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OPAL: The first placebo-controlled trial of opioid analgesia for acute spinal pain. Trial protocol

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OPAL: The first placebo-controlled trial of opioid analgesia for acute spinal pain.

Trial protocol

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Keywords

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ABSTRACT

Introduction Low back pain and neck pain are extremely prevalent and are responsible for an enormous burden of disease globally. Strong analgesics, such as opioid analgesics, are recommended by clinical guidelines for people with acute low back pain or neck pain who are slow to recover and require more pain relief. Opioid analgesics are widely and increasingly used, but there are no efficacy data supporting the use of opioid analgesics for acute low back pain or neck pain. Concerns regarding opioid use are further heightened by the risks of adverse events, some of which can be serious (e.g. dependency, misuse and overdose).

Methods and analysis OPAL is a randomised, placebo-controlled, triple-blinded trial that will investigate the judicious use of an opioid analgesic in 346 participants with acute low back pain and/or neck pain who are slow to recover. Participants will be recruited from general practice and randomised to receive the opioid analgesic (controlled release oxycodone plus naloxone up to 20 mg per day) or placebo in addition to guideline care for up to 6 weeks. Participants will be followed for 3 months for effectiveness outcomes. The primary outcome will be pain severity. Medication-related adverse events will be assessed and a cost-effectiveness analysis will be conducted. We will additionally assess long-term use and risk of misuse of opioid analgesics for up to 12 months.

Ethics and dissemination Ethical approval has been obtained. Trial results will be disseminated by publications and conference presentations, and via the media.

Registration Australian New Zealand Clinical Trials Registry: ACTRN12615000775516

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STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is the world's first placebo-controlled trial to investigate whether using a short course of an opioid analgesic, in people who are slow to recover from acute low back pain or neck pain, can effectively reduce pain, improve other outcomes (e.g. function), be reasonably tolerated and cost-effective, and have minimal risk of long-term misuse.
- The trial will inform the appropriate and judicious use of opioid analgesics.
- Results of the trial may be limited to the opioid analgesics used (controlled release oxycodone plus naloxone).

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INTRODUCTION

Low back pain and neck pain are among the most burdensome conditions globally.[1] The enormous burden of these conditions is associated with their high prevalence: the 1-year prevalence for low back pain and neck pain is 38% and 26% respectively.[2 3] There is also a high economic burden: the latest estimates show that low back pain and neck pain cost Australia $4.8 billion in healthcare costs and $8 billion in lost productivity per annum.[4 5]

Clinical guidelines recommend that first line care for people with acute low back pain or neck pain should consist of advice (patient reassurance, staying active and avoiding bed rest) and if required, simple analgesics (paracetamol or non-steroidal anti-inflammatory drugs, NSAIDs).[6] For people who do not respond to first line care, guidelines recommend stronger analgesics such as an opioid analgesic, particularly if the pain is severe.[6] There is evidence that opioid analgesics are widely and increasingly used by patients and general practitioners for low back pain and neck pain. We found that 12% of participants surveyed reported using an opioid analgesic or opioid analgesic combination (e.g. paracetamol plus codeine) as their first-choice medicine when self-managing low back pain.[7] This proportion increased to 28% for those with severe pain. We also found that opioid analgesics were prescribed for up to 19% of patients with low back pain or neck pain by general practitioners in Australia, and were second only to NSAIDs as the most prescribed medication.[8] Internationally there is a trend of increasing opioid consumption over the last decades.[9 10]

Despite guideline recommendations and the widespread use of opioid analgesics, there is no rigorous evidence to support their use.[10] Although there is evidence suggesting that opioid analgesics may be effective in the short-term for persistent low back pain,[11] there are no randomised placebo-controlled trials evaluating the use of opioid analgesics for acute low

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back pain[11] or for acute or persistent neck pain.[12] Furthermore, evidence from persistent low back pain is not compelling due to methodological issues such as high drop-out rates and the use of enrichment designs where only those participants who responded and tolerated the medicine in the run-in phase were subsequently enrolled.[10 11]

The lack of efficacy data is alarming given the adverse events associated with opioid analgesics. The most common adverse events include nausea and constipation,[11] but there are also concerns of more serious adverse events such as dependency, misuse and overdose.[10 13 14] Although some suggest that these serious adverse events are rare,[15-17] are primarily associated with long term use and may have stabilised with respect to rate,[14] there is no doubt that the use of opioid analgesics is a contentious issue globally.

We have designed the current trial to provide high quality data to inform the quality use of opioid analgesics for treating acute low back pain or neck pain in primary care. The primary aim of the trial is to investigate if taking a short course of an opioid analgesic, compared to placebo, will reduce pain severity over the 6-week treatment period in people with acute low back pain or neck pain who are slow to recover. The secondary aim is to investigate if taking a short course of an opioid analgesic, compared to placebo, will improve other clinical outcomes, be tolerated, be cost-effective and not result in long-term opioid misuse.

METHODS AND ANALYSIS

Design

OPAL: The first placebo-controlled trial of opioid analgesia for acute spinal pain, is a randomised, placebo-controlled, assessor-, clinician- and participant-blinded superiority trial, with two parallel groups randomised at a 1:1 allocation. The trial has been prospectively

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registered on the Australian New Zealand Clinical Trials Registry (ACTRN12615000775516). The current report describes the detailed trial protocol and follows the SPIRIT 2013 Statement.[18]

Setting

The OPAL trial will be conducted in primary care. Registered general practitioners in the Sydney metropolitan and surrounding areas in the state of New South Wales of Australia with no regulatory impediment to prescribe opioid analgesics will be invited to participate as trial general practitioners, who will be involved in participant screening and recruitment as well as treatment provision. It is anticipated that up to 200 general practice sites will be required.

Eligibility criteria

Participants who have not recovered from acute low back pain and/or neck pain and present to a trial general practitioner for care will be eligible if they fulfil all of the inclusion criteria and none of the exclusion criteria.

Inclusion criteria:

- Low back pain (pain between the 12th rib and buttock crease) and/or neck pain (pain in the area below the occiput to the most distal cervical spine) with or without distal radiation to the leg (for low back pain) or arm (for neck pain).
- Current episode of pain is at least 2 weeks but no more than 12 weeks since onset, and preceded by at least a 1 month pain-free period (to screen out those with recurrent pain).
    - Our trial on paracetamol for acute low back pain showed that the median time to recovery is just over 2 weeks.[19] The 2-week minimum period is to target patients who are slow to recover.

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- 12 weeks is the usual cut-off for acute or subacute pain from persistent pain.[20]

- Pain severity is at least moderate (as measured by adaptations of item 7 of the SF-36, i.e. how much low back pain or neck pain have you had in the last week? None/ very mild/ mild/ moderate/ severe/ very severe).

Exclusion criteria:

- Known or suspected serious spinal pathology (e.g. cauda equina syndrome, spinal fracture).
- Contraindications to opioid analgesics (including previous intolerance, addiction history, allergy, abuse of psychoactive drugs, alcoholism), or scoring 'high risk' on the Opioid Risk Tool.[21]
- Have taken a prescription opioid analgesic for the current episode of low back pain and/or neck pain.
- Spinal surgery in the preceding 6 months.
- Scheduled or being considered for surgery or interventional procedures for low back pain and/or neck pain during the 6-week treatment period.
- Less than 18 years of age.
- Not having sufficient English to understand trial procedures or complete assessments, or suitable translation is not available.
- For female participants: planning conception, or is pregnant or breast-feeding.

After a participant has given consent and been recruited, the general practitioner will notify the trial team via phone or fax. For a participant to be officially enrolled in the trial, a researcher (blinded) will collect baseline data directly from the participant before the

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participant starts the trial medication and within 72 hours of visiting the general practitioner. A participant timeline is shown in Figure 1.

Interventions

General practitioners will be trained on the trial protocol and receive regular monitoring visits from the trial team to ensure adherence to the trial intervention.

