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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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4 1 **DO MEASURES OF PHYSICAL FUNCTION ENHANCE THE**
5 2 **PREDICTION OF PERSISTENT PAIN AND DISABILITY**
6 3 **FOLLOWING A WHIPLASH INJURY? PROTOCOL FOR A**
7 4 **PROSPECTIVE OBSERVATIONAL STUDY**
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4 30 **ABSTRACT**

5
6 31 **Introduction**

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8 32 Not all factors that predict persistent pain and disability following whiplash injury are known.
9
10 33 In particular, few physical factors, such as changes in motor function and muscle behaviour
11
12 34 have been investigated.

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15 35 **Aims and objectives**

16
17 36 The aim of this study is to identify predictive factors that are associated with the development
18
19 37 of persistent pain and disability following a whiplash injury by combining contemporary
20
21 38 measures of physical function together with established psychological and pain-related
22
23 39 predictive factors.
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26
27 40 **Methods and analysis**

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29 41 A prospective observational study will recruit 150 consecutive eligible patients experiencing
30
31 42 whiplash-related symptoms, admitted to a private physiotherapy clinic in Spain within 15
32
33 43 days of their whiplash injury. The absolute risk of poor outcome will be measured using the
34
35 44 Neck Disability Index (NDI). Poor outcome is defined as an NDI absolute score of 30% or
36
37 45 greater at 6 months post-injury. Candidate predictors, including demographic characteristics,
38
39 46 injury characteristics, pain characteristics, self-reported psychosocial factors and physical
40
41 47 factors will be collected at baseline (within 15 days of inception). Regression analyses will be
42
43 48 performed to identify factors that are associated with persistent neck pain and disability over
44
45 49 the study period.
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49
50 50 **Ethics and dissemination**

51
52 51 The project has been approved by the University of Birmingham Research Ethics Committee
53
54 52 and the Ethics Committee of the province of Malaga, Spain (#30052019). The results of this
55
56 53 study will be published in peer-reviewed journals.
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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.

80 INTRODUCTION

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

93 High-quality evidence has shown higher pain and disability immediately post-injury
94 to be the most consistent factor predicting longer-term pain and disability (9, 10). Studies
95 have examined other factors that might predict the development of ongoing pain following
96 whiplash covering all three elements of the biopsychosocial model: demographic factors (7,
97 11-14), pre-existing comorbidities (11, 13, 14), collision factors (7, 11-13, 15-18), physical
98 factors (14, 19-24), radiological changes (2, 25-30), societal factors (31), and psychological
99 factors (7, 32, 33). Yet, there is controversial evidence concerning the predictive ability of
100 other factors including: general psychological distress, depression, previous neck pain,
101 gender, and the use of a seatbelt at the time of the collision (9, 14, 32, 34, 35). This illustrates
102 an incomplete picture regarding the predictive factors for recovery versus ongoing pain in
103 WAD.

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4 104 There has been little investigation of the predictive utility of physical factors
5
6 105 following whiplash injury; of the studies conducted, measures of physical function have been
7
8 106 limited to measures such as range of motion (19, 20, 36, 37) and cranio-cervical flexion test
9
10 107 performance (38, 39). Yet, physical factors offer potential to improve prediction accuracy.
11
12
13 108 For example, there is a wealth of evidence describing changes in motor function and muscle
14
15 109 behaviour (40-42). Decreased maximum angular velocity of neck movements has been
16
17 110 observed in individuals with chronic WAD when compared to healthy individuals (40). Such
18
19 111 changes in movement behaviour have been confirmed in individuals with WAD and insidious
20
21 112 neck pain, where lower peak velocity was observed in both groups (41). In addition, a
22
23 113 significantly larger jerk index (measure of the smoothness of neck movement) has been
24
25 114 reported in individuals with chronic neck pain of both insidious and traumatic onset, when
26
27 115 compared to asymptomatic individuals (41). Another feature reported in those with chronic
28
29 116 neck pain is increased co-activation of the neck flexors and extensors (42), which is
30
31 117 associated with reduced neck strength (42). These additional features have not been
32
33 118 investigated in individuals with acute WAD, but results from experimental pain studies
34
35 119 suggest these adaptations occur soon after pain onset and may therefore have relevance for
36
37 120 ongoing symptoms in individuals with chronic WAD (43-50).

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43 121 A number of methodological limitations of previously published studies in the field of
44
45 122 WAD prognosis have been identified. For instance, a review conducted by Walton et al. (10)
46
47 123 found that many predictors have conflicting results (11, 12, 32). Inconsistent outcome
48
49 124 measures have previously been used by to define recovery in WAD (51), with a different
50
51 125 definition of recovery used in each study (7, 52). Other reasons for inconsistency can be
52
53 126 attributed to poor reporting (11, 53) and the inclusion of subjects from different settings and
54
55 127 at different inception points. Another recent review found controversial evidence with
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4 128 regards to which demographic factors, prior pain, and psychological factors are associated
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6 129 with the transition to chronic WAD. (9).
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8 130 Collectively, these limitations impact on our understanding of factors associated with
9
10 131 the transition to chronic WAD following a whiplash injury and highlight the need for an
11
12 132 adequately powered, methodologically robust observational study to provide useful
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14 133 predictive estimates. Such knowledge could lead to the development of a new clinical care
15
16 134 pathway that matches early interventions to risk factors for poor recovery.
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21 22 136 **Aims of study** 23

24 137 The aim of the study is to identify factors soon after a whiplash injury that predict the
25
26 138 occurrence of persistent pain and disability six months later. We will include a broad range of
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28 139 candidate predictors, including measures of physical function with self-reported measures of
29
30 140 pain, disability and established psychological constructs.
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35 36 37 142 **METHODS** 38

39 40 143 **Study Design** 41

42 144 The study will be a prospective observational design. This protocol has been developed
43
44 145 in accordance with guidelines from the SPIRIT 2013 Statement (54), the Transparent Reporting
45
46 146 of a Multivariable Prediction Model for Individual Prognosis Or Diagnosis (TRIPOD)
47
48 147 statement (55), the Quality In Prognosis Studies (QUIPS) tool (56), the CHecklist for critical
49
50 148 Appraisal and data extraction for systematic Reviews of prediction Modelling Studies
51
52 149 (CHARMS) (57), and the PROGnosis RESearch Strategy (PROGRESS) framework (58).
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152 **Participants**

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

157

158 ***Eligibility criteria***

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

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

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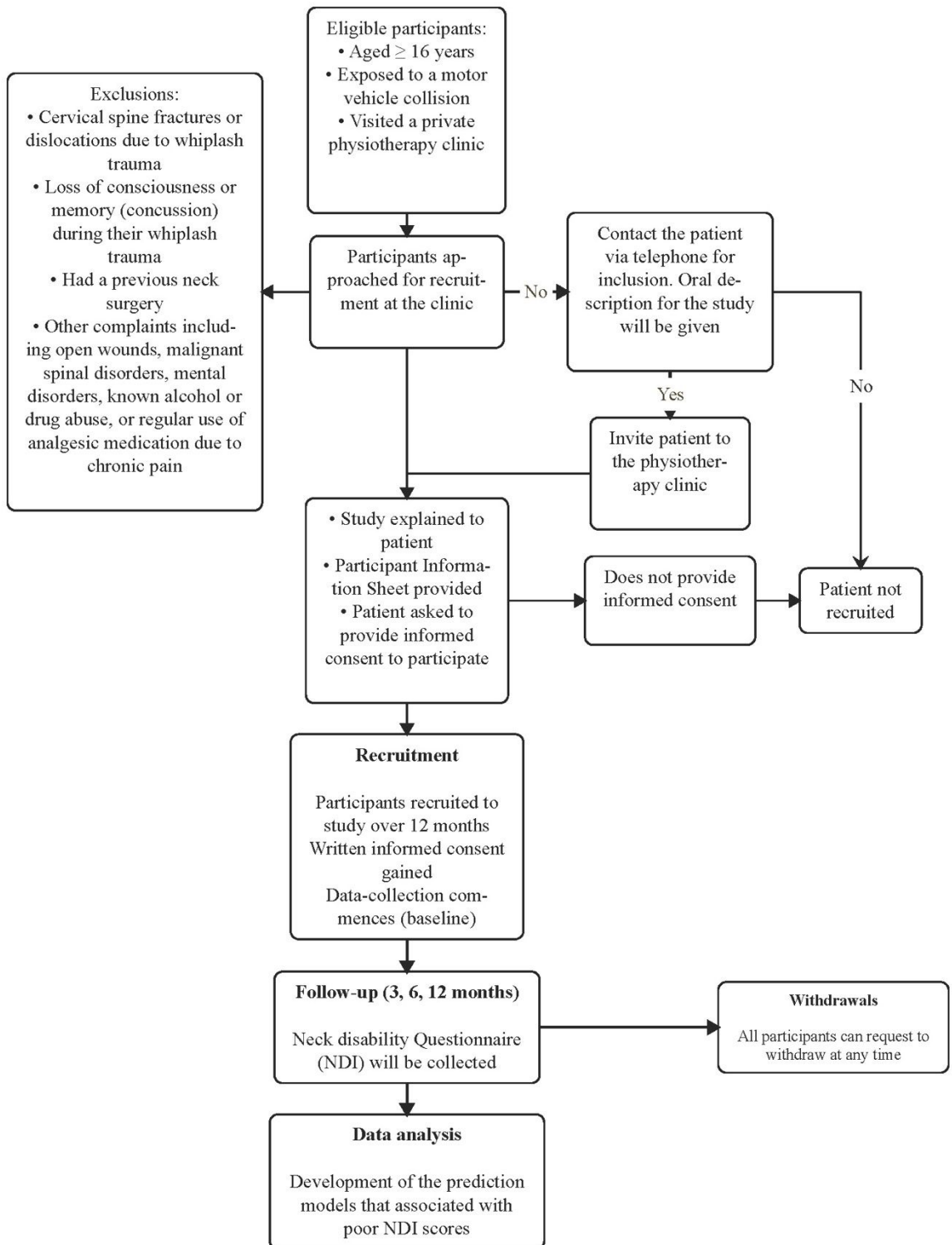
170 ***Recruitment***

