***Effectiveness of conservative multimodal physiotherapy in***

***chronic whiplash-associated disorders in individuals***

***with and without posttraumatic stress symptoms:***

***a pilot series of Single Case Experimental Designs (SCEDs)***

***Protocol***

Contact details

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**Clinical Trial Registration number**: ACTRNxxxx

# Administrative structure

This investigator-initiated study is sponsored by The University of Queensland. The study is funded by The University of Queensland. The principal investigator will be responsible for overseeing all aspects of the trial and for the preparation and publication of the principal results of the study.

The study will be coordinated from Brisbane and conducted in Brisbane, Queensland.

***Investigative team***

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## Protocol Signature Page

**Protocol Title:** Effectiveness of conservative multimodal physiotherapy in chronic whiplash-associated disorders (WAD) in individuals with or without posttraumatic stress symptoms: a pilot series of SCEDs.

**Short Title:** Physiotherapy SCEDs for chronic WAD

**Sponsor:** The University of Queensland, Recovery Injury Research Centre

*STUDY ACKNOWLEDGEMENT/CONFIDENTIALITY*

By signing this Protocol, the Investigator(s) acknowledges and agrees:

The protocol contains all necessary details for conducting the study. The Investigator will conduct this study as detailed herein, in compliance with Good Clinical Practice (GCP) and the applicable regulatory requirements, and will make every reasonable effort to complete the study within the time designated.

The Protocol and all relevant information on the Investigational Product (product information or instructions for use of registered products paracetamol and naproxen) will be made available to all physicians, nurses and other personnel who participate in the conducting of this study. The Investigator will discuss this material with them to assure they are fully informed regarding the investigational product(s) and the conduct of the study.

The University of Queensland will have access to any source documents from which the Case Report Form (CRF) information may have been generated. The CRFs and other data pertinent to this study are the property of The University of Queensland, which may utilise the data in various ways or in publication of the results of the study.

The conduct and results of this study will be kept confidential. The results of this study may be published. Upon completion of the Study it is the intention of the parties to prepare a joint publication regarding or describing the Study and all the results there from and all parties shall co-operate in this regard.

**Principal Investigator Signatory**:

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| PRINCIPAL INVESTIGATOR NAME: | SIGNATURE:  DATE: |

**Physiotherapy SCEDs for Chronic Whiplash Summary Sheet**

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| **Name of Sponsor:** The University of Queensland |
| **Title of Study:** Effectiveness of conservative multimodal physiotherapy in chronic whiplash-associated disorders in individuals with and without posttraumatic stress symptoms: a pilot series of Single Case Experimental Designs (SCEDs). |
| **Principal Investigator:** Dr Jane Nikles, RECOVER Injury Research Centre, UQ. |
| **Study Sites and recruitment:**  We will recruit participants with chronic Whiplash Associated Disorder (WAD) (> 3 months duration of symptoms). The study is based at Recover Injury Research Centre, Herston. Enrolment will utilise the RECOVER Injury Research Centre database of individuals with chronic WAD. |
| **Aims and objectives:**  The **primary aim** of this study is to conduct a series of SCEDs testing the effectiveness of conservative multimodal physiotherapy for reducing daily neck pain and increasing self-efficacy in individuals with chronic whiplash-associated disorders (WAD) with and without post-traumatic stress symptoms (PTSS).  **Secondary aims** are 1) to test the effectiveness of conservative multimodal physiotherapy in decreasing pain-related disability and improving psychological function (including depression and anxiety) and health-related quality of life at the end of the proposed intervention, and after 4 weeks follow-up in patients with chronic WAD with and without PTSS.  2) To examine whether SCEDs will be feasible, useful and acceptable in this context. |
| **Methodology:** We will assess effectiveness of conservative multimodal physiotherapy in patients with chronic WAD, with and without PTSS, using patients as their own control. Using a novel multiple baseline design, all patients will receive an advice/exercise booklet, then a variable length baseline followed by 4 weeks of conservative multimodal physiotherapy. Follow-up questionnaires will be administered during and at completion of the physiotherapy intervention, and approximately 4 weeks following treatment completion. |
| **Planned number of participants:** 6 participants |
| **Diagnosis and main criteria for inclusion:**   * Individuals with Grade II Whiplash Associated Disorder * > 12 weeks since injury * Moderate levels of pain (Numerical pain rating scale >= 5/10) and disability (Neck Disability Index > 32%) * Three individuals with moderate post-traumatic stress symptoms (revised Impact of Events Scale score > 24) and 3 individuals with minimal or no PTSS (r-IES < 20). |
| **Primary outcome:** 1. Daily neck pain intensity. Neck pain intensity is measured on the continuous numeric rating scale (NRS) of 0 to 10, and will be the patients’ self-report of average pain intensity during the last 24 hours.  2. Perceived confidence in participating in physical activity in the presence of pain-related disability at treatment completion (with 1 indicating *not at all confident*; 2 *a little confident*, 3 indicating *moderately confident*; 4 *very confident* and 5 indicating *extremely confident*). |
| **Duration:** Four weeks of intervention and then 4 weeks of follow-up during 2018. |
| **Data analysis:**  Primary outcome measures will be plotted against time and visually examined for: (1) level; (2) trend; (3) variability; (4) immediacy of the effect; (5) overlap; and (6) consistency of data patterns in similar phases. The data from the active treatment phase of the SCEDs will be aggregated using a Bayesian hierarchical model where random effects account for repeated measures (within patients) over time. |

