# Comprehensive physiotherapy exercise programme or advice for chronic whiplash (PROMISE)

## A pragmatic randomised controlled trial

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# Comprehensive physiotherapy exercise program or advice for chronic whiplash (PROMISE): a pragmatic randomised controlled trial (ACTRN12609000825257)


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**Background:** There is evidence that brief physiotherapy programs are as effective for acute whiplash associated disorders (WAD) as more comprehensive programs; however it is not clear if this is also the case for chronic WAD. We aimed to estimate the effectiveness of a physiotherapist-delivered comprehensive exercise program compared to advice for people with chronic WAD.

**Methods:** 172 participants with a chronic (> 3months and <5 years) Grade I or II WAD were randomised to receive either the comprehensive exercise program (20 sessions) or advice (1 session and telephone support). The primary outcome was pain intensity measured on a 0-10 scale; secondary outcomes were self-rated recovery, disability, health-related quality of life and neck range of motion. Outcomes were measured at baseline, 14 weeks, 6 months and 12 months by a blinded assessor. Analysis was by intention-to-treat and treatment effects were calculated using linear mixed models. Trial registration number: ACTRN12609000825257.

**Findings:** Participants were recruited from October 2009 to February 2012 with follow-up completed February 2013. 172 participants were randomised (86 participants/group) with 157 (91%) followed up at 14 weeks, 145 (84%) at 6 months and 150 (87%) at 12 months. The addition of a comprehensive exercise program was not more effective than advice in reducing pain: at 14 weeks the treatment effect was 0.0 (95%CI -0.7 to 0.7), 6 months 0.2 (-0.5 to 1.0) and at 12 months -0.1 (-0.8 to 0.6). Some of the effects on secondary outcomes were statistically significant but none were sufficiently large to be considered clinically worthwhile. Sensory hypersensitivity and symptoms of posttraumatic stress did not modify the effect of treatment. No serious adverse events were noted.

**Interpretation:** The comprehensive exercise program provided no additional benefit to a single physiotherapy advice session supplemented with telephone support.

## Introduction

Whiplash associated disorders (WAD) are recognised as a significant public health problem and are associated with substantial social and economic costs.[1] Systematic reviews on the prognosis of WAD suggest that more than half of individuals will continue to report symptoms six months after the injury,[2] with up to 30% experiencing moderate to severe pain and disability.[1] This group of people experiencing chronic symptoms accounts for a disproportionately large percentage of the burden associated with WAD due to ongoing treatment costs and loss of productivity.[3]

A broad variety of treatments have been proposed to manage people with chronic WAD however to date very few randomised controlled trials (RCTs) have been conducted to evaluate the effectiveness of these interventions.[4] One of the few quality RCTs in this field has demonstrated the efficacy of radiofrequency neurotomy[5] in patients with chronic WAD whose pain arose from the zygapophyseal joints. The limitations of neurotomies are that they are highly technical procedures, they may not provide permanent symptom relief, and even when patients are carefully selected these procedures are only effective in a moderate proportion of patients.[5] Subsequently, clinical practice guidelines recommend the use of conservative treatment approaches such as physiotherapy exercise programs for chronic WAD despite the absence of robust evidence supporting this approach.[6] Two previous trials[7, 8] provide some evidence for the effectiveness of physiotherapy exercise programs however the effects of treatments were modest with only 10-20% of patients having a successful outcome, defined as minimal to no pain and disability. Based on these findings, it was hypothesised that a comprehensive exercise program combining aspects of both specific motor relearning and graded activity may result in greater improvements in pain and disability.[9]

Evidence from the study of acute WAD suggests that longer physiotherapy programs may provide no additional benefit over and above briefer physiotherapy interventions. The UK MINT trial[10] found that six sessions of physiotherapy over 8 weeks provided short term but not long term benefits over a single advice session, and that the comprehensive package of physiotherapy was not cost-effective from the UK NHS perspective. However it is not clear if these results from MINT also apply to chronic WAD. Therefore, the aim of the PROMISE trial was to investigate the effectiveness of a physiotherapist delivered comprehensive exercise program compared to advice for people with a chronic WAD. We also tested if features suggestive of central nervous system hyper-excitability or psychological distress moderated the effect of treatment.

**Methods**

PROMISE recruited from sites in Sydney and Brisbane, Australia, from October 2009 to February 2012. Ethical approval was obtained from the University of Sydney (03-2009/11509) and the University of Queensland Human Research Ethics Committees (2008002059). PROMISE was prospectively registered with the Australian and New Zealand Clinical Trials registry (ACTRN12609000825257) and the protocol published.[9] Written informed consent was obtained from all participants prior to their entry into the study.

**Participants:**

Participants were identified via advertisements in local and metropolitan newspapers, radio and online media. The Motor Accidents Authority (MAA) of New South Wales Australia, Motor

Accident Insurance Commission (MAIC) Queensland Australia, QBE Insurance and trial clinics assisted with recruitment by inviting potentially eligible clients by mail to participate. The MAA and MAIC are statutory authorities that regulate the compulsory third party personal injury insurance schemes for motor vehicles registered in the states of New South Wales and Queensland, Australia.

Patients were eligible for inclusion if they met all of the following criteria:

- Grade I or II WAD of at least 3 months but less than 12 months duration
- Currently experiencing at least moderate pain or moderate activity limitation due to pain (modified items 7 & 8 of SF36)
- Not currently receiving care for WAD (excluding medications)
- Aged between 18 years and 65 years
- Proficient in written and spoken English
- Able to attend 4 assessment sessions at the trial centre.

Six months after the commencement of the trial the eligibility criterion relating to the duration of WAD symptoms was modified from the injury being of less than 12 months duration to less than 5 years duration. This modification was required due to recruitment difficulties.