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

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

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4 177 records of all consecutive patients attending the clinic. Once an eligible patient is identified at
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6 178 the clinic, the designated clinic physiotherapist will contact the patient to invite them to
7
8 179 participate in the study; this invitation will be done either in-person at the clinic after the first
9
10 180 treatment session or via telephone after patients have returned home from their clinic
11
12 181 appointment. A verbal and written description of the study will be provided during the
13
14 182 invitation. Those patients interested in participation will be invited to attend an initial study
15
16 183 session at the physiotherapy clinic. At this session, the researcher will again explain the study
17
18 184 design and context, patients will be given a detailed information sheet, and written informed
19
20 185 consent will be sought. Once recruited, participants (Figure 1) will be asked to complete a
21
22 186 baseline self-reported questionnaire, after which physical data will be collected (Table 1).
23
24 187 Participants will be informed that they can withdraw from the study at any time, without having
25
26 188 to provide a reason. They will also be advised to carry on with their daily routines as usual, and
27
28 189 that any interventions received during their physiotherapy sessions will be recorded for a
29
30 190 descriptive analysis.
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191
192 Figure 1: Study design



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197 **Outcome**

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

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

210 **Candidate predictors**

211 Due to the current lack of consensus on predictive factors of poor outcome, several
212 self-reported and physical measures will be collected (9). Factors have been selected based
213 on current knowledge of prognosis in whiplash (2, 7, 9, 11-13, 24, 31-34, 69) and a
214 theoretical association with prognosis in individuals with neck pain, as informed by the
215 biopsychosocial model of pain (70). These factors are also chosen due to being feasible to
216 measure in clinical practice. Candidate predictors are summarised in Table 1 with further
217 information available in the supplementary file S1. All data collection will be standardised
218 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 \leq 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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226 **Data collection**

227 *Baseline and follow-up*

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

234 **Data management**

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

242 Sensitive data management:

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

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4 250 will be securely stored at UoM for a period of 10 years, after which they will be destroyed. No
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6 251 identifiable data will be transferred outside of the UoM.
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11 253 Self-reported questionnaires management:
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13 254 Self-reported paper questionnaires, identifiable only by study ID number for each
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15 255 participant, will be sealed in another envelope and temporarily locked in a secure cabinet at the
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17 256 clinic, separate from the one in which consent forms are stored. Sealed envelopes containing
18
19 257 the pseudonymised self-reported questionnaires will be physically transferred to the UoM at
20
21 258 the end of each data collection day by one of the research team. Once transferred, self-reported
22
23 259 questionnaires will be scanned by one of the research team and saved in a password protected
24
25 260 laptop computer, owned and managed by UoM. Scanned self-reported electronic data will be
26
27 261 encrypted using a WinRAR Software before transit to the University of Birmingham (UoB)
28
29 262 (via Power Folder data sharing software, hosted locally at the University). Once received, this
30
31 263 pseudonymised data will be uploaded directly to physically secure servers at the UoB, where
32
33 264 they will remain indefinitely on secure UoB servers with access restricted to members of the
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35 265 study team. Once uploaded to UoB servers, data will be removed completely from the laptop
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37 266 at UoM. The same procedures will be followed for follow-up NDI data at 3, 6, and 12 months.
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45 268 Physical data management:
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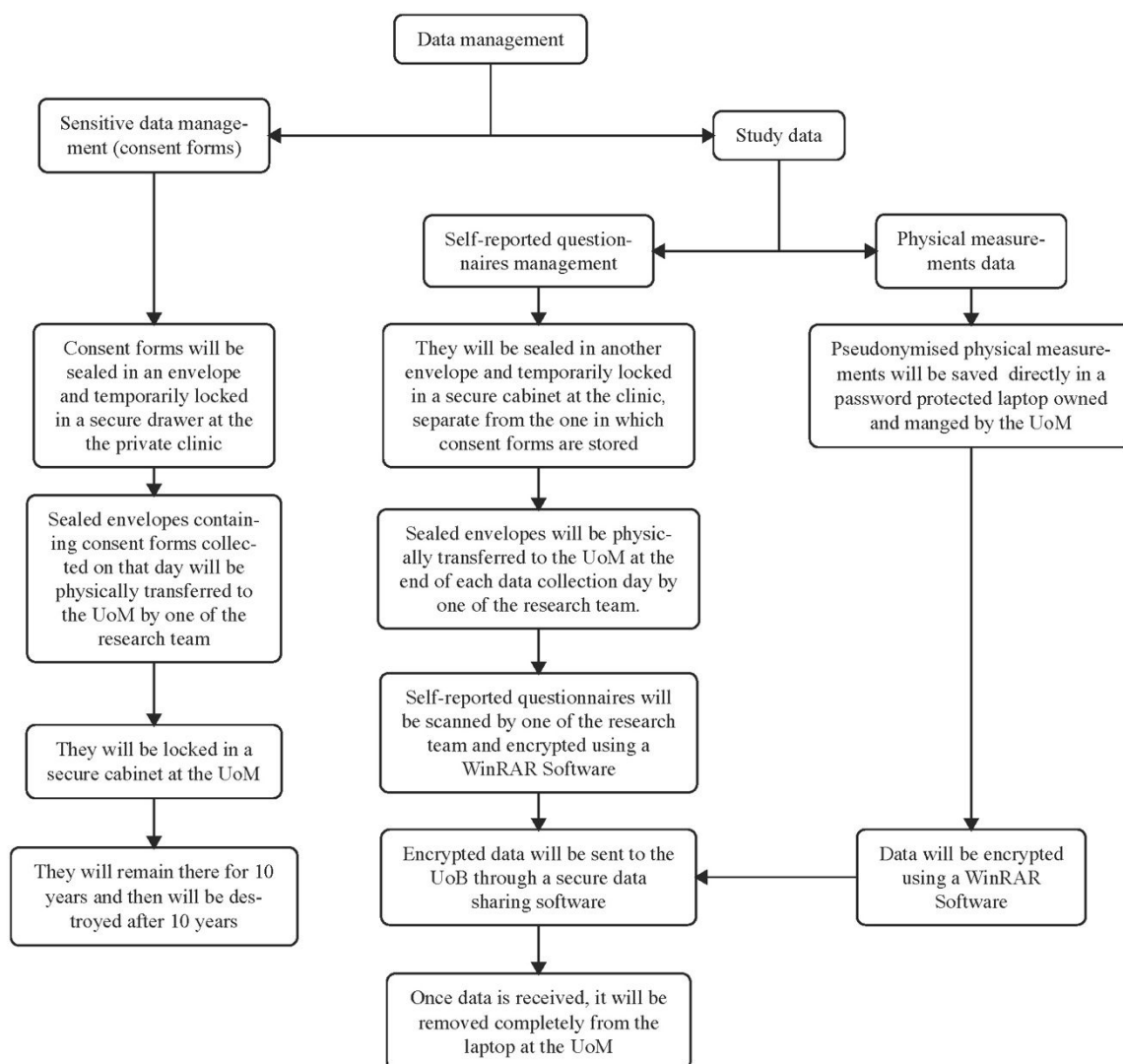
47 269 Pseudonymised physical data will be saved in a password protected laptop owned and
48
49 270 managed by UoM, whilst at the clinic study session. Access to the UoM laptop is restricted and
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51 271 only available to the local research team. As with other data, pseudonymised electronic data
52
53 272 will be encrypted using a WinRAR Software, transferred to the UoB team, and uploaded to the
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55 273 physically secure servers at UoB, where they will remain indefinitely with access restricted to
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274 study researchers. Again, once data has been received by the team at UoB, they will be removed
 275 from UoM computers.

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278 Figure 2: Data management



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281 Data analysis

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

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4 284 Loss to follow-up and withdrawals will be reported, with reasons where available. Descriptive
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6 285 analyses of participants at baseline will include participant demographics, self-reported
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8 286 questionnaires and physical assessment data.
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15 289 Linear regression analysis:

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17 290 Multivariate linear regression models will be developed as a primary analysis to
18
19 291 determine the association between candidate predictors and neck pain and disability
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21 292 (measured by NDI) at 6 months post injury. Factors with univariate associations at baseline
22
23 293 and the outcome will be established $p < 0.20$ (72) and deemed eligible to enter multivariable
24
25 294 analysis.
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29 295 Logistic regression analysis:

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31 296 Outcome (NDI) scores will be dichotomised into good or poor categories with a NDI
32
33 297 score of $\geq 30\%$ at six months post-injury defined as poor outcome, as described previously.
34
35 298 Logistic regression will be used to identify factors that are associated with poor outcomes. To
36
37 299 avoid overfitting the regression model, several steps will be taken. Firstly, linear univariate
38
39 300 associations between each predictor at baseline and the outcome will be assessed to establish
40
41 301 factors that are eligible to enter multivariable analysis. Those predictors with strong correlation
42
43 302 to the outcome ($p < 0.20$) (72), will be identified for the multivariable analysis. Secondly, a
44
45 303 univariate logistic regression model will be constructed for each baseline predictor (Table 1)
46
47 304 and its association with NDI to select those entering the final logistic model as described
48
49 305 previously (73). Next, multivariable analysis will be conducted using stepwise logistic
50
51 306 regression (74), to identify predictors that maintain significance ($p < 0.05$) when included in the
52
53 307 final model. The final logistic model will be constructed to include predictors that maintain
54
55 308 significant relationship with chronic disability at all previous steps. The final model will be
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4 309 checked for multicollinearity using variance inflation factors (VIF) to ensure no significant
5
6 310 correlations between the included candidate predictors (75).

