






STUDY PROTOCOL

Evaluating a primary care pharmacist-led intervention to reduce opioid use for persistent non-cancer pain: the PROMPPT cluster randomised controlled trial protocol

[version 1; peer review: 1 approved with reservations, 1 not approved]

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Abstract

Background

Addressing the need for evidence-based interventions to reduce opioid use for persistent pain, we developed the PROMPPT intervention (**P**roactive clinical **R**eview of patients taking **O**pioid **M**edicines long-term for persistent **P**ain led by clinical **P**harmacists in primary care **T**eams), a primary care pharmacist-led review and associated training package. This trial will evaluate whether, in patients prescribed long-term opioids for persistent pain, PROMPPT is more likely to reduce opioid use, without increasing pain/pain-related interference, compared with usual primary care and will examine the cost-effectiveness of PROMPPT from healthcare and societal perspectives.

Open Peer Review

Approval Status  

	1	2
version 1 03 Jul 2025	 view	 view

- 1. **Stephen E. Nadeau**, University of Florida
College of Medicine, Gainesville, USA
- 2. **Benjamin Lai**, Mayo Clinic Cancer Center,
Rochester, USA

Any reports and responses or comments on the article can be found at the end of the article.

Methods Patient and Public Involvement (PPI)

A group of public contributors from Keele University's Research User Group (RUG) with experience of persistent pain and opioids was convened to support the development of the PROMPPT research programme, the NIHR funding application, and subsequently to advise on delivery of the programme. As RUG members, all members of the PROMPPT PPI group have received an induction, a plain English glossary of research terms and have access to training resources (e.g. contributing assertively to meetings), are supported by a dedicated PPI support worker, and they are offered payment according to NIHR guidelines <https://www.nihr.ac.uk/nihr-public-contributor-payment-policy>.

To support the development of the PROMPPT intervention, the pharmacist training package and the feasibility study, this group attended 5 formal workshops (between Mar 2019 and July 2021). Patients were also represented in the consultation of stakeholders by 2 further RUG members, who attended 3 mixed stakeholder workshops, which informed design of the intervention¹⁷. More recently, patient advisors have influenced the design of this trial by:

- Co-producing revised pain medicines questionnaires in light of findings from the feasibility study.

- Co-producing patient-facing information with the research team including participant information sheets, invitation letters, the "Getting Ready for Your Pain Review" leaflet and self-management leaflets developed as part of the PROMPPT intervention.

- Advising on strategies to improve follow-up questionnaire response rates during the trial, including sending text notifications ahead of Minimum Data Collection (MDC) calls to non-responders and advising on the wording of text messages to participants and a Thank You Flyer to accompany follow-up questionnaires.

Further PPI group meetings are planned to discuss the findings of the main trial and the process evaluation, and to generate the key messages to disseminate these to patients and the wider public.

Design and setting: cluster randomised controlled trial, with internal pilot, in 38 general practices across England. Participants: patients ≥ 18 years prescribed one or more opioids ≥ 6 months for persistent pain who consent to participate in a questionnaire study. Practices are randomly allocated (1:1 ratio) to either: invite participants for a

PROMPPT review with the practice pharmacist, and follow-up as needed, or continue usual primary care arrangements for reviewing patients who are prescribed opioids. Co-primary outcomes, measured at 12 months, are (1) reduction in self-reported opioid use ($\geq 25\%$ reduction in daily morphine equivalent dose from their baseline) and (2) non-inferiority of the Brief Pain Inventory total score.

The trial includes an economic evaluation (within trial and longer-term cost-utility analyses) and a mixed methods process evaluation.

Analysis of consultation audio-recordings, case report forms (including an intervention delivery template), acceptability questionnaires and semi-structured interviews will explore how PROMPPT was delivered and received, and how context affected implementation and outcomes.

Conclusion

The PROMPPT trial will provide important new evidence about the effectiveness of a practice pharmacist-led primary care intervention to reduce opioid use for persistent pain.

Trial registration

ISRCTN 45616481, 13/05/2022

<https://doi.org/10.1186/ISRCTN45616481>

Plain English Summary

Persistent pain is long-lasting pain, not caused by cancer, and affects more than one in three adults in the United Kingdom. Opioids are medicines that are commonly prescribed for persistent pain, but do not help most people in the long-term and can cause serious harm.