**PROJECT OVERVIEW**

Whiplash associated disorders (WAD) are an enormous and costly burden to Australian society. Up to 50% of people who experience a whiplash injury will never fully recover. Although some individuals respond to conservative multimodal physiotherapy, the overall effect sizes are small (Teasell et al., 2010). The differential effect of conservative multimodal physiotherapy is likely due to the heterogeneous nature of the condition. We have previously shown that individuals with higher levels of post-traumatic stress symptoms (PTSS) demonstrate greater pain and disability levels (Pedler & Sterling, 2013; Sterling et al., 2010). It is hypothesized that these individuals demonstrate a poorer response to conservative physiotherapy. This is yet to be formally tested *a priori*.

We will explore commonly used multimodal conservative physiotherapy in individuals with chronic WAD and compare response to treatment in those presenting with and without PTSS, using a design which is quite novel in physiotherapy, Single Case Experimental Designs (SCEDs). In contrast to an experimental group design in which one group is compared with another, participants in single-subject research provide their own control data for the purpose of comparison in a within-subject rather than a between-subjects design. SCEDs provide a method to determine response and benefit for every individual patient. After each individual trial, patients discuss their results with their health professional based on an individually generated report. Additionally, single cases can be aggregated to arrive at a group effect. This requires a smaller sample size for a group estimate of effect than RCTs, because of greater statistical power, with implications for study design in low prevalence diseases eg WAD (106/100,000 population) (Motor Accident Authority, 2015). Results can be obtained more quickly, and, because every patient receives treatment, patients will not receive only placebo. This makes SCEDs more attractive to patients than standard RCTs.

Conservative physiotherapy is recommended in management guidelines for chronic whiplash (TRACsa, 2008), but evidence is lacking regarding its effectiveness in different sub-groups of patients. This evidence gap is of concern, particularly as recent trials demonstrate lack of effectiveness of such interventions at the group level in this heterogeneous condition (Jull et al., 2007; Lamb et al., 2012; Michaleff et al., 2014; Stewart et al., 2007). Heterogeneous conditions are particularly suited to SCEDs because of their individual focus.

We will assess effectiveness of conservative multimodal physiotherapy for chronic WAD, using patients as their own control, in a multiple baseline design. All patients will receive an advice/exercise booklet, then a variable length baseline followed by a standardized and previously published evidence-based conservative multimodal physiotherapy treatment fulfilling clinical practice guidelines (Ritchie et al., 2015b). Main outcome measures will be plotted against time and visually examined for: (1) level; (2) trend; (3) variability; (4) immediacy of the effect; (5) overlap; and (6) consistency of data patterns in similar phases.

**AIMS**

The **primary aim** of this study is to conduct a series of SCEDs comparing the effectiveness of conservative multimodal physiotherapy in reducing daily neck pain and improving self-efficacy whilst performing daily activities in chronic whiplash-associated disorders for individuals with and without PTSS.

**Secondary clinical aims** are to:

1. compare the effectiveness of conservative multimodal physiotherapy in decreasing neck disability and improving psychological function (including depression and anxiety) at the end of the proposed intervention, and at 4 weeks follow-up in individuals with chronic WAD with or without PTSS.
2. compare the impact of multimodal conservative physiotherapy on health-related quality of life, at the completion of the conservative multimodal physiotherapy intervention, and at 4 weeks follow- up in individuals with chronic WAD with or without PTSS.

**Secondary feasibility aims** are to:

1. To evaluate feasibility by documenting rates of:
   1. Recruitment (number of patients approached, number eligible to participate, number consenting to participate)
   2. Missing data and participant attrition
2. To test recruitment strategies and develop a model for recruitment to a full trial
3. To identify relevant factors that could create barriers to subsequent study completion, and develop strategies to overcome these
4. To assess the potential effectiveness of conservative multimodal physiotherapy in reducing daily neck pain and improving self-efficacy for patients with chronic WAD to determine the adequate sample size for a full trial
5. To obtain feedback from patients on their experience with the trial and areas for improvement to inform a full-scale trial.

This study will provide much-needed evidence on conservative multimodal physiotherapy in different sub-groups of patients with chronic WAD. If SCEDs are feasible in this situation, they may be useful for other treatments for chronic WAD and other sub-groups of chronic conditions.

**1.0 BACKGROUND**

Whiplash associated disorders (WAD) are an enormous and costly burden to Australian society. Up to 50% of people who experience a whiplash injury will never fully recover (Carroll et al., 2008). Whiplash is resistant to treatment and no conservative management approach has yet been shown to reduce chronic pain (Teasell et al., 2010), although it is suggested that this may be due to the heterogeneity of the condition. It is now a priority to assess the effectiveness of interventions in specific sub-groups to evaluate whether variable responses to conservative treatment exist, which will allow appropriate tailoring of future treatment.