7
8 311 Model Performance:

9
10 312 The predictive performance of the prognostic screening tool will be assessed using the
11
12 313 established traditional measures of overall prognosis, discrimination, and calibration (76).
13
14 314 Brier score will be used to quantify the overall performance of the screening tool where the
15
16 315 score ranges from 0 ('perfect model') to 0.25 ('not informative model') (76). The Receiver
17
18 316 Operator Characteristic (ROC) curve will be used to discriminate between those who did or
19
20 317 did not develop chronic whiplash. Finally, the calibration will be assessed through plotting
21
22 318 the mean predicted against observed chronic whiplash cases.
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31 321 ***Sample size***

32
33 322 This study will consider the association between 16 candidate predictors (Table 1)
34
35 323 and neck pain and disability at 6 months. The authors will ensure that at least ten participants
36
37 324 per predictor will be used to develop an adequately powered linear regression analysis (77,
38
39 325 78). It is anticipated that some predictors may be excluded due to multicollinearity between
40
41 326 predictors and/or not meeting the conditions of developing a predictive model. For example,
42
43 327 only candidate predictors that reached the stated liberal significant level with the outcome
44
45 328 ($p < 0.20$) (72) will be included. Therefore, a sample size target of 120 participants is required
46
47 329 to adequately powered a maximum of 12 candidate predictors into the multiple linear
48
49 330 regression, with the addition of 30 participants to allow for possible loss of follow-up (total =
50
51 331 150).

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53 332 For the logistic regression analysis sample size, a minimum of 5 events per predictor
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55 333 will be considered (78), as used previously (72). Based on the current knowledge about the
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4 334 transition rate from acute to chronic WAD, it is expected that 50% of patients will report
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6 335 persistent neck pain and disability (11, 79, 80). This leaves 60 out of our potential
7
8 336 participants who might develop persistent neck pain and disability 6 months post whiplash
9
10 337 injury. Therefore, a sample size of 60 participants is adequate to power a logistic regression
11
12 338 analysis of 12 candidate predictors with 5 events per predictor.
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15 339

17 340 ***Management of missing data***

19
20 341 For each variable of interest, numbers of participants with missing data will be reported.
21
22 342 Any potential bias due to loss of follow-up will be assessed and compared using baseline data
23
24 343 of subjects who withdraw or lost at follow-up (66). Multiple imputation (81) will be used to
25
26 344 deal with missing outcome data, if appropriate and necessary. Participants will be excluded
27
28 345 from the predictive model and subsequent analyses if they request to withdraw from the study
29
30 346 following recruitment (66).
31
32

33 347

36 348 **Ethics and dissemination:**

37
38 349 The study will be conducted according to the Declaration of Helsinki. The project has
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40 350 been approved by the Ethics Committee of the province of Malaga, Spain (#30052019). The
41
42 351 results of the study will be disseminated via reports published in peer-reviewed journals and
43
44 352 national and international conferences. Participant burden has been taken into consideration
45
46 353 when developing this study. The number of measures has been kept to a minimum. To ensure
47
48 354 the privacy of each patient, a unique identification number will be assigned to each
49
50 355 participant at the time of recruitment. Only pseudonymised or anonymised data will be used
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52 356 during analyses. Participants will be informed that they can withdraw from the study at any
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54 357 time, without having to provide a reason; however, where a reason is given it will be
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56 358 recorded. If a participant withdraws, no further data will be collected but data already
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4 359 collected will be retained for analyses. Baseline characteristics of any participants that
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6 360 withdraw will be compared to retained participants to assess for any differences.
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8 361 At each data collection session, confirmation to proceed will be gained before any
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10 362 data are collected. Any concerns and/or adverse events will be noted and fed back to clinical
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12 363 staff, according to the Good Clinical Practice principles. For ethical reasons, routine
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14 364 treatment will not be withheld from individuals at any point during the study. The details and
15
16 365 frequency of any received treatment will be recorded and reported. The protocol and conduct
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18 366 of this study are strengthened by the inclusion of patient and public involvement, who
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20 367 contributed to the development of study design and documentation. In addition, they will
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22 368 contribute to the processes of performing data analysis, interpretation of results, and
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24 369 producing a lay summary of findings.
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371 **DISCUSSION**

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

381 SPIRIT 2013 Statement, TRIPOD, PROGRESS, QUIPS and CHARMS statements
382 and frameworks have informed design to ensure rigorous conduct of this study (54-58) . The
383 results from this study will provide new insights into who is likely to recover versus who is
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4 384 likely to develop persistent symptoms following a whiplash injury. Using a novel
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6 385 combination of outcome measures will allow the future development of a tool to predict
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8 386 development of chronic and disabling pain following a whiplash injury providing new
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10 387 opportunities to identify precision intervention.
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15 389 **Author Contributions**

16
17 390 All authors contributed to the focus of this study. AA is a PhD student with DF as Lead
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19
20 391 Supervisor and AG and ALS as Co-Supervisors. AA drafted the initial protocol with
21
22 392 guidance from DF at all stages. DE, ALS, MFS and AG provided guidance on topic,
23
24 393 methodology and analyses. ALS and MFS will be involved in collecting data from
25
26 394 participants. All authors approved the final version for publication. DF is guarantor.
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36
37
38 399 or not-for-profit sectors.
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40 400 **Competing Interests Statement**

41
42 401 The authors have no competing interests to report.
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45 402 **Patient consent**

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47 403 Not required.
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50 404 **Ethics approval**

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52 405 Approved by Ethics Committee of the province of Malaga, Spain (#30052019).
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54 406 **Data sharing statement**

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56 407 No additional data are available.
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4 409 **Amendment Protocol**

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6 410 If changes in the protocol deemed to be necessary during conducting the study, they will be

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8 411 documented on the main report of the study.

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For peer review only

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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

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3 WAD [8]; catastrophizing increases fear of movement which leads to decreased functional
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5 self-efficacy that results in higher pain and disability [8].
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Recovery Expectation (high or low expectation of recovery)

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12 Patients will be asked if they expect to fully recover within the next six months.
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14 Recovery expectations will be assessed by the question “In your opinion, how likely is it that
15 you will be fully recovered with no persistent sequelae?” [9]. In response to this question,
16 recovery expectations will be measured using NRS where a patient need to indicate how
17 likely he/she would have completely recovered, by choosing a score from 0 (“not likely”) to
18 10 (“very likely”) [10]. Low expectation of making full recovery were found to be an
19 independent predictive factor associated (odds ratio= 4.2 [95% CI = 2.1 - 8.5]) with higher
20 disability in individuals with acute WAD [10].
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Pain characteristics

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Numeric Rating Scale (NRS)

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37 Current neck pain intensity will be measured using NRS which is a 11-point scale
38 range from 0 (no pain) to 10 (worst possible pain). Also, perceived pain intensity will be
39 measured at the end of each physical measure of neck range of motion tasks, neck maximum
40 contraction tasks, and neck submaximum contraction tasks. The reliability of NRS has been
41 established in patients with neck pain (ICC:0.76) [11]. Also, participants will be asked
42 remotely (through the app) where they have ‘experienced pain during the last week’ from
43 several body locations [12]. Based on their response of chosen areas, pain intensity will be
44 assessed using NRS. Finally, neck pain intensity following active movements will be
45 measured through NRS. High evidence of significant association shows that initial neck pain
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3 intensity was a consistent risk factor for developing persistent symptoms in whiplash [4] with
4
5 pooled odd ratio= 5.61 (95% CI = 3.74 - 8.43) [13].
6
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9

10 **Physical measures**

11 Wearable sensor for motion detection (Neck range of movement, angular velocity, movement 12 13 smoothness and proprioception) 14

15
16 A wearable BTS G-WALK® sensor system (BTS Bioengineering, Italy) will be
17
18 utilised to assess neck range of motion, angular velocity, movement smoothness, and neck
19
20 proprioception. The sensor connects to a computer via Bluetooth; at the end of each analysis
21
22 an automatic report containing all the parameters recorded during the test, is displayed.
23
24

25
26 Active neck flexion, side-flexion, extension, and rotation will be measured at
27
28 baseline. Impaired range of motion has been found in individuals with WAD compared to
29
30 healthy controls [14, 15] and has also been found to be a factor associated with persistent
31
32 disability at one year [16, 17], and neck pain and disability at 6 months [18, 19].
33
34

35
36 Besides range of motion, the angular velocity and movement smoothness will be
37
38 recorded simultaneously during each neck movement. Each movement direction will be
39
40 repeated five times and the average taken. These kinematic variables may provide more
41
42 information about motor control disturbances [20]. A study found maximum angular velocity
43
44 and acceleration were lower in subjects with chronic WAD when compared to healthy control
45
46 [20]. The same finding (lower peak velocity) was found in cohorts of both WAD and
47
48 insidious neck pain [21]. Moreover, significant differences in jerk indices were observed
49
50 during active neck movements in a study comparing healthy controls to those with chronic
51
52 neck pain of both insidious onset and traumatic onset [21].
53
54

55
56 Neck proprioception will be measured by calculating the Joint Position Error (JPE)
57
58 following active neck rotation. JPE is defined as the ability to relocate the natural head
59
60

1
2
3 position without the assistance of vision [22]. To assess this, the same wearable sensor (G-
4 Walk) will be used. Patients will repeat active neck rotation with their eyes closed and will
5 indicate when they think that they have returned to the starting position. JPE will be assessed
6 three times for both right and left rotation and the average taken for each direction. Decreased
7 head repositioning accuracy has been observed in people with idiopathic neck pain [23], but
8 with greater repositioning errors found in individuals with neck pain attributed to a trauma
9 [24], which is even more evident in those with moderate to severe pain and disability [14].