Trial medication

General practitioners will prescribe the trial medication to all participants starting at a dose of 5 mg, 2 times a day and gradually titrated up to the maximum dose of 10 mg, 2 times a day[22] until 'adequate improvement' (0 to 1 out of 10 pain for 3 consecutive days)[23] or for a maximum of exposure to oxycodone of 6 weeks. When adequate analgesic improvement is achieved or after a maximum of 5 weeks of treatment, the dose of the trial medication will be titrated down to cessation over 1 week. General practitioners will review participants, between weekly or fortnightly, to titrate the dose based on individual participant progress, tolerability and sedation score (0 = wide awake, 1 = easy to rouse, 2 = easy to rouse but cannot stay away, 3 = difficult to rouse)[22] until medication cessation. General practitioners will be asked to keep the sedation score under 2.[22]

The maximum supply of trial medication prescribed by the general practitioner at each review is 2 weeks, with the cumulative maximum supply per participant being 6 weeks. The opioid analgesic used will be controlled release oxycodone plus naloxone, the latter constituent to counter the tendency to opioid induced constipation. Participants can be given a laxative (docusate sodium and senna) in addition and advised to use this if required.[22]

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Although opioid dependency is unlikely especially when using opioid analgesics for a limited period of time for acute pain,[15 16] we have taken steps to minimise the risk further by excluding people inappropriate for opioid analgesics (history of substance abuse or addiction), implementing regular review by the trial general practitioner and limiting the supply of the trial medication. The general practitioner will also make clear agreements (Appendix 1) with participants when starting the treatment regarding dosage, frequency and duration of treatment. We will additionally contact participants up to 12 months to collect information on their spinal pain and use of treatments, including opioid analgesics (see 'Outcomes' below).

Guideline-based care

In addition to the trial medication, general practitioners will deliver guideline-based care to all participants.[6] This includes advice (patient reassurance, staying active and avoiding bed rest) and, if required, other guideline-recommended treatments. For example, spinal manipulative therapy may be offered and simple analgesics or adjuvants may be provided in addition to the trial medication in accordance to the WHO analgesic ladder.[6 24] However, no concomitant opioid analgesics should be used.

This design mimics how opioid analgesics are administered in clinical practice. The use of additional services will be recorded to investigate if this influences the trial findings, and to inform a comprehensive cost-effectiveness analysis (see 'Outcomes' below).

Outcomes

The outcomes and outcome measures chosen incorporate the core outcomes for pain trials recommended by consensus of international experts.[25] The primary outcome, collected at

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baseline and 2, 4, 6 and 12 weeks, will be pain severity measured by the Pain Severity Score of the Brief Pain Inventory.[26] The Pain Severity Score (/10) is calculated by adding the scores from four pain severity questions of the Brief Pain Inventory and dividing by four. The four pain severity questions measure worst pain in the last week, least pain in the last week, pain on average and pain right now, with each question measured by the 0 to 10 numerical pain rating scale.

Secondary outcomes, collected at baseline and 2, 4, 6 and 12 weeks (unless specified), will be:

- Physical functioning (generic) measured by the Pain Interference Score of the Brief Pain Inventory.[26]
- Physical functioning (condition-specific) measured by the Roland-Morris Disability Questionnaire[27] (24 items, for participants reporting low back pain only) and Neck Disability Questionnaire[28] (for participants reporting neck pain only) at baseline and 6 weeks only.
- Time to recovery (average daily pain of 0 or 1 out of 10 for the past 7 consecutive days)[19] measured using a pain diary, with information entered daily until recovery or up to 12 weeks (whichever is sooner).
- Quality of life measured by SF-12.[29]
- Participants' rating of global improvement measured by the global perceived effect scale.[30]

The following data will also be collected:

- Adverse events – collected at 2, 4, 6 and 12 weeks to report all adverse events that occur between baseline and 12 weeks. Serious adverse events (see section below on 'Harms' for

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definition) will be reported to an independent medical monitor and relevant bodies. We will monitor the number and severity of (serious) adverse events and consider tolerability when interpreting the results.

- Work absenteeism and use of other treatments or health care services will be collected at 2, 4, 6 and 12 weeks for a cost-effectiveness analysis.
- Adherence to trial medication – measured by participants' self-report of daily trial medication intake recorded in a diary and by counting the returned medications.
- Success of blinding – participants will be asked to guess their group allocation at the 6-week follow-up, as either opioid, placebo or don't know.

Long-term outcomes, collected at 3 (12 weeks), 6 and 12 months, will be:

- Pain severity measured by the Pain Severity Score of the Brief Pain Inventory.[26]
- If participants still experience low back pain and/or neck pain (>1/10), their use of treatments and services, including opioid analgesics.
- Use of opioid analgesics for any pain condition.
- Risk of misuse measured by the Current Opioid Misuse Measure.[31]

Sample size

Our primary outcome measure is pain severity. A sample size of 173 per group (346 total) will be sufficient to detect a between-group difference of 1 on a 10-point pain scale (Pain Severity Score of the Brief Pain Inventory), assuming a standard deviation of 2.5,[19] power of 90% and alpha of 5%, and allowing for 5% dropout and 10% non-compliance.

A previous study showed that to perceive the effect of NSAIDs as worthwhile, patients need to see a median of 30% more improvement in pain than would occur without intervention.[32]

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For opioid analgesics, no such information is available but we expect patients would need to perceive at least this level of improvement to consider the effect of opioid analgesics as worthwhile. This is estimated to be around 1 point on a 10-point pain scale taking into account the natural recovery of acute low back pain and neck pain.[33 34]

Strategies for achieving adequate participant enrolment

We plan to recruit 200 general practice (for participant screening, recruitment and provision of trial treatment) and 200 community pharmacy (for trial medication dispensing) sites over the course of the OPAL trial to complete recruitment. Strategies for achieving adequate participant enrolment to reach target sample size will include developing streamlined screening, recruitment and follow-up processes to minimise clinician and participant load, regular site monitoring visits and support from the trial team, reimbursing general practitioners and pharmacists for the time they spend on trial-related tasks, and applying with the relevant professional bodies for trial participation to be credited with continuing education points.

Assignment of interventions: allocation

The allocation sequence will be prepared *a priori* using a computerised random number generator by an independent statistician not involved in participant recruitment or data collection, in permuted blocks. Trial medication packs will be prepared according to the allocation sequence, sealed and dispatched by an independent manufacturer in small quantities to a trial pharmacy. After a participant has been recruited, the trial general practitioner will provide a prescription to the participant and the next sequentially numbered medication pack will be dispensed by the trial pharmacy, thus randomising the participant to

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either the opioid analgesic or placebo group in a 1:1 ratio. Active and placebo medicines will have an identical appearance.

Blinding

The randomisation and concealed allocation process ensure blinding of the general practitioner (treatment provider), pharmacist, participant and assessor. The Steering Committee (consisting of authors of this protocol) and data analysts will also be blinded. The success of participant blinding will be tested at the 6-week follow-up (end of treatment period) (see 'Outcomes' above).

To maintain the overall quality and rigor of the trial design, unblinding of the blinded trial personnel would occur only in exceptional circumstances when knowledge of the actual treatment is absolutely essential for further management of the participant. The decision for this will be made in consultation with the clinicians involved in the participant's management (including the trial general practitioner) and the Steering Committee.

If unblinding is deemed to be necessary, the trial team will facilitate contact between the clinicians involved in the participant's management and the independent statistician who generated the randomisation sequence, and care will be made to ensure that only the trial personnel involved in further management of the individual participant will be unblinded. Unblinding should not necessarily be a reason for trial discontinuation.

Data collection methods

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Outcomes will be collected by a blinded research assistant via phone or directly completed by the participant online or by email. Research assistants will be trained to ensure data accuracy, consistency and completeness.

The trial team will make every reasonable effort to contact and complete follow-up of every participant, including those who discontinue the trial treatment prematurely or deviate from the protocol. Attempts will be made to ensure all outcomes will be collected. At a minimum and only as a last resort, we will attempt to collect the primary outcome. Where possible, we will record the reason for loss to follow-up (e.g. consent withdrawn).

