***Personalised Treatment Trials for Acute Whiplash Injuries: a pilot study***

***Protocol***

Contact details

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**Clinical Trial Registration number**: ACTRN12618001291279

**Administrative structure**

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

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

***Investigative team***

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## Protocol Signature Page

**Protocol Title:** Personalised treatment trials for acute whiplash injury: a feasibility study

**Short Title:** N-of-1 trials for acute 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 products paracetamol and naproxen) will be made available to all physicians, nurses and other personnel who participate in the conducting of this study. The Investigator will discuss this material with them to assure they are fully informed regarding the investigational product(s) and the conduct of the study.

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

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

**Investigator Signatory**:

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

**Sponsor Signatory**:

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| THE UNIVERSITY OF QUEENSLAND RECOVER INJURY RESEARCH CENTREDr Jane Nikles Coordinating Principal Investigator | SIGNATURE:DATE:  |

**N-of-1 trials for Acute Whiplash Summary Sheet**

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| **Name of Sponsor:** The University of Queensland |
| **Title of Study:** Personalised treatment trials in acute whiplash injury: a feasibility study  |
| **Principal Investigator:** Dr Jane Nikles, RECOVER Injury Research Centre, The University of Queensland.  |
| **Study Sites:**The study will recruit participants who present to the EDs of RBWH, Caboolture, Logan, Toowoomba, Beaudesert and Redlands hospitals,or physiotherapists/GPs; or who hear about the study through social media.  |
| **Study Period:** Dec 2017 to Dec 2018 | **Phase of Development:** Phase IV |  |
| **Aims and objectives:**The **primary aim** of this feasibility study is to conduct a series of N-of-1 trials comparing the effectiveness of a) evidence-based advice (EBA), b) paracetamol and EBA, c) naproxen and EBA, and d) both paracetamol, naproxen and EBA to reduce daily neck pain and to prevent chronic pain at 3 months following whiplash injury in 15 ‘at-risk’ individuals. **Secondary aims: clinical** 1. compare the effectiveness of evidence-based advice, paracetamol plus advice, naproxen plus advice, and both paracetamol and naproxen plus advice in decreasing (1) disability, (2) depression, (3) posttraumatic stress symptoms and (4) pain catastrophizing at 3 and 6 months following whiplash injury in ‘at-risk’ individuals.
2. improve precision of individual clinical recommendations for simple analgesics in ‘at-risk’ adults with acute WAD
3. aggregate data to obtain group estimates of intervention effects.
4. to record management decision post-trial and management and compensation claim lodgment at 3 and 6 months post-injury.

**Secondary aims: feasibility** 1. Proportion of screened patients eligible
2. Proportion of eligible patients enrolled
3. Enrolment rate (i.e. number of enrolments per month)
4. Logistic model for recruitment to a full trial, including staff requirements and strategies to overcome any barriers identified.
5. Feedback from ED clinicians, local GPs, trial GPs, and patients on their experience with the trial and areas for improvement, to inform a full scale trial.
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| **Methodology:**We will assess effectiveness of evidence-based advice, paracetamol plus advice, naproxen plus advice, and naproxen and paracetamol plus advice, for at risk patients with acute WAD, using patients as their own control, and produce individual reports, a world first use of this approach. Using a novel multiple baseline design, all patients will receive a randomized sequence of three cycles of ten day treatment triplets. Followup questionnaires will be administered at approximately 3 months following trial completion.  |
| **Planned number of participants:** 15 participants  |
| **Diagnosis and main criteria for inclusion:*** Individuals with Grade II Whiplash Associated Disorder
* Within 2 weeks of injury
* Moderate to high risk according to Whiplash Risk Stratification Tool (WhipPredict)
* Numerical Rating Scale pain score of 5 or more
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| 1. **Primary outcome:** Daily neck pain intensity at baseline, during trial, at end of trial, and at 3-month follow up. Neck pain intensity is measured on the continuous Numerical Rating Scale of 0 to 10, and will represent the patients’ self-report of average pain intensity during last 24 hours.
2. Confidence to perform daily activities: patients’ self-report of confidence to perform daily activities in the presence of neck pain or disability.
3. Adverse effects: Individual adverse effects and severity using the National Cancer Institutes of Health: Common Terminology Criteria for Adverse Events v3.0 (National Cancer Institutes of Health, 2010).
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| **Duration of study:** One year |
| **Statistical methods:**We will use Bayesian techniques to model trajectory data for three prognostic groups (high, intermediate and low risk) of non-recovery, to assess whether medication/s have an additional significant effect on neck pain pain intensity (daily, at treatment completion, and 3 months later) above and beyond natural recovery.  |

**EXECUTIVE SUMMARY**

***The problem:*** Whiplash, a common and potentially disabling condition, creates a huge burden1 and enormous costs to Australia2. Current treatments are not very effective;3,4 improved outcomes are urgently needed. Clinical guidelines recommend exercise, simple analgesia and evidence-based advice,5 but in practice, opioids are used too often and physiotherapy not enough.6 Inappropriate opioids for musculoskeletal injury are a growing problem.7,8 Also, several large randomised controlled trials (RCTs) show that so far *nothing effectively prevents chronic pain.9* Why? Whiplash associated disorders (WAD) are heterogeneous.10 A one-size-fits-all approach is not working; novel individually targeted approaches are needed. There have been no trials of guideline-recommended drugs (paracetamol and non-steroidal anti-inflammatory drugs (NSAIDS), and few of *any* medications including opioids.11 An RCT to test paracetamol against NSAIDs could be done, but, a large sample size is needed, which can cause slow recruitment, often needing multiple sites at high cost. Some patients do not want to be randomised or take placebo. And, results do not necessarily apply to all patients; averages could mask individual effects.

***Our solution:*** An alternative to RCTs is N-of-1 trials. These are personalised medication effectiveness tests, to identify which drug/s work or do not work and for whom. N-of-1 trials can be designed so that all patients take every treatment. Collecting their own data and receiving feedback empowers patients;12 important as passive coping predicts poor recovery. When aggregated, they are equivalent to RCTs and need far less patients to obtain the same power.13 Our team has world-leading experience in whiplash, N-of-1 trials, single-case experimental designs (SCEDs) (where the subject is his/her own control) and Bayesian statistics, increasingly being used in N-of-1 trials. But can N-of-1 trials be used in acute situations where some recovery is expected? N-of-1 trials and multiple-baseline designs (MBD) are types of SCEDs. MBDs study treatment effects by replicating treatments across multiple participants or settings. MBD have been used previously in traumatic brain injury (TBI) and stroke,14 where baseline is changing over time. **What:** We will conduct a series of N-of-1 trials nested in a MBD, with Bayesian statistical modelling of our prior data to account for natural recovery (see Figure 1). **Why:** Nesting N-of-1s in a MBD improves overall scientific rigor; we will get both group and individual results; all patients get all interventions; patients are empowered by their own data.