Dynamometer (maximal and sub-maximal isometric contractions)

21
22
23
24 At baseline, the participants will perform maximal and sub-maximal isometric
25 contractions to measure maximum strength and control of sub-maximal forces. Cranio-
26 cervical flexion, neck flexion and extension will be tested using a hand-held dynamometer
27 for neck muscle testing (NOD, OT Bioelettronica, Italy).

1. Maximum voluntary contraction (MVC):

32
33
34
35 Two MVCs will be performed for cranio-cervical flexion, neck flexion, and
36 extension. Each maximum MVCs will last for 3 seconds, separated by 1 minute rest in
37 between [25]. The mean MVC for each direction will be calculated and used in the analysis
38 [26, 27]. Patients will perform an initial trial to familiarise themselves with each movement
39 under the guidance of a trained examiner with minimal force.

40
41
42
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45
46
47 Cranio-cervical flexion strength testing will be performed with the participant in
48 supine lying with the hip and knees flexed to approximately 90 degrees [28]. The head will
49 be placed in neutral position and the dynamometer placed behind the upper cervical spine
50 with the instruction being to nod as if saying yes but as hard as you can. Patients will be
51 seated to measure neck flexion and extension strength with the participant seated
52 comfortably on a chair with hip and knee flexed to 90 degrees with head in neutral position
53
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3 and feet flat on the ground. To measure neck flexion, the dynamometer will be placed over
4
5 the forehead and against the resistance of the examiner, the patient will be instructed to
6
7 “push as hard as you can as you try to bring your chin to your chest” [29]. The
8
9 dynamometer will then be placed on the back of the head and the patient instructed to “push
10
11 as hard as you can into the dynamometer as if trying to bring the back of the head to your
12
13 neck” [29].
14
15

16
17 Patients with neck pain commonly present with reduced neck strength [29-32],
18
19 although the extent of impaired strength is highly variable across patients [33]. Significant
20
21 lower isometric MVC force has been observed in patients with chronic WAD compared to
22
23 healthy controls [29]. Reduced neck muscle strength has been associated with the extent of
24
25 disability [25, 34] and pain [34] in people with chronic neck pain..
26
27

28 2. Sub-maximal voluntary contractions:

29
30 In the same positions described for the MVC, participants will be instructed to
31
32 perform a single submaximal contraction at 20% of their maximal force and hold this for 10
33
34 seconds for cranio-cervical flexion, flexion and extension. In addition, participants will
35
36 perform 40%, 60%, 80%, and 100% of their maximal force for the cranio-cervical flexion
37
38 only. Feedback on force will guide the participant to maintain specific degree of contraction
39
40 from their MVC over the duration of the contraction.
41
42
43
44
45
46

47 Surface electromyography (EMG) (co-activation of the sternocleidomastoid and splenius 48 49 capitis)

50
51 The amplitude of sternocleidomastoid (SCM) activity will be measured bilaterally
52
53 during the isometric maximum and submaximal voluntary contractions of cranio-cervical
54
55 flexion. In addition, both SCM and splenius capitis (SC) activity will be measured bilaterally
56
57 during the maximum and submaximal voluntary contractions of neck flexion and extension.
58
59
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2
3 Increased co-activation of the neck flexors and extensors has been observed in
4
5 patients with chronic neck pain and headache [35], and is associated with reduced neck
6
7 strength [35]. Changes in neck muscle activation has been observed in people with acute neck
8
9 pain following a whiplash injury [14, 36].
10
11

12 Following gentle skin preparation, pairs of bipolar surface electrodes will be placed
13
14 over SCM and SC bilaterally following published guidelines for electrode placement [37].
15
16 Signals will be detected using wireless EMG (Ultium® EMG, Noraxon, USA). Co-activation
17
18 indexes will be calculated as described previously [38].
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STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	_____
	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)	_____

1 Introduction

2				
3	Background and	6a	Description of research question and justification for undertaking the trial, including summary of relevant	4-6
4	rationale		studies (published and unpublished) examining benefits and harms for each intervention	
5				
6		6b	Explanation for choice of comparators	_____
7				
8	Objectives	7	Specific objectives or hypotheses	6
9				
10	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial or single group),	
11			allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7
12				
13				
14	Methods: Participants, interventions, and outcomes			
15				
16	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will	7
17			be collected. Reference to where list of study sites can be obtained	
18				
19	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and	7
20			individuals who will perform the interventions (eg, surgeons, psychotherapists)	
21				
22	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be	NA
23			administered	
24		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose	NA
25			change in response to harms, participant request, or improving/worsening disease)	
26		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence	NA
27			(eg, drug tablet return, laboratory tests)	
28		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
29				
30	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood	10
31			pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg,	
32			median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen	
33			efficacy and harm outcomes is strongly recommended	
34	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for	9
35			participants. A schematic diagram is highly recommended (see Figure 1)	
36				
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1	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
2				
3				
4	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7-8
5				
6				
7	Methods: Assignment of interventions (for controlled trials)			
8	Allocation:			
9				
10	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	_____
11				
12				
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16	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	_____
17				
18				
19				
20	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	_____
21				
22				
23				
24	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	_____
25				
26				
27		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_____
28				
29				
30				
31	Methods: Data collection, management, and analysis			
32				
33	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	_____
34				
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39		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
40				
41				
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1	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
2				
3				
4				
5	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
6				
7				
8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16
9				
10		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
11				
12				
13				
14	Methods: Monitoring			
15				
16	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	_____
17				
18				
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21				
22		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
23				
24				
25	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	_____
26				
27				
28	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_____
29				
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31				
32	Ethics and dissemination			
33				
34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	17
35				
36				
37	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
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1	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
2				
3				
4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
5				
6				
7	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
8				
9				
10	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	19
11				
12				
13	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
14				
15				
16	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
17				
18				
19				
20	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
21				
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23				
24		31b	Authorship eligibility guidelines and any intended use of professional writers	_____
25				
26		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____
27				
28				
29	Appendices			
30				
31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_____
32				
33				
34	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
35				
36				

*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](https://creativecommons.org/licenses/by-nc-nd/3.0/)" 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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Manuscript ID	bmjopen-2019-035736.R1
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Date Submitted by the Author:	17-Feb-2020
Complete List of Authors:	Alalawi, Ahmed; University of Birmingham, Centre of Precision Rehabilitation for Spinal Pain (CPR Spine); LUQUE-SUAREZ, ALEJANDRO; UNIVERSITY OF MALAGA, PHYSIOTHERAPY Fernandez-Sanchez, Manuel; Universidad De Almeria Facultad de Ciencias de la Educacion Enfermeria y Fisioterapia Gallina, Alessio; University of Birmingham, School of Sport, Exercise and Rehabilitation Sciences Evans, David; University of Birmingham, School of Sport, Exercise and Rehabilitation Sciences Falla, Deborah; University of Birmingham, School of Sport, Exercise and Rehabilitation Sciences
Primary Subject Heading:	Rehabilitation medicine
Secondary Subject Heading:	Patient-centred medicine
Keywords:	Rehabilitation medicine < INTERNAL MEDICINE, Musculoskeletal disorders < ORTHOPAEDIC & TRAUMA SURGERY, Spine < ORTHOPAEDIC & TRAUMA SURGERY

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4 1 **Do measures of physical function enhance the prediction of**
5 2 **persistent pain and disability following a whiplash injury?**
6 3 **Protocol for a prospective observational study in Spain**
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13 6 Alalawi A ^{a,b}, Luque-Suarez A ^{c,d}, Fernandez-Sanchez M ^e, Gallina A ^a,
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4 29 **ABSTRACT**

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6 30 **Introduction**

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8 31 Not all factors that predict persistent pain and disability following whiplash injury are known.

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10 32 In particular, few physical factors, such as changes in motor function and muscle behaviour
11
12 33 have been investigated. The aim of this study is to identify predictive factors that are
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14 34 associated with the development of persistent pain and disability following a whiplash injury
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16 35 by combining contemporary measures of physical function together with established
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18 36 psychological and pain-related predictive factors.