Exclusion criteria were: known or suspected serious spinal pathology (e.g. metastatic disease of the spine), nerve root compromise (Grade III WAD), confirmed fracture or dislocation at time of injury (Grade IV WAD), spinal surgery in the past 12 months and any coexisting medical condition which would severely restrict participation in the exercise program (e.g. traumatic

brain injury) or any of the contraindications to exercise listed in the American College of Sports Medicine guideline[11] as assessed using the Physical Activity Readiness Questionnaire.

## Procedures

A computer-generated randomisation sequence, stratified for recruitment site (Sydney and Brisbane), was produced prior to trial commencement by an independent researcher. Participants were randomised immediately following the baseline assessment by opening the next sealed, sequentially numbered, opaque envelope; this ensured allocation was concealed. Participants were considered to have entered the study at the time that the envelope was opened.

## Interventions

All participants were provided with the patient educational booklet 'Whiplash injury recovery: a self management guide'.[12] The booklet provided information about WAD, advice on how to manage the symptoms of WAD and outlined a simple exercise program to assist in reducing whiplash associated neck pain. In addition participants were randomly allocated to receive:

*Advice*

Participants received one, thirty-minute consultation with a physiotherapist during which they read the educational booklet, practised the exercises with minimal guidance (verbal and/or physical) from the physiotherapist and had any questions or concerns clarified; See Web appendix 1: Trial protocol (pp 21). Participants were then required to implement the advice provided and practise the exercises independently at their own discretion. No additional supervision was provided. Participants had the opportunity to contact the physiotherapist by

telephone on two occasions if they required further verbal clarification of the information covered in the consultation.

*Comprehensive exercise program*

Participants received twenty, one-hour individually-tailored and supervised exercise sessions over a 12-week period (2 physiotherapy sessions per week for 8 weeks; 1 session per week for 4 weeks); see Web appendix 2: therapist manual (pp 69-101). The comprehensive exercise program began with four weeks of specific cervical spine exercises which included craniocervical flexion training, neck extensor training, scapular training, posture re-education and, sensorimotor exercises (consisting of kinaesthetic sense, balance and eye movement control).[8] Manual therapy techniques (excluding manipulation) could only be used by physiotherapists in the first week (maximum 2 sessions) to correct any underlying musculoskeletal problems which would otherwise prevent the participant from being able to perform the specific motor relearning exercises. Between weeks four and six, participants entered a transition period where the focus shifted from specific neck motor relearning exercises to integrate this control into functional whole body exercise. By week seven all participants had commenced the graded activity program which was an individually-designed, sub-maximal program that aimed to assist participant achieve their progressively nominated functional goals. Exercises in this stage included upper and lower limb muscle strength and endurance exercises, specific functional task practice (whole or part practice) as well as progressing the aerobic, neck flexor and neck extensor endurance exercises.[7] In addition, aerobic exercise was prescribed from week one to week twelve in a manner which was submaximal and progressive.

Throughout the comprehensive exercise program, specific cognitive-behavioural therapy principles were used by the physiotherapists. These included: encouragement of skill acquisition by modelling, setting progressive goals, self-monitoring and positive reinforcement of progress.[13] By using these principles in conjunction with a progressive exercise program it was envisaged that participant's would progressively return to their pre-injury work and home activities, become more self-reliant with an improved ability to problem-solve and therefore be able to manage their condition and potential flare ups independently. Participants were provided with a 12-week home exercise program which was to be completed on days they did not attend the treatment clinic. Exercises were outlined in an exercise diary and this was also used to monitor participant's compliance with the exercises.

All treatments were delivered by physiotherapists with experience in the trial treatments. Prior to the commencement of the trial, physiotherapists were additionally trained at a one-day workshop to administer both interventions. A second training session was held half way through the trial to ensure that both interventions continued to be delivered in accordance with the trial protocol; See Web appendix 1: Trial protocol (pp 1-68). Each treating physiotherapist had one treatment and one advice session audited by experts in the field to ensure treatment fidelity.

**Outcomes**

All outcome measures were collected by an investigator unaware of group allocation at baseline, 14 weeks, 6 months and 12 months after randomisation. Demographic characteristics such as age, employment, medical history, current medications, previous investigations and treatment as well as information about their WAD symptoms, accident history, and compensation status were collected at the baseline assessment.

The primary outcome was the average pain intensity over the last week measured using a 0 (no pain) to 10 (worst possible pain) numerical rating scale.[14] Secondary outcomes were average pain intensity over the last 24 hours,[14] self-rated recovery (-5 = vastly worse 0 = unchanged +5 = completely recovered),[15] disability measured with the 10 item Neck Disability Index (scale range 0-100)[16] (NDI) and the 13 item Whiplash Disability Questionnaire[17] (scale range 0-130) (WDQ)), quality of life measured with the SF-36[18] with summary scores standardised using Australian normative values (population mean = 50, SD= 10),[19] functional ability measured using the Patient-Specific Functional Scale (scale range 0-10)[20] (PSFS)) and cervical spine range of motion measured using an inclinometer.[21] Adverse effects of treatment were identified using open-ended questioning at the 3-month follow-up assessment.