***Whiplash is a common, costly and disabling condition***

Persistent pain and disability following whiplash injury as a consequence of a road traffic crash (RTC) is common and incurs substantial personal and economic costs. Whiplash injury accounts for the vast majority (85%) of *any* submitted claims as well as the greatest incurred costs in the Queensland compulsory third party scheme (Motor Accident Insurance Commission, 2015). In Queensland the economic costs related to whiplash injury are substantial and exceeded $1.8 billion from 2003-2012 ( Motor Accident Insurance Commission, 2015). In Australia, whiplash injuries comprise ~75% of all survivable RTC injuries with total costs of more than $950 M per annum (Motor Accident Insurance Commission, 2015). Up to 50% of people who experience a whiplash injury will never fully recover and up to 30% will remain moderately to severely disabled by their condition (Carroll et al., 2008).

***Current treatment for chronic whiplash is not effective***

Following whiplash injury most recovery, if it occurs, takes place in the first 2-3 months after which time recovery plateaus (Sterling et al., 2010). Although current clinical guidelines recommend exercise and the maintenance of activity for chronic whiplash (TRACsa, 2008), it is evident from the existing literature that this approach is not working. Although it is evident (through the 95% confidence intervals) that some individuals within randomised controlled trials receive significant benefit from these interventions, systematic reviews, where results are averaged, conclude that exercise/activity based interventions provide only small effects (Southerst et al., 2014; Teasell et al., 2010).

Conservative multimodal physiotherapy consists of individualized pragmatic manual and exercise therapy directed towards the participants' specific physical impairments. As evident from the existing literature, prescribed exercise, activity and other conservative therapy can provide marginal benefit, yet these interventions have failed to significantly improve the overall health outcomes of the chronic WAD population. Thus it is abundantly clear that current treatments are not universally successful for chronic WAD. This condition continues to exist with a high chronicity rate incurring enormous costs to Australian society. Those who do not recover suffer poor physical and mental health, yet this remains largely unrecognized. New research directions are urgently required.

***Factors associated with chronic pain and disability***

Over the last decade, we have studied extensively, the clinical pathway and prognosis of whiplash injury (Sterling, 2010; Sterling et al., 2010, 2011; Sterling et al., 2005).One reason for the modest effects of current interventions may be that WAD is a heterogeneous condition. A focus of our research over recent years has been to identify factors and processes underlying the transition to chronicity. In a Phase 1 study, we identified the factors of initial levels of pain, symptoms of posttraumatic stress (eg hyperarousal), age and hyperalgesia as significant predictors of poor functional recovery at both medium and long term follow-up (Sterling et al., 2006; Sterling et al., 2005). We have shown that the same factors also predict poor mental health outcomes (Sterling et al., 2011). In a recent Phase 3 study, we externally validated this prognostic set in a large independent multicentre international cohort (Sterling et al., 2012) and have recently developed and validated a clinical prediction rule (CPR) based on this prognostic research (Ritchie et al., 2015a; Ritchie et al., 2013). There is also evidence to indicate that stress related responses are not only predictive but are actually causally related to poor recovery. Importantly, as far as rehabilitation is concerned, our recent work has shown that stress responses mediate the relationship between initial pain and later muscle/motor changes (Elliott et al., 2011) and that there is simultaneous development of PTSD and disability trajectories (Sterling et al., 2011). Additionally, Jenewein et al have demonstrated using structural equation models that PTSD symptoms appear to play a causal role in the development and/or maintenance of persistent pain in accident survivors (Jenewein et al., 2009). Thus, it is highly possible that the presence of post-traumatic stress symptoms influences the response to conservative physiotherapy.

The obvious question that arises from this work is whether the response to conservative physiotherapy is influenced by post-traumatic stress symptoms, resulting in poorer health outcomes for people with both chronic WAD and PTSD. There have been no studies to answer this question.

***Single Case Experimental Designs (SCEDs)***

The single subject design includes within-subject methods, repeated measures designs, and intra-subject replication designs. Within-subjects methods are advantageous where the sample being investigated is frequently heterogeneous or when there are only few eligible subjects available (Romeiser Logan et al., 2008). In the [ranking system](https://en.wikipedia.org/wiki/Ranking_system) of [evidence-based practice](https://en.wikipedia.org/wiki/Evidence-based_practice), randomised single subject study designs are ranked as Level I Evidence by the Oxford Centre for Evidence Based Medicine, yielding evidence of an equivalent strength to randomized controlled trials (OCEBM Levels of Evidence Working Group - Howick, 2011; Romeiser Logan et al., 2008).

The ***Single Case Experimental Design (SCED)*** provides a method to determine response and benefit for every individual patient. This approach can help patients move more quickly through a treatment pathway – e.g. if a patient is a non-responder, then an alternative could be trialled earlier, and the patient would not be subject to a treatment that does not work for them. After each individual trial, patients discuss their results with their physiotherapist based on an individual report provided by trial research staff. Thus the trial will provide direct and immediate feedback to individual patients and their physiotherapist about the effectiveness of conservative physiotherapy. Additionally, single cases can be aggregated to arrive at a group effect. Aggregated data can also be compared between groups.