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20 37 **Methods and analysis**

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22 38 A prospective observational study will recruit 150 consecutive eligible patients experiencing
23
24 39 whiplash-related symptoms, admitted to a private physiotherapy clinic in Spain within 15
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26 40 days of their whiplash injury. Poor outcome will be measured using the Neck Disability
27
28 41 Index (NDI), defined as an NDI score of 30% or greater at 6 months post-injury. Candidate
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30 42 predictors, including demographic characteristics, injury characteristics, pain characteristics,
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32 43 self-reported psychosocial factors and physical factors will be collected at baseline (within 15
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34 44 days of inception). Regression analyses will be performed to identify factors that are
35
36 45 associated with persistent neck pain and disability over the study period.

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38 46 **Ethics and dissemination**

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40 47 The project has been approved by the Ethics Committee of the province of Malaga, Spain
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42 48 (#30052019). The results of this study will be published in peer-reviewed journals.

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54 STRENGTHS AND LIMITATIONS OF THIS STUDY

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

79 INTRODUCTION

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

92 High-quality evidence has shown higher pain and disability immediately post-injury
93 to be the most consistent factor predicting longer-term pain and disability (9, 10). Studies
94 have examined other factors that might predict the development of ongoing pain following
95 whiplash covering all three elements of the biopsychosocial model: demographic factors (7,
96 11-14), pre-existing comorbidities (11, 13, 14), collision factors (7, 11-13, 15-18), physical
97 factors (14, 19-24), radiological changes (2, 25-30), societal factors (31), and psychological
98 factors (7, 32, 33). Yet, there is controversial evidence concerning the predictive ability of
99 other factors including: general psychological distress, depression, previous neck pain,
100 gender, and the use of a seatbelt at the time of the collision (9, 14, 32, 34, 35). This illustrates
101 an incomplete picture regarding the predictive factors for recovery versus ongoing pain in
102 WAD.

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4 103 There has been little investigation of the predictive utility of physical factors
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6 104 following whiplash injury; of the studies conducted, measures of physical function have been
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8 105 limited to measures such as range of motion (19, 20, 36, 37) and cranio-cervical flexion test
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10 106 performance (38, 39). Yet, physical factors offer potential to improve prediction accuracy
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12 107 (REFS). For example, there is a wealth of evidence describing changes in motor function and
13
14 108 muscle behaviour (40-42). Decreased maximum angular velocity of neck movements has
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16 109 been observed in individuals with chronic WAD when compared to healthy individuals (40).
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18 110 Such changes in movement behaviour have been confirmed in individuals with WAD and
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20 111 insidious neck pain, where lower peak velocity was observed in both groups (41). In addition,
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22 112 a significantly larger jerk index (measure of the smoothness of neck movement) has been
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24 113 reported in individuals with chronic neck pain of both insidious and traumatic onset, when
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26 114 compared to asymptomatic individuals (41). Another feature reported in those with chronic
27
28 115 neck pain is increased co-activation of the neck flexors and extensors (42), which is
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30 116 associated with reduced neck strength (42). These additional features have not been
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32 117 investigated in individuals with acute WAD, but results from experimental pain studies
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34 118 suggest these adaptations occur soon after pain onset and may therefore have relevance for
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36 119 ongoing symptoms in individuals with chronic WAD (43-50).

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43 120 A number of methodological limitations of previously published studies in the field of
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45 121 WAD prognosis have been identified. For instance, a review conducted by Walton et al. (10)
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47 122 found that many predictors have conflicting results (11, 12, 32). Inconsistent outcome
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49 123 measures have previously been used by to define recovery in WAD (51), with a different
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51 124 definition of recovery used in each study (7, 52). Other reasons for inconsistency can be
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53 125 attributed to poor reporting (11, 53) and the inclusion of subjects from different settings and
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55 126 at different inception points. Another recent review found controversial evidence with
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4 127 regards to which demographic factors, prior pain, and psychological factors are associated
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6 128 with the transition to chronic WAD. (9).

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8 129 Collectively, these limitations impact on our understanding of factors associated with
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10 130 the transition to chronic WAD following a whiplash injury and highlight the need for an
11
12 131 adequately powered, methodologically robust observational study to provide useful
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14 132 predictive estimates. Such knowledge could lead to the development of a new clinical care
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16 133 pathway that matches early interventions to risk factors for poor recovery.
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21 22 135 **Aims of study**

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24 136 The aim of the study is to identify factors soon after a whiplash injury that predict the
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26 137 occurrence of persistent pain and disability six months later. We will include a broad range of
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28 138 candidate predictors, including measures of physical function with self-reported measures of
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30 139 pain, disability and established psychological constructs.
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35 36 37 141 **METHODS**

38 39 40 142 **Study Design**

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42 143 The study will be a prospective observational design. This protocol has been developed
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44 144 in accordance with guidelines from the SPIRIT 2013 Statement (54), the Transparent Reporting
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46 145 of a Multivariable Prediction Model for Individual Prognosis Or Diagnosis (TRIPOD)
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48 146 statement (55), the Quality In Prognosis Studies (QUIPS) tool (56), the CHecklist for critical
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50 147 Appraisal and data extraction for systematic Reviews of prediction Modelling Studies
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52 148 (CHARMS) (57), and the PROGnosis RESearch Strategy (PROGRESS) framework (58).
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151 **Participants**

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

158 ***Eligibility criteria***

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

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

170 ***Recruitment***

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

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4 175 We will recruit eligible patients within 15 days of their whiplash injury. One designated
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6 176 physiotherapist working at the physiotherapy clinic will manually check electronic clinical
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8 177 records of all consecutive patients attending the clinic. Once an eligible patient is identified at
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10 178 the clinic, the designated clinic physiotherapist will contact the patient to invite them to
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12 179 participate in the study; this invitation will be done either in-person at the clinic after the first
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14 180 treatment session or via telephone after patients have returned home from their clinic
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16 181 appointment. A verbal and written description of the study will be provided during the
17
18 182 invitation. Those patients interested in participation will be invited to attend an initial study
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20 183 session at the physiotherapy clinic. At this session, the researcher will again explain the study
21
22 184 design and context, patients will be given a detailed information sheet, and written informed
23
24 185 consent will be sought. The English version of the consent form is provided in the
25
26 186 supplementary file. Once recruited, participants (Figure 1) will be asked to complete a baseline
27
28 187 self-reported questionnaire, after which physical data will be collected (Table 1). Participants
29
30 188 will be informed that they can withdraw from the study at any time, without having to provide
31
32 189 a reason. They will also be advised to carry on with their daily routines as usual, and that any
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34 190 interventions received during their physiotherapy sessions will be recorded for a descriptive
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36 191 analysis.
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45 193 **Outcome**

46
47 194 Outcome will be measured using the Neck Disability Index (NDI) (64); a neck-
48
49 195 specific self-reported questionnaire used to assess neck pain-related disability. The NDI
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51 196 consists of 10 items of daily activities including personal care, lifting, reading, work, driving,
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53 197 sleeping, and recreation (64). Each item has five ordinal response options from 0 (no
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55 198 disability) to 5 (complete disability), producing a maximum total score of 50 which can be
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4 199 expressed as a percentage (0-100%). The reliability of NDI and validity have been
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6 200 established in individuals with neck pain disorders (65).
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8 201 Outcome will be assessed at six months for the prediction model (66). Using six
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10 202 months as a cut-off for identifying outcome is supported by the finding that most individuals
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13 203 recover within three months of the whiplash injury, with fewer recovering after this (11, 67),
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15 204 and a plateau after six months (68). To investigate the course of neck pain and disability, the
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17 205 NDI scores will additionally be collected at 3 and 6 months.
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21 22 207 **Candidate predictors** 23

24 208 Due to the current lack of consensus on predictive factors of poor outcome, several
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26 209 self-reported and physical measures will be collected (9). Factors have been selected based
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29 210 on current knowledge of prognosis in whiplash (2, 7, 9, 11-13, 24, 31-34, 69) and a
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31 211 theoretical association with prognosis in individuals with neck pain, as informed by the
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33 212 biopsychosocial model of pain (70). These factors are also chosen due to being feasible to
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35 213 measure in clinical practice. Candidate predictors are summarised in Table 1 with further
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37 214 information available in the supplementary file S1. All data collection will be standardised
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39 215 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 \leq 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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6 230 **Data collection**7
8 231 ***Baseline and follow-up***

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10 232 Baseline data including self-reported questionnaires and physical assessments will be
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12 233 collected immediately following recruitment, at the physiotherapy clinic, by a trained
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14 234 assessor (MFS) within 15 days of injury. Participants will be contacted by the same assessor
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16 235 by telephone (MFS) at the University of Malaga (UoM) at three, six and twelve months
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18 236 follow-up, in order to complete the NDI, as used previously (71).
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24 238 **Data management**

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26 239 Participant data privacy will be maintained throughout data handling (collection
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28 240 transfer, storage, and processing) and will comply with data protection requirements as set out
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30 241 by the General Data Protection Regulation (GDPR) of the European Union, and UK Data
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32 242 Protection Act 2018 (Figure 2). Participant data will be tracked using only study identification
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34 243 (ID) numbers. Study ID numbers will be kept separate from study research data, which will be
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36 244 accessible only by members of the UoM research team.
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43 246 Sensitive data management:

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45 247 Some participant data will be sensitive in nature; in particular consent forms which
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47 248 contain identifiable data, name, phone, contact address and study ID numbers. Once each
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49 249 participant has completed a consent form in the clinic, it will then be sealed in an envelope and
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51 250 temporarily locked in a secure drawer at the physiotherapy clinic, with access only available
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53 251 to members of the UoM research team. Once daily data collection has ended, all sealed
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55 252 envelopes containing consent forms collected on that day will be physically transferred to the
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57 253 UoM by one of the research team and locked in a secure filing cabinet there. Identifiable data
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4 254 will be securely stored at UoM for a period of 10 years, after which they will be destroyed. No
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6 255 identifiable data will be transferred outside of the UoM.

