BMJ Open

Clinical Observation, Management and Function Of low back pain Relief Therapies (COMFORT). A cluster randomised controlled trial protocol.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2023-075286
Article Type:	Protocol
Date Submitted by the Author:	03-May-2023
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Keywords:	Primary Health Care, Back pain < ORTHOPAEDIC & TRAUMA SURGERY, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

Title:

Clinical Observation, Management and Function Of low back pain Relief Therapies (COMFORT). A cluster randomised controlled trial protocol.

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ABSTRACT

Introduction: Low back pain (LBP) is commonly treated with opioid analgesics despite evidence that these medicines provide minimal or no benefit for LBP and have an established profile of harms. International guidelines discourage or urge caution with the use of opioids for back pain; however, doctors and patients lack practical strategies to help them implement the guidelines. This trial will evaluate a multifaceted intervention to support general practitioners (GPs) and their patients with LBP implement the recommendations in the latest opioid prescribing guidelines.

Methods and analysis: This is a cluster randomised controlled trial that will evaluate the effect of educational outreach visits to GPs promoting opioid stewardship alongside non-pharmacological interventions including heat wrap and patient education about the possible harms and benefits of opioids on GP prescribing of opioids medicines dispensed. At least 40 general practices will be randomised in a 1:1 ratio to either the intervention or control (no outreach visits; GP provides usual care). A total of 410 patient-participants (205 in each arm) who have been prescribed an opioid for LBP will be enrolled via participating general practices. Follow-up of patient-participants will occur over a one year period. The primary outcome will be the cumulative dose of opioid dispensed that was prescribed by study GPs over one year from the enrolment visit (in morphine milligram equivalent dose). Secondary outcomes include prescription of opioid medicines, benzodiazepines, gabapentinoids, non-steroidal anti-inflammatory drugs by study GPs or any GP, health services utilisation and patient-reported outcomes such as pain, quality of life, and adverse events. Analysis will be by intention-to-treat, with a health economics analysis also planned.

Ethics and dissemination: The trial received ethics approval from The University of Sydney Human Research Ethics Committee (2022/511). The results will be disseminated via publications in journals, media, and conference presentations.

Trial registration number

ACTRN12622001505796

Number of Figures

1

Funding statement

The University of Sydney is the trial sponsor. The COMFORT trial is funded by a clinical trials and cohort studies grant from the National Health and Medical Research Council (NHMRC) of Australia (ID APP2000989). CM is supported by a NHMRC Investigator Fellowship (APP1194283).

Competing Interest Statement

The Sydney Pharmacy School receives funding for a postgraduate scholarship from GlaxoSmithKline for a student under the supervision of AJM. JM is an employee of the Pharmaceutical Society of Australia. BCM receives royalties for the development of an opioid risk prediction tool which is unrelated to the current study protocol. All other authors declare that they have no competing interests.

Authors contributions

All authors were involved in the conception of the trial and drafting of the protocol. CAS is principal investigator on the trial, has oversight over all trial procedures and drafted the manuscript. All authors contributed to the writing and/or critical review of the manuscript and approved the final manuscript for publication.

Acknowledgements We would like to thank the following people for their contribution:

Operations: Mr Daniel Chapman, Mrs Melissa Webb, Ms Sarah Diprose

Good Clinical Practice (GCP) training materials: Ms Joan Torony

Data Safety Monitoring Board: Prof Richard Lindley, Prof Richard O Day, Dr Nazila Jamshidi

Independent Clinical Trials Audit: The George Institute for Global Health, Rachel McGrath, Yachna Mehta

Abstract word count

296

Word count

4466

Strengths and Limitations of this study

- This is a cluster randomised trial that will evaluate simple, scalable strategies to reduce the use of opioids in the GP management of low back pain.
- A potential limitation related to trial design is that blinding of GP and patient-participants may be difficult to achieve, but we have blinded research personnel collecting patient outcomes.
- If our intervention is found effective, it has the potential to transform management of low back pain globally.

INTRODUCTION

Low back pain (LBP) is a common musculoskeletal condition, affecting 50%-80% of adults [1,2] and is the leading cause of disability in 160 countries [3]. Approximately 90% of LBP cases cannot be attributed to an identifiable cause [2,4], and the pain can be acute (self-limiting; resolving completely within 3 months) or chronic (persisting beyond 3 months) [5]. Low back pain can be complex to treat, and can adversely affect an individual's function, quality of life and mood [6-8].

Clinical practice guidelines for the management of LBP [2, 5, 9-11] recommend providing reassurance of a favourable prognosis (after screening for, and excluding, pathological conditions), encouraging physical activity, addressing potential concerns that physical activity may cause 'more damage' (e.g. fear-avoidance behaviours), and providing education around optimal pharmacological and non-pharmacological treatments. Non-pharmacological treatments may include spinal manipulation therapy or psychological interventions [5, 11], and pharmacological therapies may include non-steroidal anti-inflammatory drugs (NSAIDs) or paracetamol (acetaminophen) [12, 13].

Many clinical guidelines now discourage or urge caution with the use of opioid analgesics for LBP [13, 14]; however, opioid medicines continue to be one of the most commonly used treatments prescribed by general practitioners (GPs) for LBP globally. In the USA, chronic LBP is the leading cause for opioid prescription [15] and one in every 5 people with chronic LBP used at least one opioid in the last 30 days [16]. In Australia, half of the ~3.7 million GP encounters for LBP in 2015-16 resulted in an opioid prescription [17]. This practice has led to serious problems including dependence, overdose, hospitalisation and death [18]. In 2017-18, 823 Australians died from prescription opioids, and hospitalisations from prescription opioid poisonings have risen by 25% in the past 15 years [19]. Yet opioids provide limited benefit for LBP. Our systematic review [20] established that opioid analgesics provide only a small amount of pain relief in the short term for LBP (mean difference of −10.1 (95% Confidence Interval (CI), −12.8 to −7.4) on a 0 (no pain) to 100 (worst pain imaginable) pain scale compared with placebo [20]. Larger effects on pain (> 20 points on a 0-100 pain scale) were not reported even with high and potentially dangerous doses [20]. Adverse events such as constipation, nausea and vomiting, were common and 50% of patients stopped treatment due to adverse events or lack of efficacy [20].

We now understand that even short-term use of opioid medicines may be problematic [21]. The cumulative dose and duration of opioid use in the first month of use increases the risk of persistent opioid consumption [22, 23]. Overdose is six times more likely in patients prescribed

a long-acting opioid than those given a short-acting opioid [24]. This evidence has informed the latest opioid guidelines, which recommend treatment with a short acting opioid initially, and to use the lowest effective dose for the shortest time (ideally < 3 days) [25,26]. However, clinical practice is discordant with guidelines, and for conditions such as LBP, prescription often involves long-acting, strong opioids (e.g. oxycodone controlled release) [27,28], thereby increasing the risk of overdose, hospitalisation and persistent use.

The high rate of opioid prescribing for LBP in general practice settings strongly indicates the existing model of care needs to change. A key barrier to the uptake of the latest opioid guidelines is that patients and GPs lack the strategies to help them follow the recommendations and safely reduce opioids for this condition [29]. An effective intervention is urgently needed to support health system improvement in primary care by giving GPs and patients the tools to adopt the recommendations in the latest opioid guidelines, including using non–pharmacological measures such as heat wraps. Previous opioid reduction intervention trials have reported minimal or no benefit, and often targeted the patient or the clinician alone [30, 31].

The COMFORT trial will evaluate the effect of GP educational outreach visits promoting opioid stewardship alongside non-pharmacological treatments including heat wrap and patient education on judicious opioid use and potential harms. The intervention will be compared to no outreach visit and usual GP care to determine the effect on GP prescribing of opioid medicines dispensed to their patients with LBP over one year. The intervention provides GPs with practical strategies that they can offer patients with LBP to help them achieve adequate control of their pain and reduce the requirement for opioid medicines. We are proposing a simple, scalable intervention that, if found effective, has the potential to transform health practice and policy for LBP management globally.

METHODS AND ANALYSIS

Study design and setting

Clinical Observation, Management and Function Of low back pain Relief Therapies **(COMFORT)** is a cluster randomised controlled trial that will be undertaken in Australian general medical practices. Interested GPs from eligible practices will be trained by the research team on the study procedures and to identify and enrol eligible patient-participants into the trial. General practices will be randomised in a 1:1 ratio to receive the intervention (outreach visits to support opioid stewardship) or control (no outreach visits). The trial protocol has been

reported as per the SPIRIT 2013 Statement [32]. Recruitment of practices will take place primarily via direct contact with the practices and GPs, and through Primary Health Networks.

Eligibility criteria

General practices

General practices will be considered for the trial based on the following criteria:

Inclusion

- Has at least one practising GP registered with the Australian Health Practitioner Regulation Agency.

General practitioners

GPs in participating practices will be eligible based on the following criteria:

Inclusion

- Consult with patients who have LBP.
- Has no prescribing restrictions, that is, eligible to prescribe an opioid analgesic, including Schedule 8 opioid analgesics.
- Consent to researchers gaining access to their prescribing data.

Exclusion

- Participating GPs at that practice has received an education visit by any organisation on judicious opioid prescribing in the previous 12 months.

Note: All GPs in that practice who consent will enter the same treatment arm.

Patient-Participants

Adults with LBP will be screened for eligibility by a participating GP either during a face-to-face consultation or via telehealth. Participating GPs will determine patient eligibility against the study screening form. Patient-participants will be considered for the trial based on the following criteria:

Inclusion:

- Adults (≥18 years).
- Low back pain of any duration at the time of presentation.
- Has been prescribed an opioid analgesic for LBP by the participating GP.

- Sufficient understanding of English to complete questionnaires, or translation available.
- Holds an Australian Medicare card number (for data linkage purposes).
- Willingness to provide written informed consent to participate in the trial and grant researchers access to their Medicare/Pharmaceutical Benefits Scheme and other trial-related data.

Exclusion:

- Engaged in an opioid tapering regimen at the time of enrolment into the study i.e., have already begun to reduce their opioid medicine within the past month.
- Being actively treated for cancer or receiving palliative treatment.

Patient-participants will be informed about the consent process and receive an initial consultation with the participating GP as part of the trial. Patients will be contacted at baseline by a blinded researcher and complete a study questionnaire. Follow-up of patient-participants by the blinded researcher will then take place at the end of weeks 1, 4, 12, 26 and 52 post-baseline to complete the study questionnaire. Patients recruited into the intervention arm will also be asked to complete a heat wrap diary up to 12 weeks. Intervention arm GPs and patients will be invited to participate in a process evaluation interview (separate to this protocol).

The study flow chart is provided in Figure 1.

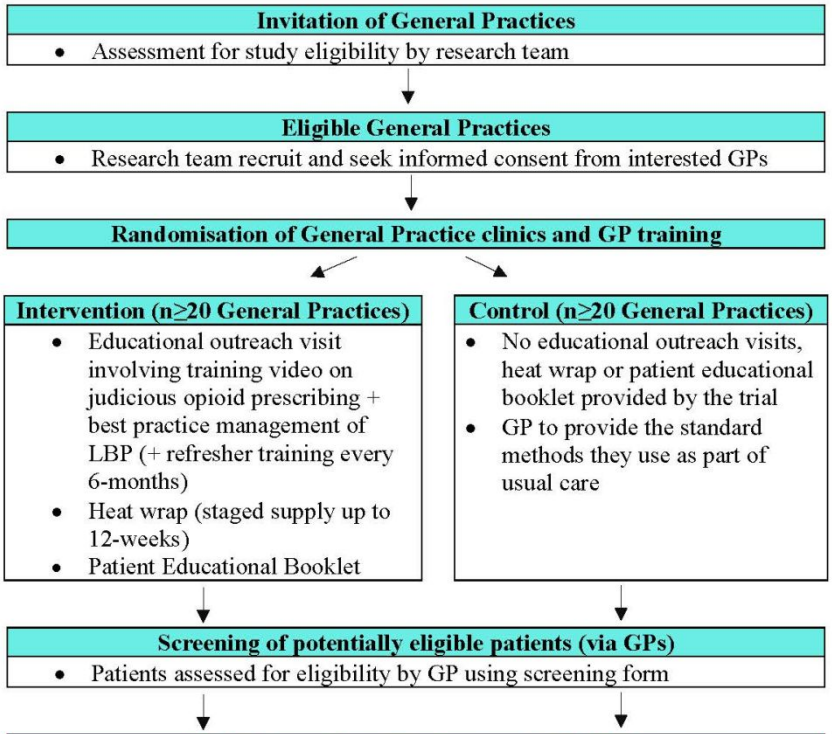

Figure 1: Study design flow Chart *Intervention only [a]Intervention only (scheduled between 12-16 weeks - standalone component).