Data management

The integrity of data will be closely monitored for omissions and errors. Data collected by phone will be directly entered into a secure, custom-built database by the trial team at the time of data collection, with a prompt for the trial team to double check the accuracy of the primary outcome. Any inconsistencies will be explored and resolved. Data directly completed by participants online will be automatically transcribed into the database. If participants return data by email, the data will be entered into the database with a prompt to check the accuracy of data entry to the primary outcome. Each trial personnel will be able to access the database only with a personal login and password. Range checks and data validation will be built-in to promote data quality. Adverse events will be coded using the preferred terms of MedDRA (Medical Dictionary for Regulatory Activities).

Statistical methods

Data analysis will be blinded, by intention-to-treat and guided by a detailed statistical analysis plan. Analysis and interpretation (also performed blinded) on the primary and key

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secondary outcomes will be conducted by the trial team and by an independent biostatistician and checked for accuracy. A p-value of < 0.05 will be considered statistically significant.

Primary analysis

Longitudinal linear models will be used to assess the effect of treatment group on pain severity over the 6-week treatment period using baseline pain as a covariate. Correlations between repeated measures (Weeks 2, 4 and 6 assessments) will be accounted for using generalised estimating equations.[35] We will conduct sensitivity analyses with duration of current pain episode and site of pain, i.e. low back or neck, as additional covariates. In case more than 10% of the primary outcome data is missing, multiple imputations will be used to conduct sensitivity analyses for the longitudinal linear mixed model of the primary outcome.

Secondary analysis

For all continuous secondary outcomes measured at Weeks 2, 4 and 6, longitudinal linear models will be used as per the primary analysis. Medium-term effects at Week 12 on the primary outcome and all secondary continuous outcomes will be analysed using a linear model with the baseline value included as a covariate. For the secondary outcome of time to recovery, the difference in survival curves will be assessed for the groups using the log-rank statistic. The median days to recovery will be used to express the time to recovery.

Adverse events will be categorised and the proportion of patients with adverse events overall and within each category will be compared between the two groups.

Cost-effectiveness analysis

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Two analyses will be conducted if between-group differences are found in effectiveness or utility over the 6-week treatment period: 1) a cost-effectiveness analysis using pain severity as a measure of effectiveness and 2) a cost-utility analysis where health state utilities (quality-adjusted life-years or QALY) will be based on measures obtained from the SF-12 and transformed into utilities via the SF-6D algorithm. The primary analysis will be conducted from the health sector's perspective to assess the incremental cost per 1-point pain reduction or per QALY gained between the two treatment groups over 12 weeks. To obtain costs, public health services will be valued at published standard rates (e.g. the Medical Benefits Scheme standard fees, the Pharmaceutical Benefits Scheme costs). Private non-medical health services (e.g. physiotherapy) will be valued at published standard rates, if available, or as reported by participants.

A secondary analysis will entail a societal perspective in which costs associated with the use of community services (e.g. exercise classes) and work absenteeism related to low back pain or neck pain will be included. Costs of community services will be based on the self-reported costs. Costs of absenteeism from paid employment will be estimated by the number of days absent from work multiplied by the average wage rate. Sensitivity analyses will test uncertainty in key parameters such as the selection of cost weights and statistical variation in quality of life scores.

Analysis of long-term outcomes

Pain severity at 6 and 12 months, and treatment utilisation and risk of opioid misuse at 3, 6 and 12 months will be reported descriptively. Between-group differences in pain severity and opioid misuse at each time point will be compared using the t-test and Chi-square test, respectively.

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Data monitoring

An independent Data and Safety Monitoring Board (DSMB) will be convened with the main purpose being to monitor (serious) adverse events, in order to ensure the safety of participants. The frequency of DSMB meetings and the stopping rules will be defined *a priori* in a charter, in consultation with the DSMB members and Steering Committee. The DSMB will have access to unblinded data, and data on the primary outcome, adverse events (after coding) and serious adverse events, however there is no planned interim analysis on efficacy data.

The DSMB will make recommendations to the Steering Committee, who will be responsible for making the final decision on the recommendations. If appropriate this will be done in consultation with the ethics committee.

Harms

Harm or safety reporting will follow a standard operating procedure on clinical trial safety reporting established by the trial sponsor, The George Institute for Global Health, which defines serious adverse events as any untoward medical occurrence that:

- Results in death
- Is life-threatening
- Requires hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is a medically significant or important event or reaction

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The relatedness and expectedness of a serious adverse event will be assessed by an independent medical monitor and, if the event occurs during the 6-week treatment period, the general practitioner. If there are differing opinions in relatedness or expectedness, we will take the most conservative opinions. Serious adverse events will be reported to the relevant bodies (e.g. ethics committee, regulatory body) within the required timeline.

Auditing

No formal auditing is planned. However if required, independent auditing of core trial processes and documents will be arranged.

ETHICS AND DISSEMINATION

Research ethics approval

Ethics approval has been granted from the Human Research Ethics Committee, The University of Sydney (Project No. 2015-004).

Protocol amendments

Any modifications to the protocol which may impact on the trial design and conduct, or the potential benefits or harms to the participants, will require a formal amendment to the protocol. Such amendments will be agreed upon by the Steering Committee and approved by the ethics committee prior to implementation.

Consent or assent

Trial general practitioners will be trained on the informed consent process, and will introduce the OPAL trial to potential participants who will also receive an information sheet and consent form. General practitioners, with support from the trial team if required, will also

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answer any questions that are raised by potential participants, and obtain written consent from those willing to participate in the trial. At any stage, participants can withdraw consent without repercussion.

Confidentiality

All data will be stored securely in either locked filing cabinets (paper files) or electronically (electronic database files) with access granted only to the trial team. Where required, general practitioners will have access to data collected from the participants they are responsible for, only after consent from the participants. After the completion of the trial, data will be archived for a minimum of 15 years.[36]

Access to data

The Steering Committee will have access to the final dataset, which may be provided to a statistician and/or a postgraduate student to assist with data analysis if required. To ensure confidentiality, the final dataset will contain de-identified information only.

Ancillary and post-trial care

During the 6-week treatment period, general practitioners may refer participants to other guideline-based treatments in addition to receiving the trial medication. The cost of such treatments will not be borne by the trial. Any post-trial care, including continuation or re-commencement of an opioid analgesic, will be determined by the participants and their clinician; whether they are trial general practitioners or other qualified clinicians.

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If non-negligent harm associated with the protocol occurs, participants will be covered by professional indemnity and clinical trials insurance of the trial. This will include cover for additional health care, compensation or damages.

Dissemination policy

The main results will be submitted for publication in a scientific journal, and presented at relevant professional conferences. The results will also be disseminated to the media and general public. Authorship eligibility guidelines of publications arising from the OPAL trial will align with those outlined by the International Committee of Medical Journal Editors (http://www.icmje.org/). There are no plans to use professional writers. There are currently no plans to grant public access to the raw data.

DISCUSSION

Low back pain and neck pain are among the most burdensome conditions globally, both in terms of disease burden to the patient and economic burden to society. Despite the widespread and increasing use of opioid analgesics and guidelines endorsing their use, there remains a lack of reliable evidence on the efficacy of opioids in acute low back pain or neck pain. Concerns are also being raised because of the risks of adverse events associated with opioid analgesics and, with persistent use, more serious consequences such as overdose.

OPAL will be the world's first placebo-controlled trial of opioid analgesics in people with acute low back pain or neck pain and will provide rigorous evidence to inform the appropriate and judicious use of this medicine. We will establish whether using a short course of an opioid analgesic in people who are slow to recover from acute low back pain or neck pain can effectively reduce pain, improve other outcomes (e.g. function), be reasonably

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tolerated and cost-effective, and have minimal risk of long-term misuse. We anticipate that participant recruitment will commence early 2016.

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AUTHORS' CONTRIBUTIONS

All authors conceived and refined the trial design and procured funding. CL was responsible for the design of the cost-effectiveness analysis. AM provided expertise in pharmacy. RD provided expertise in medicine and pharmacology. LB provided statistical expertise. CL drafted the manuscript; all authors critically contributed to the writing and approved the final manuscript for publication.

FUNDING STATEMENT

This work is supported by the National Health and Medical Research Council (NHMRC) of Australia, grant number APP1082480. CL is funded by a Career Development Fellowship from the NHMRC. CM is funded by a Principal Research Fellowship from the NHMRC. The funding source has no role in the trial design and will have no role in the trial conduct, data analysis and interpretation, or writing or reporting.