Measures of central nervous system hyper-excitability and psychological distress were also obtained at baseline and each follow-up assessment to evaluate the influence of these factors on treatment effect. The neuropathic pain measures were the S-LANSS score, a Self-report version of the Leeds Assessment of Neuropathic Symptoms and Signs pain scale[22]; pressure pain threshold measured over the cervical spine (C5 spinous process) and tibialis anterior (bilateral) using a Pressure algometer (Somedic AB, Sweden)[23] and cold pain threshold measured bilaterally over the cervical spine (level C3 to C7) using a Thermotest system (Somedic AB, Sweden)[24]. The measures of psychological distress were symptoms of posttraumatic stress measured with the Posttraumatic Stress Diagnostic Scale (PDS),[25] and symptoms of catastrophising measured with the Pain Catastrophising Scale.[26]

**Statistical analysis**

The sample size of 172 participants was calculated a priori and considered both the primary and secondary goals of this study. This sample size provides 80% power to detect a clinically worthwhile difference of at least 2 units for the primary outcome of pain intensity (estimated SD 2.0, based on previous trials that recruited similar patient cohorts.[7, 8]). This calculation assumed an alpha of 0.05 and allowed for up to 10% loss to follow up and 10% treatment non-compliance.

The analyses followed a pre-specified protocol.[9] All data were double-entered and analyses were performed on the locked data file. The statistical analyses were performed using IBM SPSS Statistics 21.0.0.0 by intention-to-treat. The investigator performing the analyses was blinded to group allocation. All analyses were double checked by a second, independent investigator.

The mean effect of the intervention on pain, function, disability, global perceived effect and quality of life were calculated using linear mixed models which incorporated terms for participant, clinician, treatment group, time, and treatment by time interactions. Treatment effect modification was tested by adding the putative effect modifier to the model and a treatment by effect modifier interaction term. An independent t-test was used to evaluate whether there was a significant difference in self-rated recovery between groups.

As PROMISE included participants with longer duration of WAD than originally pre-specified we conducted a post-hoc analysis evaluating if the duration of WAD symptoms moderated the effect of treatment.

## Role of the funding sources

PROMISE was an investigator-initiated trial funded by the National Health and Medical Research Council (NHMRC) of Australia. As the amount awarded by NHMRC was less than the submitted budget, the investigators applied for supplementary funding from the Government third party insurance regulators of the states where the trial was to be conducted (MAA of New South Wales MAIC of Queensland). Both regulators assisted with participant recruitment by sending invitational letters to claimants. The funders had no role in data analysis, data interpretation or the decision to submit for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit the manuscript.

## Results

Recruitment ran between October 2009 and February 2012 with follow-up completed in February 2013. Reasons for ineligibility and the flow of participants through the trial are shown in Figure 1. 172 participants were randomised with 157 (91%) followed up at 14 weeks, 145 (84%) at 6 months and 150 (87%) at 12 months. Two participants (one from each group) were later excluded when additional information about their health status emerged after randomisation. One participant was diagnosed with metastatic breast cancer and one participant was diagnosed with an upper motor neuron lesion. Knowledge of these conditions prior to enrolment into the study would have excluded both people from participating. A total of 25 physiotherapists delivered the trial treatments across 20 private physiotherapy clinics (Sydney: 11 physiotherapists from 8 clinics; Brisbane 14 physiotherapists from 12 clinics).

Baseline characteristics are reported in Table 1. The characteristics of the participants in the two groups were similar for all outcomes and important prognostic factors. Participants were primarily middle-aged and female and had experienced their WAD symptoms for nearly two years. Most injuries were compensable with one third having settled a compensation claim. Participants typically reported moderate levels of pain and disability and lower quality of life than the Australian population norms (Table 2).[19]

No serious adverse events were reported. Mild adverse effects were reported for five patients receiving the comprehensive exercise program and four patients receiving advice. Adverse effects were headache (n=4), musculoskeletal symptoms (n=3), exacerbation of existing symptoms (n=1) and stiffness (n=1). None of the patients withdrew from the trial due to adverse effects.

Compliance with treatment was good for both intervention groups. In the exercise group the median (interquartile range) number of comprehensive sessions attended by participants was 17 (13 to 20) of the maximum 20 sessions. In the advice group the median (interquartile range) number of advice sessions and phone follow-up sessions was 1 (1 to 3).

The unadjusted outcomes are shown in Table 2 and the treatment effects at each follow-up are shown in Table 3. To aid interpretation of the size of the treatment effects we included the clinically worthwhile effect we specified in the trial protocol[9]. In the primary analyses the comprehensive exercise program did not provide a benefit over advice. The point estimates of the effects of treatment were close to zero and the 95%CI did not include a clinically worthwhile

effect on pain reduction. For example the effect at 14 weeks was 0.0 (-0.7 to 0.7) on a 0-10 pain intensity scale whereas our pre-specified clinically worthwhile effect was 2.0 units.[9]

Most of the secondary analyses were not statistically significant. The exceptions were the results for self-rated recovery at all time points and functional ability at 14 weeks where some point estimates of treatment effect were statistically significant but did not reach the threshold we had set for being clinically worthwhile.[9]

Table 4 displays the results of the treatment effect modification analyses. None of the variables moderated the effect of treatment analyses for the primary outcome (pain intensity) at 14 weeks. Because tests of effect modification involve an interaction term in the analysis they are frequently under-powered in clinical trials[27] and hence provide imprecise estimates. To evaluate this issue we calculated the additional treatment benefit for a 1-standard deviation increase in the putative effect modifier. In all cases the point estimate and 95% CI did not include a clinically worthwhile effect on pain i.e. 2 points on a 0-10 scale. In a *post-hoc* analysis, the duration of WAD symptoms was also found to not moderate the effect of treatment on the primary outcome at 14 weeks. Post-hoc sensitivity analyses were conducted to assess the impact of missing data on the primary outcome by replacing missing data with the best or worst possible scores on the numerical rating scale (i.e. 0 or 10). These additional analyses did not change the interpretation of the results, see Web appendix 3 (pp 102).

