This approach is in line with the current recommendations for variable selection in prognostic models to address overfitting (75). Moreover, this approach is preferred when a model with fewer predictors is desired without affecting the predictive ability of the model, making it more applicable in clinical practice (73).

Model Performance:

The predictive performance of the prognostic screening tool will be assessed using the established traditional measures of overall prognosis, discrimination, and calibration (76). Brier score will be used to quantify the overall performance of the screening tool where the score ranges from 0 ('perfect model') to 0.25 ('not informative model') (76). The Receiver Operator Characteristic (ROC) curve will be used to discriminate between those who did or did not develop chronic whiplash. Finally, the calibration will be assessed through plotting the mean predicted against observed chronic whiplash cases.

Sample size

This study will consider the association between 16 candidate predictors (Table 1) and neck pain and disability at 6 months. The authors will ensure that at least ten participants per predictor will be used to develop an adequately powered linear regression analysis (77, 78). Because the shrinkage method by LASSO method creates models with fewer predictors (73), it is anticipated that the number of final predictors retained in the final linear model will fall below 12 predictors. Therefore, a sample size target of 120 participants is required to adequately powered a maximum of 12 candidate predictors into the multiple linear regression, with the addition of 30 participants to allow for possible loss of follow-up (total = 150).

For the sample size of a logistic regression model derived following the LASSO shrinkage method, a minimum of 5 events per predictor is sufficient as established previously (73). Based on the current knowledge about the transition rate from acute to chronic WAD, it is expected that 50% of patients will report persistent neck pain and disability (11, 79, 80). This leaves 60 out of our potential participants who might develop persistent neck pain and disability 6 months post WAD. Therefore, a sample size of 60 participants is adequate to power a logistic regression analysis of 12 candidate predictors with 5 events per predictor.

Management of missing data

For each variable of interest, numbers of participants with missing data will be reported. Any potential bias due to loss of follow-up will be assessed and compared using baseline data of subjects who withdraw or lost at follow-up (66). Multiple imputation (81) will be used to deal with missing outcome data, if appropriate and necessary. Participants will be excluded

from the predictive model and subsequent analyses if they request to withdraw from the study following recruitment (66).

Patients and public involvement

The research question in this study was developed following consultations with patients. Patients will not be involved in the analysis and data collection of study. The results of the study will be presented to members of the public and patients during one of our regular Patient and public involvement meetings.

Ethics and dissemination:

The study will be conducted according to the Declaration of Helsinki. The project has been approved by the Ethics Committee of the province of Malaga, Spain (#30052019). The results of the study will be disseminated via reports published in peer-reviewed journals and national and international conferences. No datasets will be created as part of this work for deposition or curation. Participant burden has been taken into consideration when developing this study. The number of measures has been kept to a minimum. To ensure the privacy of each patient, a unique identification number will be assigned to each participant at the time of recruitment. Only pseudonymised or anonymised data will be used during analyses. Participants will be informed that they can withdraw from the study at any time, without having to provide a reason; however, where a reason is given it will be recorded. If a participant withdraws, no further data will be collected but data already collected will be retained for analyses. Baseline characteristics of any participants that withdraw will be compared to retained participants to assess for any differences.

At each data collection session, confirmation to proceed will be gained before any data are collected. Any concerns and/or adverse events will be noted and fed back to clinical staff, according to the Good Clinical Practice principles. For ethical reasons, routine

treatment will not be withheld from individuals at any point during the study. The details and frequency of any received treatment will be recorded and reported. The protocol and conduct of this study are strengthened by the inclusion of patient and public involvement, who contributed to the development of study design and documentation. In addition, they will contribute to the processes of performing data analysis, interpretation of results, and producing a lay summary of findings.

DISCUSSION

This is the first protocol to describe, *a priori*, the methods and analysis for identifying predictive factors for ongoing pain and disability following acute whiplash injury. In particular, self-reported measures together with novel physical measure will be incorporated including angular velocity, smoothness of movements, force steadiness, and neck muscle co-activation to predict poor outcome in individuals with WAD recruited within 15 days of the injury. The selected candidate predictors are included based on current knowledge and the possible utilisation in clinical practice. The knowledge gained through this study can assist in the identification of personalised interventions to facilitate recovery and therefore minimise the transition to chronic whiplash.

