**TARGETING PRO-NOCICEPTIVE MECHANISMS TO PREVENT CHRONIC PAIN AFTER WHIPLASH INJURY – A RANDOMISED CONTROLLED TRIAL**

CONFIDENTIAL

**Study Protocol**

V8.0

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## Protocol Signature Page

**Protocol Title:** Targeting pro-nociceptive mechanisms to prevent chronic pain after whiplash injury – a randomised control trial

**Short Title:** Pregabalin for Whiplash

**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 Practice65 (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 product pregabalin) 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 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.

**Investigator Signatory**:

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| --- | --- |
| PRINCIPAL INVESTIGATOR NAME:SITE NAME: | SIGNATURE:DATE: |

**Sponsor Signatory**:

|  |  |
| --- | --- |
| The University of QueenslandRECOVER INJURY RESEARCH CENTREProfessor Michelle Sterling Coordinating Principal Investigator | SIGNATURE:DATE:  |

**Pregabalin for Acute Whiplash Summary Sheet**

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| --- |
| **Name of Sponsor:**The University of Queensland |
| **Title of Study:**Targeting pro-nociceptive mechanisms to prevent chronic pain after whiplash injury –a randomised controlled trial |
| **Principal Investigator:**Professor Michele Sterling, RECOVER Injury Research Centre, The University of Queensland, Australia. |
| **Study Sites:**The study will recruit participants from the EDs of hospitals at Gold Coast and regional areas of Queensland eg Ipswich Hospital. Patients who present when there is no trial staff will also be recruited as soon as practical through the Griffith Health and Medical Service at Gold Coast or Limestone Medical Centre, Ipswich.. |
| **Study Period (years):** June 2016 to June 2019. | **Phase of Development:** Phase III | **Duration:** 3 year |
| **Objectives:**The primary aim of this study is to conduct a randomised controlled trial examining the effectiveness of pregabalin to prevent chronic pain following whiplash injury in ‘at-risk’ individuals. Secondary aims are to: 1) Investigate the effectiveness of pregabalin to decrease disability, depression, posttraumatic stress symptoms, pain catastrophizing and measures of pro-nociception and2) To conduct an economic evaluation of the pregabalin intervention.  |
| **Methodology:**The study will be a randomised double blind, pilot placebo-controlled parallel design trial comparing *pregabalin 600 mg and advice* (intervention) vs *placebo and advice* (control) for patients with acute whiplash injury. Results of the intervention will be supplemented by an economic evaluation of the direct and indirect costs incurred by the pregabalin + advice participants and those receiving placebo + advice. Intervention will commence as soon as possible but within 48 hours of injury and continue for 5 weeks. Participants will be recruited from the Emergency Department of the Gold Coast Health Service District (Gold Coast University Hospital and Robina Hospital) and other Hospitals (Ipswich). Patients who present when there are no trial staff will also be recruited as soon as practical through the Griffith Health and Medical Service or Limestone Medical Centre, Ipswich. |
| **Planned number of participants:**30 participants (15/group)  |
| **Diagnosis and main criteria for inclusion:**Individuals with Grade II Whiplash Associated Disorder Within 48 hours of injury. Experiencing at least moderate pain at first measurement; Ambulance or arrival in ED (VAS: ≥ 5/10). Age 18-65 years |
| **Duration of follow-up:**One year |
| **Statistical methods:**All analyses will be conducted on an intention to treat basis and by a statistician blinded to group allocation. The primary outcome of neck pain intensity at 3 months from baseline will be compared between the treatment groups using standard analysis of variance technique, and the 95% confidence intervals of differences between the groups will be presented. |

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# Ethics and Confidentiality

The **Pregabalin for Acute Whiplash Trial** will be/has been approved by The University of Queensland and Gold Coast University Hospital Human Research Ethics Committee. Written informed consent complying with the ethical standards of University of Queensland will be obtained from each of the participants prior to their inclusion in the study. The study will not commence in any centre until all of the necessary documentation has been completed.

Any modifications to the Protocol, Participant Information Sheet or Consent Form will be submitted to the Ethics Committee for approval. Modifications will only be implemented once ethical approval has been obtained, unless an amendment is required to address immediate hazard to participants.

Prior to obtaining consent, research staff will inform potential participants of the purposes, methods, possible risks and benefits of participating in the study. All potential participants will have the opportunity to discuss the trial with study staff and their physician. The participant and the delegated doctor obtaining the informed consent will sign and date the consent form, a copy of which will be retained by the participant while the original will be stored in the participant’s case record folder. Doctors trained in the protocol will be delegated the authority to consent participants.  Participation in the study will be voluntary and any participant may withdraw from the study at any time without prejudice to their current or future medical management. In the event that a participant wishes to withdraw, they will be required to contact study staff and notify them of their decision.

All data gathered in this study will remain strictly confidential and no report will contain any information that would allow individual participants to be identified. In order to facilitate complete data collection and follow-up, individual contact details will be collected at registration and secured in locked filing cabinets with limited access. These details will be stored separately from other data. Participant records will be identified by initials and their unique randomisation number.

# Administrative structure

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

The study will be coordinated from Brisbane and conducted in Brisbane and other sites within Queensland.

**INVESTIGATIVE TEAM**

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# Introduction

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 recover1. Whiplash is resistant to treatment and no early management approach has yet been shown to prevent chronic pain2. Our research has clearly shown that the early presence of central sensitization3,4 is associated with poor recovery. WAD is the only musculoskeletal condition where the development of central sensitization prospectively from the time of injury has been extensively studied. As a result of this research, we are now in an unparalleled position to explore novel interventions to prevent the development of chronic pain and disability following injury by targeting these central processes.

Pregabalin, an anti-epileptic drug, reduces the excitability of the dorsal horn neurones after tissue damage thus blocking the development of pronociceptive mechanisms. Recent systematic reviews conclude that pregablin shows promise in *preventing* the transition from acute to chronic pain post-surgery5,6. Pregabalin’s effects on central sensitization also indicate great potential to prevent or modulate these processes after whiplash injury and improve health outcomes but this has not been investigated.

## 3.1 Background

***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 Qld compulsory third party scheme1. In Qld the economic costs related to whiplash injury are substantial and exceeded $1.8 billion from 2003-20121. In New South Wales in the period 1989-1998 there were 50,000 whiplash claims costing ~$1.5billion7 *In Australia, whiplash injuries comprise ~75% of all survivable RTC injuries1 with total costs of more than $950 M per annum7 exceeding costs for both spinal cord and traumatic brain injury*1*.*

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 condition8.

***Current treatment for acute 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. This indicates that the manner in which the whiplash-injured patient is managed in the early stages will be crucial to better recovery, yet early management has received comparatively scant attention. Although current clinical guidelines recommend exercise and the maintenance of activity for acute whiplash9 it is evident from the existing literature that this approach is not working. Systematic reviews conclude that exercise/activity based interventions provide only small effects10,2. Additionally, we have shown that early multidisciplinary management (mainly physiotherapy and psychology) is no more effective than usual care11.

As evident from the existing literature, prescribed exercise, activity and other non-pharmacological therapy can provide marginal benefit, yet these interventions have failed to significantly improve the overall health outcomes of people following whiplash injury.

Thus it is abundantly clear that current treatments do not work for acute whiplash. This condition continues to exist with a high chronicity rate incurring enormous costs to the Australian society. Those who do not recover suffer poor physical and mental health, yet this remains largely unrecognized. New clinical/research directions are urgently required.

***Factors associated with the transition to chronic pain and disability***

Over the last decade, we have studied extensively, the clinical pathway and prognosis of whiplash injury3, 12-14. Our research as well as that of others clearly shows that the strongest predictor of poor recovery is higher initial levels of pain with this factor being identified in all systematic reviews of whiplash prognosis 15. We have gone further and quantified the levels of pain with two of our prognostic validation studies showing that initial pain levels of 5.2 to 5.5/10 and greater can accurately predict poor functional recovery3, 16. *We will use this factor as an inclusion criterion to identify those at risk of poor recovery.*

Additionally the early presence of pro-nociceptive mechanisms (central sensitization reflected as hyperalgesia, allodynia and facilitated spinal withdrawal reflexes) is associated with poor recovery. In four independent cohort studies, we have shown that early cold hyperalgesia predicts persistent pain and disability post injury3,4,13,14 as well as poor mental health outcomes3. The work of other research groups supports our findings where both cold and widespread mechanical hyperalgesia have been shown to predict poor functional recovery17. These hyperalgesic responses are found both local to (over the neck) and away from (upper and lower limbs) the site of injury. This consistent evidence that patients with pain after whiplash injury display pain hypersensitivity with sensory stimulation of healthy tissues is indicative of augmented central pain processing. We have also shown that early spinal cord hyperexcitability (via nociceptive withdrawal reflexes) that does not accommodate within a few weeks is also associated with chronic moderate to severe pain and disability 12 months post injury18. These phenomena of hyperalgesia and spinal cord hyperexcitability represent the presence of pro-nociception and are important as they provide an understanding of potential mechanisms underlying the development of chronic pain after injury, **mechanisms that present as potential treatment targets.**

Pro-nociception is not a feature of individuals with whiplash who report lesser symptoms in the acute stage and have good or fair recovery4 Likewise it is not present in less severe neck pain conditions such as non-traumatic postural neck pain19,20.

We have also shown that individuals with these pro-nociceptive features do not respond to physical rehabilitation approaches21. In this randomized controlled trial of a 10 week physiotherapy program (exercise and manual therapy) for chronic whiplash, there was no clinically relevant change in either pain or disability. Nor was there any change in sensory disturbances, indicating no effect from the intervention on the underlying pain processes.

However it is important to recognize that pro-nociception is potentially modifiable. In conditions with apparently similar underlying pain processes, for example fibromyalgia, medications which target pro-nociception have been shown to be effective in reducing pain and disability22. But there have been no studies that specifically aim to address the presence of this factor in acute whiplash. This oversight may be one reason for the only small treatment effects seen with currently used physical rehabilitation based interventions.

***We propose that addressing the initial pro-nociception will improve outcomes following whiplash injury***

Pro-nociceptive mechanisms are not unique to whiplash with many *chronic* conditions manifesting these phenomena including arthritis23, temporomandibular joint pain24, and fibromyalgia25 amongst others. There is growing awareness that pro-nociceptive mechanisms should be a treatment target for these already chronic conditions. What is unique about whiplash research is that it is the only musculoskeletal condition where the development of central sensitization prospectively from the time of injury has been studied extensively. As a result of this research, we are now in an unparalleled position to explore novel interventions to prevent the development of chronic pain and disability.