Our research team has developed a new way to review people on opioids, by training pharmacists working in general practices ('practice pharmacists') to do these reviews. The new approach is called PROMPPT (Proactive clinical Review of patients taking Opioid Medicines Pain led by clinical Pharmacists in primary care Teams).

This study will test whether the PROMPPT approach is more likely to reduce opioid use, without making pain worse, compared to usual care.

General practices invite adult patients who have been prescribed opioids for at least six months to take part in a questionnaire study. The practices are then allocated at random to either offer PROMPPT or continue usual care. Practices allocated to PROMPPT invite study participants to arrange an appointment with the practice pharmacist, who is trained in the PROMPPT approach. Follow-up appointments are arranged as needed.

Some of those who arrange a PROMPPT review are asked to give their consent for the appointment to be recorded and/or consent to be interviewed. After the review, they are sent another questionnaire to find out what they thought of the review. Participants who decline the PROMPPT review will also be invited for an interview.

People with persistent pain helped design the PROMPPT review and study documents and will also advise how best to publicise the study results.

If successful, the PROMPPT approach will:

Keywords

Chronic Pain, Opioids, Tapering, Primary Care, Cluster Randomised Controlled Trial, Process Evaluation, Health Economics

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Introduction

Background and rationale

Persistent pain, defined as long-term pain not caused by cancer, is a common problem affecting an estimated one-third to one-half of adults in the United Kingdom (UK)¹ and around one in five adults in the United States (US)². Opioids are commonly prescribed for persistent pain^{3,4}, despite a lack of evidence for their long-term efficacy and the risk of serious harm⁵⁻⁷. A recent review estimated that almost one-third (31%) of patients with persistent pain are prescribed an opioid⁴ and reducing inappropriate opioid use is a key healthcare priority in many countries⁸. Most long-term opioid prescribing for persistent pain occurs in primary care and best practice guidelines recommend regular review of patients on opioids and gradual tapering of opioids (opioid deprescribing) if treatment goals are not met⁸. However, research suggests that opioid deprescribing is viewed as challenging and time-consuming by healthcare professionals⁹ and, with limited time available in UK general practitioner (GP) appointments, approaches to reviewing opioids in primary care are variable and often 'light-touch'¹⁰. Furthermore, there is a lack of practical guidance on how to implement opioid deprescribing.

Systematic reviews have found limited evidence, often of low methodological quality, supporting interventions to reduce long-term opioid use and recommended further, larger randomised controlled trials (RCTs) of theoretically grounded behaviour change interventions to support opioid deprescribing in the context of persistent pain, which measure long-term follow-up and include a health economic evaluation¹¹⁻¹³. Sandhu *et al.* evaluated a multicomponent community-based group intervention, incorporating individual tapering support, to reduce opioid use (iWOTCH¹⁴). They found that, among UK patients with persistent non-cancer pain, a group-based educational intervention significantly reduced opioid use compared with usual care without affecting perceived pain interference with daily activities¹⁴. However, less than half of participants randomised to the group intervention attended all sessions. Given the diversity of patients who are prescribed opioids for persistent pain, not all of whom will be able or willing to engage with a group intervention, a range of evidence-based strategies to reduce opioid use are likely to be needed¹⁵.

To address the need for primary care-based interventions to support opioid deprescribing in the context of persistent pain, we developed the PROMPPT intervention (**P**roactive clinical **R**eview of patients taking **O**pioid **M**edicines long-term for persistent **P**ain led by clinical **P**harmacists in primary care **T**eams). PROMPPT capitalises on an expansion in the number of clinical pharmacists working in UK general practices (practice pharmacists), who play an increasing role in managing patients on long-term medicines by conducting consultations with patients in GP surgeries¹⁶. In line with Medical Research Council (MRC) guidance on the development and evaluation of complex interventions, the PROMPPT intervention was co-designed with stakeholders¹⁷ (patients and healthcare professionals), using a person-based approach¹⁸, combined with best practice guidance and theory on behaviour change. Extensive intervention

development work included interviews with patients, pharmacists and GPs, an online qualitative study and in-practice testing of prototype PROMPPT consultations¹⁹⁻²¹, followed by a non-randomised feasibility study²². At each stage, findings informed iterative refinement of the PROMPPT review and pharmacist training. We hypothesise that the PROMPPT intervention will increase the likelihood of patients with persistent pain reducing their opioid use, compared to usual care, and that this can be achieved without increasing pain and pain-related interference.