SPIRIT 2013 Statement, TRIPOD, PROGRESS, QUIPS and CHARMS statements and frameworks have informed design to ensure rigorous conduct of this study (54-58) . The results from this study will provide new insights into who is likely to recover versus who is likely to develop persistent symptoms following a whiplash injury. Using a novel combination of outcome measures will allow the future development of a tool to predict development of chronic and disabling pain following a whiplash injury providing new opportunities to identify precision intervention.

Author Contributions

All authors contributed to the focus of this study. AA is a PhD student with DF as Lead Supervisor and AG as Co-Supervisor. AA drafted the initial protocol with guidance from DF and DWE at all stages. ALS and MFS will be involved in collecting data from participants. All authors approved the final version for publication. DF is guarantor.

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Competing Interests Statement

The authors have no competing interests to report.

Patient consent

Not required.

Ethics approval

Approved by Ethics Committee of the province of Malaga, Spain (#30052019).

Data sharing statement

No additional data are available.

Amendment Protocol

If changes in the protocol deemed to be necessary during conducting the study, they will be documented on the main report of the study.

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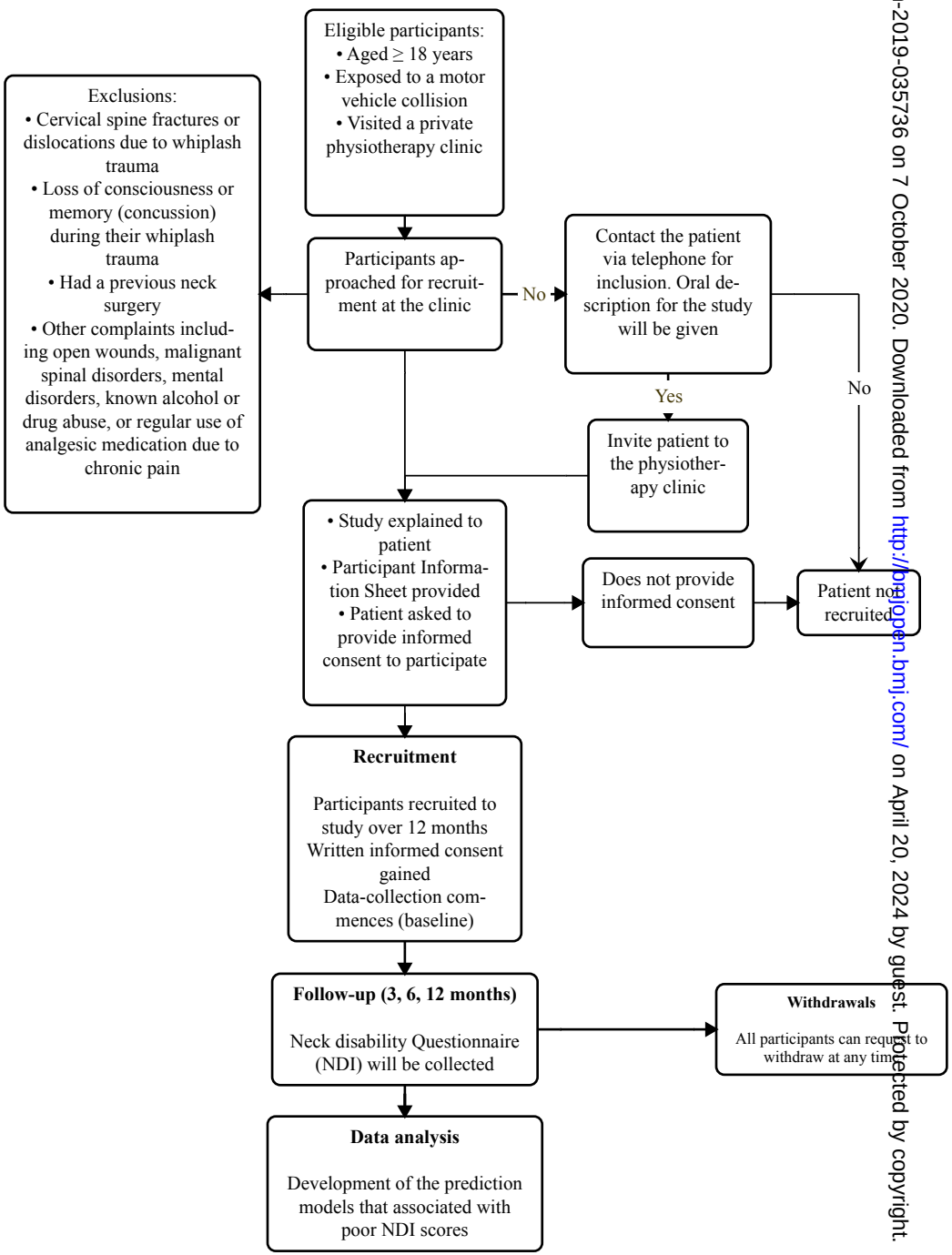
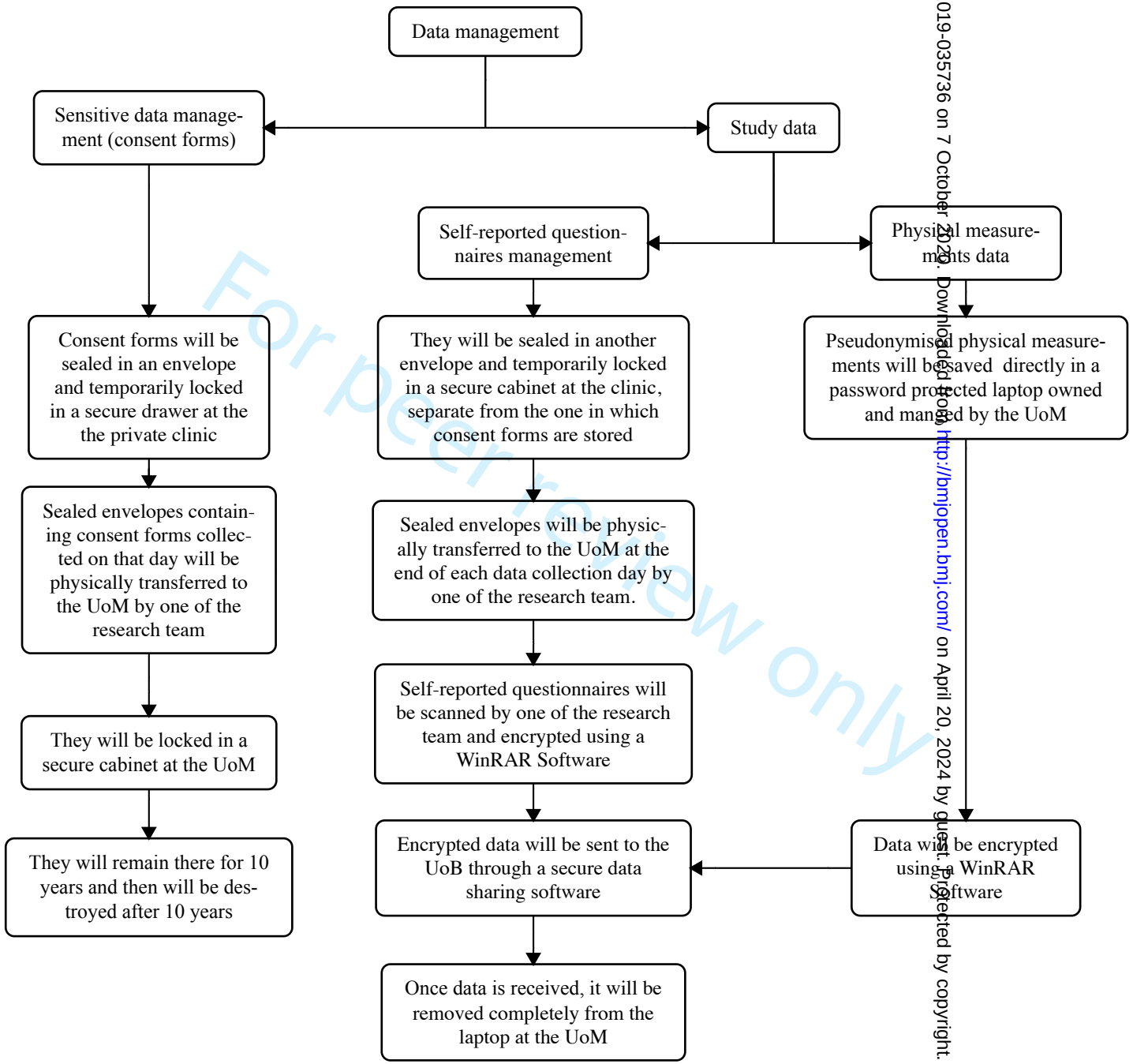
Figure Captions

Figure 1: Participant flow through the study.

Figure 2: Process for data management.





Supplementary file 1. Candidate predictors

General patient characteristics including previous musculoskeletal pain

Participants' demographic data will be recorded at baseline including gender and highest attained education level.