There are many possible interventions that could be investigated for this purpose. As outlined, the mainstay treatment for acute musculoskeletal conditions (physical rehabilitation approaches) does not seem to be effective. The use of medication in the early management of whiplash has been proposed as an urgent research need for several years26, yet very few trials have been undertaken. In a recent systematic review performed by the CIs, only two studies could be found investigating the effects of medication for acute WAD27.One found that the addition of muscle relaxants to ibuprofen was ineffective in the management of acute WAD28 and the second found that botulinum toxin injection was similarly ineffective29. People with whiplash injury are not admitted to hospital and the vast majority are managed in primary care. Therefore medications need to be easily administered, require little monitoring and with few side effects. An obvious medication choice, which fits these criteria and acts to reduce central sensitization is pregabalin.

Pregabalin is a structural analogue of the inhibitory neurotransmitter gamma-aminobutyric acid, but it is not functionally related to it. It binds to the alpha-2-delta subunit of voltage-gated calcium channels, reducing the release of several excitatory neurotransmitters and blocking the development of hyperalgesia and central sensitization30. A recent systematic review has concluded that pregabalin is effective for chronic neuropathic pain conditions such as postherpetic neuralgia and painful diabetic neuropathy as well as for fibromyalgia22. Other studies have shown that pregabalin led to improvements in pain, anxiety, depression, sleep disturbances, general health and disability in patients with chronic lumbar and cervical radiculopathy31 and decreased pain and time off work in people with refractory neck pain32. Pregabalin is approved by the TGA for neuropathic pain and attracts a PBS subsidised benefit.

However more importantly and highly relevant for our proposal is that pregabalin has been shown to prevent the development of chronic pain following acute injury, in the form of surgery. Buvanendran et al33 showed that administration of pregabalin peri-operatively and for 2 weeks postoperatively reduced the incidence of chronic neuropathic pain at 3 and 6 months after total knee arthroplasty, with less opioid consumption and better range of motion during the first 30 days of rehabilitation. Similarly less pain and improved functional outcomes have been demonstrated for pregabalin following spinal surgery34,35. Recent systematic reviews concluded that the use of pregabalin is associated with reductions in chronic postsurgical pain, it is more effective in surgical models associated with pro-nociceptive mechanisms36, and it shows promise in preventing the transition from acute to chronic pain5,6. Furthermore, pregabalin has positive effects on anxiety37 thus having potential to ameliorate symptoms of stress and arousal which are also common after whiplash injury12.

Whilst it could be argued that surgery is ‘different’ to musculoskeletal injury, the pro-nociceptive mechanisms we are aiming to target are the same. Further, there are no studies yet available that investigate effects of pregabalin following injury or trauma. In view of the promising results in surgical populations, there is, on balance sufficient evidence to support the hypothesis that pregabalin used in acute whiplash injury will prevent or modulate pro-nociceptive mechanisms and improve health outcomes for this treatment resistant condition.

In terms of safety, in a recent randomized, double-blind, placebo-controlled trial of pregabalin in patients with sciatica, patients were randomised to either pregabalin  150 mg per day adjusted to a maximum dose of 600 mg per day or matching placebo for up to 8 weeks. A total of 209 patients were randomized; 108 received pregabalin and 101 received placebo.  Treatment with pregabalin did not significantly reduce the intensity of leg pain associated with sciatica, as compared with placebo, over 8 weeks. A total of 227 adverse events were reported in the pregabalin group and 124 in the placebo group (significantly higher in the pregabalin group). Dizziness was more common in the pregabalin group (42%) than in the placebo group (19%); other less common adverse events reported were dorsalgia (19%, 13%), sweating (9%, 8%) and malaise (9%, 3%) in the pregabalin group and placebo group respectively. In addition, 2 serious adverse events were reported out of 106 Pregabalin group patients, an event of hospitalisation due to dyspnea and nausea, and one patient with suicidal ideation; no further information was given about either of these events38. Though this is a different condition, and the pain was both acute and chronic, it is a similar situation to our proposed study, being a community based study of musculosleketal pain.

## 3.2 Potential significance

We propose to establish the effectiveness and cost effectiveness of pregabalin for ‘at risk’ individuals with acute whiplash injury. This project addresses a problem of major importance to human health. Whiplash is an enormous health burden for both Australia and all countries where there are motor vehicles. The most evidence based treatment in the acute injury stage is exercise and activity but these effects are modest at best. The development of chronic pain and disability following ‘minor’ road traffic crash injuries such as whiplash is common and incurs enormous costs to the Australian community. Currently utilised treatments offer only modest benefit and improved outcomes are of great public interest. This trial will establish the effectiveness of an innovative early intervention delivered to ‘high-risk’ individuals in the Emergency Department. The results of the study will have immediate clinical applicability. If successful, this trial will provide an effective and cost-effective intervention for a costly and treatment resistant condition. It will also have implications for the early management of other traumatic conditions beyond whiplash.

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The results of the trial will be published in major journals, influencing policy and practice on how care for whiplash injury is provided at a national and international level.

# Objectives

The **primary aim** of this randomised controlled trial is to examine the effectiveness of pregabalin to prevent chronic pain following whiplash injury in ‘at-risk’ individuals.

**Secondary aims** are to:

1)Investigate the effectiveness of pregabalin to decrease disability, depression, posttraumatic stress symptoms, pain catastrophizing and measures of pro-nociception and

2) To conduct a (health) economic evaluation of the pregabalin intervention.

## 4.1 Hypotheses

The **hypotheses** are that, in people with acute whiplash injury:

1. Pregabalin and evidence-based advice will be more effective than placebo and the same advice in reducing neck pain intensity.
2. Pregabalin and evidence-based advice will be more effective than placebo and the same advice in reducing disability, depression, posttraumatic stress symptoms, pain catastrophizing and pro-nociception.
3. Pregabalin and advice will be cost-effective.

# Study Design

## 5.1 Design overview

This will be a double--blinded randomised, controlled trial of an intervention of 4 weeks active pregabalin or placebo followed by 6 days weaning, with 3, 6 month and 12 month follow-ups. A total of 30 voluntary participants (15/group) with acute whiplash (symptoms <48 hours) will be randomly allocated to receive either pregabalin and advice, or placebo and advice, for 4 weeks followed by a six day weaning process. Outcomes will be measured at baseline and at 5 weeks, 3 months, 6 months and 12 months post-randomisation. The assessors measuring outcomes will be blinded to the treatment group allocation. The overall design is illustrated in Figure 5.1.

## 5.2 Study procedure

ED staff will notify trial research staff of potentially eligible patients (ie those with a pain score ≥5 on first measurement by ambulance or on presentation to ED and cleared of being a WAD IV – fracture or dislocation or a WAD III – neurological compromise). Research staff will then screen the patients for all other inclusion/exclusion criteria and then liaise with the ED doctor to ensure the patient’s history and screening results are clear for entry to the study. Those eligible and who volunteer for the study will then complete informed consent documentation prior to being evaluated on baseline measures (see section 5.8.2 & Table 1) by the research staff. Participants will then be randomly allocated to one of two groups: pregabalin+advice or placebo+advice. See below for more details about these interventions, which will continue for 5 weeks. Outcomes will be assessed at baseline and 5 weeks, 3, 6 and 12 months later.

All participants will be required to maintain diaries in which they will record information such as other treatments and medication taken. On completion of a participant’s final assessment session, they will complete an exit questionnaire that requests information about their experience in the trial and their perceptions of what has transpired, particularly regarding group allocation and concurrent treatment.

Clinicians associated with the ongoing management of study participants will continue to provide care and support that they deem is in the patient’s best interests at all times (National Statement S1.7).

1. We will also contact patients who present to ED after hours when we have no research staff available. Triage nurses in ED will be asked to hand a permission to contact information sheet and consent form to all patients aged 18-65 years who present with neck pain. The consent form will ask for permission to contact them during office hours to explain the trial. Consent will be obtained by the treating nurse or doctor. We will call them as soon as practical after they present to ED and offer them the opportunity to participate in the trial. If they would like to proceed, we will ask them to present to Griffith Health and Medical Service or equivalent in Ipswich (Limestone Medical Centre, Ipswich).
2. Doctors there will obtain informed consent for the trial, screen, and if eligible the doctor will write a trial script and dispense the next kit in a blinded manner. The pregabalin kits will be stored onsite in a locked drug cupboard in the treatment room, where other practice drugs are stored. The scripts will go back to GCUH pharmacy for collation. Participating doctors will be trained in the protocol and sign the training and delegation logs.

## 5.3 Planned outcomes

Outcome measures with established reliability and validity and recommended by the Bone and Joint Decade Neck Pain Task Force39 and the International Whiplash Summit40 have been chosen. The protocol adheres to the IMMPACT recommendations for the design of clinical trials for chronic pain prevention41 and conforms to CONSORT guidelines. It will be registered on the Australian and New Zealand Clinical Trials Registry.

### **5.3.1 Study outcome measures**

Outcomes will be assessed at baseline and 5 weeks, 3, 6 and 12 months later. Outcome data will be obtained from all randomised participants, in so far as this is possible, regardless of compliance with the trial protocol. Outcome measurements will be made by an assessor blinded to allocation.

Table 1 (section 5.9) lists the schedule of assessments. To optimise these follow-ups, they will be done using email links from our Redcap database. If a participant does not have the internet, they will be done by phone and post.. Every attempt (within ethical guidelines) will be made to obtain outcome data, regardless of subject’s compliance with trial protocols.

*Primary Outcome:*

1. Comparison of neck pain intensity at 3 months post randomisation from baseline between the treatment groups. Neck pain intensity is measured on the continuous numeric rating scale (NRS) of 0 to10, and will represent the patients’ self-report of average pain intensity during last 24 hours42-44. The choice of efficacy evaluation at 3-month follow-up is rational from patients’ perspective and this is the most common definition of chronic WAD8.