**Primary aim**: 1) Compare effectiveness of **a)** evidence-based advice (EBA), **b)** paracetamol (P)+EBA, **c)** naproxen (N)+EBA, and **d)** both (P+N)+EBA, to reduce daily neck pain and prevent chronic pain 3 and 6 months after injury in ‘at-risk’ individuals. **Secondary aims: 1)** Compare effectiveness of EBA, P+EBA, N+EBA and P+N+EBA in reducing disability, depression, posttraumatic stress symptoms and pain catastrophizing at 3 and 6 months; **2)** Improve precision of individual clinical recommendations for simple analgesics in ‘at-risk’ adults with acute WAD; **3)** Aggregate data to obtain group estimates of intervention effects. ***Significance:*** This will significantly improve health outcomes for WAD. Because we will identify responders and nonresponders to each intervention (and describe their relevant clinical and WAD characteristics), doctors and patients can more accurately identify which intervention/s are most suitable for an individual. If positive overall, doctors will have evidence to recommend, and patients will have more faith in taking, simple analgesia rather than opioids; targeted prescribing will reduce side effects; there will be positive impacts on return to work, quality of life, health service use, opioid overuse and societal cost. If negative, we can focus on alternative options. This cutting-edge method is a significant advance for WAD research and will also be useful for other WAD treatments and other acute conditions where natural recovery is expected.

# 1.0 BACKGROUND

***WAD is a common, costly and disabling condition*** Musculoskeletal (MSK) disorders are the second most common cause of disability worldwide.1 Low back and neck pain was the most common cause of disability in all high-income countries in 2015, measured by years lived with disability.15 WAD incur greater disability than non-traumatic neck pain16, so likely contributes to much of this burden. WAD from road traffic crashes (RTC) are an enormous and costly burden,2 with 50% of those injured never fully recovering and up to 30% living with moderate to severe disability17. WAD accounts for the vast majority (85%) of *any* submitted claims as well as the greatest incurred costs in the Queensland compulsory third party scheme.2 In Queensland the economic costs related to WAD exceeded $1.8 billion from 2003-2012.2 In Australia WAD comprise ~75% of all survivable RTC injuries with total costs of over $950 M annually.2

***Current treatment for acute WAD is not very effective*** Whiplash is defined as acute for the first 12 weeks after injury.18 Most recovery, if it occurs, takes place in this time, after which recovery plateaus17. The strongest predictor of poor recovery is higher initial levels of pain;19 initial pain levels of 5.2 to 5.5/10 and more can accurately predict poor recovery20, yet there are few studies on early management. Although current clinical guidelines recommend provision of advice, encouraging return to usual activity, and exercise5 (EBA) these provide only small effects3,4 and have not significantly improved overall physical and mental health outcomes9. Additionally, early multidisciplinary management (mainly physiotherapy and psychology) is no more effective than usual care10. Individual physiotherapists, however, see some patients improve, often dramatically, with specific approaches.It is possible these RCTs show little effect because of averaging of results. For example, the Managing Injuries of the Neck Trial found no difference in Neck Disability Index (NDI) between usual care and a whiplash booklet at 4, 8 and 12 months respectively: usual care mean [Standard Deviation (SD)]: 20.4 (17.2), 16.0 (16.4), 14.4 (16.0); and whiplash booklet: mean (SD) 21.5 (17.6), 16.6 (16.5), and 14.4 (15.9).21 These SDs reflect large variability, so it is possible that the overall results disguised individual variations in response. Figure 2 shows our data for a series of N-of-1 trials for fatigue. There was no significant difference between intervention and control overall (square point - Fig 2), yet individually, 8 patients were clear responders and one patient had more fatigue on treatment.22

**Figure 2**. Variation in individual patient responses represented within a single population22 4aggregate figure

***Other issues with RCTs*****1)** To account for heterogeneity RCTs must be quite large to achieve statistical significance, especially in effectiveness trials; need more resources; validity needs multiple sites; long trial run time may result in loss of relevance; large numbers of participants must be recruited quickly, so eligibility criteria must be broad; narrower inclusion criteria make it more difficult to recruit and to generalise results. **2)**. Efficacy trials may not be widely applicable to real life (strict inclusion/exclusion criteria; highly controlled setting). **3)** Cannot ethically randomise patients unless both treatments have equal clinical support **4)** Randomisation of individual patients may not always be possible; cluster randomisation has other disadvantages. Study results can be biased when blinding is not possible; patients may drop out or be non-compliant if randomised to non-preferred treatment. New directions are needed; clinicians and researchers are calling for individualised trials.23

***N-of-1 trials*** ***are an alternative*** ***design*** N-of-1 trials (individualised randomised controlled trials) are clinical trials that involve a single patient, serving as their own control. Each participant receives both study medication and placebo/comparator, and thus learns which treatment works best specifically for him/her. **They are a patient-oriented and clinically relevant method** tooptimise individual treatment and are recommended by the JAMA working group on EBM.24 RCTs and N-of-1 trials have different and complementary roles. RCTs define what happens at a population level by giving overall probability of success, whereas N-of-1 trials examine what happens for an individual. Systematic reviews of RCTs or randomised N-of-1 trials offer Level 1 evidence regarding treatment benefits.25 When aggregated, N-of-1 trials are of equivalent strength to RCTs26, 27 yet need fewer subjects because of greater statistical power22, so results can be obtained more quickly. Collecting their own data and receiving feedback empowers patients12, important in WAD. All patients receive each medication, avoiding patients declining because they may get placebo. Currently N-of-1s are rarely conductedin acute conditions because of the need for chronic stable conditions to allow fair comparisons between multiple treatment periods.