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11 257 Self-reported questionnaires management:

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13 258 Self-reported paper questionnaires, identifiable only by study ID number for each
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15 259 participant, will be sealed in another envelope and temporarily locked in a secure cabinet at the
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17 260 clinic, separate from the one in which consent forms are stored. Sealed envelopes containing
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19 261 the pseudonymised self-reported questionnaires will be physically transferred to the UoM at
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21 262 the end of each data collection day by one of the research team. Once transferred, self-reported
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23 263 questionnaires will be scanned by one of the research team and saved in a password protected
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25 264 laptop computer, owned and managed by UoM. Scanned self-reported electronic data will be
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27 265 encrypted using a WinRAR Software before transit to the University of Birmingham (UoB)
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29 266 (via Power Folder data sharing software, hosted locally at the University). Once received, this
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31 267 pseudonymised data will be uploaded directly to physically secure servers at the UoB, where
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33 268 they will remain indefinitely on secure UoB servers with access restricted to members of the
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35 269 study team. Once uploaded to UoB servers, data will be removed completely from the laptop
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37 270 at UoM. The same procedures will be followed for follow-up NDI data at 3, 6, and 12 months.
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45 272 Physical data management:

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47 273 Pseudonymised physical data will be saved in a password protected laptop owned and
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49 274 managed by UoM, whilst at the clinic study session. Access to the UoM laptop is restricted and
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51 275 only available to the local research team. As with other data, pseudonymised electronic data
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53 276 will be encrypted using a WinRAR Software, transferred to the UoB team, and uploaded to the
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55 277 physically secure servers at UoB, where they will remain indefinitely with access restricted to
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4 278 study researchers. Again, once data has been received by the team at UoB, they will be removed
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6 279 from UoM computers.
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10 281 **Data analysis**

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13 282 Numbers of individuals will be recorded that are: potentially eligible, examined for
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15 283 eligibility, confirmed eligible, recruited into the study, completing follow-up, and analysed.

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17 284 Loss to follow-up and withdrawals will be reported, with reasons where available. Descriptive
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19 285 analyses of participants at baseline will include participant demographics, self-reported
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21 286 questionnaires and physical assessment data.
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27 288 Linear and logistic regression analysis:

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29 289 Linear regression analysis will be used as the primary analysis to develop a linear model to
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31 290 determine the association between candidate predictors and neck pain and disability (measured
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33 291 by NDI) at 6 months post injury. Linear regression analysis was included as a primary analysis
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35 292 to allow for the inclusion of the outcome (NDI) without dichotomisation. This approach
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37 293 follows the recommendations by PROGRESS series recommending of analysing continuous
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39 294 variables on their continuous scale (72), as well as to the fact that this approach method
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41 295 increases the statistical power and reduces information loss.
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45 296 In addition to the linear regression analysis, Logistic regression will be included as a
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47 297 secondary analysis to identify factors that are associated with poor outcomes. Outcome (NDI)
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49 298 scores will be dichotomised into good or poor categories with a NDI score of $\geq 30\%$ at six
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51 299 months post-injury defined as poor outcome, as described previously.
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4 303 Variable selection:

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6 304 Penalization (shrinkage) approach will be used to avoid overfitting the final prognostic
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8 305 model, given the minimum number of events (10) per variable will be adopted in this study to
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10 306 develop prognostic modes (73).

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15 308 Firstly a full model will be constructed including all baseline candidate predictors (Table1)
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17 309 with their estimated adjusted regression coefficients calculated by standard methods. Next, a
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19 310 shrinkage method, a least absolute shrinkage and selection operator (LASSO) regression, will
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21 311 be used to effectively exclude candidate predictors from the final model by shrinking their
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23 312 coefficients to exactly zero (74). Candidate predictors with zero coefficients will be excluded
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25 313 from the model, leaving the remaining candidate predictors with regression confidents of
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27 314 more than zero. This approach is in line with the current recommendations for variable
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29 315 selection in prognostic models to address overfitting (75). Moreover, this approach is
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31 316 preferred when a model with fewer predictors is desired without affecting the predictive
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33 317 ability of the model, making it more applicable in clinical practice (73).

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40 319 Model Performance:

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43 320 The predictive performance of the prognostic screening tool will be assessed using the
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45 321 established traditional measures of overall prognosis, discrimination, and calibration (76).
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47 322 Brier score will be used to quantify the overall performance of the screening tool where the
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49 323 score ranges from 0 ('perfect model') to 0.25 ('not informative model') (76). The Receiver
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51 324 Operator Characteristic (ROC) curve will be used to discriminate between those who did or
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53 325 did not develop chronic whiplash. Finally, the calibration will be assessed through plotting
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55 326 the mean predicted against observed chronic whiplash cases.

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4 328 ***Sample size***

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6 329 This study will consider the association between 16 candidate predictors (Table 1)
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8 330 and neck pain and disability at 6 months. The authors will ensure that at least ten participants
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10 331 per predictor will be used to develop an adequately powered linear regression analysis (77,
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12 332 78). Because the shrinkage method by LASSO method creates models with fewer predictors
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14 333 (73), it is anticipated that the number of final predictors retained in the final linear model will
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16 334 fall below 12 predictors. Therefore, a sample size target of 120 participants is required to
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18 335 adequately powered a maximum of 12 candidate predictors into the multiple linear
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20 336 regression, with the addition of 30 participants to allow for possible loss of follow-up (total =
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22 337 150).

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26 338 For the sample size of a logistic regression model derived following the LASSO
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28 339 shrinkage method, a minimum of 5 events per predictor is sufficient as established previously
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30 340 (73). Based on the current knowledge about the transition rate from acute to chronic WAD, it
31
32 341 is expected that 50% of patients will report persistent neck pain and disability (11, 79, 80).
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34 342 This leaves 60 out of our potential participants who might develop persistent neck pain and
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36 343 disability 6 months post WAD. Therefore, a sample size of 60 participants is adequate to
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38 344 power a logistic regression analysis of 12 candidate predictors with 5 events per predictor.
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47 347 ***Management of missing data***

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49 348 For each variable of interest, numbers of participants with missing data will be reported.
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51 349 Any potential bias due to loss of follow-up will be assessed and compared using baseline data
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53 350 of subjects who withdraw or lost at follow-up (66). Multiple imputation (81) will be used to
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55 351 deal with missing outcome data, if appropriate and necessary. Participants will be excluded
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4 352 from the predictive model and subsequent analyses if they request to withdraw from the study
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6 353 following recruitment (66).

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8 354 **Patients and public involvement**

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10 355 The research question in this study was developed following consultations with
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12 356 patients. Patients will not be involved in the analysis and data collection of study. The results
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14 357 of the study will be presented to members of the public and patients during one of our regular
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16 358 Patient and public involvement meetings.

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22 360 **Ethics and dissemination:**

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24 361 The study will be conducted according to the Declaration of Helsinki. The project has
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26 362 been approved by the Ethics Committee of the province of Malaga, Spain (#30052019). The
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28 363 results of the study will be disseminated via reports published in peer-reviewed journals and
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30 364 national and international conferences. No datasets will be created as part of this work for
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32 365 deposition or curation. Participant burden has been taken into consideration when developing
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34 366 this study. The number of measures has been kept to a minimum. To ensure the privacy of
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36 367 each patient, a unique identification number will be assigned to each participant at the time of
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38 368 recruitment. Only pseudonymised or anonymised data will be used during analyses.

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40 369 Participants will be informed that they can withdraw from the study at any time, without
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42 370 having to provide a reason; however, where a reason is given it will be recorded. If a
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44 371 participant withdraws, no further data will be collected but data already collected will be
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46 372 retained for analyses. Baseline characteristics of any participants that withdraw will be
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48 373 compared to retained participants to assess for any differences.

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50 374 At each data collection session, confirmation to proceed will be gained before any
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52 375 data are collected. Any concerns and/or adverse events will be noted and fed back to clinical
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54 376 staff, according to the Good Clinical Practice principles. For ethical reasons, routine

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4 377 treatment will not be withheld from individuals at any point during the study. The details and
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6 378 frequency of any received treatment will be recorded and reported. The protocol and conduct
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8 379 of this study are strengthened by the inclusion of patient and public involvement, who
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10 380 contributed to the development of study design and documentation. In addition, they will
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12 381 contribute to the processes of performing data analysis, interpretation of results, and
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14 382 producing a lay summary of findings.
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19 20 384 **DISCUSSION**

21
22 385 This is the first protocol to describe, *a priori*, the methods and analysis for identifying
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24 386 predictive factors for ongoing pain and disability following acute whiplash injury. In
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26 387 particular, self-reported measures together with novel physical measure will be incorporated
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28 388 including angular velocity, smoothness of movements, force steadiness, and neck muscle co-
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30 389 activation to predict poor outcome in individuals with WAD recruited within 15 days of the
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32 390 injury. The selected candidate predictors are included based on current knowledge and the
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34 391 possible utilisation in clinical practice. The knowledge gained through this study can assist in
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36 392 the identification of personalised interventions to facilitate recovery and therefore minimise
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38 393 the transition to chronic whiplash.
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43 394 SPIRIT 2013 Statement, TRIPOD, PROGRESS, QUIPS and CHARMS statements
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45 395 and frameworks have informed design to ensure rigorous conduct of this study (54-58) . The
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47 396 results from this study will provide new insights into who is likely to recover versus who is
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49 397 likely to develop persistent symptoms following a whiplash injury. Using a novel
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51 398 combination of outcome measures will allow the future development of a tool to predict
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53 399 development of chronic and disabling pain following a whiplash injury providing new
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55 400 opportunities to identify precision intervention.
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4 402 **Author Contributions**

5
6 403 All authors contributed to the focus of this study. AA is a PhD student with DF as Lead

7
8 404 Supervisor and AG as Co-Supervisor. AA drafted the initial protocol with guidance from DF

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10 405 and DWE at all stages. ALS and MFS will be involved in collecting data from participants.