Protocol

The current PROMPPT trial protocol (version 1.6 2 Apr 2024) is described below, in line with SPIRIT reporting guidelines²³. Key amendments to the protocol since initial trial registration are highlighted in the text with comments in brackets and summarised in Table 1.

Objectives

Primary objective

1. To determine, in patients prescribed opioids long-term (≥ 6 months) for persistent pain, whether providing the PROMPPT intervention (practice pharmacist-led primary care pain review and associated pharmacist training package) is more likely to reduce opioid use, without increasing pain/pain-related interference, at 12-month follow-up compared with usual primary care review.

Secondary objectives

2. To determine, in patients prescribed opioids long-term (≥ 6 months) for persistent pain, the differences, between treatment arms, in patient-reported clinical outcomes including pain, pain-related interference, use of opioid and non-opioid pain medicines, confidence to cope with pain, symptoms of depression and anxiety, presence and severity of opioid-related side-effects, and health-related quality of life at 3, 6 and 12-month follow-up.
3. To determine the differences between treatment arms in GP practice-level prescribing of opioids, non-opioid analgesics and other potentially sedating medicines commonly prescribed for patients with persistent pain at 12-month follow-up.
4. To estimate the cost-effectiveness of providing the PROMPPT intervention versus usual primary care review for patients prescribed opioids long-term (≥ 6 months) for persistent pain.
5. To explore, through a mixed methods process evaluation, how PROMPPT was delivered and received, the quantity and quality of what was delivered (fidelity and dose), how PROMPPT impacted on any change in outcomes and how context affected implementation of PROMPPT and outcomes.

Trial design and setting

The PROMPPT trial is a pragmatic, multicentre, parallel two-arm cluster randomised controlled trial (RCT) with an internal

Table 1. Protocol amendments since trial registration.

Amendment number*	Protocol section	Original protocol	Amendment details†	Date	Rationale for amendment
2 AM02 NSA 02	7.8 Long-term follow-up assessments 7.10 Withdrawal criteria	Individual clinical outcome data Where there are ambiguous or incomplete pain medicines use questionnaire entries that interfere with calculation of daily MED, a member of Keele CTU staff will try to contact participants by telephone to obtain the missing data.	Individual clinical outcome data Where there are ambiguous or incomplete pain medicines use questionnaire entries that interfere with calculation of daily MED, a member of Keele CTU staff will try to contact participants by telephone or in writing , to obtain the missing data. Withdrawal criteria Participants that have consented but advise that they do not take opioids, will be subsequently withdrawn from the study, due to not meeting the inclusion criteria.	November 2022	To improve the completeness of data collection, and ensure participant eligibility if participants cannot be contacted by telephone, participants with missing or ambiguous questionnaire entries regarding their pain medicines questionnaire may also be contacted by letter.
3 AM03 NSA02	7.9 Process Evaluation (MOPP-2 Study)	Identification and recruitment of participants (MOPP-2) <i>Patients</i> Participants from clusters in the intervention arm who consented to being contacted about a future related research study and subsequently attend a PROMPT review will be invited to participate in the process evaluation (MOPP-2 study).	Identification and recruitment of participants (MOPP-2) <i>Patients</i> Participants from clusters in the intervention arm who consented to being contacted about a future related research study and subsequently attend a PROMPT review will be invited to participate in the process evaluation (MOPP-2 study). Reminders will be sent to non-responders at 2 weeks either by email or post dependent on patient preference.	January 2023	As part of the process evaluation, participants who consented to further contact are sent a Process Evaluation (MOPP-2 study) recruitment pack including an Acceptability Questionnaire. The return rate for Acceptability Questionnaires was lower than expected and the original protocol did not allow for reminders, so this was added to the protocol and new reminder letters created.