***Nesting an N-of-1 design in a Multiple-Baseline Design (MBD) improves overall scientific rigor***. N-of-1 trials are a subtype of single-case experimental designs (SCEDs), which as noted are defined as the subject serving as his/her own control, rather than using another individual/group. The withdrawal/reversal design of N-of-1 trials is becoming more commonly used in individualised medication clinical trials, while SCEDs are frequently conducted in the behavioural sciences28. MBDs, one of the four common types of SCED, are used to study treatment effects by replicating effect of a treatment variable across multiple participants, settings or behaviours. Baselines are established by repeated observation over time. Interventions are then implemented at different times for different participants, settings or behaviours. MBDs have been used in TBI, stroke, etc, where baselines are changing over time because of natural recovery.14 Advances inBayesian statistical techniques (a mathematical procedure that applies probabilities to statistical problems, providing tools to update results with evidence from new data) now provide a powerful way to adjust for changing baselines, allowing application of N-of-1 trials to acute conditions that change over time.

**Because to date no tested nonpharmacological treatments are significantly effective for WAD, it is now a priority to assess effectiveness of medications to prevent development of chronic pain and disability following whiplash injury23.**

***There is a significant evidence gap*** ***on the use of medication in early management of WAD.*** This has been proposed as an urgent research need for several years23 , yet very few drug trials have been undertaken11. Thus recommendations of Australian WAD management guidelines about pharmacologic treatments for acute WAD are based on consensus: “*Simple analgesics may be used as first line treatment for pain relief. NSAIDs may be used if simple analgesics are ineffective. Oral opioids may be necessary to relieve severe pain. Ongoing need….….. requires reassessment.”5*

Surprisingly, there is clear lack of evidence on the effectiveness of paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs) and opioids.11 Medication trials in related conditions, soft tissue and MSK injury, have mostly been of single doses or short duration, and have not shown clear superiority of one simple analgesic regime over alternatives. The majority of people with WAD are managed in primary care, so medications need to be easily administered, require little monitoring and have few side effects. Obvious choices are ***paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs)***. These simple analgesics are cheap, commonly used and available over the counter. Paracetamol and naproxen are optimal treatments for N-of-1 trials as they have short plasma half-lives (paracetamol 1-4 hours; naproxen 14 hours29) and there is no residual impact on target symptoms after excretion. Our work in osteoarthritis has shown variation in response to both; 17% of participants had better pain relief with celecoxib, 3% with paracetamol, the rest no difference30; and paracetamol was equal or more effective than ibuprofen in 68% of 54 patients31. It is important to identify which drug, if any, works better, in order to reduce adverse events (AEs) caused by medications that provide little benefit. The pathophysiology of WAD remains an enigma but raised inflammatory biomarkers are found, especially in moderate-severe cases.32 Paracetamol, NSAIDs and selective cyclo-oxygenase (COX)-2 inhibitors all have effects on inflammation by inhibiting prostaglandin synthesis. ***Paracetamol***is a para-aminophenol derivative with analgesic and anti-pyretic activity. Its mechanism of action is believed to include inhibition of COX activity33 primarily in the central and peripheral nervous systems, and inhibition of prostaglandin synthetase.34  Paracetamol can reduce hyperalgesia,35 which is a consequence of inflammatory processes in WAD36 and associated with higher reported pain and disability.37 ***NSAIDs***Of the nonsteroidal anti-inflammatory drug (NSAIDs), we chose naproxen because it is an appropriate first-line NSAID for mild to moderate recent onset pain (based on effectiveness, adverse effect profile, cost and over-the-counter availability).38 Naproxen has anti-inflammatory, analgesic, and antipyretic activities. Its mechanism of action, like that of other NSAIDs, is primarily to inhibit cyclooxygenase (COX) and therefore prostaglandin synthesis.39

***Which medications to test: medication comparisons and combinations*** In choosing which medications to compare, because there are no studies of simple analgesia in WAD, we reviewed systematic reviews of simple analgesia trials in acute low back pain (LBP), and acute soft tissue and musculoskeletal (MSK) injury. For *soft tissue injuries and MSK pain* in adults there was no important difference between NSAIDs and paracetamol, opioids or paracetamol plus opioid.40 For acute *MSK pain* (excluding WAD), NSAIDs and opioid analgesics were modestly effective short-term,41 but NSAIDs were not consistently superior to paracetamol, and paracetamol no better than placebo in acute LBP.42,43 Though NSAIDs were significantly better than placebo for acute LBP, effect size was not clinically important.44,45 Thus there is no clear evidence for any simple analgesics in these conditions. Many primary studies were of single doses or of short duration and none were in WAD. We also reviewed clinical guidelines. According to RACGP guidelines for pain management,46 paracetamol alone is no longer first-line treatment for most mild to moderate acute MSK pain because of lack of clinical effect41, 47-49 and possible superiority of NSAIDs.45 The National Institute of Clinical Studies guidelines for pain management in Emergency Departments (EDs)34 and Australia and New Zealand College of Anaesthetists Acute Pain Management review50 note that both paracetamol and NSAIDs are effective, but more effective if used together.51,52 We chose to compare naproxen, paracetamol, and both in individuals with acute WAD over 3 months, with 3 month follow-up.

***We have found very high use of opioids and compound analgesics for WAD*** Our recent work has shown that opioids are prescribed too often in both general practice (GP) and EDs for WAD: 39% of prescribed medications for WAD in general practice were opioids6. 49.4% of 265 patients receiving medication in ED for acute WAD received opioids, and 23.9% compound analgesics. Of 113 (33.8% of 334 WAD presentations) with a discharge prescription, 62 (54.9%) received compound analgesics, and 108 (40.8%) oral opioids. Early use of opioids in ED for RTC patients is associated with continued use 6 weeks later,49 with potential risk for opioid misuse. Alarmingly, 11,698 (37.1%) of all pharmaceutical claims by people with WAD listed in an Australian insurance database (n=31,498) were for opioids including compound analgesics. Prescription opioid misuse in the US and Canada is a public health crisis, and a similar problem is developing in Australia.53 If we obtain evidence that simple analgesics are effective, this will reduce long-term opioid use in WAD.

***Our solution: N-of-1 trials for simple analgesics in acute WAD*** A variable degree of natural recovery occurs in acute whiplash injury. CI Sterling has previously studied WAD’s natural recovery trajectory and her world leading research has laid the foundation for this project, because we have data for the natural recovery trajectory17. We have chosen this design because fewer people are needed to achieve sufficient power, reducing costs; we will get both group and individual results; all patients get all interventions; patients are empowered, important because passive coping and poor expectations of recovery are consistent prognostic factors for chronic neck pain and/or disability54. N-of-1 trials are suited to WAD because of its frequent heterogeneity10, (for example differing pain and disability levels, and presence or not of posttraumatic stress disorder (PTSD) symptoms). As we will also aggregate our results, we will study the subgroup at moderate to high risk of non-recovery55.

