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To cite: Abdel Shaheed C, Ivers R, Vizza L, *et al.* Clinical Observation, Management and Function Of low back pain Relief Therapies (COMFORT): A cluster randomised controlled trial protocol. *BMJ Open* 2023;**13**:e075286. doi:10.1136/bmjopen-2023-075286

► Prepublication history for this paper is available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2023-075286>).

Received 03 May 2023
Accepted 04 October 2023



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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 1-year period. The primary outcome will be the cumulative dose of opioid dispensed that was prescribed by study GPs over 1 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.

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 general practitioner (GP) management of low back pain.
- ⇒ A potential limitation related to the 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.

Trial registration number ACTRN12622001505796.

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)⁵ or chronic (persisting beyond 3 months).⁵ LBP 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 prescription¹⁵ and one in every five 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 2015–2016 resulted in an opioid prescription.¹⁷ This practice has led to serious problems including dependence, overdose, hospitalisation and death.¹⁸ In 2017–2018, 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 review²⁰ established that opioid analgesics provide only a small amount of pain relief in the short term for LBP (mean difference of -10.1 (95% 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 Clinical Observation, Management and Function Of low back pain Relief Therapies (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 with no outreach visit and usual GP care to determine the effect on GP prescribing of opioid medicines dispensed to their patients with LBP over 1 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

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 Standard Protocol Items: Recommendations for Interventional Trials (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).
- ▶ LBP 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 (MBS/PBS) and other trial-related data.

Exclusion:

- ▶ Engaged in an opioid tapering regimen at the time of enrolment into the study, that is, 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:

Educational outreach visits to GPs promoting opioid stewardship

Baseline visit

Participating GPs will receive a face-to-face baseline educational outreach visit (duration of 0.5–1 hour) 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.

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 bed rest, and reassurance of a favourable 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, that is, 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 1-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 NSAIDs may also be considered by participating GPs if deemed appropriate for the management of LBP, based on the patients' medical and medication history.

Participant education

The training will encourage participating GPs to provide their patient-participants with an educational booklet. In