Intervention

The multifaceted intervention supports GPs to achieve judicious prescribing of opioids and supports patient-participants to use opioids judiciously. It has the following components:

1) Educational outreach visits to GPs promoting opioid stewardship

Baseline visit

Participating GPs will receive a face-to-face baseline educational outreach visit (0.5 to1 hour duration) from the study operations team involving:

- Delivery of a 10-minute training video (developed for the trial, featuring an experienced GP (RI)) on judicious opioid prescribing and best practice management of LBP in line with key messages in clinical practice guidelines [26, 33]. Key messages on judicious opioid prescribing will include recommendations to limit duration of opioid use, commence therapy with a low dose, short-acting preparation, and have a clear plan to review use and taper or cease the opioid analgesic. Participating GPs will also be advised on appropriate strategies for opioid tapering or cessation should this form part of a patient-participant's care plan [26, 33].
- Training in study procedures.
- International Committee on Harmonisation of Good Clinical Practice (ICH-GCP) training (detailed below).

Refresher training visits

We have previously shown that following an educational intervention, clinician knowledge of LBP declines after 6 months [34]. Therefore, GPs in the intervention arm will receive face-to-face refresher training visits every 6 months (until the recruitment target for that practice is met) on judicious opioid prescribing and best practice management of LBP (via an abridged training video). Live online training visits will be permitted in circumstances where face-to-face visits are not possible.

2) Non-opioid treatments

Non-pharmacological therapies and advice

Participating GPs and patient-participants in the intervention arm will be informed of alternate non-opioid pain relief strategies to manage LBP. This will involve heat wrap therapy (at no cost to the patient) and advice to remain physically active, avoid best rest, and reassurance of a favorable prognosis where appropriate. The trial will provide patient-participants up to 12

weeks staged-supply of Flexeze® heat patches, a Therapeutic Goods Administration (TGA) registered product Australian Register of Therapeutic Goods (ARTG) #209075 – Medical Devices Class IIa, i.e. low-medium risk device/product) [35]. The heat patches will be inserted inside a pouch (body wrap) to increase skin safety. Patient-participants will be informed of the use of the heat patch and advised to have a one day break after use for three consecutive days. In addition, to standardise treatment, patient-participants will be advised to apply the heat wrap for 6-8 hours during the day for up to 12 weeks, and notify the study team of any skin irritations. At the enrolment visit, patients will be provided with a 1-week initial supply of heat wraps by the participating GP.

Non-opioid analgesic medicines

Optimal dosing of paracetamol and/or oral non-steroidal anti-inflammatory medications (NSAIDs) may also be considered by participating GPs if deemed appropriate for the management of LBP based on the patients' medical and medication history.

3) Participant education

The training will encourage participating GPs to provide their patient-participants with an educational booklet. In partnership with PainAustralia Consumer Advisory Group, NPS MedicineWise and Choosing Wisely Australia, we co-developed a 2-page written booklet '*5 questions to ask about using opioids for back pain or osteoarthritis'* combining evidence-based messages on judicious opioid use with management strategies endorsed in international LBP guidelines e.g. staying active. The booklet has been modelled on the Choosing Wisely '5 questions to ask' [36] resource that was widely tested among patients and doctors and designed to empower individuals to ask questions about opioid medicines and other pain management options. The booklet contains a pain management plan to facilitate shared decision-making and review. Importantly, it allows opportunity for dialogue between the participating GP and patient-participant during the consultation about accountable opioid use.

4) Additional education resources

Participating GPs will be provided access to the NPS opioid tapering algorithm [37] to support de-prescribing of opioid medicines for their patients with LBP.

Control (no outreach visit)

Participating GPs in the control arm will not be provided with any face-to-face outreach visits discussing judicious opioid prescribing or best practice management of LBP, nor will they

receive heat wraps or the patient educational booklet to discuss with patients. These GPs will be asked to provide consenting patient-participants with the usual care methods they normally use.

Consumer Medicines Information Leaflet

All patient-participants, regardless of whether they are in the intervention or control arm will be provided with a Therapeutic Goods Administration approved Consumer Medicines Information (CMI) leaflet on the opioid medicine prescribed at enrolment by the study team. This will be provided after completion of the baseline visit.

ICH-GCP training

All participating GPs will receive ICH-GCP training at baseline and refresher training every 6 months for the duration that they are enrolling patient-participants onto the trial. This training outlines responsibilities in the conduct of clinical trials and will be delivered via a 7-minute training video.

Co-interventions

All patient-participants will not be prohibited from using other forms of pharmacological or non-pharmacological pain relief therapies during the trial. The study questionnaires will capture these details, and any therapies that may impact our study outcomes (i.e. which has the potential to provide pain relief and therefore be opioid sparing) will be documented as a co-intervention [38].

Study outcomes

Using data from Services Australia and/or patient admitted data and/or patient-report, the following outcomes will be collected over the 1-year follow up (as specified below):

Primary outcome

Cumulative opioid dose dispensed to patient-participants that was prescribed by participating GPs over one year using Medicare linkage, determined using morphine milligram equivalent (MME) [39].

Secondary outcomes

Secondary outcomes collected for patient-participants over the one year follow up will include:

- Type of opioid dispensed that was prescribed by participating GPs.
- Cumulative opioid dispensed (MME) that was prescribed by any GP.

- Number of subsidised Medicare visits to healthcare providers and services.
- Number of visits to emergency department.
- Number of hospitalisations.
- Total cost of Medicare Benefits Scheme (MBS) and Pharmaceutical Benefits Scheme (PBS) usage.
- Persistent opioid use at 6 months defined as:
    - Having had at least one opioid prescription issued in the prior 30 days AND at least 3 opioid prescriptions issued in the prior 4 months [40, 41].
- Persistent opioid use at 12 months defined as:
    - Having had 10 or more opioid prescriptions issued in the prior year with at least one prescription issued in the prior month [40, 41].
- Number of dispensations for gabapentinoids (e.g., pregabalin, gabapentin), benzodiazepines (e.g., diazepam), NSAIDs prescribed by participating GPs and any GP.
- Opioid related poisonings.
- Number of deaths.
- Economic evaluation (detailed below).

While not an outcome for this study, the trial will also determine opioid dispensation in the 1 year prior to study enrolment to determine patterns of persistent opioid use according to our pre-specified definitions of persistent opioid use outlined above.

Secondary outcomes will also assess the following patient-participant outcomes, collected online or by phone via patient-report at weeks 1, 4, 12, 26 and 52 (or as specified):

- Pain intensity (measured using the 0 to 10 Numerical Pain Rating Scale) with 0 being no pain and 10 being worst pain: a measure with acceptably high test-retest reliability (Intraclass Correlation Coefficient (ICC) of 0.95) [42].
- Disability (measured using the Roland Morris Disability Questionnaire (RMDQ)): A 24 item questionnaire, with good internal consistency and responsiveness (Cronbach's alpha 0.9-0.93) [43, 44].
- Global rating of change (using the Global Perceived Effect scale; scored from -5 to +5): A measure with acceptably high test-retest reliability (ICC 0.99) [45].
- Self-reported use of over-the-counter medicines and non-pharmacological interventions.

- Quality of life (physical component score and mental component score measured using the Short Form (SF) 12v2 questionnaire), which has been shown to have good internal consistency and validity [46].
- Pain Self Efficacy Questionnaire: A 10-item questionnaire to assess confidence levels to perform a range of activities while in pain; a measure with acceptably high good internal consistency (Cronbach's alpha 0.79 to 0.95) [47].
- Duration of opioid use: A medication diary will be used to record use of medicines (including for LBP if applicable) in the past 7 days. The opioid course will be considered to have ended after 7 continuous days of no opioid use. The medication diary has shown high concordance with clinically determined measures e.g., plasma drug concentrations and pill count or canister weight (Kappa >0.6 in 7 studies) [48], and high completion rates amongst participants was also reported be completing these diaries [49,50].
- Return of unused opioid medicine: Patient-participants will be asked if they returned any unused medicines at 12 weeks and 1 year.
- Heat wrap diary (Intervention group): To record the number of days of heat wrap use (up to 12 weeks post-enrolment).
- Severity of opioid withdrawal symptoms: Using the self-report opioid withdrawal scale at 1, 4 and 12 weeks [51].
- Proportion of people who ended an opioid course within the first month: Determined by the medication diary, and the opioid course will be considered to have ended after 7 continuous days of no opioid use.
- Harms (detailed under 'Harms' below)
    - Proportion of patient-participants in each study arm who experienced an adverse or serious adverse event.
    - Frequency and nature of any adverse or serious adverse event.
    - Cause of serious adverse event.

GP attitudes towards prescribing opioid and other analgesics

To determine whether the intervention will impact GP attitudes about prescribing, we will administer two validated surveys: the 22-item concerns about analgesics prescriptions questionnaire [52] and 10-item opioid therapy survey [53] to ascertain GP attitudes towards prescribing opioid and other analgesics. These will be administered before and after the baseline training visit and before and after the initial 6 month visit via an online questionnaire (REDCap) or paper-based version.

Sample size

A sample size of 410 patient-participants will provide the trial with 90% power to detect a difference of 210 MME over 1 year between the intervention and control arms, allowing for a withdrawal rate of 15% and a rate of non-adherence of 10%. To achieve this target we will require at least 40 general practices (at least 20 general practice clusters in each arm), with each general practice to recruit at least 12-15 participants. We have assumed an ICC of 0.045 based on 145 ICCs from cluster randomised trials in primary care [54].

This sample size will also provide at least 80% power to detect changes in secondary outcomes, including a minimum difference of 10% for pain (1 point on the 0-10 numerical rating scale; assuming SD of 1.9) [50, 55], 10% on the 24-item Roland Morris Disability Questionnaire (RMDQ) (assuming Standard Deviation (SD) of 5.4) [50, 55], and 10% on the Short Form 12 (SF-12) Mental Component Score. This sample size will also provide >80% power to detect a difference of 20% in the proportion of people who continue to use opioids at 1 year and 20% reduction in the proportion of dispensations for strong, long-acting opioids.

Strategies for achieving adequate patient-participant enrolment

Strategies to achieve the target sample size will include monthly phone calls to sites, quarterly site visits from the study team to discuss trial progress and provide ongoing support to participating GPs (or live online visits in exceptional circumstances), continuing professional development credit points for GP participation, and reimbursement to participating GPs and patient-participants for their involvement in the trial. Recruitment targets will be compared against milestones. Steering committee meetings will be held quarterly to discuss trial progress and address any challenges with recruitment.

Randomisation sequence of general practices (or allocation of interventions)

Practices will be randomised to the intervention or control group using central randomisation with allocation concealment built in. Practices will be stratified by area level socioeconomic status and geographic remoteness. Socio-Economic Indexes for Areas (SEIFA, area-level socioeconomic status) will be divided/split into tertiles (highest, middle, lowest) based on the 2021 index for relative advantage and disadvantage (IRSAD) [56]. Remoteness will be classified into two categories (ARIA+ classification), based on the Australian Statistical Geography Standard (ASGS): 1) Urban and 2) Regional/Remote/Very remote [57]. There will be two strata variables, one with two levels, and one with three levels, giving a total of six strata. Separate randomisation schedules will be generated for each of the six strata, using permuted blocks. Randomisation will also account for a planned study within a trial (SWAT) that is being embedded within the COMFORT trial. The study protocol for the SWAT is separate, and will test whether additional monetary reimbursement (versus no additional

reimbursement) will encourage greater participation of culturally and linguistically diverse patient-participants with limited English proficiency into the COMFORT trial.