## Discussion

An intensive 12-week, physiotherapist delivered comprehensive exercise program for people with chronic WAD did not provide additional benefit over advice for the primary outcome of average weekly pain intensity. A statistically significant, though clinically unimportant, benefit was found for two of the secondary outcome measures. We did not find any evidence to support the hypothesis that differential responses to treatment may occur in chronic WAD.

The PROMISE trial was prospectively registered, followed a pre-specified protocol and incorporated design features known to minimise bias such as assessor blinding, concealed allocation and an intention-to-treat analysis. The trial achieved high rates of follow-up and the participants were compliant with the interventions that were delivered. The participants were generally representative of people with chronic WAD and the study cohort was comparable to previous studies conducted in this area.[7, 8, 28] Although trial physiotherapists delivered both interventions the risk of contamination between groups was minimised by the therapists being well-trained to deliver the trial interventions, the audit of treatment sessions, and the duration of direct participant-therapist contact being significantly different between groups. The conclusions are based on precise estimates of treatment effectiveness and the interpretation of results was unaffected by the sensitivity analyses. Accordingly we believe that the trial provides a credible evaluation of the two study treatments with important implications for clinical practice and for the management of people with chronic WAD. The results of this study will also be of interest to insurers and those involved in development of future health policies.

We need to acknowledge the potential for bias in PROMISE as we were unable to blind

participants, and the nature of the intervention meant that we also could not blind the treatment providers. We are unaware of any WAD trials evaluating advice or exercise that have blinded patients or treatment providers. The only WAD trial we are aware of that has blinded patients and treatment providers, and reported that the treatment was efficacious, is the Lord et al trial[5] which evaluated radiofrequency neurotomy. The subjective nature of WAD means that in some societies the injury is associated with suspicion of malingering and fraudulent insurance claims. It is not possible to definitively say that all participants enrolled in PROMISE were genuine WAD cases however, in the in the jurisdictions where the trial took place, there is no secondary gain from participation in a trial like PROMISE. Cases of malingering also seems unlikely as participants reported consistent findings across subjective and objective measures and as discussed above the cohort enrolled were comparable to previous studies conducted in this area[7, 8, 28].

The effectiveness of an individually tailored, multi-modal treatment approach for WAD is being challenged. In keeping with the results of the current study, previous research suggests that a more comprehensive 'package' of care, designed to address the heterogeneous nature of WAD, has minimal to no additional benefit over treatments that can be delivered in a small number of sessions such as usual care or advice.[10, 28, 29] Recent studies conducted in both acute[10, 29] and chronic[28] populations have demonstrated only minimal treatment effects for tailored treatment approaches in the short term, but not at long term follow up. The complexity of WAD, including the presence of central nociceptive hyper-excitability and posttraumatic stress symptoms, may be the reason why these treatment programs are not demonstrating large improvements in outcomes compared to advice.

Musculoskeletal conditions have been identified as one of the leading causes of disability and chronic pain in the latest Global Burden of Disease study.[30] The need to identify effective and affordable strategies to prevent and treat these conditions has been highlighted as an important health priority; this is particularly true for those with chronic WAD as the majority have tried and failed previous treatments and their ongoing symptoms means that they would be unlikely to pursue more of the same approaches. The development of new therapies would be advanced with identification of specific patho-anatomical diagnoses and an improved understanding of the mechanisms responsible for the development of persistent pain and disability. It would be useful for future studies to investigate the effectiveness and timing of various pharmacological interventions for the management of nociceptive pain and central nervous system hyper-excitability, an area largely ignored to date. Alleviating or lessening pain may provide an environment in which neuromuscular and functional rehabilitation stands to have a more beneficial effect.[31] Lastly, there is a need to determine how to deliver simple advice successfully. Education and advice has been shown to be as effective as more costly interventions[32] yet we need to better understand how to deliver these to patients in the most effective manner. This may involve the use of verbal, written, or multimedia approaches.[32]

## CONTEXT OF THE PROMISE TRIAL

*Systematic review*

We searched for randomised controlled trials that addressed our study question and also searched for recent systematic reviews of treatment of chronic WAD to provide evidence for other treatment options. We searched PubMed and PEDro in September 2013 using the text search term 'chronic whiplash'. We identified 3 RCTs[7, 8, 33] and 8 systematic reviews[4, 32, 34-39] comparing a physiotherapy exercise program to advice. The three trials were of high quality, scoring 7-8/10 on the 0-10 PEDro scale and so were pooled with our outcomes for disability in the short term (the only common outcome). The additional benefit of exercise over advice was -3.3 (-5.5 to -1.1) on a 0-100 scale. Of the eight reviews that were identified, three[32, 37, 38] provided information on chronic WAD. The evidence from two reviews was of low quality[37, 38] as 27 of 45 reviewed studies were not RCTs. The third review was of higher quality.[32] The RCTs in the reviews provide evidence that exercise is effective in reducing pain though it is unclear if gains are maintained in the long term, and that radiofrequency neurotomy provides substantial, though not permanent, pain relief. There was conflicting evidence on the effectiveness of psychological therapies and a general indication that further evaluation of a multidisciplinary approach is warranted.

*Interpretation*

Our meta-analysis of the four available trials suggests that the addition of an exercise program does not provide clinically important additional benefits to advice for people with chronic WAD. The current study demonstrated that a longer program of exercise, combining two different types

of exercise, also does not provide additional benefit over advice. Furthermore, the results of this study do not support the hypothesis that there are differential responses to exercise treatment in people with chronic WAD. Radiofrequency neurotomy is effective for patients who have pain arising from the zygapophyseal joints but the procedure needs to be repeated when the nerves recover. Both the test to determine patient suitability (diagnostic nerve blocks) and radiofrequency neurotomy are technically complex and even when patients are carefully selected the procedure is only effective in a moderate proportion of patients.[5]

**Contributors**

ZM participated in the conception and design of the study, acquisition of data, analysis and interpretation of data, drafting of the report, critical revision of the report for important intellectual content, statistical analysis.