Amendment number*	Protocol section	Original protocol	Amendment details†	Date	Rationale for amendment
4 AM04 SA01	7.8 Long-term follow-up assessments	<i>Individual clinical outcome data</i> Standard Keele CTU procedures will be followed to maximise follow-up at all timepoints (3, 6 and 12 months). This includes electronic / postal reminders for non-responders after 2 and 4 weeks and contact by telephone for minimum data collection (MDC) after 6 weeks.	<i>Individual clinical outcome data</i> Standard Keele CTU procedures will be followed to maximise follow-up at all timepoints (3, 6 and 12 months). Online participants receive a text alerting them to the email containing link to follow-up questionnaire. Non-responders receive a text and email reminder after one week and a postal questionnaire after 2 weeks. Postal participants who do not respond are sent a reminder postcard after 2 weeks and a new postal questionnaire after 4 weeks Non-responders are telephoned up to 3 times for minimum data collection (MDC) after 6 weeks and receive text message prior to MDC calls. Postal MDC questionnaire sent to non-responders who are uncontactable by telephone. Those who participate in the study and return either a paper or online questionnaire at 12 months will be included in a prize draw for the opportunity to win one of three £100 prizes (e.g. Amazon voucher).	April 2023	In the internal pilot, 3 month follow-up rates were lower than expected, therefore a range of amendments to the protocol and associated patient-facing documents were made with the aim of improving follow-up data collection by: (1) improving follow-up questionnaire response rates, (2) allowing use of data from partially completed follow-up questionnaires unless participants opt out, and (3) improving minimum data collection (primary and key secondary outcomes) from non-responders.
	7.10 Withdrawal criteria		<i>Withdrawal criteria</i> Participants opting to complete the questionnaire online will be advised, in the participant information leaflet, that they can stop completing the questionnaire at any time point, without giving a reason, but that answers entered up to that point will be kept unless they contact the study team to opt out of this. New patient-facing documents - New "Thank You" flyer with all postal questionnaires and "Thank You" banner in emails for online participants - New covering letter/email with 12-month follow-up questionnaire emphasising its importance and including optional entry to a free prize draw Revised order for follow-up questionnaires, with both co-primary outcomes at the start and fewer mandatory fields in the online version		

Amendment number*	Protocol section	Original protocol	Amendment detail†	Date	Rationale for amendment
7 AM07 NSA05	8.2 Planned recruitment rate	An internal pilot will check recruitment assumptions, and we will adjust the recruitment strategy accordingly.	July 2023: Internal pilot results recommended that practices with list sizes <5000 can also be recruited to the study and practices can invite up to 350 eligible patients per practice (sampled to reflect the distribution across opioid strength groups (weak, intermediate, strong) in the practice if there are an excess of 350 patients who meet the eligibility criteria for the study).	July 2023	Following the internal pilot study, to facilitate recruitment of GP practices and the required number of participants within the planned timeframe, we adjusted the recruitment strategy to allow for smaller practices to be included whilst also raised the maximum number of eligible patients to be invited per practice.
9 AM09 NSA07	7.8 Long-term follow-up assessments	<i>Practice-level outcome data</i> We will extract and analyse aggregated data from the electronic medical records of participating practices on relevant prescriptions among adults aged ≥18 years who do not have a coded cancer diagnosis.	<i>Practice-level outcome data</i> We will extract and analyse pseudonymised data from the electronic medical records of participating practices on relevant prescriptions among adults aged ≥18 years, excluding those who have both a coded cancer diagnosis and a code for palliative care.	February 2024	To exclude patients receiving end-of-life care for cancer and avoid unnecessarily excluding patients with a historical cancer diagnosis that was no longer relevant, and cancer survivors treated for chronic non-cancer pain from data on practice-level pain-related prescribing.
10 AM10 SA02	7.2 Patient identification 9.1 Data collection tools and source document identification 9.2 Data handling and record keeping	Eligible patients who have been identified and who have a mobile phone number that is able to receive SMS on the practice record will be sent an SMS text invitation from the general practice to take part in the research. The SMS will contain a secure online link URL, hosted on Keele University managed storage services , to an embedded patient information leaflet, consent form and baseline questionnaire for online completion. Participating GP practices will send an Excel file to the study team of those patients invited, via secure transfer . A dedicated web-based Management Application will be developed and maintained by Keele University and data will be stored on Keele University managed storage services, held within the UK and protected by industry standard security tools . A study online survey will be developed and hosted on Keele University managed password protected storage services for participants that choose to complete self-report data online.	Eligible patients who have been identified and who have a mobile phone number that is able to receive SMS on the practice record will be sent an SMS text invitation from the general practice to take part in the research. The SMS will contain a secure online link URL, hosted on Keele University managed storage services , to an embedded patient information leaflet, consent form and baseline questionnaire for online completion. Participating GP practices will send an Excel file to the study team of those patients invited, via secure transfer . A dedicated web-based Management Application will be developed and maintained by Keele University and data will be stored on Keele University managed storage services, held within the UK and protected by industry standard security tools . A study online survey will be developed and hosted on Keele University managed password protected storage services for participants that choose to complete self-report data online.	April 2024	This amendment was required due to changes in how data collected to the trial is stored