Because around 70% of the population of Australia is in urban areas [58], we will recruit sites proportionally, with 70% from urban strata and 30% from regional/remote/very remote strata. This gives a target sample size of n=9-10 sites in each of the three urban strata, and n=4 sites in each of the three regional/remote/very remote strata. To maximise balance while maintaining allocation concealment, the allocation schedule will use random permuted blocks of size 2 and 4. In order to allow greater recruitment from some combinations than others without exhausting the randomisation schedule, we will allow a maximum of n=40 practices to be randomised to any particular combination of SES and remoteness.

Blinding

Randomisation allocation will not be revealed to members of the research team involved in patient-participant follow-up, the Data Safety Management Board (DSMB) and the independent statistician involved in the statistical analysis and interpretation of results. However, unblinding may be requested by the DSMB in specific cases to allow an assessment of serious adverse events.

Data collection methods

The participating GP will notify the study team when a patient-participant is enrolled into the trial. The study team will follow up with the patient-participant within 24-hours to complete the baseline telephone survey. Each patient will be followed (by phone and/or online survey via Research Electronic Data Capture (REDCap)) over one year. Collection of study outcomes will be via data linkage and patient-report. In addition, the study team will also follow-up with participating GP to complete questionnaires via REDCap (or paper based) at specified timepoints detailed above. Data will be entered and verified by the study team for data accuracy.

Other data collected

Patient-participants and participating GPs in the intervention group will also be invited to complete a process evaluation interview (reported as a separate protocol).

Data management

Data will be monitored for any errors and recorded using a secure database hosted by the University of Sydney. An electronic data capturing system e.g. REDCap [59] will be used, and

data collected over the phone will be directly entered into the database, while surveys completed online will be automatically transcribed into the database. Information recorded using paper case report forms (CRF) will be entered into the database and verified by another study team member. Data from Services Australia and patient admitted data will be stored using secure databases by the University of Sydney.

Statistical methods

The study will explore the effect of the intervention versus control as a fixed effect in a mixed effects model, including a random intercept of cluster (GP practice). Primary analyses will follow the intention-to-treat principle with the statistician blinded to treatment group.

Primary analysis

The primary outcome will be analysed using a linear mixed effects regression model with the intervention group as a covariate. Missing data is likely to be very low as our primary outcome is based on linked data.

Subgroup analyses will be performed to evaluate the difference in the primary outcome between participants using opioids persistently in the 12 months prior to study entry, versus those not using opioid medicines persistently. Subgroup analyses will be performed to examine if the following factors modify the effect of treatment on primary outcome: (i) chronicity-patient-participants with acute vs chronic LBP, (ii) type of LBP- non-specific LBP versus LBP due to specific causes (e.g., pregnancy), (iii) age and (iv) gender. In addition, subgroup analyses will also be performed to compare outcomes from patient-participants enrolled via telehealth versus face to face, years of experience of participating GPs, and geographical location of participating general practices.

Secondary analysis

Continuous secondary outcomes will be analysed with the use of repeated-measures linear mixed models. Adjusted mean differences will be tested for the end of treatment (12 weeks) and the time point for the primary analysis (one year). A binary logistic regression will be conducted for binary outcomes. Serious adverse events and adverse events will be reported descriptively for both number of events and number of patient-participants experiencing an event. Appropriate model checking will be conducted for all analyses. Balance of baseline patient-participant characteristics will be assessed and any characteristics not well balanced will be included in the model, as a secondary analysis.

Health economic analyses

A within-trial economic evaluation will be conducted. Costs (i.e., outreach visit, heat wrap therapy, patient information booklets, training) will be collected using trial financial records and staff wage rates. Health care costs will be incorporated in the analysis, using administratively linked data for MBS, PBS, and hospital admission costs, and patient-reported diaries for over-the-counter medications. The health outcome measure will use the SF-12, which will be converted to a preference-based measure of health (SF-6D) [60] to estimate quality-adjusted life years (QALYs). To calculate incremental cost-effectiveness ratios, linear mixed models will be used to analyse both costs and outcomes.
An additional analysis will be conducted to compare the total PBS cost of analgesic medicines dispensed among patient-participants randomised to the intervention versus control over a 1-year period using the dispensed price for maximum quantity (DPMQ).

Statistical Analysis Plan

A statistical analysis plan will be published separately detailing methods for statistical analysis and, where appropriate, handling of missing data.

Data monitoring

A Data Safety Management Board (DSMB) has been formed by the Steering Committee and comprises experienced clinicians with skills relevant to the trial (e.g., opioid and pain medicines specialists). The DSMB will review serious adverse events (SAE), assess causality where appropriate, review clinical trial data, and provide recommendations (i.e., trial progress and/or if changes for the trial is recommended). An initial meeting with the DSMB will be held around six months once the trial has commenced study recruitment, and quarterly follow-up meetings will be arranged, or as agreed by the DSMB and study team.

Harms

Adverse events

Adverse events (including serious adverse events) will be collected by patient-report questionnaires at weeks 1, 4, 12, 26 and 52.

Serious Adverse Events

Serious adverse events will also be collected at each of the follow up time points. These are defined as any untoward medical occurrence resulting in death; is life threatening; requires hospitalisation or prolongation of the existing hospitalisation; results in persistent or significant

disability or incapacity; is a congenital abnormality or birth defect; is a medically significant or important event or reaction [61].

Serious adverse events will be reported to the Sydney University Human Research Ethics Committee (HREC) within the required timeframe, and causality will also be reviewed and adjudicated by the DSMB where appropriate.

Auditing

An independent external audit for the trial was carried out by the George Institute for Global Health which involved a thorough review of the trial processes and study documents prior to study commencement.

Patient and Public Involvement

Consumers (PainAustralia Consumer Advisory Group) were involved in the conception and design of this trial. PainAustralia will continue to be involved throughout the study and will provide high level advocacy support and be involved in dissemination. A consumer is co-author on the work.

ETHICS AND DISSEMINATION

Ethics approval

Ethics approval has been provided by the Human Research Ethics Committee, The University of Sydney (Project number 2022/551).

Protocol amendments

Any changes to the study protocol must be agreed upon by the trial's steering committee. These will be submitted to the University of Sydney HREC for approval prior to being implemented.

Consent or assent

The study team will train participating GPs to coordinate the informed consent process, with the assistance of the study team where appropriate. Participating GPs will discuss the study with interested and potentially eligible patient-participants and provide them with a participant information sheet and consent form (paper-based or electronically). Patient-participants will have the opportunity to ask participating GPs or the research team any questions prior to consenting. Written informed consent from patient-participants will then be obtained by the participating GP. The participating GP or patient-participants can withdraw their consent at any point during the study.

Confidentiality

Study data will be securely stored in either locked cabinets (paper records) or electronically (electronic data files) and accessed only by the study team.

Access to data

The study team will have access to the final dataset, and a blinded (to treatment allocation) copy of the dataset will be provided to the trial statistician to perform the study analysis..

Ancillary and post-trial care

Costs of treatments outside of the trial will not be covered by the study. The trial will provide heat wraps at no cost to patient-participants in the intervention arm.

Non-negligent harm associated with the protocol will be covered by the trial's insurance. This includes cover for additional healthcare, compensation, or damages.

Dissemination policy

The study results will be submitted for publication in scientific journals, presented at conferences or meetings. Lay summaries will be provided to participating GPs, patient-participants, and stakeholders involved in the trial.

Trial findings will be discussed and disseminated through various media, external partners e.g. PainAustralia consumer advisory group and policymakers in Australia and overseas.

We will adhere to the International Committee of Medical Journal Editors (ICMJE) guidelines on authorship eligibility for any publications arising from this trial. We do not plan to engage professional writers.

REFERENCES

1. Fatoye F, Gebrye T, Odeyemi I. Real-world incidence and prevalence of low back pain using routinely collected data. *Rheumatol Int* 2019;39(4):619-26. doi: 10.1007/s00296-019-04273-0
2. Maher C, Underwood M, Buchbinder R. Non-specific low back pain. *Lancet* 2017;389(10070):736-47. doi: 10.1016/S0140-6736(16)30970-9.
3. World Health Organisation. Musculoskeletal Health. 2022. Available from: https://www.who.int/news-room/fact-sheets/detail/musculoskeletal-conditions.
4. Koes BW, Van Tulder M, Thomas S. Diagnosis and treatment of low back pain. *BMJ* 2006;332(7555):1430-34. doi: 10.1136/bmj.332.7555.1430
5. Qaseem A, Wilt TJ, McLean RM, et al. Noninvasive treatments for acute, subacute, and chronic low back pain: a clinical practice guideline from the American College of Physicians. *Ann Int Med* 2017;166(7):514-30. doi: 10.7326/M16-2367
6. Agnus Tom A, Rajkumar E, John R, et al. Determinants of quality of life in individuals with chronic low back pain: a systematic review. *Health Psychol Behav Med* 2022;10(1):124-44. doi: 10.1080/21642850.2021.2022487
7. Wong JJ, Tricco AC, Côté P, et al. The association between depressive symptoms or depression and health outcomes in adults with low back pain with or without radiculopathy: protocol of a systematic review. *Syst Rev* 2019;8(1):1-8. doi: 10.1186/s13643-019-1192-4
8. Sagheer MA, Khan MF, Sharif S. Association between chronic low back pain, anxiety and depression in patients at a tertiary care centre. *J Pak Med Assoc* 2013;63(6):688-90. PMID: 23901665
9. Australian Commission on Safety and Quality in Healthcare. Low Back Pain clinical care standards 2022 [Available from: https://www.safetyandquality.gov.au/sites/default/files/2022-08/low_back_pain_clinical_care_standard.pdf].
10. George SZ, Fritz JM, Silfies SP, et al. Interventions for the Management of Acute and Chronic Low Back Pain: Revision 2021. *J Orthop Sports Phys Ther* 2021;51(11):CPG1-CPG60. doi: 10.2519/jospt.2021.0304
11. Chou R, Deyo R, Friedly J, et al. Nonpharmacologic Therapies for Low Back Pain: A Systematic Review for an American College of Physicians Clinical Practice Guideline. *Ann Intern Med* 2017;166(7):493-505. doi: 10.7326/m16-2459
12. Chou R, Deyo R, Friedly J, et al. Systemic Pharmacologic Therapies for Low Back Pain: A Systematic Review for an American College of Physicians Clinical Practice Guideline. *Ann Intern Med* 2017;166(7):480-92. doi: 10.7326/m16-2458
13. Anderson DB, Shaheed CA. Medications for Treating Low Back Pain in Adults. Evidence for the Use of Paracetamol, Opioids, Nonsteroidal Anti-inflammatories, Muscle Relaxants, Antibiotics, and Antidepressants: An Overview for Musculoskeletal Clinicians. *J Orthop Sports Physi Therapy* 2022;52(7):425-31. doi: 10.2519/jospt.2022.10788
14. Oliveira CB, Maher CG, Pinto RZ, et al. Clinical practice guidelines for the management of non-specific low back pain in primary care: an updated overview. *Eur Spine J* 2018;27(11):2791-803. doi: 10.1007/s00586-018-5673-2
15. Hudson TJ, Edlund MJ, Steffick DE, et al. Epidemiology of regular prescribed opioid use: results from a national, population-based survey. *J Pain Symptom Manage* 2008;36(3):280-8. doi: 10.1016/j.jpainsymman.2007.10.003
16. Shmagel A, Ngo L, Ensrud K, et al. Prescription Medication Use Among Community-Based U.S. Adults With Chronic Low Back Pain: A Cross-Sectional Population Based Study. *J Pain* 2018;19(10):1104-12. doi: 10.1016/j.jpain.2018.04.004
17. Australian Institute of Health and Welfare 2015. Arthritis no.21. Cat.PHE 185. Canberra.