CM participated in the conception and design of the study, acquisition of data, analysis and interpretation of data, drafting of the report, critical revision of the report for important intellectual content, statistical analysis, obtaining funding, administrative, technical, or material support, and supervision;

MS participated in the conception and design of the study, acquisition of data, analysis and interpretation of data, critical revision of the report for important intellectual content, obtaining funding, administrative, technical, or material support, and supervision;

GJ participated in the conception and design of the study, training of treatment providers, acquisition of data, analysis and interpretation of data, critical revision of the report for important intellectual content, obtaining funding, administrative, technical, or material support, and supervision

CL participated in the conception and design of the study, acquisition of data, analysis and interpretation of data, critical revision of the report for important intellectual content, administrative, technical, or material support, and supervision

JL participated in the conception and design of the study, acquisition of data, analysis and interpretation of data, critical revision of the report for important intellectual content, obtaining funding, administrative, technical, or material support, and supervision

LC participated in the conception and design of the study, analysis and interpretation of data, drafting of the report, critical revision of the report for important intellectual content and obtaining funding.

TR participated in the conception and design of the study, training of treatment providers, critical revision of the report for important intellectual content, administrative, technical, or material support, and supervision.

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**Conflicts of interest:**

The authors have no conflicts of interest to declare.

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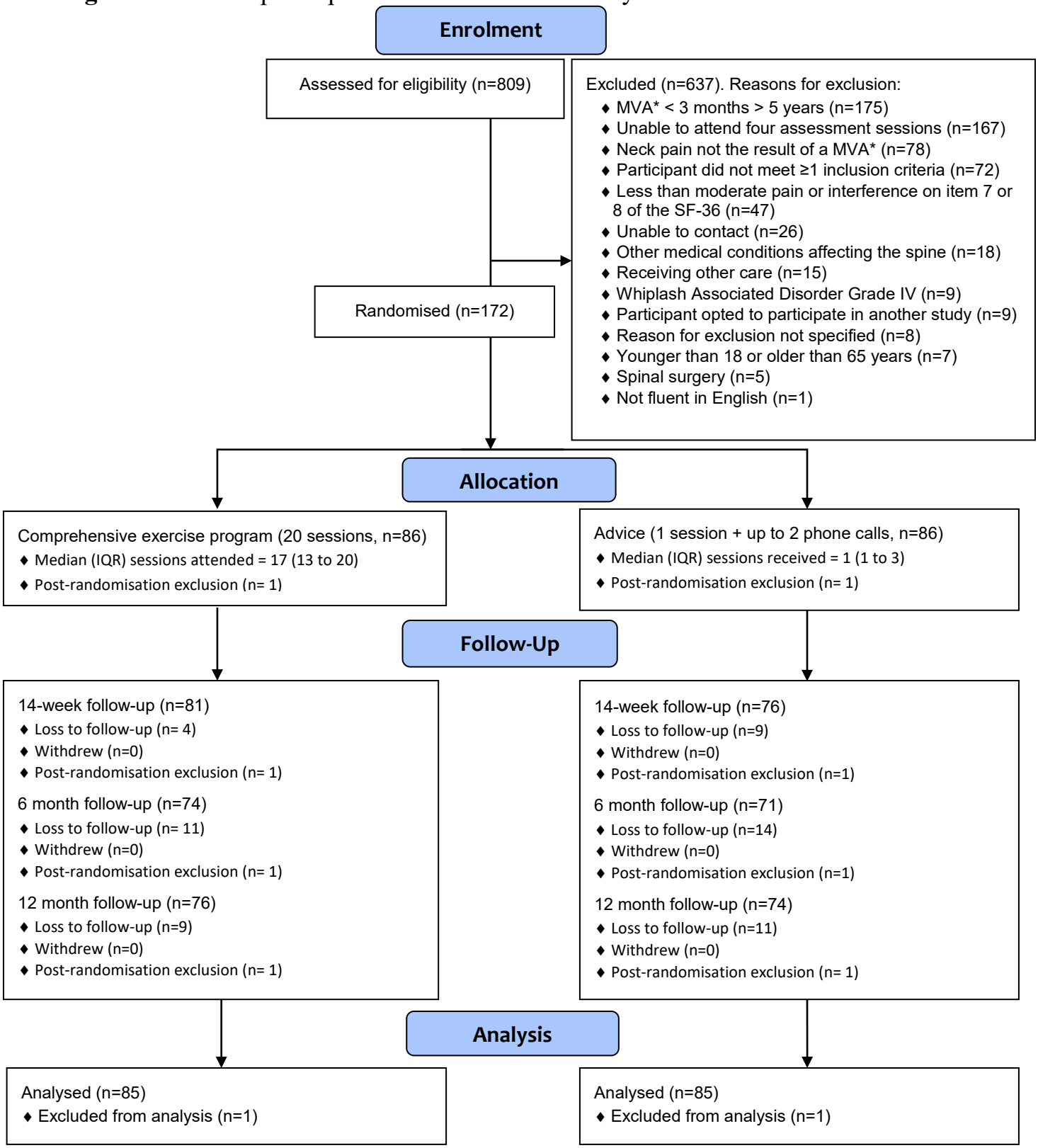
**Figure 1:** Flow of participants in the PROMISE study




* MVA: motor vehicle accident.