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12 406 All authors approved the final version for publication. DF is guarantor.

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23
24 411 or not-for-profit sectors.

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29 413 **Competing Interests Statement**

30
31 414 The authors have no competing interests to report.

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38 417 **Patient consent**

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40 418 Not required.

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45 420 **Ethics approval**

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47 421 Approved by Ethics Committee of the province of Malaga, Spain (#30052019).

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52 423 **Data sharing statement**

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54 424 No additional data are available.

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56 425 **Amendment Protocol**

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4 426 If changes in the protocol deemed to be necessary during conducting the study, they will be
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6 427 documented on the main report of the study.
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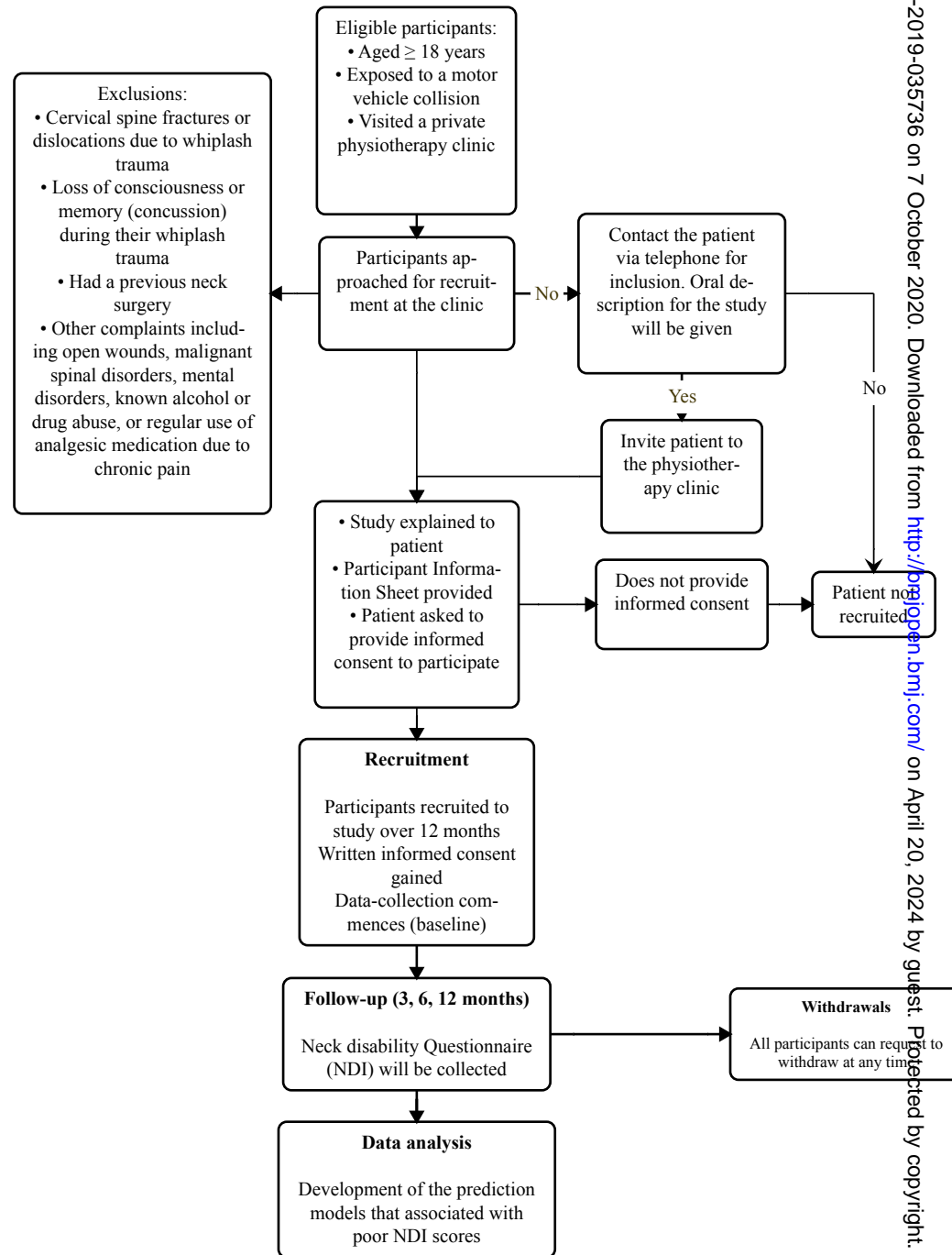
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Figure Captions

Figure 1: Participant flow through the study.

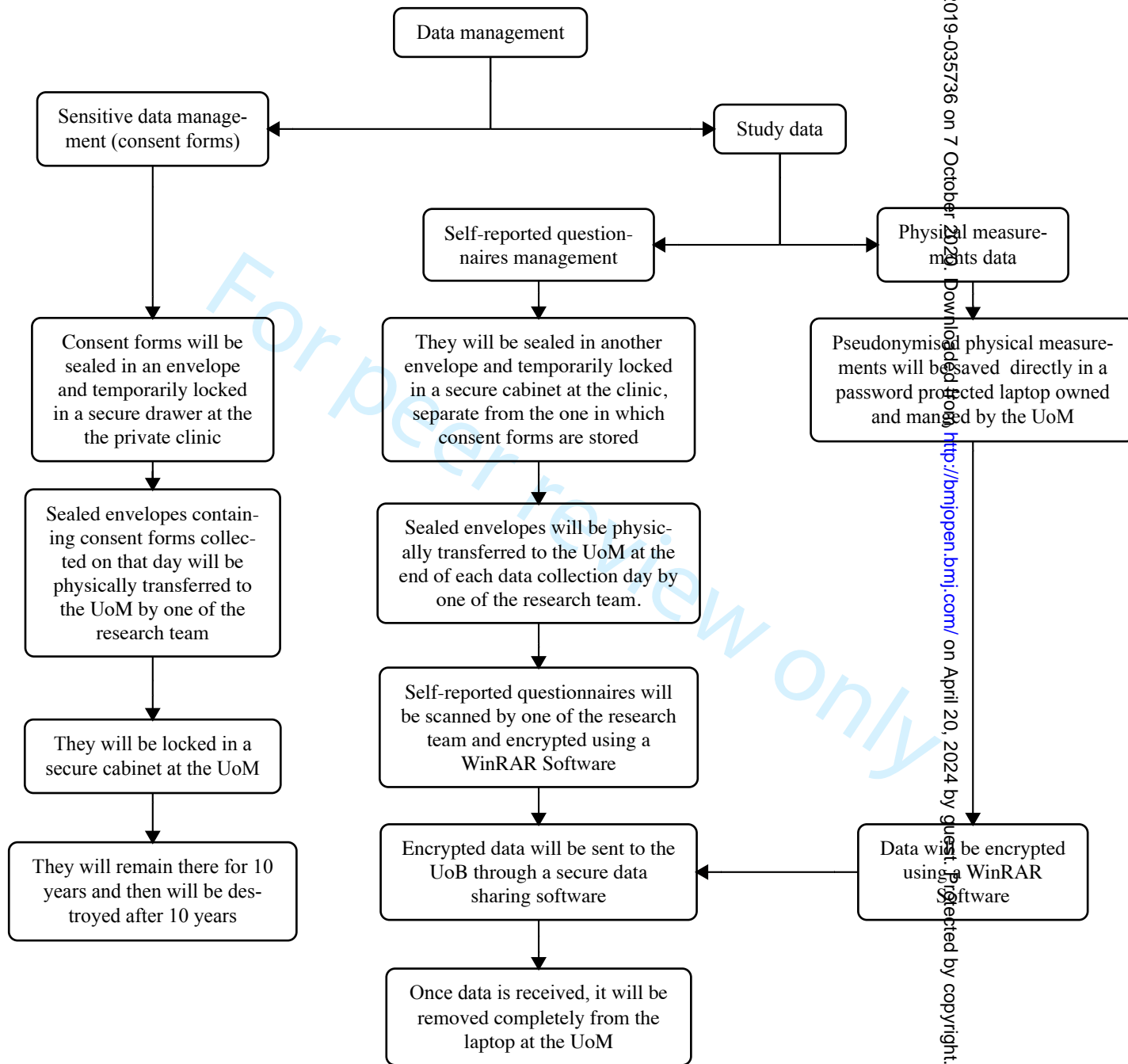
Figure 2: Process for data management.