18. Australian Institute of Health and Welfare 2019. Opioid harm in Australia and comparisons between Australia and Canada: Australian Institute of Health and Welfare. Cat.HSE 210. Canberra.
19. Australian Institute of Health and Welfare (2018). Opioid harm in Australia. HSE 210. Available at https://www.aihw.gov.au/reports/illicit-use-of-drugs/opioid-harm-in-australia/summary (Accessed 13 April, 2023).
20. Shaheed CA, Maher CG, Williams KA, et al. Efficacy, tolerability, and dose-dependent effects of opioid analgesics for low back pain: a systematic review and meta-analysis. *JAMA Intern Med* 2016;176(7):958-68.
21. Abdel Shaheed C, McLachlan AJ, Maher CG. Rethinking "long term" opioid therapy. *BMJ* 2019;367:l6691. doi: 10.1136/bmj.l6691 doi: 10.1001/jamainternmed.2016.1251
22. Shah A, Hayes CJ, Martin BC. Characteristics of Initial Prescription Episodes and Likelihood of Long-Term Opioid Use - United States, 2006-2015. *MMWR Morb Mortal Wkly Rep* 2017;66(10):265-69. doi: 10.15585/mmwr.mm6610a1
23. Deyo RA, Hallvik SE, Hildebran C, et al. Association Between Initial Opioid Prescribing Patterns and Subsequent Long-Term Use Among Opioid-Naïve Patients: A Statewide Retrospective Cohort Study. *J Gen Intern Med* 2017;32(1):21-27. doi: 10.1007/s11606-016-3810-3
24. Miller M, Barber CW, Leatherman S, et al. Prescription opioid duration of action and the risk of unintentional overdose among patients receiving opioid therapy. *JAMA Intern Med* 2015;175(4):608-15. doi: 10.1001/jamainternmed.2014.8071
25. Dowell D RK, Jones CM, Baldwin GT, Chou R. CDC Clinical Practice Guideline for Prescribing Opioids for Pain — United States, 2022. *MMWR Recomm Rep* 2022;71(No. RR-3):1–95. doi: http://dx.doi.org/10.15585/mmwr.rr7103a1
26. The Royal Australian College of General Practitioners. Prescribing drugs of dependence in general practice, Part C2: The role of opioids in pain management. *East Melbourne, Vic: RACGP* 2017.
27. Karanges EA, Blanch B, Buckley NA, et al. Twenty-five years of prescription opioid use in Australia: a whole-of-population analysis using pharmaceutical claims. *Br J Clin Pharmacol* 2016;82(1):255-67. doi: 10.1111/bcp.12937
28. Gisev N, Pearson S-A, Dobbins T, et al. Combating escalating harms associated with pharmaceutical opioid use in Australia: the POPPY II study protocol. *BMJ open* 2018;8(12):e025840. doi: 10.1136/bmjopen-2018-025840
29. Hamilton M, Mathieson S, Gnjidic D, et al. Barriers, facilitators, and resources to opioid deprescribing in primary care: experiences of general practitioners in Australia. *Pain* 2022;163(4):e518-e26. doi: 10.1097/j.pain.0000000000002340
30. Frank JW, Lovejoy TI, Becker WC, et al. Patient outcomes in dose reduction or discontinuation of long-term opioid therapy: a systematic review. *Ann Intern Med* 2017;167(3):181-91. doi: 10.7326/M17-0598
31. Mathieson S, Maher CG, Ferreira GE, et al. Deprescribing opioids in chronic non-cancer pain: systematic review of randomised trials. *Drugs* 2020;80(15):1563-76. doi: 10.1007/s40265-020-01368-y
32. Chan A-W, Tetzlaff JM, Gøtzsche PC, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013;346. doi: 10.1136/bmj.e7586.
33. Australian Commission on Safety and Quality in Health Care. Low Back Pain Clinical Care Standard. Sydney: ACSQHC; 2022.
34. Abdel Shaheed C, Maher CG, Mak W, et al. The effects of educational interventions on pharmacists' knowledge, attitudes and beliefs towards low back pain. *Int J Clin Pharm* 2015;37(4):616-25. doi: 10.1007/s11096-015-0112-5
35. Australian Register of Therapeutic Goods (ARTG): ARTG ID 209075: Public Summary.

36. Choosing Wisely. 5 questions to ask your doctor or other healthcare provider before you get any test, treatment, or procedure. Available from: https://www.choosingwisely.org.au/resources/consumers-and-carers/5questions
37. NPS Medicine Wise Opioid Tapering Algorithm. Available from: https://www.nps.org.au/assets/NPS-MedicineWise-opioid-tapering-algorithm.pdf.
38. Abdel Shaheed C, Blyth F, Furmage AM, et al. Getting the "balance" right in clinical trials. *BMJ* 2021;375:n2869. doi: 10.1136/bmj.n2869
39. Pereira J, Lawlor P, Vigano A, et al. Equianalgesic dose ratios for opioids. a critical review and proposals for long-term dosing. *J Pain Symptom Manage* 2001;22(2):672-87. doi: 10.1016/s0885-3924(01)00294-9
40. Zgierska AE, Vidaver RM, Smith P, et al. Enhancing system-wide implementation of opioid prescribing guidelines in primary care: protocol for a stepped-wedge quality improvement project. *BMC Health Serv Res* 2018;18(1):1-8. doi.org/10.1186/s12913-018-3227-2
41. Sun EC, Darnall BD, Baker LC, et al. Incidence of and risk factors for chronic opioid use among opioid-naive patients in the postoperative period. *JAMA Intern Med* 2016;176(9):1286-93. doi:10.1001/jamainternmed.2016.3298
42. Alghadir AH, Anwer S, Iqbal A, et al. Test–retest reliability, validity, and minimum detectable change of visual analog, numerical rating, and verbal rating scales for measurement of osteoarthritic knee pain. *J Pain Res* 2018;11:851. doi: 10.2147/JPR.S158847
43. Hsieh C, Phillips RB, Adams AH, et al. Functional outcomes of low back pain: comparison of four treatment groups in a randomized controlled trial. *J Manipulative Physiol Ther* 1992;15(1):4-9. PMID: 1531488
44. Kopec JA, Esdaile JM. Functional disability scales for back pain. *Spine* 1995;20(17):1943-49. doi: 10.1097/00007632-199509000-00021
45. Bobos P, MacDermid J, Nazari G, et al. Psychometric properties of the global rating of change scales in patients with neck disorders: a systematic review with meta-analysis and meta-regression. *BMJ open* 2019;9(11):e033909. doi: 10.1136/bmjopen-2019-033909
46. Bhandari NR, Kathe N, Hayes C, et al. Reliability and validity of SF-12v2 among adults with self-reported cancer. *Res Social Adm Pharm* 2018;14(11):1080-84. doi: 10.1016/j.sapharm.2018.01.007
47. Dubé M-O, Langevin P, Roy J-S. Measurement properties of the Pain Self-Efficacy Questionnaire in populations with musculoskeletal disorders: a systematic review. *Pain Rep* 2021;6(4). doi: 10.1097/PR9.0000000000000972
48. Garber MC, Nau DP, Erickson SR, et al. The concordance of self-report with other measures of medication adherence: a summary of the literature. *Med Care* 2004:649-52. doi: 10.1097/01.mlr.0000129496.05898.02
49. Mathieson S, Maher CG, McLachlan AJ, et al. Trial of pregabalin for acute and chronic sciatica. *N Engl J Med* 2017;376(12):1111-20. doi: 10.1056/NEJMoa1614292
50. Williams CM, Maher CG, Latimer J, et al. Efficacy of paracetamol for acute low-back pain: a double-blind, randomised controlled trial. *Lancet* 2014;384(9954):1586-96. doi: 10.1016/S0140-6736(14)60805-9
51. Handelsman L, Cochrane KJ, Aronson MJ, et al. Two new rating scales for opiate withdrawal. *Am J Drug Alcohol Abuse* 1987;13(3):293-308. doi: 10.3109/00952998709001515
52. McCracken LM, Velleman SC, Eccleston C. Patterns of prescription and concern about opioid analgesics for chronic non-malignant pain in general practice. *Prim Health Care Res Dev* 2008;9(2):146-56. doi: 10.1017/S1463423608000625
53. Sheehan KA, Scanlan E, Matthews M, Ross EL, Jamison RN Beliefs about prescribing opioids for chronic pain: survey of primary care practitioners. Poster session presented

at the 33rd Annual Scientific Meeting of the American Pain Society, Tampa, Florida, May 2, 2014.

54. Stuart B, Becque T, Moore M, et al. Clustering of continuous and binary outcomes at the general practice level in individually randomised studies in primary care - a review of 10 years of primary care trials. *BMC Med Res Methodol* 2020;20(1):83. doi: 10.1186/s12874-020-00971-7
55. Williams CM, Maher CG, Latimer J, et al. Efficacy of paracetamol for acute low-back pain: a double-blind, randomised controlled trial. *Lancet* 2014;384(9954):1586-96. doi: 10.1016/s0140-6736(14)60805-9
56. Statistics ABo. Technical Paper Socio-Economic Indexes for Areas (SEIFA) 2021: Australian Bureau of Statistics Canberra, 2023.
57. Pink B. Australian statistical geography standard (ASGS): volume 5—remoteness structure. *Canberra: Australian Bureau of Statistics* 2011
58. The Royal Australian College of General Practitioners. General Practice: Health of the Nation 2020. East Melbourne, Vic: RACGP, 2020.
59. Research Electronic Data Capture (REDCap). Available from: https://redcap.sydney.edu.au/.
60. Brazier JE, Roberts J. The estimation of a preference-based measure of health from the SF-12. *Med Care* 2004;42(9):851-9. doi: 10.1097/01.mlr.0000135827.18610.0d
61. National Health and Medical Research Council. Guidance: Safety monitoring and reporting in clinical trials involving therapeutic goods. Canberra: National Health and Medical Research Council 2016.

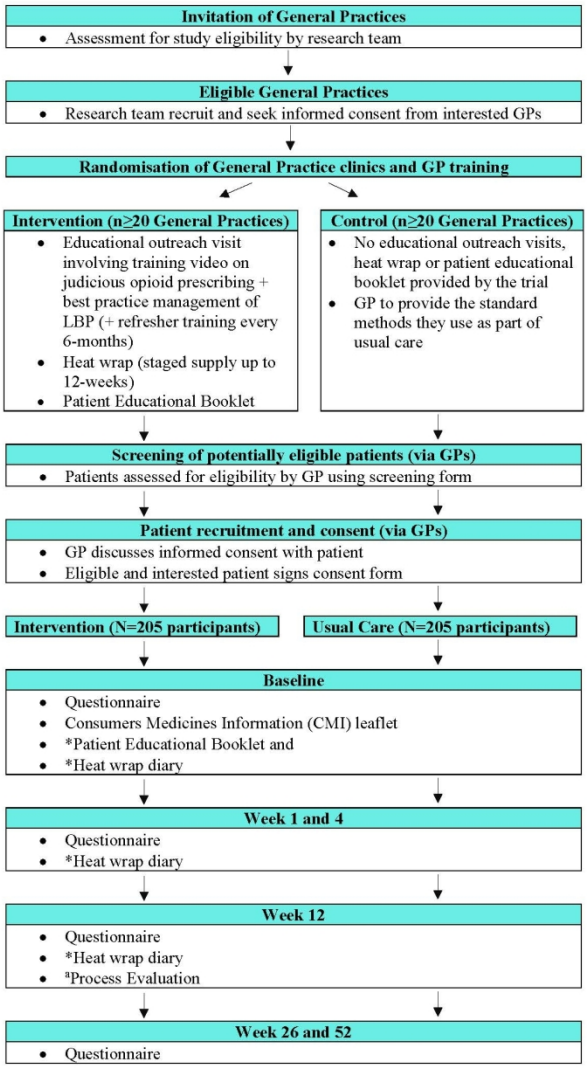

Figure 1: Study design flow Chart *Intervention only a) Intervention only (scheduled between 12-16 weeks - standalone component).