COMPETING INTERESTS STATEMENT

We have read and understood BMJ policy on declaration of interests and declare the following interests:

CL has received trial medicines from Pfizer (Australia) for an investigator-initiated trial funded by the National Health and Medical Research Council (NHMRC) of Australia, to evaluate drug treatment of low back pain.

AM has received supplementary funding and/or trial medicines from GlaxoSmithKline & Pfizer (Australia) for investigator-initiated NHMRC-funded trials evaluating drug treatment of low back pain. He is also the Program Director of the NHMRC Centre for Research Excellence in Medicines and Ageing.

JL has received supplementary funding and/or trial medicines from GlaxoSmithKline & Pfizer (Australia) for investigator-initiated NHMRC-funded trials evaluating drug treatment

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of back pain. She has received funding from Baxter Biosciences for research evaluating musculoskeletal outcomes in children with haemophilia.

RD has received supplementary funding and/or trial medicines from GlaxoSmithKline & Pfizer (Australia) for investigator-initiated NHMRC-funded trials evaluating drug treatment of back pain. RD has been a member of an advisory board about paracetamol for GlaxoSmithKline and ibuprofen for Reckitt Benckiser (Australia). Payments went to an audited hospital account for teaching and research purposes.

CM has received supplementary funding and/or trial medicines from GlaxoSmithKline & Pfizer (Australia) for investigator-initiated NHMRC-funded trials evaluating drug treatment of low back pain.

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LEGENDS

Figure 1. Participant timeline

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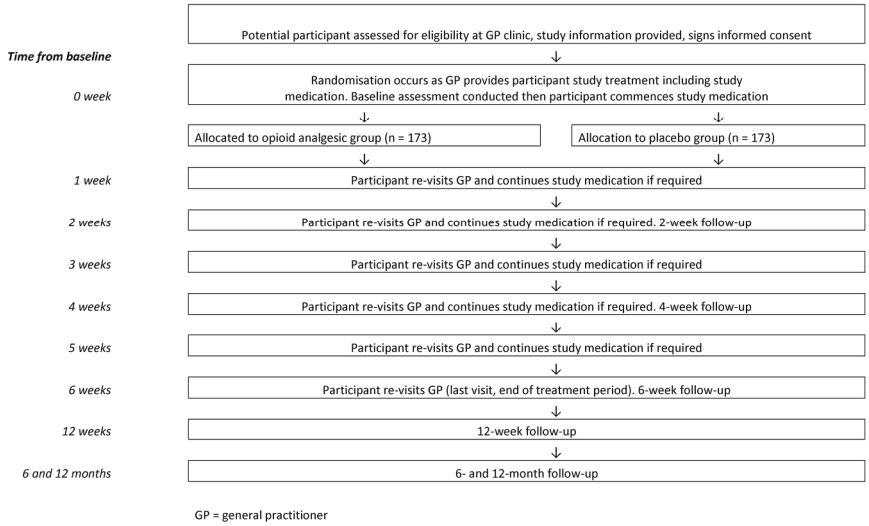

Participant timeline
A participant timeline is show
209x148mm (300 x 300 DPI)

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Opioid analgesia for acute spinal pain

TREATMENT AGREEMENT

In the OPAL study you are randomly allocated to receive an opioid analgesic or a placebo as the study medication. This document provides information about your overall pain management plan and seeks your written approval to proceed with the treatment.

Patient name:
GP name:
GP contact details:

Treatment commencement date:	____ / ____ / ____
Planned duration of treatment (max 6 weeks):	☐ 6 weeks ☐ ____ weeks
Next GP review:	____ / ____ / ____ (the recommended frequency is weekly)

Goals of treatment

Goals (e.g. walk 3 times a week for 30 min)	**Review date**	**Comments**
1. Reduce my average pain score from __/10 to __/10		
2.		
3.		
4.		
5.		

Other ways to help my pain:

1. Staying active and avoiding bed rest
2. _____
3. _____
4. _____
5. Treatments from other health professionals: ☐ physiotherapist ☐ chiropractor ☐ Other: _____

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OPAL
Opioid analgesia for acute spinal pain

If pain gets worse I can try:

Non-medicine strategies	Medicines

Please remember:

1. Only one doctor is responsible for prescribing your study medication. Arrangements can be made for an alternate prescriber to cover the absence of your doctor if needed.
2. Using the same pharmacy to re-fill your study prescription is a requirement of the OPAL study.
3. We will not give early prescriptions or replace lost prescriptions or medication, therefore you need to keep your study medication secure and take the dose as prescribed.
4. If you run out of your study medication early you may develop withdrawal symptoms which can be uncomfortable but are not life threatening.
5. If your behaviour suggests a problem with the misuse of medicines or addiction then your doctor will consider tapering and ceasing the study medication or referral to a Drug and Alcohol service. Problem behaviours include giving your medication to others, use of your medication in a non-prescribed way, excessive use of other medications (including alcohol and illicit drugs), repeated loss of medication, visiting multiple doctors to obtain medicines (doctor shopping) and worsening function at home or work.

Agreement

I have read the information provided and agree to this plan.

Patient signature: _____ **Date:** ____ / ____ / ____

GP signature: _____ **Date:** ____ / ____ / ____

Acknowledgements: adapted from 'My Pain Management Plan', National Pain Prescribing Service (NPS), and 'Opioid Treatment Agreement', Hunter New England Local Health District.

Version 1.0, 13 January 2015

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

Section/item	ItemNo	Description	Page no.
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	All
Protocol version	3	Date and version identifier	Nil
Funding	4	Sources and types of financial, material, and other support	22
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1,2
	5b	Name and contact information for the trial sponsor	2
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	22
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	14,18
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5,6

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	6b	Explanation for choice of comparators	5,6
Objectives	7	Specific objectives or hypotheses	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7,8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9,10
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	9,12
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10-12
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Fig 1

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Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12,13
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	13
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	13
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	13
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	13
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	14
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	14
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	15
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	15

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Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	15
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	15-17
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	15, 16
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	18
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	18
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	18
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	19
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	19

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Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	19
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	19
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	20
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	22
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	20
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	20
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	21
	31b	Authorship eligibility guidelines and any intended use of professional writers	21
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	21
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Nil
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

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*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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BMJ Open

OPAL: A randomised, placebo-controlled trial of opioid analgesia for the reduction of pain severity in people with acute spinal pain. Trial protocol

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Primary Subject Heading:	General practice / Family practice
Secondary Subject Heading:	Pharmacology and therapeutics
Keywords:	Opioid analgesics, low back pain, neck pain, Clinical trials < THERAPEUTICS

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OPAL: A randomised, placebo-controlled trial of opioid analgesia for the reduction of pain severity in people with acute spinal pain. Trial protocol

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Keywords

Opioid analgesics, low back pain, neck pain, clinical trials

Word count

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Trial sponsor

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ABSTRACT

Introduction Low back pain and neck pain are extremely prevalent and are responsible for an enormous burden of disease globally. Strong analgesics, such as opioid analgesics, are recommended by clinical guidelines for people with acute low back pain or neck pain who are slow to recover and require more pain relief. Opioid analgesics are widely and increasingly used, but there are no strong efficacy data supporting the use of opioid analgesics for acute low back pain or neck pain. Concerns regarding opioid use are further heightened by the risks of adverse events, some of which can be serious (e.g. dependency, misuse and overdose).

Methods and analysis OPAL is a randomised, placebo-controlled, triple-blinded trial that will investigate the judicious use of an opioid analgesic in 346 participants with acute low back pain and/or neck pain who are slow to recover. Participants will be recruited from general practice and randomised to receive the opioid analgesic (controlled release oxycodone plus naloxone up to 20 mg per day) or placebo in addition to guideline-based care (e.g. reassurance and advice of staying active) for up to 6 weeks. Participants will be followed for 3 months for effectiveness outcomes. The primary outcome will be pain severity. Secondary outcomes will include physical functioning and time to recovery. Medication-related adverse events will be assessed and a cost-effectiveness analysis will be conducted. We will additionally assess long-term use and risk of misuse of opioid analgesics for up to 12 months.