Aggregation (or meta-analysis) of SCEDs can efficiently produce a group estimate of effect. One approach for meta-analysing the results of single-cases is the use of hierarchical linear models. This allows both better inferences about the effects for individual cases to be made, and the overall effect to be estimated. They can also explore the generalizability of the effect across cases and under different conditions (Van den Noortgate & Onghena, 2007). This has implications for study design in low prevalence diseases such as WAD, which has a prevalence of 106 per 100,000 population (Motor Accident Authority, 2015).

Although SCEDs have been widely applied in the psychology, special education and rehabilitation literature, they have not had that same application in physiotherapy. Due to the average effect reported by most RCTs that does not necessarily apply to individuals, there are calls for more SCEDs in physiotherapy (Moeyaert et al., 2017; Van den Noortgate & Onghena, 2007). SCEDs have not been previously used in chronic WAD trials.

**1.1 Aims and objectives**

The **primary aim** of this study is to conduct a series of SCEDs comparing the effectiveness of conservative multimodal physiotherapy (individualized pragmatic manual and exercise therapy directed towards the participants' specific physical impairments) in reducing daily neck pain and improving self-efficacy whilst performing daily activities in chronic WAD, in 3 individuals with PTSS, and 3 individuals without PTSS.

**Secondary clinical aims** are:

1. To compare the effectiveness of conservative multimodal physiotherapy in decreasing neck disability and improving psychological function (including depression and anxiety) at the end of the proposed intervention, and after 4 weeks follow-up in individuals with chronic WAD with or without PTSS.
2. To compare the impact of multimodal conservative physiotherapy on health-related quality of life, at the completion of the conservative multimodal physiotherapy intervention, and at 4 weeks follow- up in individuals with chronic WAD with or without PTSS.

**Secondary feasibility aims** are:

1. To evaluate feasibility by documenting rates of:
   1. Recruitment (number of patients approached, number eligible to participate, number consenting to participate)
   2. Missing data and participant attrition
2. To test recruitment strategies and develop a model for recruitment to a full trial
3. To identify relevant factors that could create barriers to subsequent study completion, and develop strategies to overcome these
4. To assess the potential effectiveness of conservative multimodal physiotherapy in reducing daily neck pain and improving self-efficacy for patients with chronic WAD to determine the adequate sample size for a full trial
5. To obtain feedback from patients on their experience with the trial and areas for improvement to inform a full-scale trial.

**1.2 Hypotheses**

The **hypotheses** are that, in people with chronic WAD:

1. Multimodal conservative physiotherapy when performed in individuals without PTSS will be more effective in reducing daily neck pain intensity and improving self-efficacy whilst performing daily activities when compared to individuals with PTSS, both immediately after, and 4 weeks following completion of the intervention.
2. Multimodal conservative physiotherapy when performed in individuals without PTSS will be more effective in reducing neck pain-related disability, psychological function (including depression and anxiety) and improving health-related quality of life compared to individuals with PTSS, both immediately after, and 4 weeks following completion of the intervention.
3. SCEDs will be feasible, useful and acceptable in this context.

**2.0 METHODS**

**2.1 Overview of study design**

The study will be a series of multiple baseline SCEDs in chronic WAD comparing the effect of *conservative multimodal physiotherapy in individuals with and those without PTSS*. The efficacy of the intervention will be evaluated using a multiple-baseline design (MBD) across participants. In MBDs several tiers of the dependent variable are measured simultaneously, and the intervention is introduced across the tiers in a staggered sequence. Thus, at different stages of the study some tiers will be in the baseline (A) phase and others will be in the intervention (B) phase (see Figure 1 which illustrates this with simulated data).