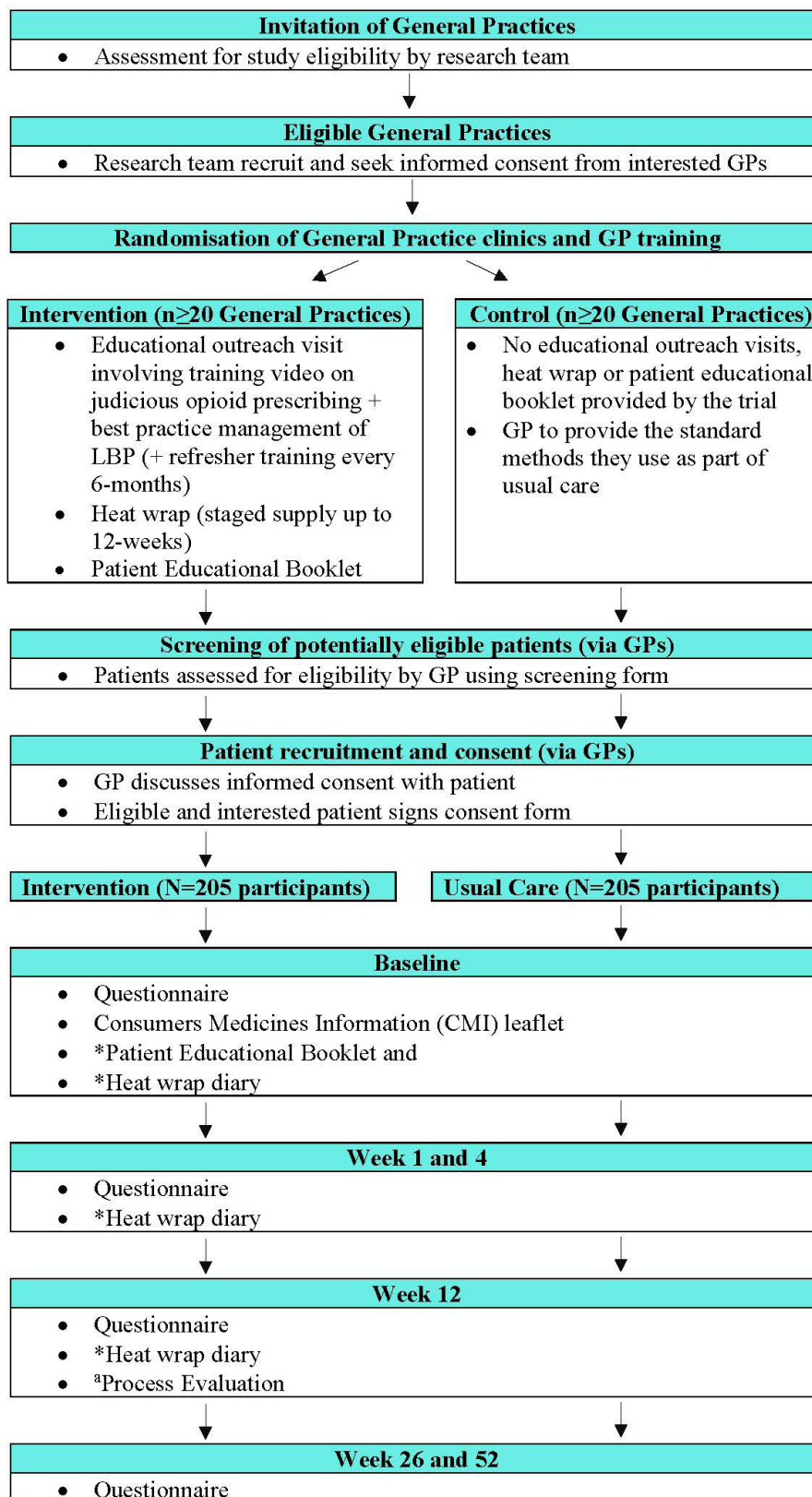


Figure 1 Study design flow chart *Intervention only, ^aIntervention only (scheduled between 12 and 16 weeks—stand-alone component). GP, general practitioner; LBP, low back pain.

partnership with PainAustralia Consumer Advisory Group, National Prescribing Service (NPS) MedicineWise and Choosing Wisely Australia, we co-developed a two-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, for example, 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.

Additional education resources

Participating GPs will be provided access to the NPS opioid tapering algorithm³⁷ to support deprescribing 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 TGA approved consumer medicines information 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 in the trial. This training outlines responsibilities in the conduct of clinical trials and will be delivered via a 7 minute training video.

Cointerventions

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 cointervention.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 1 year using Medicare linkage, determined using morphine milligram equivalent (MME).³⁹

Secondary outcomes

Secondary outcomes collected for patient-participants over the 1-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 the emergency department.
- ▶ Number of hospitalisations.
- ▶ Total cost of MBS and 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 three 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 prespecified 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 0–10 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 5 Dimension 5 Level (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 0.79–0.95).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 seven continuous days of no opioid use. The medication diary has shown high concordance with clinically determined measures, for example, plasma drug concentrations and pill count or canister weight ($\kappa > 0.6$ in seven studies),⁴⁸ and high completion rates among participants was also reported with 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 postenrolment).
- ▶ Severity of opioid withdrawal symptoms: Using the self-report opioid withdrawal scale.⁵¹
- ▶ Anxiety using the General Anxiety Disorder-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 seven 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 (SAE).
 - Frequency and nature of any adverse or SAE.
 - Cause of SAE.

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 questionnaire⁵³ and 10-item opioid therapy survey⁵⁴ 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 (Research Electronic Data Capture (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 and 10% on the 24-item RMDQ (assuming SD of 5.4).⁵⁰ 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 (area-level socioeconomic status) will be divided/split into tertiles (highest, middle, lowest) based on the 2021 Index of Relative Advantage and Disadvantage.⁵⁶ Remoteness will be classified into two categories (The Accessibility/Remoteness Index of Australia (ARIA+) classification), based on the Australian Statistical Geography Standard: (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 (vs. 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 SAEs.

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 REDCap) over 1 year. Collection of study outcomes will be via data linkage and patient-report. In addition, the study team will also follow-up with participating GPs to complete questionnaires via REDCap (or paper based) at specified time points 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, for example, REDCap⁵⁹ 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 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 are 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: (1) chronicity—patient-participants with acute versus chronic LBP, (2) type of LBP—non-specific LBP versus LBP due to specific causes (e.g., pregnancy), (3) age and (4) 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 (1 year). A binary logistic regression will be conducted for binary outcomes. SAEs 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. Healthcare 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 used⁶⁰ to estimate quality-adjusted life-years. 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.

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 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 SAEs, 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 6 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 SAEs) will be collected by patient-report questionnaires at weeks 1, 4, 12, 26 and 52.

Serious adverse events

SAEs 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

SAEs will be reported to the Sydney University Human Research Ethics Committee (HREC) within the required time frame, 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 coauthor on the work.

ETHICS AND DISSEMINATION

Ethics approval

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

Protocol amendments

Any changes to the study protocol must be agreed on 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, for example, Painaustralia consumer advisory group and policymakers in Australia and overseas.

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

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Acknowledgements We would like to thank the following people for their contribution: Operations: Daniel Chapman, Melissa Webb, Sarah Diprose, Chantay Lenord. Good Clinical Practice (GCP) training materials: 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.

Contributors CAS is principal investigator on the trial, has oversight over all trial procedures and drafted the manuscript. CAS, RI, LV, AM, PJK, FB, FS, PJC, RT, TL, LD, SR, BM, MW, RO, SF, KM, GC, HJ, SM, MB, JM, CB and CM 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.

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

Competing interests The Sydney Pharmacy School receives funding for a postgraduate scholarship from GlaxoSmithKline for a student under the supervision of AM. JM is an employee of the Pharmaceutical Society of Australia. BM receives royalties for the development of an opioid risk prediction tool which is unrelated to the current study protocol.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Consent obtained directly from patient(s).

Provenance and peer review Not commissioned; externally peer reviewed.

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