**Table 1: Baseline characteristics**

| | Comprehensive exercise program (n=85) | Advice (n=85) |
|---|---|---|
| Age, mean years (SD) | 42.6 (12.3) | 43.1 (12.7) |
| Female, n (%) | 48 (56.5) | 60 (70.6) |
| Duration of symptoms, mean months (SD) | 20.9 (15.1) | 22.0 (18.2) |
| Position in accident, n (%) | | |
| - Driver | 68 (80.0) | 70 (81.2) |
| - Front passenger | 6 (7.1) | 7 (8.2) |
| - Back seat passenger | 3 (3.5) | 4 (4.7) |
| - Motorbike | 2 (2.4) | 1 (1.2) |
| - Not applicable | 2 (2.4) | 2 (2.4) |
| - Missing | 4 (4.7) | 2 (2.4) |
| Aware of oncoming accident, n yes (%) | 16 (18.8) | 24 (28.2) |
| Collision impact, n (%) | | |
| - rear end | 38 (44.7) | 35 (41.2) |
| - rear and front | 7 (8.2) | 10 (11.8) |
| - front end | 21 (24.7) | 20 (23.5) |
| - side | 13 (15.3) | 17 (20.0) |
| - Not applicable | 1 (1.2) | 1 (1.2) |
| - Missing | 5 (5.9) | 2 (2.4) |
| Stationary at time of impact, yes (%) | 43 (50.6) | 45 (52.3) |
| Following accident neck pain started, n (%) | | |
| - Immediately | 31 (36.5) | 30 (35.3) |
| - Within 24 hours | 44 (51.8) | 35 (41.2) |
| - After 24 hours | 9 (10.6) | 20 (23.5) |
| - Missing | 1 (1.2) | 0 (0) |
| Restriction in neck movement, n (%) | | |
| - Not at all | 10 (11.8) | 3 (3.5) |
| - Mildly | 11 (12.9) | 15 (17.6) |
| - Moderately | 33 (38.8) | 32 (37.6) |
| - Severely | 31 (36.5) | 33 (38.8) |
| - Missing | 0 (0) | 2 (2.4) |
| Following accident neck restriction started, n (%) | | |
| - Immediately | 20 (23.5) | 22 (25.9) |
| - Within 24 hours | 46 (54.1) | 36 (42.4) |
| - After 24 hours | 17 (20.0) | 26 (30.6) |
| - Not applicable | 1 (1.2) | 0 (0) |
| - Missing | 1(1.2) | 1 (1.2) |
| Loss of consciousness, n yes (%) | 5 (5.9) | 8 (9.4) |
| Admitted to hospital following accident, n yes (%) | 15(17.6) | 20 (23.5) |
| Investigations, n (%)* | | |
| - X-ray | 60 (70.6) | 60 (70.6) |

| | | |
|---|---|---|
| - CT | 28 (32.9) | 32 (37.6) |
| - MRI | 24 (28.2) | 24 (28.2) |
| Previous treatment (yes), n (%) | | |
| - Physiotherapy | 68 (80.0) | 70 (82.4) |
| - Chiropractic | 23 (27.1) | 22 (25.9) |
| - Massage | 37 (43.5) | 46 (54.1) |
| - Acupuncture | 23 (26.7) | 29 (34.1) |
| - Other e.g. osteopathy | 18 (21.2) | 18 (21.2) |
| Current medication for WAD symptoms, n (%) | | |
| - No medications | 27 (15.7) | 19 (11.0) |
| - NSAID only | 31 (18) | 40 (23.3) |
| - NSAID and codeine | 5 (2.9) | 5 (2.9) |
| - NSAID gel | 2 (1.2) | 1 (0.6) |
| - Paracetamol only | 37 (21.5) | 35 (20.3) |
| - Paracetamol combination | 7 (4.0) | 4 (2.3) |
| - Opioid only | 7 (4.0) | 6 (3.5) |
| - Opioid and paracetamol | 10 (5.8) | 20 (11.9) |
| - Complementary medicines | 7 (4.0) | 4 (2.3) |
| - Anticonvulsant | 0 (0) | 1 (0.6) |
| - Benzodiazepine | 3 (1.7) | 3 (1.7) |
| - Selective serotonin reuptake inhibitors | 1 (0.6) | 1 (0.6) |
| - Tricyclic antidepressant | 0 (0) | 4 (2.3) |
| - Antiemetic | 0 (0) | 1 (0.6) |
| Antimigraine agent | 0 (0) | 1 (0.6) |
| Current employment status, n (%) | | |
| - Employed | 59 (69.4) | 57 (67.1) |
| - Self employed | 13 (15.3) | 8 (9.4) |
| - Home duties | 4 (4.7) | 2 (2.4) |
| - Unemployed | 1 (1.2) | 7 (8.2) |
| - Retired | 4 (4.7) | 6 (7.1) |
| - Entitled leave | 1 (1.2) | 3 (3.5) |
| - Student | 3 (3.5) | 1 (1.2) |
| - Missing | 0 (0) | 1 (1.2) |
| Employment hours, n (%) | | |
| - Normal hours | 57 (67.1) | 57 (67.1) |
| - Reduced hours due to whiplash injury | 12 (14.1) | 4 (4.7) |
| - Not working due to whiplash | 7 (8.2) | 6 (7.1) |
| - Not applicable | 8 (9.4) | 17 (20.0) |
| - Missing | 1 (1.2) | 1 (1.2) |
| Income, n (%) | | |
| - $1-$49999 | 31 (36.5) | 43 (50.6) |
| - $50000-$99999 | 40 (47.1) | 30 (35.3) |
| - $100000-$149999 | 9 (10.6) | 10 (11.8) |
| - >$150000 | 5 (5.9) | 2 (2.4) |
| - Missing | 0 (0) | 0 (0) |
| Compensation, n (%) | | |

| | | |
|---|---|---|
| - No | 23 (27.1) | 22 (25.9) |
| - Yes, compulsory third party claim | 48 (56.5) | 44 (51.8) |
| - Yes, workers compensation | 10 (11.8) | 15 (17.6) |
| - Yes, other e.g. personal injury claim | 1 (1.2) | 1(1.2) |
| - Missing | 3 (3.5) | 3 (3.5) |
| Compensation settled, n yes (%) | 29 (34.1) | 24 (28.2) |
| Engaged services of a solicitor, n yes (%) | 36 (42.4) | 34 (40.0) |
| Qualification, n (%) | | |
| - Bachelor degree or higher | 42 (49.4) | 37 (43.5) |
| - Diploma or certificate | 29 (34.1) | 35 (41.2) |
| - Secondary level or below | 14 (16.5) | 12 (14.1) |
| - Missing | 0 (0.0) | 1 (1.2) |