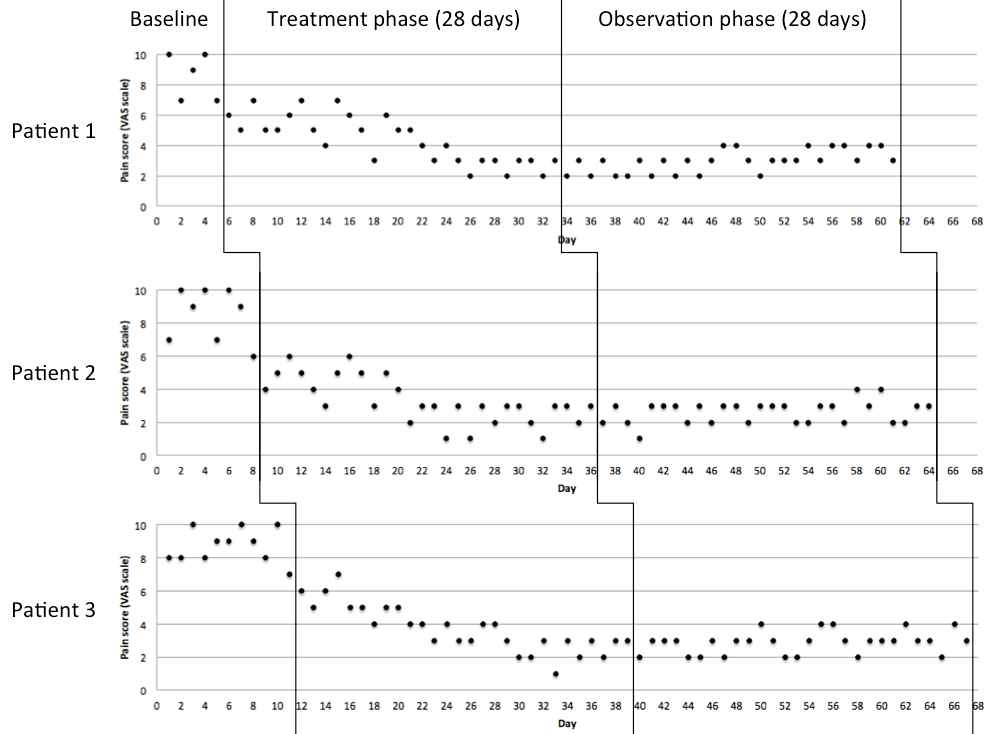
This study will utilise an A1-B-A2 design to measure the effectiveness of a standard multimodal conservative physiotherapy intervention across the three phases: a baseline phase (A1 no intervention); intervention phase (B); and a no intervention phase (A2 follow up). The onset of the intervention start point will be randomly allocated. Intervention will commence a minimum of 3 months post-whiplash injury.

In the context of sample size and sampling frequency, the study design will be based on single-subject research design guidelines (Romeiser Logan et al., 2008). In order to evaluate the efficacy of the intervention, it is recommend that a minimum of three participants and five data collection points in each phase are included in the study design (Romeiser Logan et al., 2008). The trial will be registered on the Australian and New Zealand Clinical Trials Registry. The study will be conducted and reported as per the Single Case Reporting Guidelines In Behavioural Interventions (SCRIBE) 2016 Statement (Tate et al., 2016).

**2.2 Design**

This will be a single case with randomized multiple baseline experimental design with simultaneous enrolment of 3 patients with PTSS, and 3 patients without PTSS. There will be a variable length baseline (A1) and then a randomly allocated staggered start to provide internal validity – one patient starting at 5 days, one at 8 and one at 11 days. This study will utilise an A1-B-A2 design: a baseline phase (A1 no intervention), intervention phase (B) and a no intervention phase (A2 follow up). Primary outcome measures will be collected daily during this time period. The baseline phase (A1) will be followed by a 4-week intervention period (B). Participants will have 8 one hour sessions over a 4-week period. The intervention will be delivered by an honours student physiotherapist, supervised by an experienced physiotherapist. During the intervention period, the daily collection of the primary outcome measures will coincide with the delivery of each intervention session twice per week. The intervention phase will be followed by a 4 week follow-up phase (A2) where participants will have no contact with the intervention personnel. This follow-up phase is implemented in order to determine the possible duration of improvement post intervention. Primary and secondary outcome measures will be collected at the completion of this 4 week follow-up period.

**Fig 1**: Stimulated data demonstrating a multiple baseline design across three different participants



**2.3 Setting**

Community patients recruited via RECOVER Injury Research Centre database, Facebook/social media/online and through any other appropriate sources, eg referred by GPs or physiotherapists.

**2.4 Eligibility criteria**

***Inclusion criteria*:**

* Individuals with Grade II Whiplash Associated Disorder
* > 12 weeks since injury
* Aged 35 -65 years
* Neck pain on numerical pain rating scale >= 5/10
* Neck Disability Index at start of trial > 32%
* Three individuals with moderate post-traumatic stress symptoms (revised Impact of Events Scale score > 24) and 3 individuals with minimal or no PTSS (r-IES < 20).

***Exclusion criteria:***

* Presence of dizziness symptoms
* Known or suspected serious spinal pathology (e.g. metastatic disease of the spine);
* Confirmed fracture or dislocation at time of injury (i.e., WAD Grade IV)
* Nerve root compromise (i.e., WAD Grade III)
* Spinal surgery in the past 12 months; and
* Score of 10 or more on the Patient Health Questionnaire (PHQ-9)
* Not fluent in English.

**2.5 Study Measurements**

The following outcome measures will be assessed at baseline and at follow-up times after baseline randomization. Every attempt (within ethical guidelines) will be made to obtain outcome data, regardless of subject’s compliance with trial protocols. See study schedule below.