**1.2 Aims and objectives**

The **primary aim** of this feasibility study is to conduct a series of N-of-1 trials comparing the effectiveness of a) evidence-based advice, b) paracetamol and EBA, c) naproxen and EBA, and d) both paracetamol, naproxen and EBA to reduce daily neck pain and to prevent chronic pain at 3 and 6 months following whiplash injury in ‘at-risk’ individuals.

**Secondary aims: clinical**

1)compare the effectiveness of a) evidence-based advice, b) paracetamol and EBA, c) naproxen and EBA, and d) both paracetamol, naproxen and EBA in decrease in disability, depression, posttraumatic stress symptoms and pain catastrophizing at 3 and 6 months following whiplash injury in ‘at-risk’ individuals.

2) improve precision of individual clinical recommendations for simple analgesics in ‘at-risk’ adults with acute WAD

3) aggregate data to obtain group estimates of intervention effects.

**Secondary aims: feasibility**

1. Proportion of screened patients eligible
2. Proportion of eligible patients enrolled
3. Enrolment rate (i.e. number of enrolments per month per site)
4. Protocol compliance
5. Logistic model for recruitment to a full trial, including staffing requirements and strategies to overcome any barriers identified.
6. Feedback from ED clinicians, local GPs, trial GPs, and patients on their experience with the trial and areas for improvement, to inform a full scale trial.

**Objectives** are to:

1. To conduct N-of-1 trials comparing effectiveness and safety of a) evidence-based advice (EBA), b) paracetamol plus advice, c) naproxen plus advice, and d) paracetamol and naproxen plus advice to reduce daily neck pain and to prevent chronic pain 3 and 6 months after whiplash injury in ‘at-risk’ individuals.
2. To compare effectiveness of a) EBA; b) paracetamol plus advice, c) naproxen plus advice, and d) paracetamol and naproxen plus advice to decrease disability, depression, posttraumatic stress symptoms and pain catastrophizing; and improve health status and satisfaction with treatment, 3 and 6 months after whiplash injury in ‘at-risk’ individuals
3. To aggregate data from the series of n-of-1 trials to arrive at group estimates of effect for intervention effect
4. To record management decision post-trial, and management and compensation claim lodgment at 3 and 6 months post-injury.

**1.3 Hypotheses**

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

1. Paracetamol, naproxen, and evidence-based advice will be more effective and safer than (i) paracetamol plus advice (ii) naproxen plus advice or (iii) advice alone in reducing neck pain intensity at 3 and 6 months following whiplash injury.
2. Paracetamol, naproxen, and evidence-based advice will be more effective and safer (i) paracetamol plus advice (ii) naproxen plus advice or (iii) advice alone in reducing disability, depression, posttraumatic stress symptoms and pain catastrophizing at 3 and 6 months following whiplash injury.

**2.0 METHODS**

 **2.1 Overview of study design**

The study will be a series of N-of-1 trials nested in multiple-baseline design (MBD) comparing

**1)** *evidence-based advice (EBA)* (intervention 1, phase B);

**2)** *paracetamol + EBA* (intervention 2, phase C);

**3)** *naproxen + EBA* (intervention 3, phase D); and

**4)** *paracetamol +naproxen + EBA* (intervention 4, phase E) for patients with recent onset WAD.

Intervention will commence as soon as possible but within 2 weeks of injury.

The trial protocol conforms to CENT guidelines and will be registered on the Australian and New Zealand Clinical Trials Registry. It also adheres to the IMMPACT recommendations for the design of clinical trials for chronic pain prevention (Gewandter et al, 2015).

**2.2 Design**

***Detailed description of trial design***

This is a series of N-of-1 trials nested in a multiple-baseline design (MBD) comparing **1)** *evidence-based advice (EBA)* (intervention 1, phase B); **2)** *paracetamol + EBA* (intervention 2, phase C); **3)** *naproxen + EBA* (intervention 3, phase D); and **4)** *paracetamol +naproxen + EBA* (inter-vention 4, phase E) for patients with recent onset WAD. Baseline NRS pain scores will be collected for 5, 8, or 11 days in phase A (no intervention), followed by Phase B (Intervention 1, EBA). for 5 days.  Effectiveness will be evaluated using a series of MBDs across 3 participants at a time28; that is, each MBD will contain 3 tiers, one per participant (Fig 3; simulated data).  After phase B (intervention 1, EBA), there will be 3 cycles of randomised CDE triplets in each tier (ie for each patient) to control for sequencing effects. This design controls for threats to internal validity as the lengths of phases A are staggered across the 3 patients (phase B starts 5, 8, 11 days post enrolment. Each group of 3 participants will begin Phase A at the same time as far as is practical. External events are one of the major threats to internal validity. If one such event coincides with onset of treatment, it is not possible to know whether the intervention or the external event is responsible for any change in the target symptom.  It is unlikely that this will occur for each participant exactly at commencement of the interventions, because of staggering of phase A length. Internal validity is further bolstered by replication across the 3 participants within each MBD, each having 3 cycles of CDE intervention.

***Interventions***

**Advice booklet**All patients will receive an evidence-based advice (EBA) booklet to use from the start of phase B until the end of the last treatment phase. Based on current Australian Guidelines for WAD Management,5 and input from consumers and health care professionals, *WAD Injury Recovery: A Self Help Guide56* provides information about WAD; assurance about prognosis; advice to stay active and resume working; information on correct posture; pictures of specific exercises for the neck and upper limbs; and information on resuming daily activities. Effect size from this booklet itself is unknown, though there is some evidence for small effects from staying active and doing specific exercises for the neck and upper limbs.5

**Medications** There will be 3 cycles of 10-day triplets of paracetamol 1g four times daily (phase C) or naproxen sodium 137.5 mg four times daily (phase D) or both (phase E) (90 days active treatment), then a 10-day observation phase (phase F), using a double dummy design, so the timing of doses does not unblind. Data from first 3 days of each treatment period will be discarded to ensure no carryover.

**2.3 Setting**

Community patients recruited via EDs of RBWH, Logan, Toowoomba, Beaudesert, Redlands and Caboolture hospitals, online via social media/websites, through local GPs and physiotherapists, and pamphlets and posters.

**2.4 Eligibility criteria**

***Inclusion criteria*:**

* Individuals with Grade II WAD and within 2 weeks of injury.
* Moderate to high risk according to the Whiplash Risk Stratification Tool (WhipPredict), a validated tool for predicting ongoing moderate/severe disability following acute whiplashinjury57. See Figure 4 for the algorithm used by WhipPredict to predict the risk of disability following acute whiplash injury.
* Initial Numerical Rating Score (NRS) pain score58 of 5 or greater.