210x297mm (200 x 200 DPI)

SPIRIT CHECKLIST

Item	Item n	Description	Checked
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Y
Trial Registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Y
	2b	2b All items from the World Health Organization Trial Registration Data Set	N/A
Protocol Version	3	Date and version identifier	Y
Funding	4	Sources and types of financial, material, and other support	Y
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	
	5b	Name and contact information for the trial sponsor	Y
	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	Y
	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)	Y
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	Y
	6b	Explanation for choice of comparators	Y
Objectives	7	Specific objectives or hypotheses	Y
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)	Y
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	Y
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and	Y

		individuals who will perform the interventions (eg, surgeons, psychotherapists)	
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Y
	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)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Y
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Y
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	Y
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)	Y
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	Y
Recruitment	**15**	Strategies for achieving adequate participant enrolment to reach target sample size	Y
Methods: Assignment for 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	Y
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	Y

Implementation	**16c**	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Y
Blinding (masking)	**17a**	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Y
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Y
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	Y
	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	Y
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	Y
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	Y
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Y
	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)	Y
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	Y

	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	Y
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	Y
Auditing	**23**	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Y
Ethics and Dissemination			
Research Ethics approval	**24**	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Y
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)	Y
Consent or assent	**26a**	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Y
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Y
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	Y
Declaration of interests	**28**	Financial and other competing interests for principal investigators for the overall trial and each study site	Y
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	Y
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	Y
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	Y
	31b	Authorship eligibility guidelines and any intended use of professional writers	Y

	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Y
Appendices			
Informed consent materials	**32**	Model consent form and other related documentation given to participants and authorised surrogates	Y
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	N/A

BMJ Open

Clinical Observation, Management and Function Of low back pain Relief Therapies (COMFORT). A cluster randomised controlled trial protocol.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2023-075286.R1
Article Type:	Protocol
Date Submitted by the Author:	21-Aug-2023

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Primary Subject Heading:	Public health
Secondary Subject Heading:	Anaesthesia
Keywords:	Primary Health Care, Back pain < ORTHOPAEDIC & TRAUMA SURGERY, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

Title:

Clinical Observation, Management and Function Of low back pain Relief Therapies (COMFORT). A cluster randomised controlled trial protocol.

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ABSTRACT

Introduction: Low back pain (LBP) is commonly treated with opioid analgesics despite evidence that these medicines provide minimal or no benefit for LBP and have an established profile of harms. International guidelines discourage or urge caution with the use of opioids for back pain; however, doctors and patients lack practical strategies to help them implement the guidelines. This trial will evaluate a multifaceted intervention to support general practitioners (GPs) and their patients with LBP implement the recommendations in the latest opioid prescribing guidelines.

Methods and analysis: This is a cluster randomised controlled trial that will evaluate the effect of educational outreach visits to GPs promoting opioid stewardship alongside non-pharmacological interventions including heat wrap and patient education about the possible harms and benefits of opioids, on GP prescribing of opioids medicines dispensed. At least 40 general practices will be randomised in a 1:1 ratio to either the intervention or control (no outreach visits; GP provides usual care). A total of 410 patient-participants (205 in each arm) who have been prescribed an opioid for LBP will be enrolled via participating general practices. Follow-up of patient-participants will occur over a one year period. The primary outcome will be the cumulative dose of opioid dispensed that was prescribed by study GPs over one year from the enrolment visit (in morphine milligram equivalent dose). Secondary outcomes include prescription of opioid medicines, benzodiazepines, gabapentinoids, non-steroidal anti-inflammatory drugs by study GPs or any GP, health services utilisation and patient-reported outcomes such as pain, quality of life, and adverse events. Analysis will be by intention-to-treat, with a health economics analysis also planned.

Ethics and dissemination: The trial received ethics approval from The University of Sydney Human Research Ethics Committee (2022/511). The results will be disseminated via publications in journals, media, and conference presentations.

Trial registration number

ACTRN12622001505796

Number of Figures

1

Funding statement

National Health and Medical Research Council (NHMRC) of Australia (ID APP2000989).

Competing Interest Statement

The Sydney Pharmacy School receives funding for a postgraduate scholarship from GlaxoSmithKline for a student under the supervision of AJM. JM is an employee of the Pharmaceutical Society of Australia. BCM receives royalties for the development of an opioid risk prediction tool which is unrelated to the current study protocol. All other authors declare that they have no competing interests.

Authors contributions

CAS is principal investigator on the trial, has oversight over all trial procedures and drafted the manuscript. CAS, RI, LV, AM, PK, FB, FS, PC, RT, TL, LD, SR, BM, MW, RO, SF, KM, GC, HJ, SM, MB, JM, CB, CGM were involved in the conception of the trial and drafting of the protocol, writing and/or critical review of the manuscript and approved the final manuscript for publication.

Acknowledgements We would like to thank the following people for their contribution:

Operations: Mr Daniel Chapman, Mrs Melissa Webb, Ms Sarah Diprose

Good Clinical Practice (GCP) training materials: Ms Joan Torony

Data Safety Monitoring Board: Prof Richard Lindley, Prof Richard O Day, Dr Nazila Jamshidi

Independent Clinical Trials Audit: The George Institute for Global Health, Rachel McGrath, Yachna Mehta

Abstract word count

296

Word count

4466

Strengths and Limitations of this study

- This is a cluster randomised trial that will evaluate simple, scalable strategies to reduce the use of opioids in the GP management of low back pain.

- A potential limitation related to trial design is that blinding of GP and patient-participants may be difficult to achieve, but we have blinded research personnel collecting patient outcomes.
- If our intervention is found effective, it has the potential to transform management of low back pain globally.

INTRODUCTION

Low back pain (LBP) is a common musculoskeletal condition, affecting 50%-80% of adults [1,2] and is the leading cause of disability in 160 countries [3]. Approximately 90% of LBP cases cannot be attributed to an identifiable cause [2,4], and the pain can be acute (self-limiting;

resolving completely within 3 months) or chronic (persisting beyond 3 months) [5]. Low back pain can be complex to treat, and can adversely affect an individual's function, quality of life and mood [6-8].

Clinical practice guidelines for the management of LBP [2, 5, 9-11] recommend providing reassurance of a favourable prognosis (after screening for, and excluding, pathological conditions), encouraging physical activity, addressing potential concerns that physical activity may cause 'more damage' (e.g. fear-avoidance behaviours), and providing education around optimal pharmacological and non-pharmacological treatments. Non-pharmacological treatments may include spinal manipulation therapy or psychological interventions [5, 11], and pharmacological therapies may include non-steroidal anti-inflammatory drugs (NSAIDs) or paracetamol (acetaminophen) [12, 13].

Many clinical guidelines now discourage or urge caution with the use of opioid analgesics for LBP [13, 14]; however, opioid medicines continue to be one of the most commonly used treatments prescribed by general practitioners (GPs) for LBP globally. In the USA, chronic LBP is the leading cause for opioid prescription [15] and one in every 5 people with chronic LBP used at least one opioid in the last 30 days [16]. In Australia, half of the ~3.7 million GP encounters for LBP in 2015-16 resulted in an opioid prescription [17]. This practice has led to serious problems including dependence, overdose, hospitalisation and death [18]. In 2017-18, 823 Australians died from prescription opioids, and hospitalisations from prescription opioid poisonings have risen by 25% in the past 15 years [19]. Yet opioids provide limited benefit for LBP. Our systematic review [20] established that opioid analgesics provide only a small amount of pain relief in the short term for LBP (mean difference of −10.1 (95% Confidence Interval (CI), −12.8 to −7.4) on a 0 (no pain) to 100 (worst pain imaginable) pain scale compared with placebo [20]. Larger effects on pain (> 20 points on a 0-100 pain scale) were not reported even with high and potentially dangerous doses [20]. Adverse events such as constipation, nausea and vomiting, were common and 50% of patients stopped treatment due to adverse events or lack of efficacy [20].

We now understand that even short-term use of opioid medicines may be problematic [21]. The cumulative dose and duration of opioid use in the first month of use increases the risk of persistent opioid consumption [22, 23]. Overdose is six times more likely in patients prescribed a long-acting opioid than those given a short-acting opioid [24]. This evidence has informed the latest opioid guidelines, which recommend treatment with a short acting opioid initially, and to use the lowest effective dose for the shortest time (ideally < 3 days) [25,26]. However, clinical practice is discordant with guidelines, and for conditions such as LBP, prescription

often involves long-acting, strong opioids (e.g. oxycodone controlled release) [27,28], thereby increasing the risk of overdose, hospitalisation and persistent use.

The high rate of opioid prescribing for LBP in general practice settings strongly indicates the existing model of care needs to change. A key barrier to the uptake of the latest opioid guidelines is that patients and GPs lack the strategies to help them follow the recommendations and safely reduce opioids for this condition [29]. An effective intervention is urgently needed to support health system improvement in primary care by giving GPs and patients the tools to adopt the recommendations in the latest opioid guidelines, including using non–pharmacological measures such as heat wraps. Previous opioid reduction intervention trials have reported minimal or no benefit, and often targeted the patient or the clinician alone [30, 31].

The COMFORT trial will evaluate the effect of GP educational outreach visits promoting opioid stewardship alongside non-pharmacological treatments including heat wrap and patient education on judicious opioid use and potential harms. The intervention will be compared to no outreach visit and usual GP care to determine the effect on GP prescribing of opioid medicines dispensed to their patients with LBP over one year. The intervention provides GPs with practical strategies that they can offer patients with LBP to help them achieve adequate control of their pain and reduce the requirement for opioid medicines. We are proposing a simple, scalable intervention that, if found effective, has the potential to transform health practice and policy for LBP management globally.

METHODS AND ANALYSIS

Study design and setting

Clinical Observation, Management and Function Of low back pain Relief Therapies **(COMFORT)** is a cluster randomised controlled trial that will be undertaken in Australian general medical practices. Interested GPs from eligible practices will be trained by the research team on the study procedures and to identify and enrol eligible patient-participants into the trial. General practices will be randomised in a 1:1 ratio to receive the intervention (outreach visits to support opioid stewardship) or control (no outreach visits). The trial protocol has been reported as per the SPIRIT 2013 Statement [32]. Recruitment of practices will take place primarily via direct contact with the practices and GPs, and through Primary Health Networks.

Eligibility criteria

General practices

General practices will be considered for the trial based on the following criteria:

Inclusion

- Has at least one practising GP registered with the Australian Health Practitioner Regulation Agency.

General practitioners

GPs in participating practices will be eligible based on the following criteria:

Inclusion

- Consult with patients who have LBP.
- Has no prescribing restrictions, that is, eligible to prescribe an opioid analgesic, including Schedule 8 opioid analgesics.
- Consent to researchers gaining access to their prescribing data.

Exclusion

- Participating GPs at that practice has received an education visit by any organisation on judicious opioid prescribing in the previous 12 months.

Note: All GPs in that practice who consent will enter the same treatment arm.

Patient-Participants

Adults with LBP will be screened for eligibility by a participating GP either during a face-to-face consultation or via telehealth. Participating GPs will determine patient eligibility against the study screening form. Patient-participants will be considered for the trial based on the following criteria:

Inclusion:

- Adults (≥18 years).
- Low back pain of any duration at the time of presentation.
- Has been prescribed an opioid analgesic for LBP by the participating GP.
- Sufficient understanding of English to complete questionnaires, or translation available.
- Holds an Australian Medicare card number (for data linkage purposes).
- Willingness to provide written informed consent to participate in the trial and grant researchers access to their Medicare/Pharmaceutical Benefits Scheme and other trial-related data.

Exclusion:

- Engaged in an opioid tapering regimen at the time of enrolment into the study i.e., have already begun to reduce their opioid medicine within the past month.
- Being actively treated for cancer or receiving palliative treatment.

Patient-participants will be informed about the consent process and receive an initial consultation with the participating GP as part of the trial. Patients will be contacted at baseline by a blinded researcher and complete a study questionnaire. Follow-up of patient-participants by the blinded researcher will then take place at the end of weeks 1, 4, 12, 26 and 52 post-baseline to complete the study questionnaire (with the option of completing the questionnaires online also available). Patients recruited into the intervention arm will also be asked to complete a heat wrap diary up to 12 weeks. GPs and patients in the intervention arm will be invited to participate in a process evaluation interview (separate to this protocol).

The study flow chart is provided in Figure 1.

Intervention

The multifaceted intervention supports GPs to achieve judicious prescribing of opioids and supports patient-participants to use opioids judiciously. It has the following components:

1) Educational outreach visits to GPs promoting opioid stewardship

Baseline visit

Participating GPs will receive a face-to-face baseline educational outreach visit (0.5 to 1 hour duration) from the study research team involving:

- Delivery of a 10-minute training video (developed for the trial, featuring an experienced GP (RI)) on judicious opioid prescribing and best practice management of LBP in line with key messages in clinical practice guidelines [26, 33]. Key messages on judicious opioid prescribing will include recommendations to limit duration of opioid use, commence therapy with a low dose, short-acting preparation, and have a clear plan to review use and taper or cease the opioid analgesic. Participating GPs will also be advised on appropriate strategies for opioid tapering or cessation should this form part of a patient-participant's care plan [26, 33].
- Training in study procedures.