*Secondary Outcomes:*

1. Comparison neck pain intensity (NRS 24 hours) at 6-and 12-month follow-up from baseline between the treatment groups;
2. Comparison of proportion of patients maintaining or further reducing neck pain at 6- and 12-month follow-up from neck pain intensity observed at 3-month;
3. Neck Disability Index (NDI)45 at 3-, -6 and 12-month from baseline, compared between the treatments;
4. Pain Catastrophising Scale (PCS)46 during follow-up from baseline, compared between treatments;
5. Between treatment differences in Posttraumatic Stress Diagnostic Scale (PDS) symptom score47, measured during follow-up;
6. Between treatment differences in Depression, Anxiety & Stress scale (DASS-21)48, measured during follow-up;
7. Comparison of generic measure of health status scores (SF-12)49 during follow-up between the treatment groups;
8. Comparison of proportion of patients who lodge a compensation claim during follow-up, between the treatment groups.
9. S-LANSS during follow-up from baseline, compared between treatments;

10. Number of doses of breakthrough medication taken compared between treatments.

## 5.4 Study Design

*Exclusion criteria:*

* Known or suspected serious spinal pathology (e.g. metastatic disease of the spine)
* Confirmed fracture or dislocation at time of injury (WAD IV)
* WAD III (neurological compromise eg decreased reflexes, muscle power)
* Previous whiplash injury or neck pain condition requiring treatment
* PHQ-2 score 3 or more
* Patients using gabapentin/pregabalin; Patients with known peripheral neuropathy
* Known hypersensitivity to pregabalin use (hives, blisters, rash, dyspnoea and wheezing)
* History of renal insufficiency
* Women who are pregnant or breastfeeding
* History of psychiatric illness or substance abuse
* Inability to speak and write in English

PREGABALIN PLUS ADVICE

1 pregabalin capsule (75 mg) orally twice daily with the first dose taken at the time of the initial consultation.

3 month assessment (outcomes, claim lodgement)

6 month assessment (outcomes, claim lodgement)

Concealed random allocation

(medication pack supplied to participant)

PLACEBO PLUS ADVICE

1 placebo capsule (75 mg) orally twice daily with the first dose taken at the time of the initial consultation.

Placebo dose titration: Trial GP will evaluate all patients via telephone review (3 days after randomisation and then weekly thereafter) to titrate the dose. 28 days then 6 days weaning

Baseline assessment

* Age, gender, accident date, symptoms
* Some outcomes – primary and secondary
* Expectations

Invitation to participate in the study by ED doctor in Emergency departments

Volunteers respond. Informed consent obtained.

Potential participants screened for eligibility

*Inclusion criteria:*

* Grade II whiplash (duration <48 hours)
* Experiencing moderate pain (VAS:≥5/10)
* Aged between 18 and 65 years old
* Proficient in written and spoken English

12 month assessment (outcomes, claim lodgement)

Pregabalin dose titration: Trial GP will evaluate all patients via telephone review (3 days after randomisation and then weekly thereafter) to titrate the dose. 28 days then 6 days weaning

5 week assessment (outcomes, side effects, claim lodgement)

Patients with neck pain who have presented to ED after hours when we have no research staff available – triage nurses will be asked to hand them an information sheet and consent form which will ask for permission to contact them during office hours to explain the trial. We will call them as soon as practical after they present and offer them participation in the trial. If they would like to proceed, we will ask them to present to Griffith Health and Medical Service or Limestone Medical Centre, Ipswich. Doctors there will obtain informed consent.

## 5.5 Participants

### **5.5.1 Eligibility criteria**

**Inclusion criteria**

Participants will be included if they meet all of the following inclusion criteria:

*Inclusion criteria*:

* Individuals with Grade II WAD and within 48 hours of injury. (The evidence for effectiveness of pregabalin in preventing ch**ronic pain has been in surgical populations with the drug administered peri-operatively. This** time frame is not possible for whiplash injury, so we aim to administer pregabalin as soon as is practicable in the ED. We will place an upper time frame limit of 48 hours post injury).
* Experiencing at least moderate pain (VAS≥5/10) on first measurement by ambulance or on arrival in ED. As outlined in section 3.1, initial pain intensity is the most consistent predictor or poor recovery. We have identified a score of greater than 5.2 /10 as the best cut-point for optimal sensitivity and specificity16. Others have identified 5.5/10 as a cut-point50. Based on these results we will use a score of ≥5/10 for the identification of at-risk patients.
* Age 18-65 years
* Proficient in written and spoken English.

**Exclusion criteria**

Participants will be excluded if they have any of the following:

*Exclusion criteria:*

* Known or suspected serious spinal pathology (e.g. metastatic disease of the spine);
* Confirmed fracture or dislocation at time of injury (WAD IV);
* WAD III (neurological compromise eg decreased reflexes, muscle power);
* Previous whiplash injury or neck pain condition requiring treatment;
* PHQ-2 score 3 or more
* Patients using gabapentin/pregabalin;
* Patients with known peripheral neuropathy;
* Known hypersensitivity to pregabalin use (hives, blisters, rash, dyspnea and wheezing);
* History of renal insufficiency or liver disease:
* Women who are pregnant or breastfeeding;
* History of psychiatric illness or substance abuse;
* Inability to speak and write in English (participants will be required to complete questionnaires written in English only).

### **5.5.2 Participant recruitment**

Recruitment will be from the Emergency Departments of Gold Coast Health Service District (Gold Coast University Hospital, Robina Hospital if needed) and Ipswich Hospital..

Griffith Health [and Medical services](https://www.griffith.edu.au/student-services/health-counselling-wellbeing/health-and-medical-services) and Limestone Medical Centre, Ipswich, will also be involved. During office hours, we will contact patients with neck pain who present to ED after hours when we have no research staff available. Triage nurses in ED will be asked to hand an information sheet and consent form – permission to contact to all patients aged 18-65 years who present with neck pain. The consent form will ask for permission for research staff to contact them during office hours to explain the trial. Informed consent for permission to contact them will be obtained by the treating nurse or doctor. We plan to call them as soon as practical after they present and offer them participation in the trial.

If they would like to proceed, we will ask them to present to Griffith Health [and Medical services](https://www.griffith.edu.au/student-services/health-counselling-wellbeing/health-and-medical-services) or Limestone Medical Centre, Ipswich.

### Doctors there will fully screen the patients for inclusion/exclusion criteria, obtain informed consent, and if eligible will write a trial script and dispense the next kit in a blinded manner. The pregabalin kits will be stored onsite in a locked drug cupboard in the treatment room, where other practice drugs are stored. The scripts will go back to GCUH pharmacy for collation.

Recruiting through EDs means that our cohort of patients will not be entirely representative of the entire population of whiplash patients. However by recruiting participants through EDs, we will be most likely to enrol participants with greater pain and distress and therefore at higher risk of poor recovery – the very group we aim to target. Data from our current trials51 would support this, where patients with acute injury recruited from ED reported average higher pain levels (6.2 ± 1.5) compared to those recruited from primary care and advertisement (4.5 ± 1.0).

A total of 30 participants will be recruited for this pilot. Participants will be initially screened to identify those who are unsuitable for the treatment because of significant co-morbidity such as serious spinal pathology as per the exclusion criteria.

## 5.6 Study interventions

**Advice**

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; advice to stay active and resume working as well as information on correct posture; pictorial descriptions of specific exercises for the neck and upper limbs 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 Management9.

**Pregabalin**

*Dose Titration*

Patients randomized to the experimental arm of the study will receive 1 pregabalin capsule (75 mg) orally twice daily with the first dose taken before discharge during the initial ED presentation. Patients will continue on this dose for 3 days after which time the dose could be titrated to 150mg twice daily if the previous dose is well tolerated. The dose could be further increased to 300 mg twice daily after the second week if 150 mg twice daily is well tolerated. The dose will be reduced to the previously tolerated level if the higher dose is not well tolerated after 3 days. The study medication will be continued up to 28 days, after which a dose of 300 mg twice daily will be weaned to 150 mg twice daily for 3 days and then 75 mg twice daily for 3 days, a dose of 150 mg twice daily will be weaned to 75 mg twice daily for 6 days and a dose of 75 mg twice daily continued for 6 days. Dose de-escalation in lower maximum tolerated doses will use proportionately lower doses over the same time schedule. The dose escalation/reduction regimen for our trial has been used in previous pregabalin trials52-54 . All patients will be asked to continue taking the medicines (active or placebo) for a period of 28 days with a subsequent 6 days of weaning. The prescription of pregabalin in this way is standard clinical practice. See the dosing algorithm below. Patients will be stabilised on a lower dose of pregabalin if the 600mg is not tolerated despite a challenge period.

Dosing schedules for morning start and evening start are given below.

*Morning start*

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Day** | **Date** | **Dose** | **Number of capsules Morning dose** | **Number of capsules** **Evening dose** | **Telephone call or text to remind patient re dose change next day** |
| 1 |   | 75mg TWICE a day | 1 | 1 |  |
| 2 |   | 75mg TWICE a day | 1 | 1 |  |
| 3 |   | 75mg TWICE a day | 1 | 1 | x |
| 4 |   | 150mg TWICE a day | 2 | 2 |  |
| 5 |   | 150mg TWICE a day | 2 | 2 |  |
| 6 |   | 150mg TWICE a day | 2 | 2 |  |
| 7 |   | 150mg TWICE a day | 2 | 2 |  |
| 8 |   | 150mg TWICE a day | 2 | 2 |  |
| 9 |   | 150mg TWICE a day | 2 | 2 |  |
| 10 |   | 150mg TWICE a day | 2 | 2 |  |
| 11 |   | 150mg TWICE a day | 2 | 2 |  |
| 12 |   | 150mg TWICE a day | 2 | 2 |  |
| 13 |   | 150mg TWICE a day | 2 | 2 |  |
| 14 |   | 150mg TWICE a day | 2 | 2 | x |
| 15 |   | 300mg TWICE a day | 4 | 4 |  |
| 16 |   | 300mg TWICE a day | 4 | 4 |  |
| 17 |   | 300mg TWICE a day | 4 | 4 |  |
| 18 |   | 300mg TWICE a day | 4 | 4 |  |
| 19 |   | 300mg TWICE a day | 4 | 4 |  |
| 20 |   | 300mg TWICE a day | 4 | 4 |  |
| 21 |   | 300mg TWICE a day | 4 | 4 |  |
| 22 |   | 300mg TWICE a day | 4 | 4 |  |
| 23 |   | 300mg TWICE a day | 4 | 4 |  |
| 24 |   | 300mg TWICE a day | 4 | 4 |  |
| 25 |   | 300mg TWICE a day | 4 | 4 |  |
| 26 |   | 300mg TWICE a day | 4 | 4 |  |
| 27 |   | 300mg TWICE a day | 4 | 4 |  |
| 28 |   | 300mg TWICE a day | 4 | 4 | x |
| 29 |   | 150mg TWICE a day | 2 | 2 |  |
| 30 |   | 150mg TWICE a day | 2 | 2 |  |
| 31 |   | 150mg TWICE a day | 2 | 2 | x |
| 32 |   | 75mg TWICE a day | 1 | 1 |  |
| 33 |   | 75mg TWICE a day | 1 | 1 |  |
| 34 |   | 75mg TWICE a day | 1 | 1 | XReminder to stop taking the medication on this date + return the pregabalin bottles |