Ethics and dissemination Ethical approval has been obtained. Trial results will be disseminated by publications and conference presentations, and via the media.

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Registration Australian New Zealand Clinical Trials Registry: ACTRN12615000775516

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is the world's first placebo-controlled trial to investigate whether using a short course of an opioid analgesic, in people who are slow to recover from acute low back pain or neck pain, can effectively reduce pain, improve other outcomes (e.g. function), be reasonably tolerated and cost-effective, and have minimal risk of long-term misuse.
- The trial will inform the appropriate and judicious use of opioid analgesics.
- Misuse data will be collected via self-report and therefore subject to reporting bias.

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INTRODUCTION

Low back pain and neck pain are among the most burdensome conditions globally.[1] The enormous burden of these conditions is associated with their high prevalence: the 1-year prevalence for low back pain and neck pain is 38% and 26% respectively.[2 3] There is also a high economic burden: the latest estimates show that low back pain and neck pain cost Australia $4.8 billion in healthcare costs and $8 billion in lost productivity per annum.[4 5]

Clinical guidelines recommend that first line care for people with acute low back pain or neck pain should consist of advice (patient reassurance, staying active and avoiding bed rest) and if required, simple analgesics (paracetamol or non-steroidal anti-inflammatory drugs, NSAIDs).[6] For people who do not respond to first line care, guidelines recommend stronger analgesics such as an opioid analgesic, particularly if the pain is severe.[6] There is evidence that opioid analgesics are widely and increasingly used by patients and general practitioners for low back pain and neck pain. We found that 12% of participants surveyed reported using an opioid analgesic or opioid analgesic combination (e.g. paracetamol plus codeine) as their first-choice medicine when self-managing low back pain.[7] This proportion increased to 28% for those with severe pain. We also found that opioid analgesics were prescribed for up to 19% of patients with low back pain or neck pain by general practitioners in Australia, and were second only to NSAIDs as the most prescribed medication.[8] Internationally there is a trend of increasing opioid consumption over the last decades.[9 10]

Despite guideline recommendations and the widespread use of opioid analgesics, there is no rigorous evidence to support their use for acute low back pain and neck pain.[10] Although there is evidence suggesting that opioid analgesics may be effective in the short-term for persistent low back pain,[11] there are no randomised placebo-controlled trials evaluating the

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use of opioid analgesics for acute low back pain[11] or for acute or persistent neck pain.[12] Furthermore, evidence from persistent low back pain is not compelling due to methodological issues such as high drop-out rates and the use of enrichment designs where only those participants who responded and tolerated the medicine in the run-in phase were subsequently enrolled.[10 11]

The lack of efficacy data is alarming given the adverse events associated with opioid analgesics. The most common adverse events include nausea and constipation,[11] but there are also concerns of more serious adverse events such as dependency, misuse and overdose.[10 13 14] Australian data suggest that hospital separations for opioid poisoning doubled between 2005 to 2006 and 2006 to 2007,[15] and there has been a multi-fold increase in drug overdose deaths in the United States in the last 15 years, primarily driven by opioid analgesics.[16] Alarmingly, since 2003 more overdose deaths have involved opioid analgesics than heroin and cocaine combined.[17] Although some suggest that these serious adverse events are rare,[18-20] are primarily associated with long term use and may have stabilised with respect to rate,[14] there is no doubt that the use of opioid analgesics is a contentious issue globally.

We have designed the current trial to provide high quality data to inform the use of opioid analgesics for treating acute low back pain or neck pain. The primary aim of the trial is to investigate if taking a short course of an opioid analgesic, compared to placebo, will reduce pain severity over the 6-week treatment period in people with acute low back pain or neck pain who are slow to recover. The secondary aim is to investigate if taking a short course of an opioid analgesic, compared to placebo, will improve other clinical outcomes, be tolerated, be cost-effective and not result in long-term opioid misuse.

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METHODS AND ANALYSIS

Design

OPAL: a randomised, placebo-controlled trial of opioid analgesia for the reduction of pain severity in people with acute spinal pain, is a randomised, placebo-controlled, assessor-, clinician- and participant-blinded superiority trial, with two parallel groups randomised at a 1:1 allocation. We have chosen a randomised, placebo-controlled design in order to provide high-level evidence on the efficacy or safety of opioid analgesics in those with acute spinal pain. The trial has been prospectively registered on the Australian New Zealand Clinical Trials Registry (ACTRN12615000775516). The current report describes the detailed trial protocol and follows the SPIRIT 2013 Statement.[21]

Setting

The OPAL trial will be conducted in primary care. Registered general practitioners in the Sydney metropolitan and surrounding areas in the state of New South Wales of Australia with no regulatory impediment to prescribe opioid analgesics will be invited to participate as trial general practitioners, who will be involved in participant screening and recruitment as well as treatment provision. It is anticipated that up to 200 general practice sites will be required.

Eligibility criteria

Participants who have not recovered from acute low back pain and/or neck pain and present to a trial general practitioner for care will be eligible if they fulfil all of the inclusion criteria and none of the exclusion criteria. Trial general practitioners will determine a participant's eligibility via a history and physical examination.

Inclusion criteria:

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- Low back pain (pain between the 12th rib and buttock crease) and/or neck pain (pain in the area below the occiput to the most distal cervical spine) with or without distal radiation to the leg (for low back pain) or arm (for neck pain).
- Current episode of pain is at least 2 weeks but no more than 12 weeks since onset, and preceded by at least a 1 month pain-free period (to screen out those with recurrent pain).
    - Our trial on paracetamol for acute low back pain showed that the median time to recovery is just over 2 weeks.[22] The 2-week minimum period is to target patients who are slow to recover.
    - 12 weeks is the usual cut-off for acute or subacute pain from persistent pain.[23]
- Pain severity is at least moderate (as measured by adaptations of item 7 of the SF-36, i.e. how much low back pain or neck pain have you had in the last week? None/ very mild/ mild/ moderate/ severe/ very severe).

Exclusion criteria:

- Known or suspected serious spinal pathology (e.g. cauda equina syndrome, spinal fracture).
- Contraindications to opioid analgesics (including previous intolerance, addiction history, allergy, abuse of psychoactive drugs, alcoholism), or scoring 'high risk' on the Opioid Risk Tool.[24]
- Have taken a prescription opioid analgesic for the current episode of low back pain and/or neck pain.
- Spinal surgery in the preceding 6 months.
- Scheduled or being considered for surgery or interventional procedures for low back pain and/or neck pain during the 6-week treatment period.
- Less than 18 years of age.

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- Not having sufficient English to understand trial procedures or complete assessments, or suitable translation is not available.
- For female participants: planning conception, or is pregnant or breast-feeding.

After a participant has given consent and been recruited, the general practitioner will notify the trial team via phone or fax. For a participant to be officially enrolled in the trial, a researcher (blinded) will collect baseline data directly from the participant before the participant starts the trial medication and within 72 hours of visiting the general practitioner. A participant timeline is shown in Figure 1.

Interventions

General practitioners will be trained on the trial protocol and receive regular monitoring visits from the trial team to ensure adherence to the trial intervention.

Trial medication

General practitioners will prescribe the trial medication to all participants starting at a dose of 5 mg, 2 times a day and gradually titrated up to the maximum dose of 10 mg, 2 times a day[25] until 'adequate improvement' (0 to 1 out of 10 pain for 3 consecutive days)[26] or for a maximum of exposure to oxycodone of 6 weeks. When adequate analgesic improvement is achieved or after a maximum of 5 weeks of treatment, the dose of the trial medication will be titrated down to cessation over 1 week. General practitioners will review participants, between weekly or fortnightly, to titrate the dose based on individual participant progress, tolerability and sedation score (0 = wide awake, 1 = easy to rouse, 2 = easy to rouse but cannot stay awake, 3 = difficult to rouse)[25] until medication cessation. General practitioners will be asked to keep the sedation score under 2.[25]

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The maximum supply of trial medication prescribed by the general practitioner at each review is 2 weeks, with the cumulative maximum supply per participant being 6 weeks. The opioid analgesic used will be controlled release oxycodone plus naloxone, the latter constituent to counter the tendency to opioid induced constipation. Participants can be given a laxative (docusate sodium and senna) in addition and advised to use this if required.[25]

Although opioid dependency is unlikely especially when using opioid analgesics for a limited period of time for acute pain,[18 19] we have taken steps to minimise the risk further by excluding people inappropriate for opioid analgesics (history of substance abuse or addiction), implementing regular review by the trial general practitioner and limiting the supply of the trial medication. The general practitioner will also make clear agreements (Appendix 1) with participants when starting the treatment regarding dosage, frequency and duration of treatment. We will additionally contact participants up to 12 months to collect information on their spinal pain and use of treatments, including opioid analgesics (see 'Outcomes' below).