* Performed on the neck at any time since the motor vehicle accident

**Table 2: Unadjusted outcomes, mean (SD) for each treatment group**

| | Baseline | | 14 weeks | | 6 months | | 12 months | |
|---|---|---|---|---|---|---|---|---|
| | **Comprehensive exercise program (n= 85)** | **Advice (n = 85)** | **Comprehensive exercise program (n = 81)** | **Advice (n = 76)** | **Comprehensive exercise program (n = 74)** | **Advice (n = 71)** | **Comprehensive exercise program (n = 76)** | **Advice (n = 74)** |
| **PRIMARY OUTCOME** | | | | | | | | |
| **Pain over previous week**[a] | 5.5 (2.1) | 5.9 (1.9) | 3.9 (2.3) | 4.4 (2.5) | 4.4 (2.7) | 4.7 (2.3) | 3.7 (2.6) | 4.4 (2.5) |
| **SECONDARY OUTCOME** | | | | | | | | |
| **Pain previous 24 hours**[a] | 4.7 (2.0) | 5.5 (2.0) | 3.5 (2.2) | 4.0 (2.5) | 3.9 (2.7) | 4.3 (2.5) | 3.6 (2.6) | 4.1 (2.4) |
| **Self-rated recovery**[b] | N/A | N/A | 2.4 (1.6) | 1.2 (2.0) | 2.2 (2.0) | 1.3 (2.0) | 2.2 (2.0) | 1.5 (2.1) |
| **Neck disability index (%)**[c] | 34.3 (16.3) | 37.7 (15.4) | 27.1 (17.7) | 31.3 (18.8) | 26.8 (18.0) | 31.7 (18.5) | 25.9 (19.6) | 30.0 (18.9) |
| **Whiplash disability questionnaire**[d] | 51.9 (29.3) | 59.7 (27.9) | 39.8 (29.7) | 44.9 (31.3) | 40.6 (31.4) | 45.0 (33.3) | 37.1 (32.1) | 41.6 (32.5) |
| **SF36-physical**[e] | 40.6 (7.8) | 39.4 (7.8) | 43.4 (9.0) | 42.6 (9.9) | 44.5 (9.7) | 43.1 (9.5) | 45.1 (9.2) | 42.7 (9.9) |
| **SF36-mental**[f] | 42.2 (13.4) | 41.8 (13.3) | 47.0 (12.1) | 43.7 (12.6) | 45.6 (12.3) | 44.5 (9.7) | 46.0 (12.4) | 45.3 (13.0) |
| **Functional ability**[g] | 4.0 (1.4) | 3.9 (1.6) | 5.9 (2.4) | 4.8 (2.2) | 6.0 (2.5) | 5.3 (2.5) | 6.3 (2.5) | 5.6 (2.5) |
| **Cervical spine flexion (deg)**[h] | 44.5 (16.1) | 44.2 (15.8) | 48.0 (16.9) | 48.1 (17.7) | 46.8 (16.3) | 48.9 (16.6) | 46.7 (15.6) | 50.8 (17.1) |
| **Cervical spine extension, (deg)**[h] | 42.2 (15.4) | 41.5 (17.1) | 46.0 (15.6) | 43.2 (15.4) | 46.5 (15.7) | 44.0 (15.6) | 45.6 (14.2) | 43.8 (14.4) |
| **Cervical spine right rotation (deg)**[h] | 53.1 (20.3) | 52.5 (20.7) | 58.5 (19.3) | 54.7 (17.4) | 59.8 (19.2) | 56.2 (18.4) | 60.2 (20.5) | 55.7 (16.9) |
| **Cervical spine left rotation (deg)**[h] | 53.7 (20.0) | 52.2 (18.9) | 58.2 (19.2) | 57.2 (17.4) | 60.0 (18.9) | 54.8 (18.7) | 58.6 (18.1) | 58.2 (17.6) |

Values are unadjusted mean (SD). Self-rated recovery was not measured at baseline.

[a] Numerical pain rating scale scored from 0 (no pain) to 10 (worst pain possible)
[b] Global perceived effect scale scored from -5 (vastly worse) 0 (unchanged) to +5 (completely recovered)
[c] Neck Disability Index Score: 10 items, scored on a 0–50 scale which is converted to a percentage with 0% (no disability) to 100% (high disability)
[d] Whiplash disability questionnaire: 13 items, scored from 0 (no disability) to 130 (high disability)
[e] Physical component score from the SF-36 Health Survey (Australian population norm standardised mean = 50, SD=10)
[f] Mental component score from the SF-36 Health Survey (Australian population norm standardised mean = 50, SD=10)
[g] Patient-Specific Functional Scale score: average of 3 scores, 0 (unable to perform activity) to 10 (able to perform activity at pre-injury level)
[h] Cervical spine range of motion measured with an inclinometer: average of 3 measures