*Evening start*

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Day** | **Date** | **Dose** | **Number of capsules Morning dose** | **Number of capsules Evening dose** | **Telephone call or text to remind patient re dose change next day** |
| 1 |  | 75mg TWICE a day | - | 1 |  |
| 2 |  | 75mg TWICE a day | 1 | 1 |  |
| 3 |  | 75mg TWICE a day | 1 | 1 | x |
| 4 |  | 150mg TWICE a day | 1 | 2 |  |
| 5 |  | 150mg TWICE a day | 2 | 2 |  |
| 6 |  | 150mg TWICE a day | 2 | 2 |  |
| 7 |  | 150mg TWICE a day | 2 | 2 |  |
| 8 |  | 150mg TWICE a day | 2 | 2 |  |
| 9 |  | 150mg TWICE a day | 2 | 2 |  |
| 10 |  | 150mg TWICE a day | 2 | 2 |  |
| 11 |  | 150mg TWICE a day | 2 | 2 |  |
| 12 |  | 150mg TWICE a day | 2 | 2 |  |
| 13 |  | 150mg TWICE a day | 2 | 2 |  |
| 14 |  | 150mg TWICE a day | 2 | 2 | x |
| 15 |  | 300mg TWICE a day | 2 | 4 |  |
| 16 |  | 300mg TWICE a day | 4 | 4 |  |
| 17 |  | 300mg TWICE a day | 4 | 4 |  |
| 18 |  | 300mg TWICE a day | 4 | 4 |  |
| 19 |  | 300mg TWICE a day | 4 | 4 |  |
| 20 |  | 300mg TWICE a day | 4 | 4 |  |
| 21 |   | 300mg TWICE a day | 4 | 4 |  |
| 22 |   | 300mg TWICE a day | 4 | 4 |  |
| 23 |   | 300mg TWICE a day | 4 | 4 |  |
| 24 |   | 300mg TWICE a day | 4 | 4 |  |
| 25 |   | 300mg TWICE a day | 4 | 4 |  |
| 26 |   | 300mg TWICE a day | 4 | 4 |  |
| 27 |   | 300mg TWICE a day | 4 | 4 |  |
| 28 |   | 300mg TWICE a day | 4 | 4 | x |
| 29 |   | 150mg TWICE a day | 4 | 2 |  |
| 30 |   | 150mg TWICE a day | 2 | 2 |  |
| 31 |   | 150mg TWICE a day | 2 | 2 | x |
| 32 |  | 75mg TWICE a day | 2 | 1 |  |
| 33 |   | 75mg TWICE a day | 1 | 1 |  |
| 34 |   | 75mg TWICE a day | 1 | 1 | x |
| 35 |  | 75mg in the MORNING | 1 | CEASE |  Reminder to stop taking the medication on this date + return the pregabalin bottles |

*Conditions surrounding temporary discontinuation and permanent discontinuation*.

In terms of adverse effects, if the patient is dizzy or drowsy, but this is not interfering with their daily life activities, we will wait till they are tolerant of that dose for 5 days, then increase the dose. However if dizziness or drowsiness is interfering with their daily life activities, we will drop to the previous dose for 2 days, then if this is tolerated, increase the dose again. If the dizziness recurs, then the dose will drop to the previous dose and remain on that for the remainder of the trial.

If the patient does not tolerate the medication and is symptomatic to the point where their symptoms interfere with life, the trial medication will be ceased. For example, if there is serious dizziness or other significant symptom, so that the patient cannot drive or work, the patient will be withdrawn from the trial and trial medication ceased. See the section on adverse events. If serious dizziness or other significant symptom persists after stopping the medication, then the patient will be advised to see their GP immediately for further management.

Any significant symptoms that develop in which a patient is withdrawn from the study as a result of the trial medication will trigger a visit to a Research team physician to review the patient. This would be an Adverse Drug Reaction in which causality would be assessed. Outcomes of that review would be liaised with their usual GP to resume ongoing care. The participant will be asked to return with their trial medications during the visit. Intention-To-Treat principles would apply regarding follow-up.

Participants may withdraw or stop the medication out of patient preference should they choose to no longer continue.

*Dosing algorithm*

Tolerated – continue 150 mg bd and no escalation

Not tolerated and interfering with life– stop

Not tolerated but not interfering with life – drop to 150 mg bd and no escalation

Not tolerated and interfering with life–

– drop to 150 mg bd for up to 5 extra days

Not tolerated but not interfering with life – drop to 75 mg bd and no escalation

Not tolerated and interfering with life - stop

Not tolerated but not interfering

with life -

stay at 300 mg bd for up to 5 extra days

Tolerated – continue 75mg bd and no escalation

Tolerated - wean off as per schedule

Not tolerated but not interfering with life– stay at 150 mg bd for up to 5 extra days

Tolerated – increase to 150 mg bd

Not tolerated and interfering with life– drop to 75 mg bd for up to five extra days

Not tolerated and interfering with life – stop

Not tolerated but not interfering with life - stop.

Tolerated – increase to 300 mg bd

Not tolerated –but symptoms not interfering with life– stay at 75 mg bd for up to 5 days

Not tolerated and interfering with life - stop

75 mg bd

*Rationale for duration of treatment*

Our aim is to prevent the development of chronic pain. There are no firm guidelines on what the duration of treatment should be. Surgical studies have used pregabalin for 10 days to 2 weeks in a post-op setting6 whilst for chronic neuropathic pain, recommendations are for 2-4 weeks of treatment54. We want to avoid missing a benefit that may occur and have therefore, taken a pragmatic approach of a 28 day treatment period before weaning.

*Placebo*

The placebo will consist of a capsule containing only the filler Avicel®, and will look identical to the pregabalin capsule to ensure blinding of research staff, participants, ED staff and trial GPs. The dosage pattern for the placebo will be the same as the dosage pattern for pregabalin: i.e. titration, maintenance and titration down phases (total of 5 weeks), at identical time points. The placebo will be titrated based on patients’ tolerance in the same way that the pregabalin will be titrated.

After discharge from the ED, the trial GP will evaluate all patients via telephone review (3 days after randomisation and then weekly thereafter) to titrate the dose based on the patient’s tolerance and adverse effects and in consultation with CI Mitchell. Participants will be offered an optional GP visit (to Griffith Health and Medical Services or Limestone Medical Centre) during the titration phase or active intervention phase if they wish. Participants will also be able to contact the trial GP if they have questions regarding the medication dose or any side effects. At the end of the 5 week intervention period, in respect of the compensable nature of a whiplash injury, the patients in the both intervention groups will be permitted to seek further treatment if required. Information about any additional treatments sought by participants (eg additional medication, physiotherapy etc.) will be gained via the cost diaries at the follow-up time points (see 5.14).

## 5.7 Breakthrough medication

Participants (in either intervention group) who experience high levels of continuing or worsening pain will be able to return for an earlier review with the GP. Further assessment will be provided by the GP and in some instances, rescue medication (Paracetamol 1000 mg qid prn or oxycodone 5mg prn if paracetamol is not sufficient for pain control) can be provided in addition to the study medicine. These medications are consistent with current clinical practice guidelines for WAD management9. Rescue medication will be provided by the GP at their discretion and will be based on continuing and worsening pain that is debilitating in nature (in the short term) or continuing high levels of pain that have not improved after 7 days of treatment, despite following the trial regimen.

The researchers will provide care and support that they deem is in the patient’s best interests at all times (*National Statement S1.7*).

## 5.8 Concomitant medications

Participants in both groups will be asked not to seek other treatments and where possible not to change current medications for the 5 week trial period. Furthermore, the nominated general practitioner will be notified in writing of the individual’s participation in the trial. They will be asked within reason to refrain from referring or suggesting additional or alternative treatments to the individual for the initial 5 weeks after randomisation.

All participants will be required to maintain diaries in which they will record information such as other treatments and medication taken. If clinically indicated, treatments will be amended. Patients will be asked at each time point if their medications have changed – and to identify the medications and doses added.

## 5.9 Investigator/Site Personnel Training

Investigator and site personnel will undergo training prior to performing any study-related procedures. All training will be documented. Study training requirements will include the following topics as relevant:

* Protocol review
* Delegation of authority for study-related tasks
* Informed consent process, including any relevant IRB/IEC requirements
* Case report forms and completion instructions
* Documentation of protocol deviations
* Adverse Event and Serous Adverse Event reporting
* Responsibilities and obligations of the investigator/research staff
* General guidelines for good clinical practice
* Study documentation management (essential documents)

The Lead Investigator, and the Principal Investigator, who have co-developed the protocol, will train Site Personnel. Once trained, study site personnel as appropriate will provide training to incoming trial team members who have been delegated new tasks. Training will be documented in a training log and reflect the duties in the delegation log.

## 5.10 Study sequence

### **5.10.1 Screening**

* Assess eligibility, willingness and ability of participants to join the trial.
* Complete screening assessment forms including Patient Health Questionnaire-2

### **5.10.2 Baseline assessment**

Participants who meet the inclusion criteria will complete informed consent documentation prior to being evaluated on all primary and secondary baseline measures obtained by a blinded investigator.

Forms will include the following:

* Contact details form
* Baseline demographic form and information about symptoms of whiplash
* Questionnaires
	1. NRS (Pain) on arrival at ED (0-10 scale)
	2. Depression, Anxiety and Stress Scale (DASS-21)
	3. SF-12
	4. S-LANSS, a self-report version of the Leeds Assessment of Neuropathic Symptoms and Signs pain scale55

9. Patient expectations of a beneficial treatment effect will be scored from 1 to 4 with higher scores indicating higher expectations.

Participants in both groups will be provided with the MAIC *Whiplash Injury Recovery: A Self Help Guide* booklet. This booklet aims to help people who have a whiplash injury on the road to recovery. It provides information about whiplash associated disorders, an explanation of whiplash, an exercise program which has been proven to assist in reducing neck pain and advice on how to manage your neck to prevent unnecessary strain and to aid recovery. The booklet is a self-help resource to aid recovery and to supplement any care being provided by a health care practitioner.