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***Exclusion criteria:***

* Pre-existing 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, and still symptomatic;
* Long term use of Paracetamol or NSAIDs for other chronic conditions (e.g. back pain, joint pain/arthritis)
* Long term analgesics such as opiates, tramadol, etc and adjunctive analgesics for neuropathic pain such as pregabalin, amitriptyline, etc
* Known hypersensitivity to paracetamol or naproxen or to any excipients (hives, blisters, rash, dyspnea and wheezing);
* Asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs;
* History of renal insufficiency (eGFR<60ml/min/1.73m2 or ACR >3 mg/mmol)
* Patients on diuretics, angiotensin converting enzyme inhibitors or angiotensin receptor blockers
* Severe active liver disease that in the clinican’s judgement excludes the patient;
* Patients who are severely malnourished, anorexic, septic, have a low body mass index or are chronic heavy users of alcohol.
* Women who are pregnant or breastfeeding
* History of severe or uncontrolled psychiatric illness or substance abuse
* Patients who are smokers or obese (BMI > 30)
* Inability to speak and write in English (participants will be required to complete questionnaires written in English only)
* Older than 65 years
* Use of concomitant drugs that increase the risk of upper GI bleeds/perforation e.g. anticoagulants, antiplatelet drugs, or corticosteroids
* Current H. pylori infection or past infection where the clinician considers a risk of upper GI bleeding persists.
* Prior history of peptic ulcer disease and/or gastrointestinal bleeding
* History of inflammatory bowel disease
* Uncontrolled hypertension, symptomatic heart failure and persistent peripheral edema.
* Cardiovascular risk/history  ≥10% within 5 years or history of established CVD (eg unstable angina or MI, not including hypertension).
* Patients undergoing or planning to have surgery during the next three months.

**2.5 Study Measurements**

The following outcome measures will be assessed at baseline and at follow-up. Every attempt (within ethical guidelines) will be made to obtain outcome data, regardless of subjects’ compliance with trial protocols.

**Primary outcomes** *Assessed at baseline, during trial, at end of trial and at 3-month follow-up*

1. Daily neck pain intensity: patients’ self-report of average pain intensity during last 24 hours on Numeric Rating Scale (NRS) 0-10.58
2. Confidence to perform daily activities: patients’ self-report of confidence to perform daily activities in the presence of neck pain or disability.

**3)** Adverse events and severity using National Cancer Institutes of Health: Common Terminology Criteria for Adverse Events.59

**Secondary Outcomes**

*At end of each treatment period, end of trial and at 3-month follow-up*: Neck Disability Index;60 Patient global impression of change (-5 to +5 scale);61 Patient Global Assessment of Treatment Satisfaction scale;62 Pain Catastrophising Scale;63 PTSD Checklist for DSM-564 (PCL-5); [Depression & Anxiety Stress Scales](http://www.psy.unsw.edu.au/research/research-tools/depression-anxiety-stress-scales-dass) (DASS-21);65 generic measure of health status scores (EQ-5D-5L).66

*Throughout the trial*: daily number of oxycodone doses taken

**3)** *At post-trial F/U*: Management decision at review 2 weeks post N-of-1 trial; compensation claim lodgement.

**4)** *At 3-month F/U only*: Concordance with post N-of-1 trial decision; compensation claim lodgement.

**2.6 Trial Procedure**

The trial process can be likened to a pathology test, testing for medication effectiveness.

***Recruitment and Screening***

Community patients with WAD will hear about the trial through pamphlets and posters in the rooms of private physiotherapists, flyers, Recover Injury Research Centre website and other online methods/social media (eg. Twitter)and Emergency Departments of RBWH, , Logan, Toowoomba, Beaudesert, Redlands , and Caboolture Hospitals. Patients diagnosed with grade II WAD by doctors will be referred to ED physiotherapists, who will present patients with the permission to contact form. After signing the permission to contact form or registering on the Recover website, the RA will pre-screen participants for inclusion and exclusion criteria (Form P Prescreening form). If they pass prescreening, wewill contact their GP to do further screening (i.e. more extensive exclusion criteria) using Form SC. Eligible participants will provide informed consent and receive the medication script from either the trial GP or their own GP.

***Baseline***

A baseline questionnaire will be completed on personal characteristics and information about symptoms of whiplash, specifically:

1. Neck pain intensity (NRS average over 24 hours)
2. Neck disability index (NDI)
3. Depression, Anxiety and Stress Scale (DASS-21)
4. PTSD Checklist for DSM-5 (PCL-5)
5. Pain Catastrophising Scale (PCS)
6. Generic measure of health status scores (EQ-5D-5L)
7. Patient expectations of a beneficial treatment effect, scored from 1 to 4 with higher scores indicating higher expectations.

The research staff provide medication instructions, and answer any queries. The patient is allocated a randomisation number, and the RA organises for a kit to be given or posted to the patient containing medication, medication instructions, patient safety card, and return envelope to patient’s nearest pharmacy. The RA then goes through the trial documents, the method of recording the symptom diary data is explained, and a patient safety card is given to the patient. Contact details of the RA, including mobile number, are left with the patient, who is asked to contact the RA immediately if they have any questions or concerns. RA will send the advice booklet via post for patients to receive one day before Phase B begins for them. RA will instruct the patient when to start using the advice booklet and commence the Phase B diary.

***Trial phase***

During the trial, all participants will be required to maintain symptom diaries in which they will record information such as pain scores, other treatments, and medication taken. Patients will be asked about progress, any queries and adverse events weekly by the RA during followup phone calls. During the trial, the trial GP will evaluate the patients via telephone review as needed, if the patient’s pain is uncontrolled or they are having any adverse effects. Participants will also be able to contact trial research staff if they have questions regarding the medication or any side effects.

***Individual report***

After 12 weeks, the data are analysed. We want to avoid missing a benefit that may occur and have therefore, taken a pragmatic approach in a trial of 12 weeks of treatment in total. An individual report on the effectiveness of the interventions is produced and sent to the referring doctor for discussion with the patient. Patients will be unblinded during the process of discussing their results with their doctor based on the individual report provided by trial staff. Thus the trial will provide direct and immediate feedback to patients about effectiveness and safety of paracetamol/NSAIDs/EBA for them. This is an advantage of N-of-1 trial methodology over other epidemiological approaches.