**2.6 Study schedule**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Protocol Activity** | **Baseline** | **At the end of week 2 of treatment** | **End of Treatment (end of week 4)** | **End of week 4 post-treatment completion**  **(F/U)** |
| Clinic | Phone/Clinic | Phone/Clinic | Phone/post/online |
| Informed consent | X |  |  |  |
| Screening | X |  |  |  |
| Demographics | X |  |  |  |
| Clinical Assessment | X |  |  |  |
| Randomise | X |  |  |  |
| Expectations of treatment effect | X |  |  |  |
| **Daily** |  |  |  |  |
| NRS (pain) average over last 24 hours | X | X | X | X |
| General self-efficacy | X | X | X | X |
| **Secondary outcomes** |  |  |  |  |
| NDI | X | X | X | X |
| DASS-21 | X | X | X | X |
| EQ-5D-5L | X | X | X | X |
| PCS | X | X | X | X |
| 3 Patient Specific questions from Self Efficacy Questionnaire | X | X | X | X |
| Global Impression of Change |  | X | X | X |
| Concomitant medications | X | X | X | X |
| Adverse events |  | X | X | X |

**2.7Outcomes**

**Primary outcomes**

1. Neck pain intensity at trial completion, and at 4 week follow-up. Neck pain intensity will be measured on the VAS scale of 0 to 10, and will represent the patient’s self-report of average pain intensity during last 24 hours (Williamson et al, 2005; Michaleff et al, 2014).
2. Self-efficacy whilst performing daily activities in chronic WAD. This question will ask participants to identify “how confident are you in your ability to perform your daily tasks in the presence of your neck pain or disability?” with 1 *indicating not at all confident*, 2 a *little confident,* 3 *moderately confident*, 4 *very confident* and 5 *extremely confident* (adapted from[Nicholas 2007)](https://www.ncbi.nlm.nih.gov/pubmed/?term=Nicholas%20MK%5BAuthor%5D&cauthor=true&cauthor_uid=16446108).

**Secondary Outcomes**

#### All secondary outcome measures will be collected at the commencement of the baseline data collection period; at the end of week 2 and 4 during the intervention period; and at the end of the follow up period; totaling 4 sampling points during the study protocol. All secondary outcome measures will be delivered using an online survey medium. It is anticipated that the surveys will take no longer than 20 minutes to complete in total. Surveys will be administered and completion monitored by physiotherapy honours students. The following will be collected:

1. Neck Disability Index (NDI) (Vernon & Mior, 1991)
2. Patient global impression of change (-3 to +3 scale) (Hurst & Bolton, 2004)
3. [Depression & Anxiety Stress Scales](http://www.psy.unsw.edu.au/research/research-tools/depression-anxiety-stress-scales-dass) (DASS-21) (Lovibond & Lovibond, 1995)
4. The Pain Catastrophizing Scale (PCS) (Sullivan et al., 1995)
5. Generic measure of health status (EQ-5D-5L) (Herdmann et al, 2011)
6. 3 patient-specific questions from self-efficacy questionnaire (Nicholas 2007), individualised per patient (see Appendix One).

**2.8 Trial Procedure**

***Recruitment***

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| Individuals with chronic WAD who have previously contacted Recover Injury Research Centre, Brisbane, and expressed interest in participating in experimental studies will be contacted by telephone and prescreened for eligibility for the study. Individuals who are potentially eligible and interested will be provided with information regarding the study and invited to participate. |

If interested, patients will be screened for all inclusion/exclusion criteria over the phone. Initial Neck Disability Index (NDI) needs to be greater than 32%. Current VAS pain rating of 5/10 or greater and a PHQ-9 score below 10 is also required. These scales can be completed online. If volunteers are eligible, they will be invited to the trial clinic to complete informed consent documentation and ensure their history and screening results are clear for entry to the study. Treatment will be delivered at The University of Queensland, Centre for Clinical Research, Herston by physiotherapy honors students supervised by an experienced physiotherapist.

***Baseline***

Questionnaires will be completed on personal characteristics and baseline measures:

1. Neck pain intensity (VAS average over last 24 hours)

1. Patient expectations of a beneficial treatment effect, scored from 1 to 5 with higher scores indicating higher expectations
2. Depression, Anxiety and Stress Scale (DASS-21)
3. The Pain Catastrophizing Scale (PCS)
4. Generic measure of health status scores (EQ-5D-5L)
5. 3 patient - specific questions from self-efficacy questionnaire (SEQ)
6. Patient Health Questionnaire (PHQ-9)

***Trial phase***

During the trial, all participants will be required to maintain symptom diaries in which they will record information such as pain scores, self-efficacy scores, and other treatments and medication taken, if any. During the trial, the trial physiotherapists (PT) will evaluate the patients via weekly re-examination to check for pain and any adverse effects. Patients will be asked about progress, and any queries, and will also be able to contact trial staff if they have questions regarding the treatment or any side effects.

***Post-trial and follow-up***

At the completion of physiotherapy treatment, patients will repeat all primary and secondary outcome measures. Trial staff will produce a report that provides feedback on the impact of the physiotherapy treatment on their symptoms. Patients will visit the PT to receive their results. 4 weeks after the completion of the treatment, patients will repeat all primary and secondary outcome measures. After this, they will complete an exit questionnaire that requests information about their experience in the trial and their perceptions of its usefulness to them.