Guideline-based care

In addition to the trial medication, general practitioners will deliver guideline-based care to all participants.[6] This includes advice (patient reassurance, staying active and avoiding bed rest) delivered by the general practitioners and, if required, other guideline-recommended treatments delivered either by the general practitioners or by referral to other health professionals. For example, spinal manipulative therapy may be offered and simple analgesics or adjuvants may be provided in addition to the trial medication in accordance to the WHO analgesic ladder.[6 27] However, no concomitant opioid analgesics should be used.

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We have not protocolised guideline-based care, other than that all participants will receive advice, to allow the care to be tailored to participants.

This design mimics how opioid analgesics are administered in clinical practice. The use of additional services will be recorded to investigate if this influences the trial findings, and to inform a comprehensive cost-effectiveness analysis (see 'Outcomes' below).

Outcomes

The outcomes and outcome measures chosen incorporate the core outcomes for pain trials recommended by consensus of international experts.[28] The primary outcome, collected at baseline and 2, 4, 6 and 12 weeks, will be pain severity measured by the Pain Severity Score of the Brief Pain Inventory.[29] The Pain Severity Score (/10) is calculated by adding the scores from four pain severity questions of the Brief Pain Inventory and dividing by four. The four pain severity questions measure worst pain in the last week, least pain in the last week, pain on average and pain right now, with each question measured by the 0 to 10 numerical pain rating scale.

Secondary outcomes, collected at baseline and 2, 4, 6 and 12 weeks (unless specified), will be:

- Physical functioning (generic) measured by the Pain Interference Score of the Brief Pain Inventory.[29]
- Physical functioning (condition-specific) measured by the Roland-Morris Disability Questionnaire[30] (24 items, for participants reporting low back pain only) and Neck Disability Questionnaire[31] (for participants reporting neck pain only) at baseline and 6 weeks only.

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- Time to recovery (average daily pain of 0 or 1 out of 10 for the past 7 consecutive days)[22] measured using a pain diary, with information entered daily until recovery or up to 12 weeks (whichever is sooner).
- Quality of life measured by SF-12.[32]
- Participants' rating of global improvement measured by the global perceived effect scale.[33]

The following data will also be collected:

- Adverse events – collected at 2, 4, 6 and 12 weeks by self-report on all adverse events that occur between baseline and 12 weeks. Additionally we will ask general practitioners to report adverse events (if any) at each participant follow-up visit. Serious adverse events (see section below on 'Harms' for definition) will be reported to an independent medical monitor and relevant bodies. We will monitor the number and severity of (serious) adverse events and consider tolerability when interpreting the results.
- Work absenteeism and use of other treatments or health care services will be collected by self-report at 2, 4, 6 and 12 weeks for a cost-effectiveness analysis.
- Adherence to trial medication – measured by participants' self-report of daily trial medication intake recorded in a diary and by counting the returned medications. This will be compared against prescription data of trial medication reported by the general practitioner at each participant visit during the 6-week treatment period.
- Success of blinding – participants will be asked to guess their group allocation at the 6-week follow-up, as either opioid, placebo or don't know.

Long-term outcomes, collected at 3 (12 weeks), 6 and 12 months, will be:

- Pain severity measured by the Pain Severity Score of the Brief Pain Inventory.[29]

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- If participants still experience low back pain and/or neck pain (>1/10), their use of treatments and services, including opioid analgesics.
- Risk of misuse measured by the Current Opioid Misuse Measure.[34]

Sample size

Our primary outcome measure is pain severity. A sample size of 173 per group (346 total) will be sufficient to detect a between-group difference of 1 on a 10-point pain scale (Pain Severity Score of the Brief Pain Inventory) at 6 weeks, assuming a standard deviation of 2.5,[22] power of 90% and alpha of 5%, and allowing for 5% dropout (based on our previous study)[22] and 10% non-compliance.

A previous study showed that to perceive the effect of NSAIDs as worthwhile, patients need to see a median of 30% more improvement in pain than would occur without intervention.[35] For opioid analgesics, no such information is available but we expect patients would need to perceive at least this level of improvement to consider the effect of opioid analgesics as worthwhile. This is estimated to be around 1 point on a 10-point pain scale taking into account the natural recovery of acute low back pain and neck pain.[36 37]

Strategies for achieving adequate participant enrolment

We plan to recruit 200 general practice (for participant screening, recruitment and provision of trial treatment) and 200 community pharmacy (for trial medication dispensing) sites over the course of the OPAL trial to complete recruitment. Strategies for achieving adequate participant enrolment to reach target sample size will include developing streamlined screening, recruitment and follow-up processes to minimise clinician and participant load, regular site monitoring visits and support from the trial team, reimbursing general

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practitioners and pharmacists for the time they spend on trial-related tasks, and applying with the relevant professional bodies for trial participation to be credited with continuing education points.

Assignment of interventions: allocation

The allocation sequence will be prepared *a priori* using a computerised random number generator by an independent statistician not involved in participant recruitment or data collection, in permuted blocks. Trial medication packs will be prepared according to the allocation sequence, sealed and dispatched by an independent manufacturer in small quantities to a trial pharmacy. After a participant has been recruited, the trial general practitioner will provide a prescription to the participant and the next sequentially numbered medication pack will be dispensed by the trial pharmacy, thus randomising the participant to either the opioid analgesic or placebo group in a 1:1 ratio. Active and placebo medicines will have an identical appearance.

Blinding

The randomisation and concealed allocation process ensure blinding of the general practitioner (treatment provider), pharmacist, participant and assessor. The Steering Committee (consisting of authors of this protocol) and data analysts will also be blinded. Blinding will be maintained for the entire duration of the trial until all data have been collected and data analysis and interpretation have been completed and agreed upon. The success of participant blinding will be tested at the 6-week follow-up (end of treatment period) (see 'Outcomes' above).

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To maintain the overall quality and rigor of the trial design, unblinding of the blinded trial personnel would occur only in exceptional circumstances when knowledge of the actual treatment is absolutely essential for further management of the participant. The decision for this will be made in consultation with the clinicians involved in the participant's management (including the trial general practitioner) and the Steering Committee.

If unblinding is deemed to be necessary, the trial team will facilitate contact between the clinicians involved in the participant's management and the independent statistician who generated the randomisation sequence, and care will be made to ensure that only the trial personnel involved in further management of the individual participant will be unblinded. Unblinding should not necessarily be a reason for trial discontinuation.

Data collection methods

Outcomes will be collected by a blinded research assistant via phone or directly completed by the participant online or by email. Research assistants will be trained to ensure data accuracy, consistency and completeness. For participants completing data assessment online, an email reminder will be sent prior to the due date, with a unique link to complete the data online. For participants completing data assessment by email, a blank assessment form will be provided which can be emailed to the trial team upon completion. Additionally, at each participant visit general practitioners will be asked to complete data on trial medication prescription and adverse events (if any, excluding the initial visit).

The trial team will make every reasonable effort to contact and complete follow-up of every participant, including those who discontinue the trial treatment prematurely or deviate from the protocol. Attempts will be made to ensure all outcomes will be collected. At a minimum

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and only as a last resort, we will attempt to collect the primary outcome. Where possible, we will record the reason for loss to follow-up (e.g. consent withdrawn).

Data management

The integrity of data will be closely monitored for omissions and errors. Data collected by phone will be directly entered into a secure, custom-built database by the trial team at the time of data collection, with a prompt for the trial team to double check the accuracy of the primary outcome. Any inconsistencies will be explored and resolved. Data directly completed by participants online will be automatically transcribed into the database. If participants return data by email, the data will be entered into the database with a prompt to check the accuracy of data entry to the primary outcome. Each trial personnel will be able to access the database only with a personal login and password. Range checks and data validation will be built-in to promote data quality.