**Table 3: Treatment effects, mean (95%CI) at 14 weeks, 6 & 12 months**

| | Clinically worthwhile effect | 14 weeks | 6 months | 12 months |
|---|---|---|---|---|
| **PRIMARY OUTCOME** | | | | |
| **Pain over previous week**[a] | 2.0 | 0.0 (-0.7 to 0.7) | 0.2 (-0.5 to 1.0) | -0.1 (-0.8 to 0.6) |
| **SECONDARY OUTCOMES** | | | | |
| **Pain previous 24 hours**[a] | 2.0 | 0.3 (-0.4 to 1.0) | 0.5 (-0.2 to 1.2) | 0.2 (-0.4 to 0.9) |
| **Self-rated recovery**[b] | 2.0 | 0.7 (0.3 to 1.1)* | 0.9 (0.3 to 1.6)* | 0.8 (0.1 to 1.4)* |
| **Neck disability index (%)**[c] | 12 | -1.2 (-4.9 to 2.4) | -1.1 (-4.8 to 2.6) | -0.1 (-3.8 to 3.5) |
| **Whiplash disability questionnaire**[d] | 30 | 2.3 (-4.6 to 9.2) | 3.8 (-3.2 to 10.9) | 3.2 (-3.7 to 10.2) |
| **SF36-physical**[e] | 15 | 0.3 (-2.3 to 2.9) | 0.7 (-1.9 to 3.3) | 1.2 (-1.4 to 3.8) |
| **SF-36-mental**[f] | 15 | 2.4 (-1.0 to 5.8) | 0.0 (-3.4 to 3.4) | 0.4 (-3.6 to 3.9) |
| **Functional ability**[g] | 1.5 | 1.0 (0.3 to 1.7)* | 0.7 (0.0 to 1.5) | 0.6 (-0.1 to 1.4) |
| **Cervical spine flexion (deg)**[h] | | -1.0 (-6.0 to 3.9) | -3.2 (-8.2 to 1.9) | -4.9 (-9.9 to 0.1) |
| **Cervical spine extension, (deg)**[h] | | 0.7 (-3.4 to 4.9) | 0.9 (-3.2 to 5.1) | 0.1 (-4.1 to 4.2) |
| **Cervical spine right rotation (deg)**[h] | | -0.7 (-5.3 to 3.9) | 2.5 (-2.2 to 7.2) | 0.7 (-4.0 to 5.4) |
| **Cervical spine left rotation (deg)**[h] | | 0.6 (-4.5 to 5.7) | 3.6 (-1.6 to 8.8) | 1.0 (-4.2 to 6.1) |

Values are point estimates and 95% confidence intervals. The treatment effects for self-rated recovery are from an un-paired t test. The second column contains the clinically worthwhile effect pre-specified in the trial protocol.

[a] Numerical pain rating scale scored from 0 (no pain) to 10 (worst pain possible)
[b] Global perceived effect scale scored from -5 (vastly worse) 0 (unchanged) to +5 (completely recovered)
[c] Neck Disability Index Score: 10 items, scored on a 0–50 scale which is converted to a percentage with 0% (no disability) to 100% (high disability)
[d] Whiplash disability questionnaire: 13 items, scored from 0 (no disability) to 130 (high disability)
[e] Physical component score from the SF-36 Health Survey (Australian population norm standardised mean = 50, SD=10)
[f] Mental component score from the SF-36 Health Survey (Australian population norm standardised mean = 50, SD=10)
[g] Patient-Specific Functional Scale score: average of 3 scores, 0 (unable to perform activity) to 10 (able to perform activity at pre-injury level)
[h] Cervical spine range of motion measured with an inclinometer: average of 3 measures
* Statistically significant, p = <0.05

NB: For outcomes where a high score is preferred e.g. range of motion a positive effect favours exercise, for outcomes where a low score is preferred a negative effect favours exercise.

**Table 4. Evaluation of treatment effect modification on primary outcome at 14 weeks**

| | Estimate (95%CI) p value | Effect for 1 SD increase |
|---|---|---|
| **EFFECT MODIFIER** | | |
| Neuropathic pain score[a] | 0.04 (-0.08 to 0.16) p = 0.480 | 0.24 (-0.48 to 0.96) |
| Post traumatic stress symptom score[b] | -0.03 (-0.08 to 0.03) p = 0.288 | -0.36 (-0.96 to 0.36) |
| Pressure pain threshold-peripheral[c] | 0.00 (0.00 to 0.00) p = 0.769 | N/A |
| Pressure pain threshold-neck[d] | 0.00 (0.00 to 0.00) p = 0.228 | N/A |
| Cold pain threshold-neck[e] | 0.01 (-0.08 to 0.10) p = 0.776 | 0.10 (-0.64 to 0.80) |
| Catastrophising score[f] | -0.01 (-0.06 to 0.05) p = 0.732 | -0.13 (-0.78 to 0.65) |
| WAD duration[g] | -0.02 (-0.06 to 0.02) p = 0.259 | -0.34 (-0.78 to 0.65) |

Estimates of treatment effect modification from the linear mixed models analysis at 14 weeks. The second column is the point estimate and 95% confidence interval for the treatment x time interaction term. The third column quantifies the size of the interaction for a 1 standard deviation increase in the putative effect modifier.

[a]Self report version of Leeds Assessment of Neuropathic pain Symptoms and Signs scale
[b]Post-traumatic stress Diagnostic Scale score
[c]Mean of three pressure pain threshold tests over right and left tibialis anterior
[d]Mean of three PPT tests over lower cervical spine
[e]Mean of six cold pain threshold tests
[f]Pain Catastrophising Scale total score sum of 13 items
[g]Duration of WAD symptoms (Post-hoc analysis)