***Followup***

At 3 months after the post trial consultation, a brief questionnaire will assess pain and current medication, any other treatments, secondary outcome measures, and their perceptions of the trial’s usefulness.

**2.7 Interventions**

***Advice booklet***

All patients will be provided with an evidenced-based 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, from the start of phase B until the end of the last treatment phase. 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 Management (MAA 2014). Effect size from this booklet itself is unknown, though there is some evidence for small effects from staying active and doing specific exercises for the neck and upper limbs.

***Medications***

There will be 3 cycles of 10-day triplets of paracetamol 1g four times daily (phase C) or naproxen sodium 137.5 mg four times daily (phase D) or both (phase E) (90 days active treatment), then a 10-day observation phase (phase F), using a double dummy design, so the timing of doses does not unblind. Data from first 3 days of each treatment period will be discarded to ensure no carryover.

To ensure blinding of doctors, research staff and participants, both Paracetamol and Naproxen Tablets will be identical in every way by using encapsulation. Study medication will be prepared according to the randomisation schedule by a pharmacist not involved with data collection, then sealed in medication kits. Upon recruitment, the pharmacy staff will provide a sealed medication pack to the participant (blinded).

**2.8 Co-interventions**

Participants who experience high levels of continuing or worsening pain will be able to contact research staff to return for an earlier review with the GP. In some instances, rescue medication (oxycodone 5mg prn) can be provided in addition to the study medicine. These medications are consistent with current clinical practice guidelines for WAD management. Patients will be provided with the rescue medication if they have continuing and worsening pain that is debilitating in nature (in the short term) or continuing high levels of pain that have not improved after 2 days of treatment, despite following the trial regimen. Participants will be provided with rescue medication for 2 days duration.

At the end of the trial, in respect of the compensable nature of a whiplash injury, the patients will be permitted to seek further treatment if required. Information about any additional treatments sought by participants (eg additional medication, physiotherapy etc.) will be gained via patient diaries at the 3 month follow-up time point.

**2.9 Adherence to Study Medication**

Adherence with the study medications will be assessed in three ways: (1) daily self-recorded medication intake, (2) the trial staff will ask about adherence during the planned telephone-based reviews starting at 1 week post randomization and (3) counts of returned tablets following the completion of treatment. Participants will be asked to return all unused tablets for counting at the end of the treatment period in a reply paid post satchel.

* 1. **Randomisation**

The randomisation codes in variable block sizes of 4-6 will be generated by the study statistician following standard statistical procedures and sent to the study dispensing pharmacy. Each individual receives interventions 2, 3 and 4 in a randomised sequence within a triplet, over three treatment triplets, which controls for sequencing effects. Each tier is randomised separately; each MBD is independent of the others. Figure 2 illustrates a hypothetical randomisation sequence. The schedule will be kept in a sealed envelope in a locked filing cabinet in the pharmacy, and 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 an independent pharmacist, and sealed in medication kits. Following baseline assessment, research staff will provide the next kit to the participant.

**2.11 Blinding**

 The randomisation process and double dummy design will ensure concealed allocation and triple blinding of research staff, trial GPs, participants, investigators, health care providers, and data analyst. Study drugs and placebos (needed for double dummy design) will be identical in every way (appearance, volume, weight, odour, taste) by using overencapsulation of powdered original drugs.

### 2.11.1 *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 criteria 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 request 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 randomisation 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 The 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, to 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 PI that a participant is unblinded, or off trial treatment. The PI will advise the investigative team and research assistants. After being off-treatment, the PI 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.**

## 2.11.2 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.

**2.12 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 RA. Participants will be able to contact trial staff at any time of the day 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 doctor 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. All adverse events will be reported to the relevant ethics committees. The most common side effects reported with paracetamol usage are nausea, vomiting, constipation and with naproxen, gastrointestinal (heartburn, abdominal pain, constipation) and CNS (headaches, somnolence, tinnitus, vertigo) symptoms. More severe side-effects are rare and are listed in sections 2.12.12 and 2.12.13.

**2.12.1 *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.

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.

## 2.12.2 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 the end of the treatment phase, and 3 and 6 month follow-up if the participant remains on trial medication. 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.

## 2.12.3 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.

## 2.12.4 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.

## 2.12.5 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-threatening to the TGA within 7 calendar days, and all other SUSARs, no later than 15 calendar days of being made aware.

**2.12.6 *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.

##  2.12.7 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.

## 2.12.8 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.

## 2.12.9 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.

## 2.12.10 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 gastrointestinal ulcers, bleeds, perforation, stomach pain, heartburn, blood in the stool, or black and tarry stools, heart attack, stroke.

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 UQ 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.

**2.12.11 *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.

**2.12.12 *Existing known adverse drug reactions of paracetamol***

### Hepatic

### Common (1% to 10%): Increased aspartate aminotransferaseRare (less than 0.1%): Increased hepatic transaminases Frequency not reported: Liver failure

### Gastrointestinal

Very common (10% or more): Nausea (up to 34%), Vomiting (up to 15%)
Common (1% to 10%): Abdominal pain, diarrhea, constipation, dyspepsia, enlarged abdomen
Frequency not reported: Dry mouth

### Hypersensitivity

Postmarketing reports: Anaphylaxis, hypersensitivity reactions

### Hematologic

Common (1% to 10%): Anemia, postoperative hemorrhage
Very rare (less than 0.01%): Thrombocytopenia, leucopenia, neutropenia

### Dermatologic

Common (1% to 10%): Rash, pruritus
Rare (less than 0.1%): Serious skin reactions such as acute generalized exanthematous pustulosis, Stevens-Johnson syndrome, and toxic epidermal necrolysis
Very rare (less than 0.01%): Pemphigoid reaction, pustular rash, Lyell syndrome

### Respiratory

Common (1% to 10%): Dyspnea, abnormal breath sounds, pulmonary edema, hypoxia, pleural effusion, stridor, wheezing, coughing

### Cardiovascular

Common (1% to 10%): Peripheral edema, hypertension, hypotension, tachycardia, chest pain