- International Committee on Harmonisation of Good Clinical Practice (ICH-GCP) training (detailed below).

Refresher training visits

We have previously shown that following an educational intervention, clinician knowledge of LBP declines after 6 months [34]. Therefore, GPs in the intervention arm will receive face-to-face refresher training visits every 6 months (until the recruitment target for that practice is met) on judicious opioid prescribing and best practice management of LBP (via an abridged training video). Live online training visits will be permitted in circumstances where face-to-face visits are not possible.

2) Non-opioid treatments

Non-pharmacological therapies and advice

Participating GPs and patient-participants in the intervention arm will be informed of alternate non-opioid pain relief strategies to manage LBP. This will involve heat wrap therapy (at no cost to the patient) and advice to remain physically active, avoid best rest, and reassurance of a favorable prognosis where appropriate. The trial will provide patient-participants up to 12 weeks staged-supply of Flexeze® heat patches, a Therapeutic Goods Administration (TGA) registered product (Australian Register of Therapeutic Goods (ARTG) #209075 – Medical Devices Class IIa, i.e. low-medium risk device/product) [35]. The heat patches will be inserted inside a pouch (body wrap) to increase skin safety. Patient-participants will be informed of the use of the heat patch and advised to have a one day break after use for three consecutive days. In addition, to standardise treatment, patient-participants will be advised to apply the heat wrap for 6-8 hours during the day for up to 12 weeks, and notify the study team of any skin irritations. At the enrolment visit, patients will be provided with a 1-week initial supply of heat wraps by the participating GP.

Non-opioid analgesic medicines

Optimal dosing of paracetamol and/or oral non-steroidal anti-inflammatory medications (NSAIDs) may also be considered by participating GPs if deemed appropriate for the management of LBP, based on the patients' medical and medication history.

3) Participant education

The training will encourage participating GPs to provide their patient-participants with an educational booklet. In partnership with PainAustralia Consumer Advisory Group, NPS

MedicineWise and Choosing Wisely Australia, we co-developed a 2-page written booklet '*5 questions to ask about using opioids for back pain or osteoarthritis'* combining evidence-based messages on judicious opioid use with management strategies endorsed in international LBP guidelines e.g. staying active. The booklet has been modelled on the Choosing Wisely '5 questions to ask' [36] resource that was widely tested among patients and doctors and designed to empower individuals to ask questions about opioid medicines and other pain management options. The booklet contains a pain management plan to facilitate shared decision-making and review. Importantly, it allows opportunity for dialogue between the participating GP and patient-participant during the consultation about accountable opioid use.

4) Additional education resources

Participating GPs will be provided access to the NPS opioid tapering algorithm [37] to support de-prescribing of opioid medicines for their patients with LBP.

Control (no outreach visit)

Participating GPs in the control arm will not be provided with any face-to-face outreach visits discussing judicious opioid prescribing or best practice management of LBP, nor will they receive heat wraps or the patient educational booklet to discuss with patients. These GPs will be asked to provide consenting patient-participants with the usual care methods they normally use.

Consumer Medicines Information Leaflet

All patient-participants, regardless of whether they are in the intervention or control arm will be provided with a Therapeutic Goods Administration approved Consumer Medicines Information (CMI) leaflet on the opioid medicine prescribed at enrolment by the study team. This will be provided after completion of the baseline visit.

ICH-GCP training

All participating GPs will receive ICH-GCP training at baseline and refresher training every 6 months for the duration that they are enrolling patient-participants onto the trial. This training outlines responsibilities in the conduct of clinical trials and will be delivered via a 7-minute training video.

Co-interventions

All patient-participants will not be prohibited from using other forms of pharmacological or non-pharmacological pain relief therapies during the trial. The study questionnaires will capture these details, and any therapies that may impact our study outcomes (i.e. which has the potential to provide pain relief and therefore be opioid sparing) will be documented as a co-intervention [38].

Study outcomes

Using data from Services Australia and/or patient admitted data and/or patient-report, the following outcomes will be collected over the 1-year follow up (as specified below):

Primary outcome

Cumulative opioid dose dispensed to patient-participants that was prescribed by participating GPs over one year using Medicare linkage, determined using morphine milligram equivalent (MME) [39].

Secondary outcomes

Secondary outcomes collected for patient-participants over the one year follow up will include:

- Type of opioid dispensed that was prescribed by participating GPs.
- Cumulative opioid dispensed (MME) that was prescribed by any GP.
- Number of subsidised Medicare visits to healthcare providers and services.
- Number of visits to emergency department.
- Number of hospitalisations.
- Total cost of Medicare Benefits Scheme (MBS) and Pharmaceutical Benefits Scheme (PBS) usage.
- Persistent opioid use at 6 months defined as:
    - Having had at least one opioid prescription issued in the prior 30 days AND at least 3 opioid prescriptions issued in the prior 4 months [40, 41].
- Persistent opioid use at 12 months defined as:
    - Having had 10 or more opioid prescriptions issued in the prior year with at least one prescription issued in the prior month [40, 41].
- Number of dispensations for gabapentinoids (e.g., pregabalin, gabapentin), benzodiazepines (e.g., diazepam), NSAIDs prescribed by participating GPs and any GP.
- Opioid related poisonings.
- Number of deaths.

- Economic evaluation (detailed below).

While not an outcome for this study, the trial will also determine opioid dispensation in the 1 year prior to study enrolment to determine patterns of persistent opioid use according to our pre-specified definitions of persistent opioid use outlined above.

Secondary outcomes will also assess the following patient-participant outcomes, collected online or by phone via patient-report at weeks 1, 4, 12, 26 and 52 (or as specified):

- Pain intensity (measured using the 0 to 10 Numerical Pain Rating Scale) with 0 being no pain and 10 being worst pain: a measure with acceptably high test-retest reliability (Intraclass Correlation Coefficient (ICC) of 0.95) [42].
- Disability (measured using the Roland Morris Disability Questionnaire (RMDQ)): A 24 item questionnaire, with good internal consistency and responsiveness (Cronbach's alpha 0.9-0.93) [43, 44].
- Global rating of change (using the Global Perceived Effect scale; scored from -5 to +5): A measure with acceptably high test-retest reliability (ICC 0.99) [45].
- Self-reported use of over-the-counter medicines and non-pharmacological interventions.
- Quality of life (measured using the EuroQol EQ-5D-5L questionnaire), which has been shown to have good internal consistency and validity [46].
- Pain Self Efficacy Questionnaire: A 10-item questionnaire to assess confidence levels to perform a range of activities while in pain; a measure with acceptably high good internal consistency (Cronbach's alpha 0.79 to 0.95) [47].
- Duration of opioid use: A medication diary will be used to record use of medicines (including for LBP if applicable) in the past 7 days. The opioid course will be considered to have ended after 7 continuous days of no opioid use. The medication diary has shown high concordance with clinically determined measures e.g., plasma drug concentrations and pill count or canister weight (Kappa >0.6 in 7 studies) [48], and high completion rates amongst participants was also reported be completing these diaries [49,50].
- Return of unused opioid medicine: Patient-participants will be asked if they returned any unused medicines at 12 weeks and 1 year.
- Heat wrap diary (Intervention group): To record the number of days of heat wrap use (up to 12 weeks post-enrolment).
- Severity of opioid withdrawal symptoms: Using the self-report opioid withdrawal scale [51].

- Anxiety using the General Anxiety Disorder-7 (GAD-7) at baseline, 4, 12, 26 and 52 weeks [52].
- Proportion of people who ended an opioid course within the first month: Determined by the medication diary, and the opioid course will be considered to have ended after 7 continuous days of no opioid use.
- Harms (detailed under 'Harms' below)
    - Proportion of patient-participants in each study arm who experienced an adverse or serious adverse event.
    - Frequency and nature of any adverse or serious adverse event.
    - Cause of serious adverse event.

GP attitudes towards prescribing opioid and other analgesics

To determine whether the intervention will impact GP attitudes about prescribing, we will administer two validated surveys: the 22-item concerns about analgesics prescriptions questionnaire [53] and 10-item opioid therapy survey [54] to ascertain GP attitudes towards prescribing opioid and other analgesics. These will be administered before and after the baseline training visit and before and after the initial 6 month visit via an online questionnaire (REDCap) or paper-based version.

Sample size

A sample size of 410 patient-participants will provide the trial with 90% power to detect a difference of 210 MME over 1 year between the intervention and control arms, allowing for a withdrawal rate of 15% and a rate of non-adherence of 10%. To achieve this target we will require at least 40 general practices (at least 20 general practice clusters in each arm), with each general practice to recruit at least 12-15 participants. We have assumed an ICC of 0.045 based on 145 ICCs from cluster randomised trials in primary care [55].

This sample size will also provide at least 80% power to detect changes in secondary outcomes, including a minimum difference of 10% for pain (1 point on the 0-10 numerical rating scale; assuming SD of 1.9) [50, 56], and 10% on the 24-item Roland Morris Disability Questionnaire (RMDQ) (assuming Standard Deviation (SD) of 5.4) [50, 56]. This sample size will also provide >80% power to detect a difference of 20% in the proportion of people who continue to use opioids at 1 year and 20% reduction in the proportion of dispensations for strong, long-acting opioids.

Strategies for achieving adequate patient-participant enrolment

Strategies to achieve the target sample size will include monthly phone calls to sites, quarterly site visits from the study team to discuss trial progress and provide ongoing support to participating GPs (or live online visits in exceptional circumstances), continuing professional development points for GP participation, and reimbursement to participating GPs and patient-participants for their involvement in the trial. Recruitment targets will be compared against milestones. Steering committee meetings will be held quarterly to discuss trial progress and address any challenges with recruitment.

Randomisation sequence of general practices (or allocation of interventions)

Practices will be randomised to the intervention or control group using central randomisation with allocation concealment built in. Practices will be stratified by area level socioeconomic status and geographic remoteness. Socio-Economic Indexes for Areas (SEIFA, area-level socioeconomic status) will be divided/split into tertiles (highest, middle, lowest) based on the 2021 index for relative advantage and disadvantage (IRSAD) [57]. Remoteness will be classified into two categories (ARIA+ classification), based on the Australian Statistical Geography Standard (ASGS): 1) Urban and 2) Regional/Remote/Very remote [58]. There will be two strata variables, one with two levels, and one with three levels, giving a total of six strata. Separate randomisation schedules will be generated for each of the six strata, using permuted blocks. Randomisation will also account for a planned study within a trial (SWAT) that is being embedded within the COMFORT trial. The study protocol for the SWAT is separate, and will test whether additional monetary reimbursement (versus no additional reimbursement) will encourage greater participation of culturally and linguistically diverse patient-participants with limited English proficiency into the COMFORT trial.

Because around 70% of the population of Australia is in urban areas [59], we will recruit sites proportionally, with 70% from urban strata and 30% from regional/remote/very remote strata. This gives a target sample size of n=9-10 sites in each of the three urban strata, and n=4 sites in each of the three regional/remote/very remote strata. To maximise balance while maintaining allocation concealment, the allocation schedule will use random permuted blocks of size 2 and 4. In order to allow greater recruitment from some combinations than others without exhausting the randomisation schedule, we will allow a maximum of n=40 practices to be randomised to any particular combination of SES and remoteness.

Blinding

Randomisation allocation will not be revealed to members of the research team involved in patient-participant follow-up, the Data Safety Management Board (DSMB) and the

independent statistician involved in the statistical analysis and interpretation of results. However, unblinding may be requested by the DSMB in specific cases to allow an assessment of serious adverse events.

Data collection methods

The participating GP will notify the study team when a patient-participant is enrolled into the trial. The study team will follow up with the patient-participant within 24-hours to complete the baseline telephone survey. Each patient will be followed (by phone and/or online survey via Research Electronic Data Capture (REDCap)) over one year. Collection of study outcomes will be via data linkage and patient-report. In addition, the study team will also follow-up with participating GP to complete questionnaires via REDCap (or paper based) at specified timepoints detailed above. Data will be entered and verified by the study team for data accuracy.