**2.9 Interventions**

***Advice booklet***

All patients will be provided with an advice booklet *Whiplash Injury Recovery: A Self Help Guide (2nd edition),* co-authored by Prof Sterling and published by the Motor Accident Insurance Commission (MAIC), Qld. It provides information about whiplash, assurance about prognosis and advice to stay active and resume working; as well as information on correct posture, with pictorial descriptions of specific neck and upper limbs exercises and information on resuming functional daily activities. This second edition of the booklet was written based on consumer and health care professional feedback via focus groups. The booklet is based on the recommendations of the current Australian Guidelines for Whiplash Management (TRACsa, 2008).

***Conservative Multimodal Physiotherapy***

The 4-week exercise program will be carried out by the honors students under the supervision of the experienced physiotherapist (2 sessions per week). The exercise program will comprise specific exercises to improve the movement and control of the neck and shoulder girdle. Exercises will be tailored by the physiotherapist for each individual participant. The exercises will be of a low load nature and designed to be pain free. At the same time, the physiotherapist will guide the participant’s return to normal activities. The program begins with a clinical examination of the cervical and axio-scapular-girdle muscles and includes tests that assess an individual’s ability to recruit the muscles in a coordinated manner, and tests of muscle endurance at low levels of maximum voluntary contraction. The specific impairments identified are then addressed with an exercise program that is supervised and progressed by the physiotherapist. This specific treatment program as described in Jull et al (2008) focuses on activating and improving the coordination and endurance capacity of neck flexor, extensor and scapular muscles in specific exercises and functional tasks, and a graded program directed to the postural control system including exercises for balance, head relocation and eye movement control. Participants will also perform the exercises at home, once per day. Written and illustrated exercise instructions will be provided. A log book will be completed by participants to record compliance with the exercises. The exercise program follows the current Australian guidelines for the management of chronic whiplash (TRACsa, 2008).

*Physiotherapists providing the intervention and control*

Physiotherapy honours students who successfully complete a face-to-face, trial specific training workshop run by Prof Michele Sterling (MS) will provide the therapeutic interventions for this study. They will be supervised by a physiotherapist experienced in the management of whiplash injured individuals. The physiotherapy exercise sessions will be audited twice per honours student/physiotherapist (face to face by MS) to check for adherence to the exercise protocol.

**2.10 Co-interventions**

Participants who experience high levels of continuing or worsening pain will be able to contact research staff to return for an earlier review with the PT. Medication (paracetamol or NSAIDs) can be recommended consistent with current clinical practice guidelines for WAD management. The criteria for recommending medication will be based on worsening pain that is debilitating in nature (in the short term) or continuing high levels of pain that have not improved after the first week of treatment.

At the end of the trial, in respect of the compensable nature of a whiplash injury, the patients will be permitted to seek further treatment if required. Information about any additional treatments sought by participants (eg additional medication, physiotherapy etc.) will be obtained via patient diaries at the follow-up time points.

**2.11 Adverse Events**

Although adverse events are not anticipated, mild exacerbation of symptoms may occur with treatment. Manual [therapy](https://www.ncbi.nlm.nih.gov/pubmedhealth/PMHT0022340) can sometimes have side effects such as sore neck [muscles](https://www.ncbi.nlm.nih.gov/pubmedhealth/PMHT0022447) and temporary stiff or painful neck. In addition to weekly open-ended questioning, at the end of the trial phase, information about adverse effects of treatment will be sought from all participants using open-ended questioning. Practitioners will be requested to report any significant adverse event to Prof Michele Sterling. If this does occur, the usual ethics committee requirements for reporting of adverse effects will be followed. Those with elevated symptoms (from the iES-R) at baseline that remain elevated at the study's completion (after the intervention) will be referred to their GP.

**2.12 Data management and integrity**

A regulatory approved electronic data capture system (Redcap) with web hosting facility will be used to collect all clinical and safety data for this proposed study, following Good Clinical Practice (GCP) standards. All database development and management activities, and the management of baseline randomisation for the study will be the responsibility of the investigative team. Standard operating procedures are in place to conduct these activities to GCP standard. The integrity of trial data will be monitored by regularly scrutinising the data for omissions and errors.

**2.13 Blinding**

In order to compare patients with and without PTSD, a member of the research team will initially prescreen patients for PTSD symptoms, and the results will not be disclosed to the honors students. The honors students will then continue the prescreening process. This will ensure that the honors students do not know the PTSD status of the patients. They will be randomized in groups of three to commencement of intervention at 5, 8 or 11 days post enrolment. After the end of followup the honors students will be unblinded so that they can analyse the data.

**3.1 Statistical considerations**

***3.1.1* *Statistical approach***

Primary outcome measures will be plotted against time and visually examined for: (1) level; (2) trend; (3) variability; (4) immediacy of the effect; (5) overlap; and (6) consistency of data patterns in similar phases.