### Metabolic

Common (1% to 10%): Hypokalemia, hyperglycemia

### Nervous system

Common (1% to 10%): Headache, dizziness
Frequency not reported: Dystonia

### Musculoskeletal

Common (1% to 10%): Muscle spasms, trismus

### Psychiatric

Common (1% to 10%): Insomnia, anxiety

### Genitourinary

Common (1% to 10%): Oliguria

### Local

Common (1% to 10%): Infusion site pain, injection site reactions

### Ocular

Common (1% to 10%): Periorbital edema

### Other

Common (1% to 10%): Pyrexia, fatigue
Rare (0.01% to 0.1%): Malaise

***2.12.13 Existing known adverse drug reactions of naproxen***

**Gastrointestinal**

Common (3-9%): abdominal pain, constipation, nausea, heartburn

Less common (1-4%): GI bleeding, GI perforation, GI ulcers

Less common (1-3%): diverticulitis, stomatitis, diarrhea, dyspepsia

Rare (<1%): glossitis, colitis, hematemesis, pancreatitis, aphthous stomatitis, melena

NSAIDs including this drug, can cause serious gastrointestinal (GI) events which can occur at any time, with or without warning. For patients who develop a serious upper GI event, only about 20% were symptomatic. Upper GI ulcers, gross bleeding, or perforation occurred in approximately 1% of patients treated with NSAIDs for 3 to 6 months and 2% to 4% of patients treated for 1 year. Patients with a prior history of peptic ulcer disease and/or GI bleeding had a greater than 10-fold increased risk for developing a GI bleed than patients with neither of these risk factors.

**Hepatic**

Very common (1-10%): increased liver enzymes

Rare (<1%): hepatitis, hepatic failure, hepatotoxicity, jaundice

**Renal**

Common (1-10%): Renal function abnormality

Rare (<1%): interstitial nephritis, oliguria, polyuria, dysuria, renal failure, renal papillary necrosis, proteinuria

**Dermatological**

Common (3-9%): pruritus, skin rash, ecchymosis

Less common (<3%): diaphoresis

Rare (<1%): exfoliative dermatitis

**Hematological**

Common (3-9%): hemolysis

Less common (<3%): purpura, anemia, prolonged bleeding time

Rare (<1%): thrombocytopenia, leukopenia

**Hypersensitivity**

Rare (<1%): angioedema, anaphylaxis, Stevens-Johnson syndrome, epidermal necrolysis, urticaria

**Metabolic**

Common (3-9%): fluid retention

Less common (<3%): increased thirst

Rare (<1%): hypoglycemia, hyperglycemia

**Nervous** **System**

Common (3-9%): dizziness, drowsiness, headache

Less common (<3%): vertigo

Rare (<1%): paresthesia, seizure, syncope, coma, confusion, aseptic meningitis

**Respiratory**

Common (3-9%): dyspnea, pneumonia

Rare (<1%): asthma, respiratory depression

**Cardiovascular**

Common (3-9%): edema

Less common (<3%): palpitations

Rare (<1%): myocardial infarction, hypertension, vasculitis, tachycardia

Clinical trials of several cyclooxygenase (COX)-2 selective and nonselective NSAIDs of up to 3 years duration have shown an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. All NSAIDs appear to have a similar risk. There is no consistent evidence that concurrent use of aspirin mitigates this increased risk and may be associated with an increased risk of serious gastrointestinal events.

**Ophthalmic**

Less common (<3%): visual disturbance

Rare (<1%): conjunctivitis, blurred vision

**Otic**

Common (3-9%): tinnitus

Less common (<3%): auditory disturbance

**Psychiatric**

Rare (<1%): abnormal dreams, hallucination, depression

* 1. ***Trial Data management***

 A regulatory approved electronic data capture system (Redcap) with web hosting facility will be used to collect all clinical and safety data for this proposed study, following 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 the investigative team. Standard operating procedures are in place to conduct these activities to GCP standard.

 ***Data management and monitoring***Data will be collected and managed at Recover Injury Research Centre, UQ (Recover),

The trial protocol conforms to the Single-Case Reporting guideline In Behavioural interventions67 and Consort Extension for reporting N-of-1 trials guidelines68 is registered on Australian and New Zealand Clinical Trials Registry; and adheres to IMMPACT recommendations for design of clinical trials for chronic pain prevention.69

***2.14 Ethics:***

Approved by The University of Queensland HREC #2017001870 and Darling Downs Hospital and Health Service HREC (HREC/18/QTDD/36). All patients will give written informed consent.

***2. 15 Data Safety and 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. Members of the DSMB include Jacelle Warren, biostatistician, Kathryn Steadman, pharmacist and Michaela Kelly, GP.

**2.16 Study schedule**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Protocol Activity** | **Screening** | **Phase A** **(Baseline)** | **Phase B** | **Phases C-E****(Treatment)** | **Phase F** | **3 month follow up** |
|  | Clinic  | Phone/Clinic  | Clinic |  Phone/Online/Post  | Phone/Online/Post  |
| Informed Consent | X |  |  |  |  |  |
| Screening | X |  |  |  |  |  |
| Demographics | X |  |  |  |  |  |
| Clinical Assessment | X |  |  |  |  |  |
| Expectations of beneficial treatment effect | X |  |  |  |  |  |
| Randomise | X |  |  |  |  |  |
| Dispense medication |  |  |  | x |  |  |
| **Daily during trial (A-F in Figure 2)** |  |  |  |  |  |  |
| NRS (pain) 24 hours |  | X | X | X | X | X |
| Confidence to perform daily activities |  | X | X | X | X | X |
| **At end of each treatment period** |  |  |  |  |  |  |
| NDI |  | X | X | X | X | X |
| PGATS |  |  |  | X | X |  |
| PGIC |  |  |  | X | X | X |
| PCL-5 |  | X | X | X | X | X |
| PCS |  | X | X | X | X | X |
| DASS-21 |  | X | X | X | X | X |
| EQ-5D-5L |  | X | X | X | X | X |
| Adverse events |  |  |  | X | X | X |
| Concomitant medications |  | X | X | X | X | X |
| Management decision |  |  |  |  |  | X |
| Drug accountability and returns |  |  |  |  |  | X |
| Claim lodgement |  |  |  |  | X | X |

**Forms are listed in the order given to participants**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Protocol Activity** | **Pretrial** | **Phase A** **(Baseline)** | **Phase B** | **Phases C-E****(Treatment)** | **Phase F** | **3 month follow up** |
| **Permission to contact form**  | **X** |  |  |  |  |  |
| **Participant Information Sheet** | **X** |  |  |  |  |  |
| **Consent to Participate** | **X** |  |  |  |  |  |
| **Form P Pre-Screening** | **X** |  |  |  |  |  |
| **Form SC**  | **X** |  |  |  |  |  |
| **Form Z**  | **X** |  |  |  |  |  |
| **Baseline Questionnaire**  | X |  |  |  |  |  |
| **Phase A Observational Diary** |  | X |  |  |  |  |
|  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |
| **Phase B Observational Diary**  |  |  | X |  |  |  |
| **Participant Symptom Diary (Cycle 1, 2, 3)**  |  |  |  | X |  |  |
| **Phase F Observational Diary**  |  |  |  |  | X |  |
| **FUM3**  |  |  |  |  |  | X |