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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

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3 WAD [8]; catastrophizing increases fear of movement which leads to decreased functional
4
5 self-efficacy that results in higher pain and disability [8].
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Recovery Expectation (high or low expectation of recovery)

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12 Patients will be asked if they expect to fully recover within the next six months.
13
14 Recovery expectations will be assessed by the question “In your opinion, how likely is it that
15 you will be fully recovered with no persistent sequelae?” [9]. In response to this question,
16
17 recovery expectations will be measured using NRS where a patient need to indicate how
18
19 likely he/she would have completely recovered, by choosing a score from 0 (“not likely”) to
20
21 10 (“very likely”) [10]. Low expectation of making full recovery were found to be an
22
23 independent predictive factor associated (odds ratio= 4.2 [95% CI = 2.1 - 8.5]) with higher
24
25 disability in individuals with acute WAD [10].
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Pain characteristics

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Numeric Rating Scale (NRS)

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37 Current neck pain intensity will be measured using NRS which is a 11-point scale
38
39 range from 0 (no pain) to 10 (worst possible pain). Also, perceived pain intensity will be
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41 measured at the end of each physical measure of neck range of motion tasks, neck maximum
42
43 contraction tasks, and neck submaximum contraction tasks. The reliability of NRS has been
44
45 established in patients with neck pain (ICC:0.76) [11]. Also, participants will be asked
46
47 remotely (through the app) where they have ‘experienced pain during the last week’ from
48
49 several body locations [12]. Based on their response of chosen areas, pain intensity will be
50
51 assessed using NRS. Finally, neck pain intensity following active movements will be
52
53
54
55
56 measured through NRS. High evidence of significant association shows that initial neck pain
57
58
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60

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2
3 intensity was a consistent risk factor for developing persistent symptoms in whiplash [4] with
4
5 pooled odd ratio= 5.61 (95% CI = 3.74 - 8.43) [13].
6
7
8
9

10 **Physical measures**

11 Wearable sensor for motion detection (Neck range of movement, angular velocity, movement 12 13 smoothness and proprioception) 14

15
16 A wearable BTS G-WALK® sensor system (BTS Bioengineering, Italy) will be
17
18 utilised to assess neck range of motion, angular velocity, movement smoothness, and neck
19
20 proprioception. The sensor connects to a computer via Bluetooth; at the end of each analysis
21
22 an automatic report containing all the parameters recorded during the test, is displayed.
23
24

25
26 Active neck flexion, side-flexion, extension, and rotation will be measured at
27
28 baseline. Impaired range of motion has been found in individuals with WAD compared to
29
30 healthy controls [14, 15] and has also been found to be a factor associated with persistent
31
32 disability at one year [16, 17], and neck pain and disability at 6 months [18, 19].
33
34

35
36 Besides range of motion, the angular velocity and movement smoothness will be
37
38 recorded simultaneously during each neck movement. Each movement direction will be
39
40 repeated five times and the average taken. These kinematic variables may provide more
41
42 information about motor control disturbances [20]. A study found maximum angular velocity
43
44 and acceleration were lower in subjects with chronic WAD when compared to healthy control
45
46 [20]. The same finding (lower peak velocity) was found in cohorts of both WAD and
47
48 insidious neck pain [21]. Moreover, significant differences in jerk indices were observed
49
50 during active neck movements in a study comparing healthy controls to those with chronic
51
52 neck pain of both insidious onset and traumatic onset [21].
53
54

55
56 Neck proprioception will be measured by calculating the Joint Position Error (JPE)
57
58 following active neck rotation. JPE is defined as the ability to relocate the natural head
59
60

1
2
3 position without the assistance of vision [22]. To assess this, the same wearable sensor (G-
4 Walk) will be used. Patients will repeat active neck rotation with their eyes closed and will
5 indicate when they think that they have returned to the starting position. JPE will be assessed
6 three times for both right and left rotation and the average taken for each direction. Decreased
7 head repositioning accuracy has been observed in people with idiopathic neck pain [23], but
8 with greater repositioning errors found in individuals with neck pain attributed to a trauma
9 [24], which is even more evident in those with moderate to severe pain and disability [14].

Dynamometer (maximal and sub-maximal isometric contractions)

23
24 At baseline, the participants will perform maximal and sub-maximal isometric
25 contractions to measure maximum strength and control of sub-maximal forces. Cranio-
26 cervical flexion, neck flexion and extension will be tested using a hand-held dynamometer
27 for neck muscle testing (NOD, OT Bioelettronica, Italy).

1. Maximum voluntary contraction (MVC):

32
33 Two MVCs will be performed for cranio-cervical flexion, neck flexion, and
34 extension. Each maximum MVCs will last for 3 seconds, separated by 1 minute rest in
35 between [25]. The mean MVC for each direction will be calculated and used in the analysis
36 [26, 27]. Patients will perform an initial trial to familiarise themselves with each movement
37 under the guidance of a trained examiner with minimal force.

38
39 Cranio-cervical flexion strength testing will be performed with the participant in
40 supine lying with the hip and knees flexed to approximately 90 degrees [28]. The head will
41 be placed in neutral position and the dynamometer placed behind the upper cervical spine
42 with the instruction being to nod as if saying yes but as hard as you can. Patients will be
43 seated to measure neck flexion and extension strength with the participant seated
44 comfortably on a chair with hip and knee flexed to 90 degrees with head in neutral position
45
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3 and feet flat on the ground. To measure neck flexion, the dynamometer will be placed over
4
5 the forehead and against the resistance of the examiner, the patient will be instructed to
6
7 “push as hard as you can as you try to bring your chin to your chest” [29]. The
8
9 dynamometer will then be placed on the back of the head and the patient instructed to “push
10
11 as hard as you can into the dynamometer as if trying to bring the back of the head to your
12
13 neck” [29].
14
15

16
17 Patients with neck pain commonly present with reduced neck strength [29-32],
18
19 although the extent of impaired strength is highly variable across patients [33]. Significant
20
21 lower isometric MVC force has been observed in patients with chronic WAD compared to
22
23 healthy controls [29]. Reduced neck muscle strength has been associated with the extent of
24
25 disability [25, 34] and pain [34] in people with chronic neck pain..
26
27

28 2. Sub-maximal voluntary contractions:

29
30 In the same positions described for the MVC, participants will be instructed to
31
32 perform a single submaximal contraction at 20% of their maximal force and hold this for 10
33
34 seconds for cranio-cervical flexion, flexion and extension. In addition, participants will
35
36 perform 40%, 60%, 80%, and 100% of their maximal force for the cranio-cervical flexion
37
38 only. Feedback on force will guide the participant to maintain specific degree of contraction
39
40 from their MVC over the duration of the contraction.
41
42
43
44
45
46

47 Surface electromyography (EMG) (co-activation of the sternocleidomastoid and splenius 48 49 capitis)

50
51 The amplitude of sternocleidomastoid (SCM) activity will be measured bilaterally
52
53 during the isometric maximum and submaximal voluntary contractions of cranio-cervical
54
55 flexion. In addition, both SCM and splenius capitis (SC) activity will be measured bilaterally
56
57 during the maximum and submaximal voluntary contractions of neck flexion and extension.
58
59
60

1
2
3 Increased co-activation of the neck flexors and extensors has been observed in
4
5 patients with chronic neck pain and headache [35], and is associated with reduced neck
6
7 strength [35]. Changes in neck muscle activation has been observed in people with acute neck
8
9 pain following a whiplash injury [14, 36].
10

11
12 Following gentle skin preparation, pairs of bipolar surface electrodes will be placed
13
14 over SCM and SC bilaterally following published guidelines for electrode placement [37].
15
16 Signals will be detected using wireless EMG (Ultium® EMG, Noraxon, USA). Co-activation
17
18 indexes will be calculated as described previously [38].
19
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STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	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

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1	Introduction			
2				
3	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
4				
5				
6		6b	Explanation for choice of comparators	NA
7				
8	Objectives	7	Specific objectives or hypotheses	6
9				
10	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial or single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7
11				
12				
13				
14	Methods: Participants, interventions, and outcomes			
15				
16	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
17				
18				
19	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
20				
21				
22	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	NA
23				
24		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
25				
26		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	NA
27				
28				
29		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
30				
31				
32	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
33				
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40	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
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1	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
2				
3				
4	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7-8
5				
6				
7	Methods: Assignment of interventions (for controlled trials)			
8	Allocation:			
9				
10	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
11				
12				
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16	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
17				
18				
19				
20	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	NA
21				
22				
23				
24	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA
25				
26				
27		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
28				
29				
30				
31	Methods: Data collection, management, and analysis			
32				
33	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
34				
35				
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38		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
39				
40				
41				
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1	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
2				
3				
4				
5	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
6				
7				
8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16
9				
10		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
11				
12				
13				
14	Methods: Monitoring			
15				
16	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
17				
18				
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21				
22		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
23				
24				
25	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
26				
27				
28	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
29				
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32	Ethics and dissemination			
33				
34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	17
35				
36				
37	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
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1	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
2				
3				
4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
5				
6				
7	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
8				
9				
10	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	19
11				
12				
13	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
14				
15				
16	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
17				
18				
19				
20	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
21				
22				
23				
24		31b	Authorship eligibility guidelines and any intended use of professional writers	NA
25				
26		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
27				
28				
29	Appendices			
30				
31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	185
32				
33				
34	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
35				
36				

*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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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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