Other data collected

Patient-participants and participating GPs in the intervention group will also be invited to complete a process evaluation interview (reported as a separate protocol).

Data management

Data will be monitored for any errors and recorded using a secure database hosted by the University of Sydney. An electronic data capturing system e.g. REDCap [60] will be used, and data collected over the phone will be directly entered into the database where possible, while surveys completed online will be automatically transcribed into the database. Information recorded using paper case report forms (CRF) will be entered into the database and verified by another study team member. Data from Services Australia and patient admitted data will be stored using secure databases by the University of Sydney.

Statistical methods

The study will explore the effect of the intervention versus control as a fixed effect in a mixed effects model, including a random intercept of cluster (GP practice). Primary analyses will follow the intention-to-treat principle with the statistician blinded to treatment group.

Primary analysis

The primary outcome will be analysed using a linear mixed effects regression model with the intervention group as a covariate. Missing data is likely to be very low as our primary outcome is based on linked data.

Subgroup analyses will be performed to evaluate the difference in the primary outcome between participants using opioids persistently in the 12 months prior to study entry, versus those not using opioid medicines persistently. Subgroup analyses will be performed to examine if the following factors modify the effect of treatment on primary outcome: (i) chronicity-patient-participants with acute vs chronic LBP, (ii) type of LBP- non-specific LBP versus LBP due to specific causes (e.g., pregnancy), (iii) age and (iv) gender. In addition, subgroup analyses will also be performed to compare outcomes from patient-participants enrolled via telehealth versus face to face, years of experience of participating GPs, and geographical location of participating general practices.

Secondary analysis

Continuous secondary outcomes will be analysed with the use of repeated-measures linear mixed models. Adjusted mean differences will be tested for the end of treatment (12 weeks) and the time point for the primary analysis (one year). A binary logistic regression will be conducted for binary outcomes. Serious adverse events and adverse events will be reported descriptively for both number of events and number of patient-participants experiencing an event. Appropriate model checking will be conducted for all analyses. Balance of baseline patient-participant characteristics will be assessed and any characteristics not well balanced will be included in the model, as a secondary analysis.

Health economic analyses

A within-trial economic evaluation will be conducted. Costs (i.e., outreach visit, heat wrap therapy, patient information booklets, training) will be collected using trial financial records and staff wage rates. Health care costs will be incorporated in the analysis, using administratively linked data for MBS, PBS, and hospital admission costs, and patient-reported diaries for over-the-counter medications. The health outcome measure will use the EQ-5D-5L, which will be used [61] to estimate quality-adjusted life years (QALYs). To calculate incremental cost-effectiveness ratios, linear mixed models will be used to analyse both costs and outcomes.

An additional analysis will be conducted to compare the total PBS cost of analgesic medicines dispensed among patient-participants randomised to the intervention versus control over a 1-year period using the dispensed price for maximum quantity (DPMQ).

Statistical Analysis Plan

A statistical analysis plan will be published separately detailing methods for statistical analysis and, where appropriate, handling of missing data.

Data monitoring

A Data Safety Management Board (DSMB) has been formed by the Steering Committee and comprises experienced clinicians with skills relevant to the trial (e.g., opioid and pain medicines specialists). The DSMB will review serious adverse events (SAE), assess causality where appropriate, review clinical trial data, and provide recommendations (i.e., trial progress and/or if changes for the trial is recommended). A meeting with the DSMB will be held around six months once the trial has commenced study recruitment, and quarterly follow-up meetings will be arranged, or as agreed by the DSMB and study team.

Harms

Adverse events

Adverse events (including serious adverse events) will be collected by patient-report questionnaires at weeks 1, 4, 12, 26 and 52.

Serious Adverse Events

Serious adverse events will also be collected at each of the follow up time points. These are defined as any untoward medical occurrence resulting in death; is life threatening; requires hospitalisation or prolongation of the existing hospitalisation; results in persistent or significant disability or incapacity; is a congenital abnormality or birth defect; is a medically significant or important event or reaction [62].

Serious adverse events will be reported to the Sydney University Human Research Ethics Committee (HREC) within the required timeframe, and causality will also be reviewed and adjudicated by the DSMB where appropriate.

Auditing

An independent external audit for the trial was carried out by the George Institute for Global Health which involved a thorough review of the trial processes and study documents prior to study commencement.

Patient and Public Involvement

Consumers (PainAustralia Consumer Advisory Group) were involved in the conception and design of this trial. PainAustralia will continue to be involved throughout the study and will provide high level advocacy support and be involved in dissemination. A consumer is co-author on the work.

ETHICS AND DISSEMINATION

Ethics approval

Ethics approval has been provided by the Human Research Ethics Committee, The University of Sydney (Project number 2022/551).

Protocol amendments

Any changes to the study protocol must be agreed upon by the trial's steering committee. These will be submitted to the University of Sydney HREC for approval prior to being implemented.

Consent or assent

The study team will train participating GPs to coordinate the informed consent process, with the assistance of the study team where appropriate. Participating GPs will discuss the study with interested and potentially eligible patient-participants and provide them with a participant information sheet and consent form (paper-based or electronically). Patient-participants will have the opportunity to ask participating GPs or the research team any questions prior to consenting. Written informed consent from patient-participants will then be obtained by the participating GP. The participating GP or patient-participants can withdraw their consent at any point during the study.

Confidentiality

Study data will be securely stored in either locked cabinets (paper records) or electronically (electronic data files) and accessed only by the study team.

Access to data

The study team will have access to the final dataset, and a blinded (to treatment allocation) copy of the dataset will be provided to the trial statistician to perform the study analysis.

Ancillary and post-trial care

Costs of treatments outside of the trial will not be covered by the study. The trial will provide heat wraps at no cost to patient-participants in the intervention arm.

Non-negligent harm associated with the protocol will be covered by the trial's insurance. This includes cover for additional healthcare, compensation, or damages.

Dissemination policy

The study results will be submitted for publication in scientific journals, presented at conferences or meetings. Lay summaries will be provided to participating GPs, patient-participants, and stakeholders involved in the trial.

Trial findings will be discussed and disseminated through various media, external partners e.g. PainAustralia consumer advisory group and policymakers in Australia and overseas.

We will adhere to the International Committee of Medical Journal Editors (ICMJE) guidelines on authorship eligibility for any publications arising from this trial. We do not plan to engage professional writers.

Figure Legend

Figure 1: Study design flow Chart *Intervention only [a]Intervention only (scheduled between 12-16 weeks - standalone component).

REFERENCES

1. Fatoye F, Gebrye T, Odeyemi I. Real-world incidence and prevalence of low back pain using routinely collected data. *Rheumatol Int* 2019;39(4):619-26. doi: 10.1007/s00296-019-04273-0
2. Maher C, Underwood M, Buchbinder R. Non-specific low back pain. *Lancet* 2017;389(10070):736-47. doi: 10.1016/S0140-6736(16)30970-9.
3. World Health Organisation. Musculoskeletal Health. 2022. Available from: https://www.who.int/news-room/fact-sheets/detail/musculoskeletal-conditions.
4. Koes BW, Van Tulder M, Thomas S. Diagnosis and treatment of low back pain. *BMJ* 2006;332(7555):1430-34. doi: 10.1136/bmj.332.7555.1430
5. Qaseem A, Wilt TJ, McLean RM, et al. Noninvasive treatments for acute, subacute, and chronic low back pain: a clinical practice guideline from the American College of Physicians. *Ann Int Med* 2017;166(7):514-30. doi: 10.7326/M16-2367
6. Agnus Tom A, Rajkumar E, John R, et al. Determinants of quality of life in individuals with chronic low back pain: a systematic review. *Health Psychol Behav Med* 2022;10(1):124-44. doi: 10.1080/21642850.2021.2022487
7. Wong JJ, Tricco AC, Côté P, et al. The association between depressive symptoms or depression and health outcomes in adults with low back pain with or without radiculopathy: protocol of a systematic review. *Syst Rev* 2019;8(1):1-8. doi: 10.1186/s13643-019-1192-4
8. Sagheer MA, Khan MF, Sharif S. Association between chronic low back pain, anxiety and depression in patients at a tertiary care centre. *J Pak Med Assoc* 2013;63(6):688-90. PMID: 23901665
9. Australian Commission on Safety and Quality in Healthcare. Low Back Pain clinical care standards 2022 [Available from: https://www.safetyandquality.gov.au/sites/default/files/2022-08/low_back_pain_clinical_care_standard.pdf].
10. George SZ, Fritz JM, Silfies SP, et al. Interventions for the Management of Acute and Chronic Low Back Pain: Revision 2021. *J Orthop Sports Phys Ther* 2021;51(11):CPG1-CPG60. doi: 10.2519/jospt.2021.0304
11. Chou R, Deyo R, Friedly J, et al. Nonpharmacologic Therapies for Low Back Pain: A Systematic Review for an American College of Physicians Clinical Practice Guideline. *Ann Intern Med* 2017;166(7):493-505. doi: 10.7326/m16-2459
12. Chou R, Deyo R, Friedly J, et al. Systemic Pharmacologic Therapies for Low Back Pain: A Systematic Review for an American College of Physicians Clinical Practice Guideline. *Ann Intern Med* 2017;166(7):480-92. doi: 10.7326/m16-2458
13. Anderson DB, Shaheed CA. Medications for Treating Low Back Pain in Adults. Evidence for the Use of Paracetamol, Opioids, Nonsteroidal Anti-inflammatories, Muscle Relaxants, Antibiotics, and Antidepressants: An Overview for Musculoskeletal Clinicians. *J Orthop Sports Physi Therapy* 2022;52(7):425-31. doi: 10.2519/jospt.2022.10788
14. Oliveira CB, Maher CG, Pinto RZ, et al. Clinical practice guidelines for the management of non-specific low back pain in primary care: an updated overview. *Eur Spine J* 2018;27(11):2791-803. doi: 10.1007/s00586-018-5673-2
15. Hudson TJ, Edlund MJ, Steffick DE, et al. Epidemiology of regular prescribed opioid use: results from a national, population-based survey. *J Pain Symptom Manage* 2008;36(3):280-8. doi: 10.1016/j.jpainsymman.2007.10.003
16. Shmagel A, Ngo L, Ensrud K, et al. Prescription Medication Use Among Community-Based U.S. Adults With Chronic Low Back Pain: A Cross-Sectional Population Based Study. *J Pain* 2018;19(10):1104-12. doi: 10.1016/j.jpain.2018.04.004
17. Australian Institute of Health and Welfare 2015. Arthritis no.21. Cat.PHE 185. Canberra.