Psychosocial features

Pain Catastrophizing Scale (PCS)

The PCS will be used to evaluate the extent to which patients ruminate, magnify or feel helpless about controlling their pain [1]. It is a 13-item self-reported outcome consisting of three dimensions including rumination, magnification and helplessness to measure pain related catastrophizing. Subjects rate the frequency of experiencing catastrophic thoughts as 0 (not at all) or 4 (all the times) which produces an overall score of from 0-52 with higher scores indicating greater negative pain thoughts. The reliability and validity of the PCS have been established [1], and it has been used in patients with WAD [2, 3]. Moderate evidence of significant association shows that initial catastrophising was a risk factor for developing persistent symptoms in whiplash [4] with pooled odd ratio=3.77 (95% confidence intervals = 1.33 - 10.74) [5].

Tampa Scale of Kinesiophobia [TSK-11]

The TSK-11 is a self-reported outcome used to evaluate fear of movement or injury during activities [6]. It consists of 11-item of which each is scored from 1 ('totally agree') to 4 ('totally disagree') producing a total score from 11 to 44, with higher scores indicating higher fear of movement. The TSK-11 has showed excellent test-retest reliability and good construct validity in detecting changed in pain and disability [7]. Indirect association was found between fear of movement and higher neck pain and disability in patients with acute

WAD [8]; catastrophizing increases fear of movement which leads to decreased functional self-efficacy that results in higher pain and disability [8].

Recovery Expectation (high or low expectation of recovery)

Patients will be asked if they expect to fully recover within the next six months. Recovery expectations will be assessed by the question "In your opinion, how likely is it that you will be fully recovered with no persistent sequelae?" [9]. In response to this question, recovery expectations will be measured using NRS where a patient need to indicate how likely he/she would have completely recovered, by choosing a score from 0 ("not likely") to 10 ("very likely") [10]. Low expectation of making full recovery were found to be an independent predictive factor associated (odds ratio= 4.2 [95% CI = 2.1 - 8.5]) with higher disability in individuals with acute WAD [10].

Pain characteristics

Numeric Rating Scale (NRS)

Current neck pain intensity will be measured using NRS which is a 11-point scale range from 0 (no pain) to 10 (worst possible pain). Also, perceived pain intensity will be measured at the end of each physical measure of neck range of motion tasks, neck maximum contraction tasks, and neck submaximum contraction tasks. The reliability of NRS has been established in patients with neck pain (ICC:0.76) [11]. Also, participants will be asked remotely (through the app) where they have 'experienced pain during the last week' from several body locations [12]. Based on their response of chosen areas, pain intensity will be assessed using NRS. Finally, neck pain intensity following active movements will be measured through NRS. High evidence of significant association shows that initial neck pain

intensity was a consistent risk factor for developing persistent symptoms in whiplash [4] with pooled odd ratio= 5.61 (95% CI = 3.74 - 8.43) [13].

Physical measures

Wearable sensor for motion detection (Neck range of movement, angular velocity, movement smoothness and proprioception)

A wearable BTS G-WALK® sensor system (BTS Bioengineering, Italy) will be utilised to assess neck range of motion, angular velocity, movement smoothness, and neck proprioception. The sensor connects to a computer via Bluetooth; at the end of each analysis an automatic report containing all the parameters recorded during the test, is displayed.

Active neck flexion, side-flexion, extension, and rotation will be measured at baseline. Impaired range of motion has been found in individuals with WAD compared to healthy controls [14, 15] and has also been found to be a factor associated with persistent disability at one year [16, 17], and neck pain and disability at 6 months [18, 19].

Besides range of motion, the angular velocity and movement smoothness will be recorded simultaneously during each neck movement. Each movement direction will be repeated five times and the average taken. These kinematic variables may provide more information about motor control disturbances [20]. A study found maximum angular velocity and acceleration were lower in subjects with chronic WAD when compared to healthy control [20]. The same finding (lower peak velocity) was found in cohorts of both WAD and insidious neck pain [21]. Moreover, significant differences in jerk indices were observed during active neck movements in a study comparing healthy controls to those with chronic neck pain of both insidious onset and traumatic onset [21].

Neck proprioception will be measured by calculating the Joint Position Error (JPE) following active neck rotation. JPE is defined as the ability to relocate the natural head

position without the assistance of vision [22]. To assess this, the same wearable sensor (G-Walk) will be used. Patients will repeat active neck rotation with their eyes closed and will indicate when they think that they have returned to the starting position. JPE will be assessed three times for both right and left rotation and the average taken for each direction. Decreased head repositioning accuracy has been observed in people with idiopathic neck pain [23], but with greater repositioning errors found in individuals with neck pain attributed to a trauma [24], which is even more evident in those with moderate to severe pain and disability [14].