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**5.10.3 Blinding**

The trial will be triple-blinded (participant, investigators, health care providers). Study personnel will not be unblinded until the end of the study. The placebo will have the same appearance, volume, weight, odour, and taste as active product.

**5.10.4 Randomisation**

Participants will be randomly allocated to either treatment group. The randomisation codes will be generated following appropriate statistical procedures by the study statistician. The study statistician will provide a randomization list in variable block sizes of 4-6 for the whole trial to the study dispensing pharmacy which will then hold it for the duration of the study. The randomisation schedule, which includes patient initials, date of birth and randomisation code, will be kept in a sealed envelope in a locked filing cabinet in the pharmacy. The randomisation schedule will be kept concealed from the research team. In order to balance potential confounders and to conceal allocation, there will be separate randomisation schedules for each site,

The pharmacy will hold the randomisation schedule during working hours and it will be in the 24hr on-call bag after hours in case unblinding is needed.

Study medication will be prepared according to the randomisation schedule by a pharmacist not involved with data collection, then sealed in an opaque medication kit and stored in a locked drug roomin ED or at the general practice.. Allocation will occur immediately following the baseline assessment. Upon recruitment, the doctor or nurse (blinded) will select the next kit in the box, record the participant’s randomisation number and provide the sealed medication kit to the participant (blinded), thus randomising the participant to one of two groups: pregabalin or placebo. Placebo capsules will have an identical appearance to the active pregabalin capsules. The randomisation process will ensure concealed allocation and blinding of the ED research staff, the trial GPs, participants and outcome assessors. Participants will be considered to have entered the study at the time that the kit is opened.

### **5.10.5 Unblinding Process**

The trial participants, investigators, clinicians and research staff will not know the treatment allocation. Principal Investigators will be able to unblind individual cases if the following crtieria are met:

* 1. Emergency Unblinding - To make a clinical treatment decision or when an unexpected serious adverse event occurs .
	2. During an unmasked analysis in accordance with the study analysis plan or at the requestion of the Data Safety Monitoring Board.
	3. At the conclusion of the study to determine the effect of intervention.

Any unblinding that occurs outside of these criteria must be reported as a protocol violation such as premature unblinding (e.g. accidental unblinding or unblinding due to a serious adverse event).

### The investigator will follow the trial's randomization procedures, and the code will be broken only in accordance with the protocol. The investigator will promptly document and explain to the sponsor any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event) of the investigational product.

The safety of the participant always comes first. It is important to seriously consider if unblinding the study therapy is necessary to ensure a participant’s safety and if unblinding will change clinical management.The investigator must inform University of Queensland of all participants whose treatment was unblinded within 24 hours by phone or fax, followed by a written narrative of the event within 48 hours of unblinding occurring.

Physicians providing care to a participant on trial who require unblinding to provide effective clinical care have been advised to contact the medically qualified investigator, Professor Geoffrey Mitchell, in an event where unblinding may be necessary, and discuss the nature of the emergency that requires the unblinding.

If a medically qualified investigator requires the identification of the trial medication composition, they must quote the randomisation code, participant initials, participant D.o.B. and trial title to the Principal Investigator, who will contact the pharmacy and quote the randomisation code and trial title. The pharmacy will unblind for the specific participant only. The medically qualified investigator will talk to and unblind the participant.

Unblinding should only occur if relevant to clinical treatment. If the medically qualified investigator does not believe unblinding should occur in this situation, he/she will consult with the participant and Principal Investigator and discuss alternative procedures in which the participant can come off trial medications for the short-term, or withdraw from the trial without unblinding. Alternatively, these discussions may provide indication for unbinding to occur.

Premature unblinding (e.g.: accidental unblinding or unblinding due to a serious adverse event) would be a protocol violation and must be recorded by the medically qualified investigator as a protocol violation or deviation on form PVD. If the participant withdraws, the investigator must complete the withdrawal form.

The medically qualified investigator will notify the trial GP that a participant is unblinded, or off trial treatment. The trial GP will advise the investigative team and research assistants.

After being off-treatment, the trial GP will follow-up on the participant’s care to ascertain if they are willing and safe to return to trial medication.

**It is a requirement that all research staff follow the agreed unblinding process. Unnecessary unblinding can affect the scientific integrity of the trial.**

## 5.10.6 Stopping Criteria

The study will be stopped if new literature indicates findings that can be applied to the research question in terms of benefit or side effects, or if the DSMB decide that serious adverse events indicate that review of the study protocol is required. Alternatively, the DSMB may recommend protocol review or changes without stopping the trial.

After 30 participants have been enrolled, or after one year, whichever occurs first, the DSMB will supervise one interim analysis for safety only. They will be provided with treatment labels (A and B) without knowledge of the identity of each label, to determine if there is an excess of adverse events in one group. A p-value of 0.01 will be used as a decision criterion for stopping the study for harm. As no efficacy endpoint will be evaluated, there will be no need to adjust the sample size.

### **5.10.7 Follow up: 5 weeks, 3 months, 6 months and 12 months**

Outcome measures will be assessed at baseline, immediately after the intervention, and at 3, 6 months and 12 months post randomisation. To optimise completion of measures via online survey or paper copy at these follow-ups, reminders will be made by phone, followed by an email or letter. Every attempt (within ethical guidelines) will be made to obtain outcome data, regardless of subject’s compliance with trial protocols.

To be completed by all participants at 5 weeks, 3 months, 6 months and 12 months, using either the online survey tool or by paper copy. Questionnaires will include:

1. NRS (Pain) average pain over the last 24 hours (0-10 scale)
2. Neck Disability Index (NDI)
3. Hyper-arousal subscale of the Posttraumatic Stress Diagnostic Scale (PDS)
4. Depression, Anxiety and Stress Scale (DASS-21)
5. Pain Catastrophising Scale (PCS)
6. SF-12
7. S-LANSS
8. Claim lodgement

9. Adverse effects of treatment

### **5.10.8 Exit assessment**

On completion of a participant’s final assessment session, they will complete an exit questionnaire that requests information about their experience in the trial and their perceptions of what has transpired, particularly regarding group allocation and concurrent treatment.

## 5.11 Time and Events schedule

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Protocol Activity** | **Baseline** | **Treatment** | **Follow-up (F/U)** | **Study** **Discharge** |
| Day 1 | Day 2 - Day 35 | Day 90 | Day 180 | Day 365 |
| Hospital/Clinic  | ***Dose Titration***Phone/Clinic (*optional*) |  Phone/Online/Post  | Phone/Online/Post  |
| Window |  | Day 3, 14, 28, 31 | **CEASE**Day 35-1/+5d | +/-14d | +/- 30d |
| Screening | X |  |  |  |  |  |
| Inclusion/Exclusion | X |  |  |  |  |  |
| Informed consent | X |  |  |  |  |  |
| Demographics | X |  |  |  |  |  |
| Clinical Assessment | X |  |  |  |  |  |
| Randomise | X |  |  |  |  |  |
| Dispense medication | X |  |  |  |  |  |
| NRS (pain) 24 hours | X |  | X | X |  | X |
| NDI |  |  | X | X |  | X |
| PDS |  |  | X | X |  | X |
| PHQ-2 | X |  |  |  |  |  |
| PCS |  |  | X | X | X | X |
| DASS-21 | X |  | X | X | X | X |
| SF12 | X |  | X | X | X | X |
| S-LANSS | X |  | X | X | X | X |
| Concomitant medications | X | X | X |  |  |  |
| Drug Accountability and Returns |  |  | X |  |  |  |
| Adverse events | X | X | X | X | X | X |
| Claim lodgement |  |  | X | X | X | X |
| Cost diary |  |  | X | X | X | X |

## 5.12 Adherence to Study Medication

Adherence with the study medications will be assessed by: (1) weekly self-recorded medication intake, (2) counts of returned tablets following the completion of treatment and (3) the trial GP will ask questions about adherence during the planned telephone-based reviews starting at 3-days post randomisation. Participants will be asked to return all unused tablets for counting at the end of the treatment period in a reply paid post satchel. There will be full accountability for all drug given out to patients.

## 5.13 Adverse Events

Information about adverse effects of the medication will be sought from all participants using open-ended questioning at weekly intervals following randomisation during their contact with the trial GP. Participants will be able to contact trial staff at any time if they have questions or concerns about the medication. In the event that a participant reports an adverse event or side effect, the trial staff will liaise with the trial GP. The trial GP will then call the participant to assess further and to make a determination on what action should be taken. This may include dose alteration or withdrawal from the study if deemed necessary.

The most common side effects reported with pregabalin usage are dizziness and sedation and we have taken this into account with the dose titration as tolerated. Leg oedema can also develop and may require discontinuation of pregabalin. More severe side-effects are rare.

**5.13.1 Definitions**

An **Adverse Event (AE) is a**ny untoward medical occurrence in a patient or clinical trial participant administered a medicinal product and that does not necessarily have a causal relationship with this treatment. Anticipated, brief fluctuations of pre-existing condition(s) or disease(s) which were present or detected at the start of the study which do not worsen do not constitute AE.

**An Adverse Reaction (AR)** is any untoward and unintended response to an investigational medicinal product related to any dose administered.

Comment: All adverse events judged by either the reporting investigator or the sponsor as having a reasonable possibility of a causal relationship to an investigational medicinal product would qualify as adverse reactions. The expression ‘reasonable causal relationship’ means to convey, in general, that there is evidence or argument to suggest a causal relationship.

A **Serious Adverse Event (SAE)** is any adverse event/adverse reaction that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.

Note: Life-threatening in the definition of a serious adverse event or serious adverse reaction refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

Note: Medical and scientific judgement should be exercised in deciding whether an adverse event/ reaction should be classified as serious in other situations. Important medical events that are not immediately life-threatening or do not result in death or hospitalisation, but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious.

**A Suspected Unexpected Serious Adverse Reaction (SUSAR)** is an adverse reaction that is both serious and unexpected.

Note: Hospitalisations for treatment planned prior to randomisation and hospitalisation for elective treatment of a pre-existing condition will not be considered as an AE. However the trial should be suspended till the patient is stable once again.

Complications occurring during such hospitalisation will be AEs.

## 5.13.2 Detecting AEs and SAEs

All AEs and SAEs are to be recorded from the time a participant consents to join the study until the last study visit.