18. Australian Institute of Health and Welfare 2019. Opioid harm in Australia and comparisons between Australia and Canada: Australian Institute of Health and Welfare. Cat.HSE 210. Canberra.
19. Australian Institute of Health and Welfare (2018). Opioid harm in Australia. HSE 210. Available at https://www.aihw.gov.au/reports/illicit-use-of-drugs/opioid-harm-in-australia/summary (Accessed 13 April, 2023).
20. Shaheed CA, Maher CG, Williams KA, et al. Efficacy, tolerability, and dose-dependent effects of opioid analgesics for low back pain: a systematic review and meta-analysis. *JAMA Intern Med* 2016;176(7):958-68.
21. Abdel Shaheed C, McLachlan AJ, Maher CG. Rethinking "long term" opioid therapy. *BMJ* 2019;367:l6691. doi: 10.1136/bmj.l6691 doi: 10.1001/jamainternmed.2016.1251
22. Shah A, Hayes CJ, Martin BC. Characteristics of Initial Prescription Episodes and Likelihood of Long-Term Opioid Use - United States, 2006-2015. *MMWR Morb Mortal Wkly Rep* 2017;66(10):265-69. doi: 10.15585/mmwr.mm6610a1
23. Deyo RA, Hallvik SE, Hildebran C, et al. Association Between Initial Opioid Prescribing Patterns and Subsequent Long-Term Use Among Opioid-Naïve Patients: A Statewide Retrospective Cohort Study. *J Gen Intern Med* 2017;32(1):21-27. doi: 10.1007/s11606-016-3810-3
24. Miller M, Barber CW, Leatherman S, et al. Prescription opioid duration of action and the risk of unintentional overdose among patients receiving opioid therapy. *JAMA Intern Med* 2015;175(4):608-15. doi: 10.1001/jamainternmed.2014.8071
25. Dowell D RK, Jones CM, Baldwin GT, Chou R. CDC Clinical Practice Guideline for Prescribing Opioids for Pain — United States, 2022. *MMWR Recomm Rep* 2022;71(No. RR-3):1–95. doi: http://dx.doi.org/10.15585/mmwr.rr7103a1
26. The Royal Australian College of General Practitioners. Prescribing drugs of dependence in general practice, Part C2: The role of opioids in pain management. *East Melbourne, Vic: RACGP* 2017.
27. Karanges EA, Blanch B, Buckley NA, et al. Twenty-five years of prescription opioid use in Australia: a whole-of-population analysis using pharmaceutical claims. *Br J Clin Pharmacol* 2016;82(1):255-67. doi: 10.1111/bcp.12937
28. Gisev N, Pearson S-A, Dobbins T, et al. Combating escalating harms associated with pharmaceutical opioid use in Australia: the POPPY II study protocol. *BMJ open* 2018;8(12):e025840. doi: 10.1136/bmjopen-2018-025840
29. Hamilton M, Mathieson S, Gnjidic D, et al. Barriers, facilitators, and resources to opioid deprescribing in primary care: experiences of general practitioners in Australia. *Pain* 2022;163(4):e518-e26. doi: 10.1097/j.pain.0000000000002340
30. Frank JW, Lovejoy TI, Becker WC, et al. Patient outcomes in dose reduction or discontinuation of long-term opioid therapy: a systematic review. *Ann Intern Med* 2017;167(3):181-91. doi: 10.7326/M17-0598
31. Mathieson S, Maher CG, Ferreira GE, et al. Deprescribing opioids in chronic non-cancer pain: systematic review of randomised trials. *Drugs* 2020;80(15):1563-76. doi: 10.1007/s40265-020-01368-y
32. Chan A-W, Tetzlaff JM, Gøtzsche PC, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013;346. doi: 10.1136/bmj.e7586.
33. Australian Commission on Safety and Quality in Health Care. Low Back Pain Clinical Care Standard. Sydney: ACSQHC; 2022.
34. Abdel Shaheed C, Maher CG, Mak W, et al. The effects of educational interventions on pharmacists' knowledge, attitudes and beliefs towards low back pain. *Int J Clin Pharm* 2015;37(4):616-25. doi: 10.1007/s11096-015-0112-5
35. Australian Register of Therapeutic Goods (ARTG): ARTG ID 209075: Public Summary.

36. Choosing Wisely. 5 questions to ask your doctor or other healthcare provider before you get any test, treatment, or procedure. Available from: https://www.choosingwisely.org.au/resources/consumers-and-carers/5questions
37. NPS Medicine Wise Opioid Tapering Algorithm. Available from: https://www.nps.org.au/assets/NPS-MedicineWise-opioid-tapering-algorithm.pdf.
38. Abdel Shaheed C, Blyth F, Furmage AM, et al. Getting the "balance" right in clinical trials. *BMJ* 2021;375:n2869. doi: 10.1136/bmj.n2869
39. Pereira J, Lawlor P, Vigano A, et al. Equianalgesic dose ratios for opioids. a critical review and proposals for long-term dosing. *J Pain Symptom Manage* 2001;22(2):672-87. doi: 10.1016/s0885-3924(01)00294-9
40. Zgierska AE, Vidaver RM, Smith P, et al. Enhancing system-wide implementation of opioid prescribing guidelines in primary care: protocol for a stepped-wedge quality improvement project. *BMC Health Serv Res* 2018;18(1):1-8. doi.org/10.1186/s12913-018-3227-2
41. Sun EC, Darnall BD, Baker LC, et al. Incidence of and risk factors for chronic opioid use among opioid-naive patients in the postoperative period. *JAMA Intern Med* 2016;176(9):1286-93. doi:10.1001/jamainternmed.2016.3298
42. Alghadir AH, Anwer S, Iqbal A, et al. Test–retest reliability, validity, and minimum detectable change of visual analog, numerical rating, and verbal rating scales for measurement of osteoarthritic knee pain. *J Pain Res* 2018;11:851. doi: 10.2147/JPR.S158847
43. Hsieh C, Phillips RB, Adams AH, et al. Functional outcomes of low back pain: comparison of four treatment groups in a randomized controlled trial. *J Manipulative Physiol Ther* 1992;15(1):4-9. PMID: 1531488
44. Kopec JA, Esdaile JM. Functional disability scales for back pain. *Spine* 1995;20(17):1943-49. doi: 10.1097/00007632-199509000-00021
45. Bobos P, MacDermid J, Nazari G, et al. Psychometric properties of the global rating of change scales in patients with neck disorders: a systematic review with meta-analysis and meta-regression. *BMJ open* 2019;9(11):e033909. doi: 10.1136/bmjopen-2019-033909
46. McCaffrey N, Kaambwa B, Currow DC, Ratcliffe J. Health-related quality of life measured using the EQ-5D-5L: South Australian population norms. *Health Qual Life Outcomes*. 2016;14(1):133. doi: 10.1186/s12955-016-0537-0.
47. Dubé M-O, Langevin P, Roy J-S. Measurement properties of the Pain Self-Efficacy Questionnaire in populations with musculoskeletal disorders: a systematic review. *Pain Rep* 2021;6(4). doi: 10.1097/PR9.0000000000000972
48. Garber MC, Nau DP, Erickson SR, et al. The concordance of self-report with other measures of medication adherence: a summary of the literature. *Med Care* 2004:649-52. doi: 10.1097/01.mlr.0000129496.05898.02
49. Mathieson S, Maher CG, McLachlan AJ, et al. Trial of pregabalin for acute and chronic sciatica. *N Engl J Med* 2017;376(12):1111-20. doi: 10.1056/NEJMoa1614292
50. Williams CM, Maher CG, Latimer J, et al. Efficacy of paracetamol for acute low-back pain: a double-blind, randomised controlled trial. *Lancet* 2014;384(9954):1586-96. doi: 10.1016/S0140-6736(14)60805-9
51. Handelsman L, Cochrane KJ, Aronson MJ, et al. Two new rating scales for opiate withdrawal. *Am J Drug Alcohol Abuse* 1987;13(3):293-308. doi: 10.3109/00952998709001515
52. Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med* 2006;166(10):1092-1097. doi: 10.1001/archinte.166.10.1092.

53. McCracken LM, Velleman SC, Eccleston C. Patterns of prescription and concern about opioid analgesics for chronic non-malignant pain in general practice. *Prim Health Care Res Dev* 2008;9(2):146-56. doi: 10.1017/S1463423608000625
54. Sheehan KA, Scanlan E, Matthews M, Ross EL, Jamison RN Beliefs about prescribing opioids for chronic pain: survey of primary care practitioners. Poster session presented at the 33rd Annual Scientific Meeting of the American Pain Society, Tampa, Florida, May 2, 2014.
55. Stuart B, Becque T, Moore M, et al. Clustering of continuous and binary outcomes at the general practice level in individually randomised studies in primary care - a review of 10 years of primary care trials. *BMC Med Res Methodol* 2020;20(1):83. doi: 10.1186/s12874-020-00971-7
56. Williams CM, Maher CG, Latimer J, et al. Efficacy of paracetamol for acute low-back pain: a double-blind, randomised controlled trial. *Lancet* 2014;384(9954):1586-96. doi: 10.1016/s0140-6736(14)60805-9
57. Statistics ABo. Technical Paper Socio-Economic Indexes for Areas (SEIFA) 2021: Australian Bureau of Statistics Canberra, 2023.
58. Pink B. Australian statistical geography standard (ASGS): volume 5—remoteness structure. *Canberra: Australian Bureau of Statistics* 2011
59. The Royal Australian College of General Practitioners. General Practice: Health of the Nation 2020. East Melbourne, Vic: RACGP, 2020.
60. Research Electronic Data Capture (REDCap). Available from: https://redcap.sydney.edu.au/.
61. Craig BM, Rand K. Choice Defines QALYs: A US Valuation of the EQ-5D-5L. *Med Care*. 2018;56(6):529-536. doi: 10.1097/MLR.0000000000000912.
62. National Health and Medical Research Council. Guidance: Safety monitoring and reporting in clinical trials involving therapeutic goods. Canberra: National Health and Medical Research Council 2016.

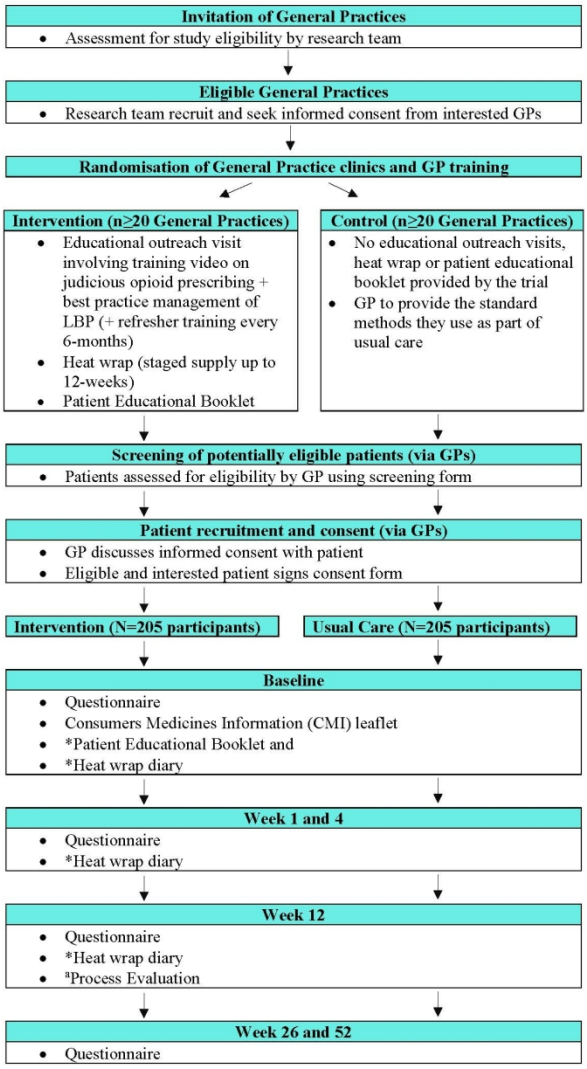

Figure 1: Study design flow Chart *Intervention only a) Intervention only (scheduled between 12-16 weeks - standalone component).

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SPIRIT CHECKLIST

Item	Item n	Description	Checked
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Y
Trial Registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Y
	2b	2b All items from the World Health Organization Trial Registration Data Set	N/A
Protocol Version	3	Date and version identifier	Y
Funding	4	Sources and types of financial, material, and other support	Y
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	
	5b	Name and contact information for the trial sponsor	Y
	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	Y
	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)	Y
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	Y
	6b	Explanation for choice of comparators	Y
Objectives	7	Specific objectives or hypotheses	Y
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)	Y
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	Y
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and	Y

		individuals who will perform the interventions (eg, surgeons, psychotherapists)	
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Y
	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)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Y
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Y
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	Y
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)	Y
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	Y
Recruitment	**15**	Strategies for achieving adequate participant enrolment to reach target sample size	Y
Methods: Assignment for 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	Y
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	Y

Implementation	**16c**	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Y
Blinding (masking)	**17a**	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Y
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Y
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	Y
	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	Y
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	Y
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	Y
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Y
	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)	Y
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	Y

	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	Y
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	Y
Auditing	**23**	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Y
Ethics and Dissemination			
Research Ethics approval	**24**	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Y
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)	Y
Consent or assent	**26a**	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Y
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Y
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	Y
Declaration of interests	**28**	Financial and other competing interests for principal investigators for the overall trial and each study site	Y
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	Y
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	Y
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	Y
	31b	Authorship eligibility guidelines and any intended use of professional writers	Y

	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Y
Appendices			
Informed consent materials	**32**	Model consent form and other related documentation given to participants and authorised surrogates	Y
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	N/A