The magnitude of change (i.e. effect size) between two phases (e.g. baseline versus intervention (Parker et al., 2009)) will be measured using the improvement rate difference (IRD). IRD is an overlap measure that calculates the difference in ‘‘improvement rates’’ between two phases. For example, to measure a decrease from baseline (A) to intervention phase (B), an ‘‘improved’’ intervention average pain VAS score at the end of active treatment is lower than most or all of the baseline data points (by 1.5 VAS points). Parker et al. provided guidelines for interpretation of IRD scores, which were established based on their evaluation of 166 single case data sets comparing IRD results with visual analyses. They suggest that IRD of 0.50 or lower implies small or no effects, scores between about 0.50 and 0.70 indicate moderate effects, and scores of about 0.70 or 0.75 or higher indicate large or very large intervention effects. Parker et al. (2009) provide a detailed description of and the method of calculating IRD. A significant difference between the averaged IRD for each category (with or without PTSS) will be defined as lack of overlap in the confidence intervals for the two categories.

Next, the data from each active treatment phase of the SCEDs will be aggregated using a Bayesian hierarchical model where random effects account for repeated measures (within patients) over time.  Upon developing and estimating an appropriate model including treatment effects and overall participant response against baseline, will be considered as follows for each of the two groups (with and without PTSS): 1) the posterior mean differences in group and individual expected outcomes at the end of the SCED and at 3 months follow up will be evaluated with associated 95% credible intervals, and 2) the posterior probability that the treatment effect is different from zero (in the direction of active treatment over baseline) will be calculated.

***3.1.2* *Study Sample Size***

For this pilot study we will enrol 6 patients. We will commence patients in 2 groups of three (n=3 with PTSS and n=3 without PTSS) with randomised staggered starts ie different lengths of baseline (5, 8 and 11 days), to increase external validity (Tate and Perdices, 2015).

***3.1.3* *Time Line***

Study protocol/ethics/set up Jan-April 2018; commence recruitment May 2018, complete all follow-ups by Sept 2018, analysis and manuscript preparation by Dec 2018.

***3.1.4* *Feasibility of the Study***

1. Recruitment is very achievable. We have conducted multiple studies by recruiting through the Recover database of interested patients.
2. We have assembled a research team with the experience and expertise to successfully undertake this trial.
3. CI Sterling has been internationally instrumental in conducting the extensive foundation research of whiplash injury that has led to the undertaking of this trial.

***3.1.5* *Outcomes and significance***

*Outcomes and significance*

The evidence gap on treatment in different whiplash sub-groups is of concern. This trial will assess the effectiveness of interventions used commonly and recommended by clinical guidelines in discretely defined whiplash populations (with or without PTSS) to establish evidence for their use in these respective sub-groups. The intervention will be assessed using an innovative clinical tool, SCEDs. The identification of responders to conservative multimodal physiotherapy in this costly and treatment resistant condition would be of benefit. If treatment is shown to be more effective in the group without PTSS, the study will provide evidence for conservative multimodal physiotherapy to be targeted to specific subpopulations of patients with chronic WAD (those without PTSS).

Also, if SCEDs are feasible to use in this situation, there are implications for trial design in a range of other chronic whiplash sub-groups, other chronic conditions (including low prevalence conditions) and for a range of other treatments. We anticipate that this trial may ultimately better target the therapeutic options available to clinicians, whiplash sufferers and their families.

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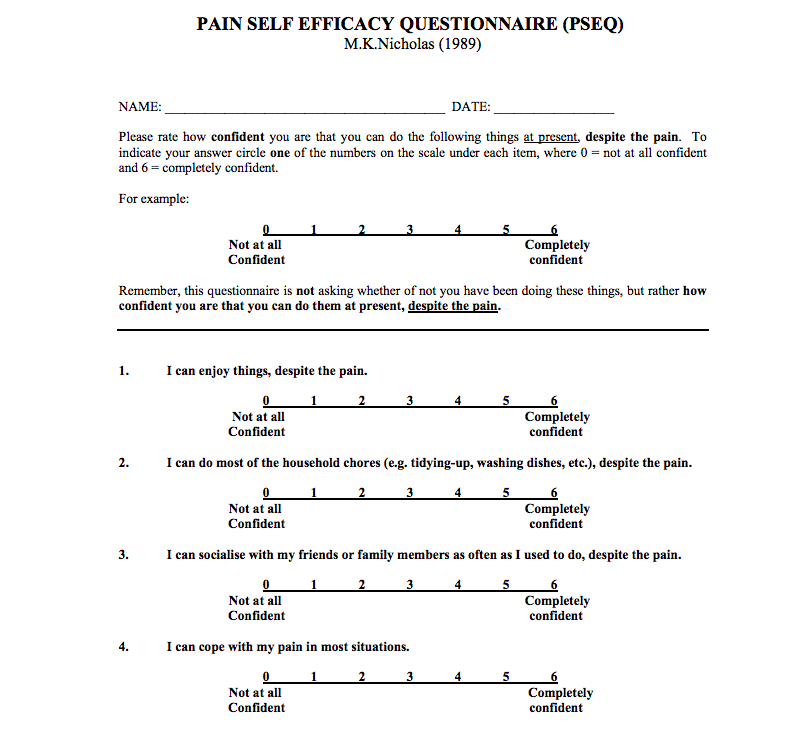
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**APPENDIX 1**

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