* Amendments 1,5,6, 8 & 11 not included as they relate only to minor changes to patient-facing documents and did not have implications for the trial protocol.

† Additions to the protocol are in bold italics.

pilot, linked health economic evaluation and mixed methods process evaluation. A cluster RCT design was chosen to (a) reduce treatment contamination risk between arms and (b) to facilitate recruitment, as practice level randomisation has previously been highlighted as a potential strategy for addressing the challenges of recruiting patients who may be apprehensive about changes to their opioid analgesics^{24,25}.

The setting is UK primary care, specifically 38 general practices from across the West Midlands, East Midlands, Wessex, Thames Valley and South Midlands. Participating practices identify eligible patients from their electronic health records and invite them to participate in a questionnaire study (patient facing name: Management of Opioids & Persistent Pain (MOPP) Study). Practices are randomised (1:1) to either offer PROMPPT (intervention arm) or continue usual primary care arrangements for reviewing patients prescribed long-term opioids (control arm). The units of randomisation are the general practices, and the units of observation are MOPP study participants, who receive the care to which their practice is randomised. Participant flow through the trial is shown in Figure 1.

To minimise the risk of post-randomisation selection bias²⁶, identification of eligible potential participants is completed prior to practice randomisation. In addition, practices are requested to provide pseudonymised demographic data for patients invited

(including National Health Service (NHS) number, age, sex, and opioid strength grouping (defined below)) to the research team to allow any evidence of selection bias to be assessed. To reduce the risk of participation bias, all potential participants receive identical information inviting them to participate in the MOPP study and all patient participants complete identical MOPP study questionnaires at baseline and all follow-up time points, regardless of which treatment arm their practice is randomised to.

Ethical approval

Ethical approval was obtained from North East, Newcastle & North Tyneside 2 Research Ethics Committee (REC) (Ref:22/NE/0044). Following initial approval, the REC has been informed of all substantial changes to the management of the trial.

General practice eligibility, recruitment and consent

General practices are eligible to participate in this trial if they use either the EMIS Web (Optum: <https://www.emishealth.com/products/emis-web>) or SystmOne (TPP: <https://tpp-uk.com/products/>) electronic health record (EHR) system and have at least one practice pharmacist, who is an Independent Prescriber and consults with patients face-to-face and/or remotely, working within the practice for at least one session per week. Initially practices were also required to have at least 5000 registered