Dynamometer (maximal and sub-maximal isometric contractions)

At baseline, the participants will perform maximal and sub-maximal isometric contractions to measure maximum strength and control of sub-maximal forces. Cranio-cervical flexion, neck flexion and extension will be tested using a hand-held dynamometer for neck muscle testing (NOD, OT Bioeletronica, Italy).

1. Maximum voluntary contraction (MVC):

Two MVCs will be performed for cranio-cervical flexion, neck flexion, and extension. Each maximum MVCs will last for 3 seconds, separated by 1 minute rest in between [25]. The mean MVC for each direction will be calculated and used in the analysis [26, 27]. Patients will perform an initial trial to familiarise themselves with each movement under the guidance of a trained examiner with minimal force.

Cranio-cervical flexion strength testing will be performed with the participant in supine lying with the hip and knees flexed to approximately 90 degrees [28]. The head will be placed in neutral position and the dynamometer placed behind the upper cervical spine with the instruction being to nod as if saying yes but as hard as you can. Patients will be seated to measure neck flexion and extension strength with the participant seated comfortably on a chair with hip and knee flexed to 90 degrees with head in neutral position

and feet flat on the ground. To measure neck flexion, the dynamometer will be placed over the forehead and against the resistance of the examiner, the patient will be instructed to "push as hard as you can as you try to bring your chin to your chest" [29]. The dynamometer will then be placed on the back of the head and the patient instructed to "push as hard as you can into the dynamometer as if trying to bring the back of the head to your neck" [29].

Patients with neck pain commonly present with reduced neck strength [29-32], although the extent of impaired strength is highly variable across patients [33]. Significant lower isometric MVC force has been observed in patients with chronic WAD compared to healthy controls [29]. Reduced neck muscle strength has been associated with the extent of disability [25, 34] and pain [34] in people with chronic neck pain..

2. Sub-maximal voluntary contractions:

In the same positions described for the MVC, participants will be instructed to perform a single submaximal contraction at 20% of their maximal force and hold this for 10 seconds for cranio-cervical flexion, flexion and extension. In addition, participants will perform 40%, 60%, 80%, and 100% of their maximal force for the cranio-cervical flexion only. Feedback on force will guide the participant to maintain specific degree of contraction from their MVC over the duration of the contraction.

Surface electromyography (EMG) (co-activation of the sternocleidomastoid and splenius capitis)

The amplitude of sternocleidomastoid (SCM) activity will be measured bilaterally during the isometric maximum and submaximal voluntary contractions of cranio-cervical flexion. In addition, both SCM and splenius capitis (SC) activity will be measured bilaterally during the maximum and submaximal voluntary contractions of neck flexion and extension.

Increased co-activation of the neck flexors and extensors has been observed in patients with chronic neck pain and headache [35], and is associated with reduced neck strength [35]. Changes in neck muscle activation has been observed in people with acute neck pain following a whiplash injury [14, 36].

Following gentle skin preparation, pairs of bipolar surface electrodes will be placed over SCM and SC bilaterally following published guidelines for electrode placement [37]. Signals will be detected using wireless EMG (Ultium® EMG, Noraxon, USA). Co-activation indexes will be calculated as described previously [38].

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Not intended
	2b	All items from the World Health Organization Trial Registration Data Set	NA
Protocol version	3	Date and version identifier	NA
Funding	4	Sources and types of financial, material, and other support	19
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	NA
	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)	NA

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-6
	6b	Explanation for choice of comparators	NA
Objectives	7	Specific objectives or hypotheses	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
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)	7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	NA
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	NA
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	NA
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure 1)	9

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	16
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7-8
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	NA
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	NA
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	NA
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	NA
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	10-11

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12-14
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	15-16
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	17
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	NA
	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	7
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	NA
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	17
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	20

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	12-13
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	19
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	12-13
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	NA
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	17
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	185
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

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

Correction: *Do measures of physical function enhance the prediction of persistent pain and disability following a whiplash injury? Protocol for a prospective observational study in Spain*

Alalawi A, Luque-Suarez A, Fernandez-Sanchez M, *et al*. Do measures of physical function enhance the prediction of persistent pain and disability following a whiplash injury? Protocol for a prospective observational study in Spain. *BMJ Open* 2020;**10:**e035736. doi: 10.1136/bmjopen-2019-035736

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