The research team will ask about the occurrence of AEs/SAEs at least weekly during the study, and at 5 weeks, and 3, 6 and 12 month follow-up. Open-ended and non-leading verbal questioning of the participant will be used to enquire about AE/SAE occurrence. Participants will also be asked if they have been admitted to hospital, had any accidents, used any new medicines or changed concomitant medication regimens. If there is any doubt as to whether a clinical observation is an AE, the event should be recorded.

## 5.13.3 Recording AEs and SAEs

At each contact with the participant, the research staff will seek information on adverse events by specific questioning. During the trial GP’s calls to patients, all medications and doses used will be recorded, including prescription and over-the-counter medications and Natural Health Products, to include important co-variables in the final analysis. If a serious adverse event is identified the trial GP will forward this information immediately to the PI and Data Safety Monitoring Board (DSMB).

Depending on severity, when an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g. hospital notes, laboratory and diagnostic reports) related to the event. The Investigator will record all relevant information in the Case Report Form (CRF) and on the AE/SAE form. Information to be collected includes dose, type of event, onset date, Investigator assessment of severity and causality, date of resolution as well as treatment required, investigations needed and outcome.

All adverse events occurring during the study period will be recorded immediately in the source document, and also in the appropriate adverse event form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedure results should be recorded in the source document, though should be grouped under one diagnosis.

The clinical course of each event will be followed until resolution, stabilisation, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

## 5.13.4 Evaluation of AEs and SAEs

SAEs need to be notified within 24 hours of their occurrence or within 24 hrs of being brought to the attention of the Investigator.

### ***Assessment of Causality***

The Investigator will make an assessment of whether the AE/SAE is likely to be related to treatment according to the following definitions:

**Unrelated:** where an event is not considered to be related to the study drug.

**Possibly:** although a relationship to the study drug cannot be completely ruled out, the nature of the event, the underlying disease, concomitant medication or temporal relationship make other explanations possible.

**Probably:** the temporal relationship and absence of a more likely explanation suggest the event could be related to the study drug.

**Definitely:** The known effects of the study drug or its therapeutic class, or based on challenge testing, suggest that study drug is the most likely cause.

All AEs/SAEs judged as having a reasonable suspected causal relationship (e.g. possibly, probably, definitely) to the study drug will be considered as ARs/SARs. All AEs/SAEs judged as being related (e.g. possibly, probably, definitely) to an interaction between the study drug and another drug will also be considered to be ARs/SAR.

Alternative causes such as natural history of the underlying disease, concomitant therapy, other risk factors and the temporal relationship of the event to the treatment should be considered. The blind will not be broken for the purpose of making this assessment.

### ***Assessment of Severity***

The Investigator should make an assessment of severity for each AE/SAE and record this on the CRF according to one of the following categories:

**Grade 1**: mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

**Grade 2**: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL\*

**Grade 3**: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL\*\*

**Grade 4**: Life-threatening consequences; urgent intervention indicated

**Grade 5**:Death related to adverse event

*\*instrumental ADL: preparing meals, shopping for groceries or clothes, using the telephone, etc.

\*\*self-care ADL: bathing, dressing and undressing, feeding self, using toilet, taking medications and not bedridden*

Note: the term ‘severe’, used to describe the intensity, should not be confused with ‘serious’ which is a regulatory definition based on participant/event outcome or action criteria. For example, a headache may be severe but not serious, while a minor stroke is serious but may not be severe.

### ***Assessment of Expectedness***

If an event is judged to be an AR/SAR, the evaluation of whether the event is expected should be made based on knowledge of the reaction and the relevant product information.

## 5.13.4 Monitoring of SAE/SARS/SUSARS

All SAE/SARS/SUSARS will be closely monitored for any relationship to the study procedures and protocol or clustering of events at a particular site while blinded to treatment allocation; In addition, all SAE/SARS/SUSARS will be submitted to the DSMB for review. Seriousness, causality, severity and expectedness will be evaluated by the DSMB as though the participant is taking active drug. The protocol will be amended or the study stopped early if an excess of particular SAE/SARS/SUSARS appear to be protocol related.

The sponsor will report all SUSARs that are fatal or life-threathening to the TGA within 7 calendar days, and all other SUSARs, no later than 15 calendar days of being made aware.

**5.13.5 Pre-existing Condition**

A pre-existing condition is one that is present at the start of the study. A pre-existing condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

### General Physical Examination Findings

At screening, any clinically significant abnormality should be recorded as a pre-existing condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

##  5.13.6 Post-study Adverse Event

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each participant to report any subsequent event(s) that the subject, or the participant’s personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a participant has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a participant that has participated in this study.

##  5.13.7 Abnormal Laboratory Values

A clinical laboratory abnormality should be documented as an adverse event if any one of the following conditions is met:

* The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
* The abnormality suggests a disease and/or organ toxicity
* The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

## 5.13.8 Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition requiring surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

* Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a pre-existing condition. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
* Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
* Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

##  5.13.9 Reporting of Serious Adverse Events and Unanticipated Problems

Investigators must conform to the adverse event reporting timelines, formats and requirements of the various entities to which they are responsible, but at a minimum those events that must be reported are all deaths, all events meeting SAE criteria and adverse events of interest.

Adverse events of interest for this study are overdose and suicidal ideation.

SAEs need to be notified within 24 hours of their occurrence or within 24 hrs of being brought to the attention of the Investigator.

If the report is supplied as a narrative, the minimum necessary information to be provided at the time of the initial report includes:

|  |  |
| --- | --- |
| * Study identifier
* Study site
* Subject number
* A description of the event
* Date of onset
 | * Current status
* Whether study treatment was discontinued
* The reason why the event is classified as serious
* Investigator assessment of the association between the event and study treatment
 |

### **Investigator reporting: Notifying the sponsor**

Any study-related unanticipated problem posing risk of harm to participants or others, and any type of serious adverse event, must be reported to the study sponsor by telephone and email immediately the event is reported to the PI. To report such events, a Serious Adverse Event form (Form SAE) must be completed by the investigator and faxed/scanned to the study sponsor immediately. The investigator will keep a copy of this Serious Adverse Event form on file at the study site.

Within the following 24 hours, the investigator must provide further information on the serious adverse event or the unanticipated problem in the form of a written narrative. This should include a copy of the completed Serious Adverse Event form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing serious adverse events should be provided promptly to the study sponsor as relevant. We will combine the data so as to not miss any signals that may be emerging.

### **Investigator reporting: Notifying a Site HREC/HREB**

Investigators at research sites are responsible for safety reporting to their local HREC. Investigators are responsible for complying with their local reporting requirements. Copies of each report and documentation of HREC notification and receipt will be kept in the investigator’s study file. The study site must supply University of Queensland with copies of all HREC notifications and correspondence.

### **Sponsor reporting: Notifying participating investigators**

It is the responsibility of the study sponsor to notify all participating investigators, in a written safety report, of any adverse event associated with the use of the drug that is both serious and unexpected. Additionally, the study sponsor will identify in safety reports all previous reports concerning similar adverse events and analyze the significance of the current event in light of the previous reports.

**5.13.10 Premature Termination or Suspension**

If the trial is terminated prematurely or suspended for any reason, the investigator will promptly inform the trial participants, assure appropriate therapy and follow-up for the participants, and, where required by the applicable regulatory requirement(s), will inform the regulatory authority(ies).

In addition, if the investigator terminates or suspends a trial, the investigator will inform the HREC, and will provide the HREC a detailed written explanation of the termination or suspension.

**5.13.11 Existing known adverse drug reactions of pregabalin**

### **Cardiovascular**

Common (1% to 10%): Chest pain
Uncommon (0.1% to 1%): Hypotension, hypertension, hot flushes, flushing, peripheral coldness, heart failure, postural hypotension, syncope
Rare (less than 0.1%): ST depressed, ventricular fibrillation

### **Dermatologic**

Common (1% to 10%): Ecchymosis, pruritus
Uncommon (0.1% to 1%): Angioedema, rash papular, urticaria, hyperhidrosis, abscess, cellulitis, alopecia, dry skin, eczema, hirsutism, skin ulcer, urticaria, vesiculobullous rash
Rare (less than 0.1%): Stevens Johnson syndrome, cold sweat, angioedema, exfoliative dermatitis, lichenoid dermatitis, melanosis, nail disorder, petechial rash, purpuric rash, pustular rash, skin atrophy, skin necrosis, skin nodule, subcutaneous nodule.

Symptoms of angioedema have included swelling of the face, mouth (tongue, lips, and gums), and neck (throat and larynx). There have also been reports of life-threatening angioedema with respiratory compromise requiring emergency treatment. Therapy should be discontinued immediately in patients with these symptoms. Caution is recommended if this drug is used in patients who have had a previous episode of angioedema. Patients who are taking other drugs associated with angioedema (e.g., angiotensin converting enzyme inhibitors [ACE inhibitors]) may be at increased risk of developing angioedema.

### **General**

The most common adverse reactions to this drug are dizziness, somnolence, dry mouth, edema, blurred vision, weight gain, and "thinking abnormal" (primarily difficulty with concentration/attention).

### **Gastrointestinal**

Common (1% to 10%): Dry mouth, constipation, nausea, vomiting, diarrhea, flatulence, abdominal distention, gastroenteritis
Uncommon (0.1% to 1%): Gastroesophageal reflux disease, salivary hypersecretion, hypoesthesia oral, cholecystitis, cholelithiasis, colitis, dysphagia, esophagitis, gastritis, GI hemorrhage, melena, mouth ulceration, pancreatitis, rectal hemorrhage, tongue edema
Rare (less than 0.1%): Ascites, granuloma.

### **Genitourinary**

Common (1% to 10%): Urinary incontinence, erectile dysfunction, impotence, urinary frequency, urinary incontinence
Uncommon (0.1% to 1%): Sexual dysfunction, ejaculation delayed, dysmenorrhea, breast pain, anorgasmia, albuminuria, dysuria, hematuria, kidney calculus, leukorrhea, menorrhagia, metrorrhagia, oliguria, urinary retention, urine abnormality, abnormal ejaculation, albuminuria, amenorrhea, dysmenorrhea, kidney calculus, menorrhagia, metrorrhagia, oliguria
Rare (less than 0.1%): Breast discharge, breast enlargement, gynecomastia, pelvic pain, balanitis, bladder neoplasm, cervicitis, dyspareunia, epididymitis, glomerulitis, ovarian disorder.