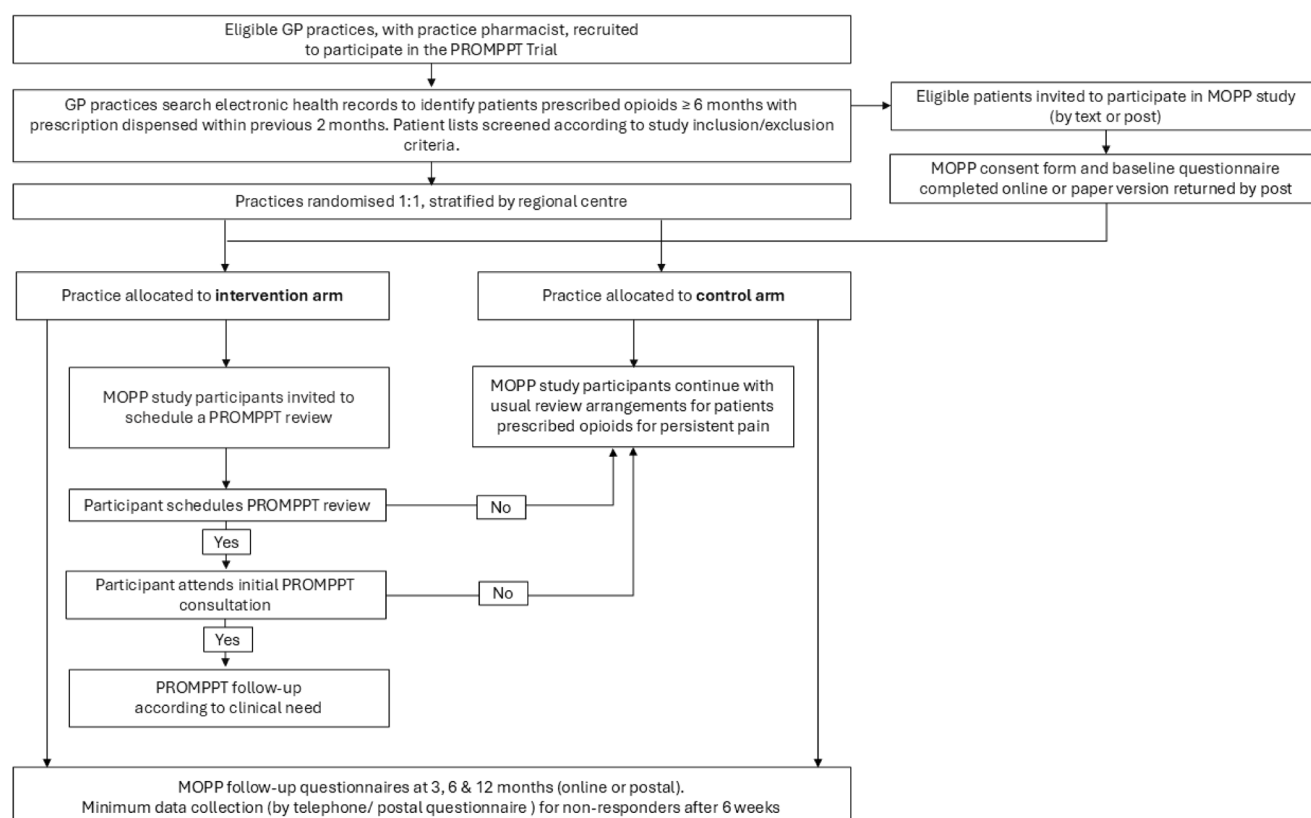


Figure 1. PROMPPT Trial Recruitment Flowchart.

patients but from July 2023, practices with <5000 registered patients were also included (Amendment 7, see [Table 1](#)).

Recruitment of general practices is facilitated by National Institute for Health and Care Research (NIHR) Clinical Research Networks (CRNs) in the West Midlands, East Midlands, Wessex and Thames Valley & South Midlands to identify eligible general practices with a range of patient list size and setting (urban, semi-urban, and rural). Members of the research team meet with a GP, practice pharmacist and practice manager (face-to-face or remotely) to explain the study and describe the study requirements. GP practices are recruited in batches until the required number of participants is recruited. Informed written consent for practices to participate is provided by the authorised person in each practice, as a guardian for patients in their care, following agreement with the practice team to provide either the PROMPT intervention or usual care (dependent on random allocation) for the period of the trial and to participate in the process evaluation.

Individual patient participants

Inclusion criteria

- Adult patients aged 18 years and over, registered at a participating practice, and prescribed any opioid analgesic (defined as any opioid or opioid/paracetamol combination analgesic from sections 4.7.2 and 4.7.1 British National Formulary (BNF))²⁷ for persistent non-cancer pain for at least 6 months, with at least one prescription issued within the previous 2 months.

Exclusion criteria

- Patients being treated for acute pain (self-limiting pain, for example after injury or surgery), pain associated with cancer and patients with terminal illness (life expectancy <6m),

- vulnerable patients (as assessed by general practices e.g. severe mental illness, learning difficulties, dementia),
- patients currently receiving treatment for substance misuse.