Statistical methods

Data analysis will be blinded, by intention-to-treat and guided by a detailed statistical analysis plan. Analysis and interpretation (also performed blinded) on the primary and key secondary outcomes will be conducted by the trial team and by an independent biostatistician and checked for accuracy. A p-value of < 0.05 will be considered statistically significant.

Primary analysis

Repeated-measure linear mixed models will be used to assess the effect of treatment group on pain severity over the 6-week treatment period using baseline pain as a covariate. Correlations between repeated measures (Weeks 2, 4 and 6 assessments) will be modelled using a repeated effect.[38] We will conduct sensitivity analyses with duration of current pain

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episode and site of pain, i.e. low back or neck, as additional covariates. In case more than 10% of the primary outcome data is missing, multiple imputations will be used to conduct sensitivity analyses for the longitudinal linear mixed model of the primary outcome.

Secondary analysis

For all continuous secondary outcomes measured at Weeks 2, 4 and 6, repeated-measure linear mixed models will be used as per the primary analysis. Medium-term effects at Week 12 on the primary outcome and all secondary continuous outcomes will be analysed using a linear mixed model with the baseline value included as a covariate. For the secondary outcome of time to recovery, the difference in survival curves will be assessed for the groups using the log-rank statistic. The median days to recovery will be used to express the time to recovery.

Adverse events will be categorised and the proportion of patients with adverse events overall and within each category will be compared between the two groups. Self-reported data will be used as the primary source of data and supported by data reported by the general practitioners.

Cost-effectiveness analysis

Two analyses will be conducted if between-group differences are found in the primary analysis: 1) a cost-effectiveness analysis using pain severity as a measure of effectiveness and 2) a cost-utility analysis where health state utilities (quality-adjusted life-years or QALY) will be based on measures obtained from the SF-12 and transformed into utilities via the SF-6D algorithm. The primary analysis will be conducted from the health sector's perspective to assess the incremental cost per 1-point pain reduction or per QALY gained between the two

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treatment groups over 12 weeks. To obtain costs, public health services will be valued at published standard rates (e.g. the Medical Benefits Scheme standard fees, the Pharmaceutical Benefits Scheme costs). Private non-medical health services (e.g. physiotherapy) will be valued at published standard rates, if available, or as reported by participants.

A secondary analysis will entail a societal perspective in which costs associated with the use of community services (e.g. exercise classes) and work absenteeism related to low back pain or neck pain will be included. Costs of community services will be based on the self-reported costs. Costs of absenteeism from paid employment will be estimated by the number of days absent from work multiplied by the average wage rate. Sensitivity analyses will test uncertainty in key parameters such as the selection of cost weights and statistical variation in quality of life scores.

Analysis of long-term outcomes

Pain severity at 6 and 12 months, and treatment utilisation and risk of opioid misuse at 3, 6 and 12 months will be reported descriptively. Between-group differences in pain severity and opioid misuse at each time point will be compared using the t-test and Chi-square test, respectively.

Data monitoring

An independent Data and Safety Monitoring Board (DSMB) will be convened with the main purpose being to monitor (serious) adverse events, in order to ensure the safety of participants. The frequency of DSMB meetings and the stopping rules will be defined *a priori* in a charter, in consultation with the DSMB members and Steering Committee. The DSMB will have access to unblinded data, and data on the primary outcome, adverse events

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(after coding) and serious adverse events, however there is no planned interim analysis on efficacy data.

The DSMB will make recommendations to the Steering Committee, who will be responsible for making the final decision on the recommendations. If appropriate this will be done in consultation with the ethics committee.

Harms

Harm or safety reporting will follow a standard operating procedure on clinical trial safety reporting established by the trial sponsor, The George Institute for Global Health, which defines serious adverse events as any untoward medical occurrence that:

- Results in death
- Is life-threatening
- Requires hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is a medically significant or important event or reaction

The relatedness and expectedness of a serious adverse event will be assessed by an independent medical monitor and, if the event occurs during the 6-week treatment period, the general practitioner. If there are differing opinions in relatedness or expectedness, we will take the most conservative opinions. Serious adverse events will be reported to the relevant bodies (e.g. ethics committee, regulatory body) within the required timeline.

Auditing

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No formal auditing is planned. However if required, independent auditing of core trial processes and documents will be arranged.

ETHICS AND DISSEMINATION

Research ethics approval

Ethics approval has been granted from the Human Research Ethics Committee, The University of Sydney (Project No. 2015-004).

Protocol amendments

Any modifications to the protocol which may impact on the trial design and conduct, or the potential benefits or harms to the participants, will require a formal amendment to the protocol. Such amendments will be agreed upon by the Steering Committee and approved by the ethics committee prior to implementation.

Consent or assent

Trial general practitioners will be trained on the informed consent process, and will introduce the OPAL trial to potential participants who will also receive an information sheet and consent form. General practitioners, with support from the trial team if required, will also answer any questions that are raised by potential participants, and obtain written consent from those willing to participate in the trial. At any stage, participants can withdraw consent without repercussion.

Confidentiality

All data will be stored securely in either locked filing cabinets (paper files) or electronically (electronic database files) with access granted only to the trial team. Where required, general

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practitioners will have access to data collected from the participants they are responsible for, only after consent from the participants. After the completion of the trial, data will be archived for a minimum of 15 years.[39]

Access to data

The Steering Committee will have access to the final dataset, which may be provided to a statistician and/or a postgraduate student to assist with data analysis if required. To ensure confidentiality, the final dataset will contain de-identified information only.

Ancillary and post-trial care

During the 6-week treatment period, general practitioners may refer participants to other guideline-based treatments in addition to receiving the trial medication. The cost of such treatments will not be borne by the trial. Any post-trial care, including continuation or re-commencement of an opioid analgesic, will be determined by the participants and their clinician; whether they are trial general practitioners or other qualified clinicians.

If non-negligent harm associated with the protocol occurs, participants will be covered by professional indemnity and clinical trials insurance of the trial. This will include cover for additional health care, compensation or damages.

Dissemination policy

The main results will be submitted for publication in a scientific journal, and presented at relevant professional conferences. The results will also be disseminated to the media and general public. Authorship eligibility guidelines of publications arising from the OPAL trial will align with those outlined by the International Committee of Medical Journal Editors

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(http://www.icmje.org/). There are no plans to use professional writers. There are currently no plans to grant public access to the raw data.

DISCUSSION

Low back pain and neck pain are among the most burdensome conditions globally, both in terms of disease burden to the patient and economic burden to society. Despite the widespread and increasing use of opioid analgesics and guidelines endorsing their use, there remains a lack of reliable evidence on the efficacy of opioid analgesics in acute low back pain or neck pain. Concerns are also being raised because of the risks of adverse events associated with opioid analgesics and, with persistent use, more serious consequences such as overdose.

OPAL will be the world's first placebo-controlled trial of opioid analgesics in people with acute low back pain or neck pain and will provide rigorous evidence to inform the appropriate and judicious use of this medicine. We will establish whether using a short course of an opioid analgesic in people who are slow to recover from acute low back pain or neck pain can effectively reduce pain, improve other outcomes (e.g. function), be reasonably tolerated and cost-effective, and have minimal risk of long-term misuse.

The strengths of the OPAL trial include that it is adequately powered and incorporates features that reduces bias, such as concealed allocation and blinding. Because the trial is delivered at the point of care, the results can be directly translated to clinical practice and inform clinical guidelines. The choice of modified release oxycodone plus naloxone as the opioid analgesic for the OPAL trial relates to the ease of dosing (twice daily) compared to the immediate release opioid preparations that need to be taken more frequently. The combination with naloxone is known to reduce the frequency and severity of opioid-induced

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constipation which will be important for protecting the blinding of the OPAL trial. A weakness is that although we will monitor opioid misuse, we rely on self-report which can be prone to reporting bias. There are alternative sources, such as government prescription data or urine or blood samples, which may provide more objective data. However, after considering trial resources, the burden on participants, the recruitment of an acute population with a short term prescription of opioid analgesics, and the exclusion of those with a history or at high risk of addiction, drug abuse or alcoholism, we have decided to use self-report to capture such information.