### **Hematologic**

Uncommon (0.1% to 1%): Neutropenia, blood creatine phosphokinase increased, alanine aminotransferase increased, aspartate aminotransferase increased, platelet count decreased, blood creatinine increased, blood potassium decreased, deep thrombophlebitis
Rare (less than 0.1%): White blood cell count decreased, anemia, eosinophilia, hypochromic anemia, leukocytosis, leukopenia, lymphadenopathy, thrombocytopenia
Rare (0.01% to 0.1%): Myelofibrosis, polycythemia, prothrombin decreased, purpura.

### **Hypersensitivity**

Uncommon (0.1% to 1%): Hypersensitivity
Rare (0.01% to 0.1%): Allergic reaction, anaphylactic reaction.

### **Immunologic**

Very common (10% or more): Infection (up to 14%)
Common (1% to 10%): Influenza syndrome.

### **Musculoskeletal**

Common (1% to 10%): Myasthenia, muscle cramp, arthralgia, back pain, pain in limb, cervical spasm, leg cramps
Uncommon (0.1% to 1%): Joint swelling, myalgia, muscle twitching, neck pain, muscle stiffness, neck rigidity, arthrosis
Rare (less than 0.1%): Rhabdomyolysis, chondrodystrophy, generalized spasm.

### **Nervous system**

Very common (10% or more): Dizziness (up to 37%), somnolence (up to 25%)
Common (1% to 10%): Neuropathy, ataxia, vertigo, incoordination, tremor, abnormal gait, headache, speech disorder, twitching
Uncommon (0.1% to 1%): Syncope, stupor, myoclonus, psychomotor hyperactivity, dyskinesia, dizziness postural, intention tremor, nystagmus, hyporeflexia, hyperesthesia, burning sensation, ageusia, malaise
Rare (less than 0.1%): Convulsions, parosmia, hypokinesia, dysgraphia, shock, circumoral paresthesia, dysarthria, hyperalgesia, hyperkinesia, hypokinesia, hypotonia, myoclonus, neuralgia cerebellar syndrome, cogwheel rigidity, coma, dysautonomia, dystonia, encephalopathy, extrapyramidal syndrome, Guillain-Barre syndrome, hypalgesia, intracranial hypertension, torticollis, trismus, peripheral neuritis.

### **Ocular**

Very common (10% or more): Visual field changes (13%)
Common (1% to 10%): Blurry vision, abnormal vision, diplopia, conjunctivitis
Uncommon (0.1% to 1%): Peripheral vision loss, visual disturbance, eye swelling, visual field defect, visual acuity reduced, eye pain, asthenopia, photopsia, photosensitivity reaction, dry eye, lacrimation increased, eye irritation, retinal vascular disorder, abnormality of accommodation, blepharitis, dry eyes, eye hemorrhage, hyperacusis, photophobia, retinal edema
Rare (0.01% to 0.1%): Vision loss, keratitis, oscillopsia, altered visual depth perception, mydriasis, strabismus, visual brightness, anisocoria, blindness, corneal ulcer, exophthalmos, extraocular palsy, iritis, keratitis, keratoconjunctivitis, miosis, mydriasis, night blindness, ophthalmoplegia, optic atrophy, papilledema, parosmia, ptosis, uveitis.

### **Other**

Very common (10% or more): Peripheral edema (up to 12%)
Common (1% to 10%): Asthenia, accidental injury, face edema, pain, otitis media, tinnitus
Uncommon (less than 0.1% to 1%): Generalized edema, pain, pyrexia, chills, thirst
Rare (0.01% to 0.1%): Retroperitoneal fibrosis, retinal vascular disorder, taste loss, taste perversion.

### **Respiratory**

Common (1% to 10%): Dyspnea, bronchitis, nasopharyngitis
Uncommon (0.1% to 1%): Epistaxis, cough, nasal congestion, rhinitis, snoring, nasal dryness
Rare (less than 0.1%): Pulmonary edema, throat tightness, apnea, atelectasis, bronchiolitis, hiccup, laryngismus, lung fibrosis, yawn.

### **Metabolic**

Common (1% to 10%): Weight gain, edema, hypoglycemia, increased appetite
Uncommon (0.1% to 1%): Weight decreased, blood glucose increased
Rare (0.01% to 0.1%): Glucose tolerance decreased, urate crystalluria.

### **Psychiatric**

Common (1% to 10%): Confusion, euphoria, amnesia, nervousness, irritability, disorientation, insomnia, libido decreased, disturbance in attention, anxiety, depersonalization, stupor, abnormal thinking
Uncommon (0.1% to 1%): Cognitive disorder, mental impairment, abnormal dreams, agitation, apathy, aphasia, hallucinations, hostility
Rare (less than 0.1%): Delirium, delusions, manic reaction, paranoid reaction, personality disorder, psychotic depression, schizophrenic reaction, sleep disorder, disinhibition.

### **Renal**

Uncommon (0.1% to 1%): Nephritis
Rare (0.01% to 0.1%): Acute kidney failure, pyelonephritis.

**5.13.12 The risk of suicidal ideation in participants**

***Brief literature review of depression and suicidal ideation in new users of pregabalin***

Two of 1373 first time users of pregabalin for neuropathic pain experienced suicidal ideation in a observational, Web-based, prospective cohort study in the Netherlands using patients as a source of information over a six month period56. However, in a case control study, out of 453 patients with epilepsy who had exhibited self-harm or suicidal behaviour, there were no patients who had been using pregabalin57.

Depressed mood and suicidal ideation occurred in 5 of approximately 50 patients commencing pregabalin for the treatment of chronic neuropathic pain58. All 5 patients had a long history of mental health issues, including moderate/severe depression, and were taking a number of medications. This is not unusual in a persistent-pain patient population. However, they were carefully assessed for depression on presentation and their mood had been stable prior to commencement of pregabalin. Similarly, use of all other psychoactive medication was stable at the point of initiation of pregabalin.

**Patient Health Questionnaire-2 (PHQ-2)**

The Patient Health Questionnaire (PHQ)59 is the most commonly used measure to screen for depression in primary care60. This easy to use patient questionnaire is a self-administered version of the PRIME-MD diagnostic instrument for common mental disorders. When screening for depression the Patient Health Questionnaire-2 (PHQ-2) can be used first. The PHQ-2 has been found to be up to 97 percent sensitive and 67 percent specific in adults, with a 38 percent positive predictive value and 93 percent negative predictive value61.

The PHQ-2 comprises 2 items and the total score ranges from 0 to 6, with a cut-off score of 3 and above indicating higher levels of depressed mood and anhedonia59, 62. Ultrashort screening instruments, such as the PHQ-2 may rule out, but not definitively diagnose, depression. However, the PHQ-2, which asks two simple questions about mood and anhedonia, has strengths. It is as effective as longer screening instruments, such as the Beck Depression Inventory or Zung Depression Scale59,62.

#### Patient Health Questionnaire-2: Screening Instrument for Depression

| ***OVER THE PAST TWO WEEKS, HOW OFTEN HAVE YOU BEEN BOTHERED BY ANY OF THE FOLLOWING PROBLEMS?*** | ***NOT AT ALL*** | ***SEVERAL DAYS*** | ***MORE THAN ONE-HALF THE DAYS*** | ***NEARLY EVERY DAY*** |
| --- | --- | --- | --- | --- |
| Little interest or pleasure in doing things | 0 | 1 | 2 | 3 |
| Feeling down, depressed, or hopeless | 0 | 1 | 2 | 3 |

A negative response to both questions is considered a negative result for depression60.

**Screening** [**Go to:**](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2709995/)

**The Depression Anxiety Stress Scale (DASS) was designed to efficiently measure the core symptoms of anxiety and depression and has demonstrated positive psychometric properties in adult samples of anxiety and depression patients and student samples. Despite these findings, the psychometric properties of the DASS remain untested in older adults, for whom the identification of efficient measures of these constructs is especially important.**

**To determine the psychometric properties of the DASS 21-item version in older adults, we analyzed data from 222 medical patients seeking treatment to manage worry. Consistent with younger samples, a three-factor structure best fit the data. Results also indicated good internal consistency, excellent convergent validity, and good discriminative validity, especially for the depression scale. Receiver operating curve analyses indicated that the DASS-21 predicted the diagnostic presence of generalized anxiety disorder and depression as well as other commonly used measures.**

**These data suggest that the DASS may be used with older adults in lieu of multiple scales designed to measure similar constructs, thereby reducing participant burden and facilitating assessment in settings with limited assessment resources.**

**Process**

We will screen potential participants using the PHQ-2. If the potential participant is not depressed or moderately depressed (score 2 or below on the PHQ-2), we will continue screening for the trial. If they meet criteria for severe depression (3 or more), further assessment will be conducted by medical staff to determine whether they are at risk of suicide. They will be excluded, with follow-up by their GP (or ED if acutely suicidal).

Given that the participants will be assessed while in ED or at a general practice, if they are at risk of suicide, patients will be referred to a health professional in ED or at the practice who is qualified to further assess for suicide risk. To ensure the safety of the patient if at risk of suicide, the patient’s GP will also be contacted to monitor the patient’s mood/suicide risk if/when discharged from ED or after leaving the general practice.

Additionally, participants will be given contact details for the trial GP and asked to call if their mood becomes depressed or if they are having suicidal thoughts. Participants will be able to contact the trial GP during business hours, and outside working hours they will be provided with the Lifeline phone number (13 11 14) should they become distressed and/or experience suicidal thoughts.

The trial GP will follow up all participants with routine questions about “how is your mood?” at each weekly phone call. Patients will be monitored for deterioration in mood. If there are any minor concerns, the trial GP will advise the patient to see their GP. If during the weekly phone call a patient is found to be getting increasingly depressed then the trial GP will conduct further assessment to check level of negative mood and suicidal risk. Based on this assessment, the trial GP will then take the appropriate steps to ensure the participant’s safety.

**Team members with skills and experience in this area:**

Prof Geoff Mitchell is an experienced GP with skills and experience in management of depression.

Dr Gerben Keijzers is a senior staff specialist in the GCUH ED who has extensive experience in the processes related to mental health assessment in the ED.

**5.13.13 Overdose**

An overdose of pregabalin causes an exaggeration of the side effects that occur with normal doses.

## Drowsiness

In normal doses, pregabalin causes dizziness and drowsiness. When taken in excess, the medication causes profound drowsiness as well as excessive sleepiness. Pregabalin can also cause an abnormal gait that presents as uncoordinated movements of the muscles, including twitching and sudden involuntary jerking of the limbs. This predisposes a patient to falls, serious bodily harm and injuries related to falling. If an overdose of pregabalin is suspected, the patient should be watched and, when possible, remain seated or lie down until medical intervention is available.