Recruitment and consent for outcome data collection

Participating practices search their electronic health record systems, using a Search and Report, designed by a health informatics specialist from Keele Clinical Trials Unit (CTU), to systematically identify adults prescribed opioid-containing pain medicines for 6 months or longer (with at least one prescription dispensed in the last two months), grouped according to the strength of opioid medicine (weak, intermediate, strong, see [Table 2](#)), based on a published categorisation for prescribed analgesics in primary care²⁸. Practices then screen patients identified according to study inclusion and exclusion criteria, excluding ineligible patients.

To avoid individual practices being overrepresented in the overall study population, the maximum number of patients invited to participate per practice is capped. Initially a maximum of 250 eligible patients per practice were invited, but the cap was increased to 350 from July 2023 to facilitate recruitment within the planned timeframe (Amendment 7, see [Table 1](#)). Where practices identify an excess of potentially eligible patients, a representative sample (randomly sampled by Keele CTU staff to reflect the distribution across the opioid strength groups (weak, intermediate, strong) in the practice overall) is invited by the GP practice.

Using general practices' existing systems for bulk text messaging, potentially eligible patients with a mobile phone number on the practice record are sent a text message from their practice inviting them to participate in the Management of Opioids & Persistent Pain (MOPP) Study. The text message

Table 2. Categorisation of patients by opioid strength*.

Weak	Intermediate	Strong
Co-codamol 8mg/500 mg	Codeine 30mg	Morphine
Co-codamol 15mg/500 mg	Co-codamol 30mg/500mg	Oxycodone
Codeine 15mg	Dihydrocodeine 30mg	Fentanyl
Codeine 20mg	Buprenorphine patch ≥15mcg/hour	Tapentadol
Co-dydramol 10mg/500mg	Buprenorphine SL 400mcg	Diamorphine
Co-dydramol 20mg/500mg	Tramadol >37.5mg	Hydromorphone
Dihydrocodeine 20mg	Pethidine	Dipipanone
Co-proxamol 32.5mg/325mg	Pentazocine	Dextromoramide
Tramadol 37.5mg/500mg	Meptazinol	
Buprenorphine patch 5 or 10 mcg/hour		
Buprenorphine Sublingual 200mcg		

* Hierarchy of analgesic potency arising from a consensus study of UK general practitioners²⁸

contains a secure online link to a web page, hosted by Keele University, with an embedded participant information leaflet, consent form and baseline questionnaire for online completion. A reminder text is sent after 2 to 3 days and includes information on how to contact Keele CTU for assistance completing the online questionnaire, or to request a postal version of the information leaflet, consent form and questionnaire. Potentially eligible patients who cannot be invited by text are sent a postal invitation pack via Docmail, a secure remote document compilation, print and mailing solution. To facilitate inclusion of patients, Keele CTU offer telephone support for questionnaire completion and reassurance that family members can assist; and for patients whose first language is not English, questionnaire completion can also be facilitated online by an interpreter on request.

Given the cluster RCT design, patient participants are not individually consented to randomisation; written informed consent for practices to participate in the trial is provided by the general practice lead acting as 'guardian' for patients in their care.

Written consent is obtained from patient participants for:

- Participation in the MOPP questionnaire study (read and understood the participant information leaflet, voluntary participation, completion of baseline and 3,6,12-month follow up questionnaires)
- Access to their electronic health record (EHR).

Written consent (optional) from patient participants is also requested for:

- Contact about future related research studies, including the linked process evaluation (MOPP 2 study), which is described separately below.

Randomisation and blinding

General practices are randomised (1:1) in balanced blocks, stratified by regional centre, by an independent statistician affiliated with Keele CTU. The randomisation sequence is generated using the randomisation lists module in the **Power Analysis and Sample Size** software (PASS: [Sample Size Software | Power Analysis Software | PASS | NCSS.com](#)). Allocation concealment is ensured by each practice having an anonymised code. Practices are randomised either to offer the PROMPPT review (intervention arm) or to continue with usual practice arrangements for reviewing patients prescribed opioids for persistent pain (control arm). Participants receive the care to which their practice is randomised.