The inclusion and exclusion criteria have been kept as broad as possible so the results can be applicable to the heterogeneous population that present to primary care with acute, non-specific spinal pain. OPAL is specifically designed to establish the effects of opioid analgesics in acute spinal pain. If the results show that opioid analgesics are indeed efficacious and well-tolerated, future research can further investigate if factors such as patient prognostic characteristics, treatment expectation, medication dosage and the type of opioid analgesics used will influence treatment responsiveness.

We have chosen outcomes that are patient-oriented, clinically relevant and recommended by international consensus.[28] Because the trial intervention will be implemented over a short period of time for an acute condition where patients in general make an initial, rapid improvement,[36 40] we will collect outcomes frequently (every 2 weeks) during the 6-week treatment period to assess treatment effects. We will also collect outcomes at 12 weeks to assess whether treatment effects, if any, can be sustained in the medium term. While we do not expect that a short term treatment will influence long term clinical outcomes, we will collect our primary outcome at 6 and 12 months, as well as long term opioid use and misuse

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data, to inform our results. We anticipate that participant recruitment will commence early 2016.

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AUTHORS' CONTRIBUTIONS

All authors conceived and refined the trial design and procured funding. CL was responsible for the design of the cost-effectiveness analysis. AM provided expertise in pharmacy. RD provided expertise in medicine and pharmacology. LB provided statistical expertise. CL drafted the manuscript; all authors critically contributed to the writing and approved the final manuscript for publication.

FUNDING STATEMENT

This work is supported by the National Health and Medical Research Council (NHMRC) of Australia, grant number APP1082480. CL is funded by a Career Development Fellowship from the NHMRC. CM is funded by a Principal Research Fellowship from the NHMRC. The funding source has no role in the trial design and will have no role in the trial conduct, data analysis and interpretation, or writing or reporting.

COMPETING INTERESTS STATEMENT

We have read and understood BMJ policy on declaration of interests and declare the following interests:

CL has received trial medicines from Pfizer (Australia) for an investigator-initiated trial funded by the National Health and Medical Research Council (NHMRC) of Australia, to evaluate drug treatment of low back pain.

AM has received supplementary funding and/or trial medicines from GlaxoSmithKline & Pfizer (Australia) for investigator-initiated NHMRC-funded trials evaluating drug treatment of low back pain. He is also the Program Director of the NHMRC Centre for Research Excellence in Medicines and Ageing.

JL has received supplementary funding and/or trial medicines from GlaxoSmithKline & Pfizer (Australia) for investigator-initiated NHMRC-funded trials evaluating drug treatment

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of back pain. She has received funding from Baxter Biosciences for research evaluating musculoskeletal outcomes in children with haemophilia.

RD has received supplementary funding and/or trial medicines from GlaxoSmithKline & Pfizer (Australia) for investigator-initiated NHMRC-funded trials evaluating drug treatment of back pain. RD has been a member of an advisory board about paracetamol for GlaxoSmithKline and ibuprofen for Reckitt Benckiser (Australia). Payments went to an audited hospital account for teaching and research purposes.

CM has received supplementary funding and/or trial medicines from GlaxoSmithKline & Pfizer (Australia) for investigator-initiated NHMRC-funded trials evaluating drug treatment of low back pain.

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LEGENDS

Figure 1. Participant timeline

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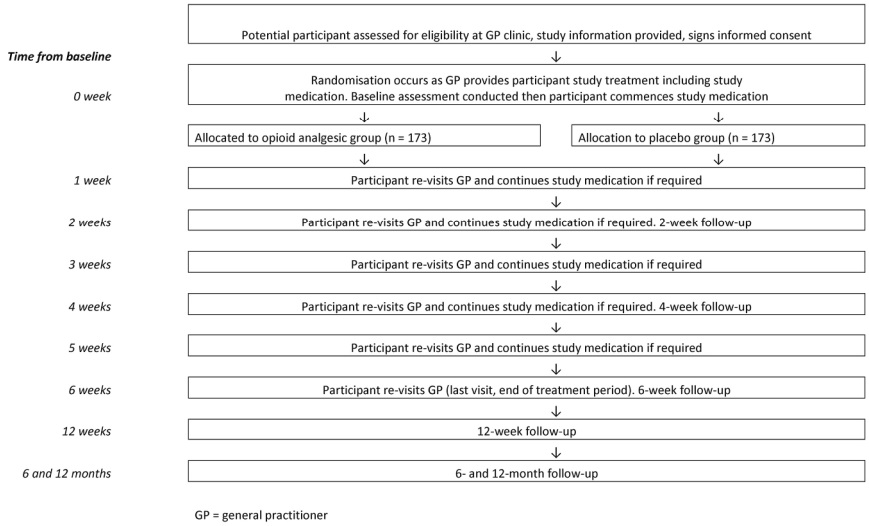

Participant timeline
A participant timeline is show
209x148mm (300 x 300 DPI)

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Opioid analgesia for acute spinal pain

TREATMENT AGREEMENT

In the OPAL study you are randomly allocated to receive an opioid analgesic or a placebo as the study medication. This document provides information about your overall pain management plan and seeks your written approval to proceed with the treatment.

Patient name:
GP name:
GP contact details:

Treatment commencement date:	____ / ____ / ____
Planned duration of treatment (max 6 weeks):	☐ 6 weeks ☐ ____ weeks
Next GP review:	____ / ____ / ____ (the recommended frequency is weekly)

Goals of treatment

Goals (e.g. walk 3 times a week for 30 min)	**Review date**	**Comments**
1. Reduce my average pain score from __/10 to __/10		
2.		
3.		
4.		
5.		

Other ways to help my pain:

1. Staying active and avoiding bed rest
2. _____
3. _____
4. _____
5. Treatments from other health professionals: ☐ physiotherapist ☐ chiropractor ☐ Other: _____

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OPAL
Opioid analgesia for acute spinal pain

If pain gets worse I can try:

Non-medicine strategies	Medicines

Please remember:

1. Only one doctor is responsible for prescribing your study medication. Arrangements can be made for an alternate prescriber to cover the absence of your doctor if needed.
2. Using the same pharmacy to re-fill your study prescription is a requirement of the OPAL study.
3. We will not give early prescriptions or replace lost prescriptions or medication, therefore you need to keep your study medication secure and take the dose as prescribed.
4. If you run out of your study medication early you may develop withdrawal symptoms which can be uncomfortable but are not life threatening.
5. If your behaviour suggests a problem with the misuse of medicines or addiction then your doctor will consider tapering and ceasing the study medication or referral to a Drug and Alcohol service. Problem behaviours include giving your medication to others, use of your medication in a non-prescribed way, excessive use of other medications (including alcohol and illicit drugs), repeated loss of medication, visiting multiple doctors to obtain medicines (doctor shopping) and worsening function at home or work.

Agreement

I have read the information provided and agree to this plan.

Patient signature: _____ **Date:** ____ / ____ / ____

GP signature: _____ **Date:** ____ / ____ / ____

Acknowledgements: adapted from 'My Pain Management Plan', National Pain Prescribing Service (NPS), and 'Opioid Treatment Agreement', Hunter New England Local Health District.

Version 1.0, 13 January 2015

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SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	ItemNo	Description	Page no.
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	All
Protocol version	3	Date and version identifier	Nil
Funding	4	Sources and types of financial, material, and other support	22
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1,2
	5b	Name and contact information for the trial sponsor	2
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	22
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	14,18
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5,6

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	6b	Explanation for choice of comparators	5,6
Objectives	7	Specific objectives or hypotheses	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7,8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9,10
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	9,12
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10-12
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Fig 1

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Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12,13
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	13
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	13
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	13
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	13
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	14
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	14
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	15
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	15

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Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	15
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	15-17
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	15, 16
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	18
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	18
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	18
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	19
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	19

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Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	19
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	19
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	20
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	22
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	20
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	20
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	21
	31b	Authorship eligibility guidelines and any intended use of professional writers	21
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	21
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Nil
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

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*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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