## Confusion

Pregabalin can cause amnesia as well as confusion, euphoria and speech disturbances when taken in normal doses. In an overdose condition, these symptoms can escalate and the patient can be at risk of additional injury and possible fatality due to inability to remember simple but important things such as how much of the other prescription medications should be taken. When a patient taking pregabalin is confused or sounds incoherent, an overdose should be suspected and reported immediately to a physician.

## Headaches

Normal and over-dosage of pregabalin can also cause headaches, numbness and blurred vision. This also increases the risk of falls and injuries, especially in the elderly, seizure patients and other patients predisposed to falls. Pregabalin also cause fatigue and weakness.

## Blood Effects

Overdose of pregabalin can cause a breakdown in muscle fibers. Some of the fibers can deposit in the kidney and cause kidney damage. Possible symptoms of accumulation of fibers in the kidney include fatigue, pain in the joint and seizures. Breakdown of muscle fibers is sometimes difficult to diagnose in patients who are being treated with pregabalin for joint pain and seizures.

**5.13.14 Data Safety Monitoring Board (DSMB)**

An independent DSMB will be constituted to evaluate the safety aspects of the study, involving experts in the field of study. A charter for the DSMB will be in place. It will be responsible for safety reporting for the study, and assessing causality of the intervention for Serious Adverse Reactions (SAR) and Suspected Unexpected Serious Adverse Reactions (SUSAR). An annual safety report will be provided to the HREC by the committee.

## 5.14 Withdrawals

Participants can withdraw from the study at any time without prejudice to their current or future management. A participant must give verbal notification to study staff of their decision to withdraw. Regardless of whether a participant continues with the intervention arms, the follow-up schedule should continue unchanged for all randomised participants unless a participant chooses to withdraw from all follow-ups. If participants cannot complete follow-up outcome measures via the online survey tool or by mailed paper copy, alternative means (such as telephone survey or clinic visits) for completion will be explored. Participants will also be withdrawn it they develop any of the exclusion criteria.

Patients who withdraw during dosing will be made aware of the need to be weaned from the study medication.

Procedures for participants that are lost-to-follow-up and/or non-compliant with dosing will include possible home visits and communication with their GP as needed by the investigative team.

## 5.15 Statistical and methodological considerations

### **5.14.1 Sample size**

The primary outcome is change in neck pain intensity at 3 months post randomisation. For the full trial, a sample size of 180 participants (90/group) will provide 90% power to detect a difference of 1.5 out of 10 units of pain on the NRS, assuming a standard deviation of 2.542 , at 5% type 1 error level, and allowing for the possibility of dropout of 30% (Emergency Department (ED) patients). We have based the sample-size calculation on a between-group difference of 1.5/10 on the NRS on IMMPACT recommendations for clinical trials of chronic pain prevention41,50.

This is a pilot feasibility study so we will aim for 30 participants.

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### **5.14.2 Data analysis**

***Primary outcome***

All analyses will be conducted on an intention to treat basis and by a statistician blinded to group allocation. The primary outcome of change in neck pain intensity at 3 months from baseline will be compared between the treatment groups using standard analysis of variance technique, and the 95% confidence intervals of changes between the groups will be presented. Analyses of data from earlier studies and our simulation studies suggest approximate normality of the distribution of change in intensity score. Missing data will be examined for its randomness and addressed with multiple imputations, if required.

***Secondary Outcomes***

1. Neck pain intensity (NRS) at 3-, 6- and 12-month follow-up will be compared between treatment groups using standard analysis of variance technique, and the confidence intervals of changes will be presented from baseline between the treatment groups;
2. The proportions of patients maintaining or further reducing neck pain at , 6- and 12-month follow-up from neck pain intensity at 3-months will be compared between the treatment groups using logistic regression models. The odds ratios and 95% confidence intervals for the intervention group will be presented, compared to the standard treatment group.
3. NDI & PCS scores during follow-up will be analysed by non-parametric quantile regression technique (median regression), owing to the skewed distribution of these outcome measures.
4. Between treatment differences in PDS and DASS-21 measures will be analysed using the non-parametric quantile regression technique.
5. Differences in SF-12 scores between treatment groups will be analysed using non-parametric quantile regression techniques.
6. Differences in S-LANSS scores between treatment groups will be analysed using non-parametric quantile regression techniques.
7. Between treatment differences in breakthrough medication use will be analysed by non-parametric quantile regression technique (median regression), owing to the skewed distribution of these outcome measures.

For all measures of differences in scores described above, the median and the 95% confidence intervals of the median will be presented for both treatment groups.

Proportion of patients lodging a compensation claim will be compared using logistic regression. Odds ratio and 95% confidence intervals will be presented.

* + 1. **Data Storage**

The study data will be retained for a minimum of 15 years from the completion of the study, as per GCP and section 2.1.1 of the *Australian Code on the Responsible Conduct of Research*. While patients are in ED, each patient file containing the CRFs will be placed in a locked filing cabinet in the research office at the GCUH ED. After the patient has been discharged, the patient file will be transferred to a locked filing cabinet in the research office at the University of Queensland. Electronic records will be stored securely on a password–protected database on the University of Queensland server, accessible only to the research team.

## 5.16 Cost related data and analyses

***Direct costs***

Determined by cost diaries collected at each follow-up assessment over the 12 months duration of the trial (e.g. general practitioner, physiotherapy, chiropractor and pharmaceutical services) will be calculated using market prices estimated from the Medicare Benefits Schedule (MBS), worker’s compensation scheme payment schedules and the Pharmaceutical Benefits Scheme (PBS).

***Direct health-care cost*** (e.g., consumer co-payments) and non-health care costs, which are not captured by insurer payments will be identified using patient cost diaries. Patients will be asked to complete cost diaries in order to capture the direct costs; for example, other professional care, transportation costs and time spent by family members or volunteers providing care. Cost diaries have been shown to be a reliable and valid method to determine costs in cost-effectiveness research.

***The indirect costs*** associated with their injury include the patient’s lost economic productivity due to poor health. A shadow wage rate will be used to identify the ***opportunity cost*** of time spent away from work due to their injury. These costs will be calculated using income and employment data collected via a baseline questionnaire. We have successfully used these methods in our previous trials and have not had problems with participant compliance. Utility weights will be generated using trial participants’ SF-12 responses, translated to SF-6D utilities63. This study will use the new Australian algorithm that has been developed by Norman and colleagues64. The resulting cost-effectiveness measure will be a cost per QALY saved and we will subject the results to *n-*way sensitivity analyses, modelling second-order uncertainty (e.g., uncertainty the magnitudes of probabilities, treatment effects) where appropriate.

## 5.17 Quality assurance and data integrity

This trial will be conducted in accordance with the protocol, Manual of Procedures, ICH Guidelines for Good Clinical Research Practice and within all relevant local ethical regulations.

The integrity of trial data will be monitored by regularly scrutinising data sheets for omissions and errors. Data will be double entered and the source of any inconsistencies will be explored and resolved.

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, strictly following the GCP standards. The database will have the option for automated real-time alert on adverse events. All database development and management activities, and the management of randomisation for the study will be the responsibility of University of Queensland. Standard operating procedures are in place to conduct these activities to GCP standard.

## 5.18 Feasibility of the Study

* We have completed large RCTs and prospective studies on patients with whiplash and other musculoskeletal conditions and so have experience recruiting this patient group and delivering interventions within a trial environment and measuring outcome. We have experience and established channels to recruit participants from the EDs of the respective hospitals.
* Recruitment is very achievable. The trial research staff will be based in the EDs of the respective hospitals and will be available within the hours of 8am to 8pm, 6days/week. We have been recruiting from Gold Coast University Hospital (GCUH) ED for another trial and in the 6 month period Sept 2015-Feb 2016, have recruited 26 participants with acute WAD and pain ≥5/10. Therefore we anticipate it will take approximately 6 months to recruit 30 patients from GCUH.
* We have assembled a research team with the experience and expertise to successfully undertake this trial. The team have international reputations in the areas of management of whiplash injury (Sterling, McLean), acute pain medicine (Schug, Mitchell, McLean), emergency medicine (McLean, Keijzers), primary care (Mitchell, Nikles), pro-nociceptive measures (Sterling, Gibson), psychological factors (Gibson), health economics (Connelly) and statistics (Ware).
* CI Sterling and AI McLean have been internationally instrumental in conducting the extensive foundation research of whiplash injury that has led to the undertaking of this trial.
* AI McLean is conducting an ongoing sister trial in the US; CIA Sterling is a co-investigator on this study. Like the proposed study, this study is an ED-based intervention study evaluating the potential feasibility and efficacy of administering a medication to individuals at high risk of transitioning from acute to chronic musculoskeletal pain after MVC. (AI McLean is testing the serotonin-norepinephrine reuptake inhibitor venlafaxine.) To date in this ongoing study, 26 patients have been recruited in ED. All patients have had initial assessments successfully performed in ED. These data support the feasibility of ED-based studies to improve pain outcomes after whiplash injury, and the experience of members of the study team in performing the proposed study.

## 5.19 Outcomes and significance

The development of chronic pain and disability following ‘minor’ road traffic crash injuries such as whiplash is common and incurs enormous costs to the Australian community. Currently utilised treatments offer only modest benefit and improved outcomes are of great public interest. This trial will establish the effectiveness of an innovative early intervention delivered to ‘high-risk’ individuals in the Emergency Department. If successful, this trial will provide an effective and cost-effective intervention for a costly and treatment resistant condition. It will also have implications for the early management of other traumatic conditions beyond whiplash. The results of the trial will be published in major journals, influencing policy and practice on how care for whiplash injury is provided at a national and international level.

## 5.20 Funding

This trial is funded by NHMRC CRE in Road Traffic Injury Recovery and Menzies Health Institute Queensland, The University of Queensland.

## 5.21 Timeline

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Activity** | 2016 | 2017 | 2018 | 2019 |
| Ethics approval and trial setup |  |  |  |  |
| Accrual 1 years |  |  |  |  |
| Follow up 1 year |  |  |  |  |
| Data analysis and reporting 6 months |  |  |  |  |  |

## 5.22 Indemnity

The University of Queensland shall at all times indemnify their study investigators and their staff from claims that may be made against them for any injury sustained by a trial participant as a consequence of interventions used in this study in accordance with this protocol.

## 5.23 Publications and reports

The main results of this study will be submitted for publication in a prominent journal and all actively collaborating investigators will be acknowledged.

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