***Statistical approach and methods*** In SCEDs, a model-based approach is flexible, and allows aggregated analysis. A sophisticated approach for analysing N-of-1 data is to fit a hierarchical model within a Bayesian framework70,71 to take into account variability at all levels, and facilitate use of prior data. We will use a Bayesian modelling framework which accounts for a changing baseline and also provides inference at individual and group level. We have developed an empirical Bayesian hierarchical model for the pain trajectory of natural recoveryfor the moderate to high-risk group (Whip-Predict55) with initial NRS>=5 (Figure 4). Data are from a prospective longitudinal study of prognostic factors for poor functional recovery72  and from the control arm (usual care) of an RCT.10 Thus, we can predict the recovery expected. Figure 5 shows actual data for individual pain trajectories for those in the moderate to high-risk group (Whip-Predict55) with initial NRS >= 5.Data fromEBA alone and from each phase of the N-of-1 trials with active medication treatment will be aggregated using a Bayesian hierarchical model where random effects account for repeated measures (within patients) over time.  As the patients in Sterling et al (2010) are different from those in this study, we cannot assume our empirical model will be directly transferrable. Demographics of our sample will be compared to those of the moderate to high risk group with NRS >=5 from Sterling et al (2010). We will calibrate the model using data from phase A to ensure our model for natural recovery is applicable to this study. Then, when on an intervention, the outcome will be judged based on what is predicted by the empirical model (for a given point in time).  It is unknown how (or if) each intervention will affect pain. Typically, in N-of-1 trials where natural recovery does not need to be accounted for, treatment effects are assumed to be additive. This will be explored in our analysis but we will also consider including treatment effects in other ways, eg treatment effect may depend on severity, and thus multiplicative effects would be appropriate.  Further, treatment may increase the rate of recovery so treatment effect may need to be included in a non-additive manner.  This is a problem of model choice, and, as no prior data are available to inform this problem, we will be guided by what information is available in the data, adopting formal model selection techniques from Bayesian statistics to determine the preferred approach.  The inclusion of additional covariates eg age, gender, will also be explored, and decisions about inclusion made through formal model choice procedures. On estimating the model for natural recovery and appropriately including intervention effects, overall participant response against natural recovery will be calculated as follows: **1)** posterior mean differences in population and individual expected outcomes compared to natural recovery at the end of the trial and at 3 months follow up will be evaluated with associated 95% credible intervals; and **2)** the posterior probability that the intervention effect is >= average of 1.5 NRS points better than natural recovery will be estimated. We will take >= 1.5 points on NRS scale to be a clinically significant difference.69 For each intervention, a patient will be deemed a responder to that intervention if the corresponding individual level difference to natural recovery is >= 1.5 NRS points.  If there is >= 1.5 NRS points difference between two interventions, they will be deemed to respond better to that intervention. Effect sizes will be calculated when we know how the interventions will be included in the model (additive, multiplicative, etc).

* 1. ***Study Sample Size***

We will recruit 15 patients to this pilot study.

**3.15 *Study Sites***

Participants will be recruited from RBWH, , Logan, Toowoomba, Beaudesert, Redlands and Caboolture EDs. Patients will also be recruited through local physiotherapists and GPs, and may also hear about the study through online sources/social media.

**3.16 *Time Line***

Study/protocol set up Oct-Nov 2017; commence recruitment June 2018, complete recruitment September 2018, analysis & manuscript preparation by December 2018.

|  |  |  |
| --- | --- | --- |
| **Activity** | Jan-June 2018 | July-Dec 2018 |
| Ethics approval 2 months |  |  |  |
| Trial setup 4 months |  |  |  |
| Accrual 6 months |  |  |
| Analysis and reporting |  |  |

**3.18 *Feasibility of the Study***

1. Recruitment is very achievable. Based on recruitment rates to our other trials using similar recruitment methods, 15 patients in one year is feasible for a 4-month trial, allowing 5 months setup time, 6 months for conducting the trial and 1 month for data analysis and reporting.For APP1069443 CI Sterling recruited 120 participants from Gold Coast ED in 18 months, and for APP1075736 is recruiting at a similar rate from each of 2 other EDs in Queensland.
2. We have assembled a research team with the experience and expertise to successfully undertake this trial.
3. CI Sterling has been internationally instrumental in conducting the extensive foundation research of whiplash injury that has led to the undertaking of this trial. **CI Sterling has a history of successful retention and compliance in RCTs:** eg a 90-95% retention rate in recently completed RCTs for WADand APP1069443.

**3.19 *Outcomes and significance***

*Outcomes*

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 assess the effectiveness of early interventions used commonly because they are recommended by clinical guidelines, however there is no evidence for their use. The intervention will be delivered to ‘moderate to high-risk’ individuals recruited through Emergency Departments using an innovative clinical tool, N-of-1 trials. If successful, this trial will provide evidence for effective simple interventions for a costly and treatment resistant condition.

*Significance*

The evidence gap on pharmacological treatment of whiplash is of concern, particularly in the light of recent work on low back pain, which shows that paracetamol is not effective (Williams et al, 2014), and NSAIDs are of limited benefit (effect sizes are small and not clinically significant)(Machado et al, 2016). Because 15 patients will provide sufficient inter-subject replications, if any tested treatment is shown to be effective (or more effective) with clear, consistent, significant effect sizes, study results will be directly translatable to clinical practice, as these medications are readily available and recommended in WAD management guidelines. Our results will also give a probability of response and side effects to each treatment, which can guide treatment recommendations. This has potential to confirm or change current practice on how care for WAD is provided at a national and international level. Results will be disseminated via Q1 journals, conferences and professional networks of the team and Recover, and consumer networks of Chronic Pain Australia. If N-of-1 trials are feasible to use in this situation, there are implications for trial design in other WAD treatments, and for other acute conditions where natural recovery occurs, eg in rehabilitation (stroke, TBI), postoperative pain, and deteriorating chronic conditions with changing baselines. Some of these are suitable for using observation periods rather than relying on prior data, which may not exist. *We anticipate this study will determine the best intervention/s for each individual, and overall, will strengthen the evidence on EBA and simple analgesics for people with WAD and their clinicians.*

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