Blinding for participating practice pharmacists and GPs is not possible. The main trial statistician, outcome data entry staff, and members of the research team involved in calculating daily morphine equivalent dose from self-reported pain medicines data are blinded to allocation (at cluster (practice) and individual participant level) until the analysis is finalised. The independent Trial Steering Committee (TSC) is also blinded to allocation, but unblinded data is shared with the independent

Data Monitoring Committee (DMC) so that outcomes, such as patient safety, can be fully monitored.

Interventions

PROMPPT intervention

The PROMPPT intervention, comprising a proactive practice pharmacist-led review for patients who have been prescribed opioids for at least 6 months and an associated pharmacist training package, is described below, informed by the TIDieR guidance²⁹. Both the approach to delivering the PROMPPT review, and the content of the training package were shaped by earlier intervention development work^{17,19–22}. They incorporate best practice guidance^{30,31}, contemporary behaviour change theories and key communication skills to support shared decision-making^{32–35}. The intervention aims to respect patient values and autonomy, ensuring that decisions about when and how to change are patient centred.

PROMPPT review. General practices in the intervention arm invite MOPP study participants, by letter, to arrange a review with the practice pharmacist. The invitation letter is accompanied by an information leaflet called 'Getting Ready for Your Pain Review'. This leaflet aims to inform participants about what to expect at the initial review consultation and help them identify their priorities to discuss with the pharmacist during the consultation. The initial PROMPPT consultation (approximately 30 min) is conducted face-to-face or remotely (by video or telephone) according to patient preference.

The consultation begins with a holistic assessment of the participant's pain and the impact of persistent pain on their life, followed by a personalised discussion to explore the participant's personal experience of the effects (wanted/unwanted, useful/bothersome) of opioids. Pharmacists are encouraged to explore participants' reasons for considering changing their use of opioids, their readiness to change and any ambivalence, before agreeing an individualised management plan.

The agreed plan may include opioid tapering, but this is not mandatory, for example if a participant obtains continued useful benefit from moderate opioid doses without experiencing troublesome side-effects. Where changes to medicines are agreed, goal setting is used to facilitate translation of intentions into action. Important barriers to reducing opioids specific to the individual, such as fear of pain worsening and/or withdrawal symptoms following opioid reduction, are addressed. Practice pharmacists are encouraged to signpost to information resources, which are hosted on a dedicated website. These resources include strategies for living well with pain and reducing opioids. Pharmacists may also signpost or refer to appropriate community services (for example physiotherapy and mental health support services) and, if needed for more complex cases, discussion/collaboration with the GP and/or referral to specialist services is advised. Follow-up is encouraged and arranged according to pharmacists' clinical judgment and participant preference. Follow-up appointments, conducted face-to-face or remotely by video or telephone, according to pharmacists' assessment of clinical need and patient preference,

are anticipated to be shorter in duration (up to 15 minutes) on average. Pharmacists are also encouraged to agree and document a clear plan for contact, if needed, between scheduled appointments. A written summary of the agreed plan ('Your Pain Action Plan'), including a link to the information resources webpage, is provided in either paper or electronic form, according to patient preference.

Practice pharmacists delivering PROMPPT are independent prescribers and have completed trial-specific training to deliver the PROMPPT intervention, as described below. Intervention fidelity is assessed in the process evaluation (described in detail below) using pharmacist completed intervention delivery templates and audio-recorded consultations.

Pharmacist training. A comprehensive training package, developed by experts in pain management, primary care clinicians, behaviour change experts and medical/pharmacy educationalists, aims to equip practice pharmacists to deliver PROMPPT reviews. The training comprises an e-learning course and two half-day online workshops delivered via Microsoft Teams. The e-learning course, delivered via the PROMPPT study website, includes video presentations by experts in pain management and behaviour change, as well as videos of four simulated consultations aligned with readiness to change³⁵.

The training covers communication skills, how to conduct person-centred discussions about persistent pain and opioids, negotiating treatment plans, creating opioid tapering plans, optimising non-opioid pain management, supporting patients to live well with persistent pain, signposting to patient information resources and when to seek help (e.g. from a GP). Training also includes guidance to help practice pharmacists manage any emotional impact of conducting pain reviews.

The online workshops are facilitated by members of the research team with clinical and academic expertise in persistent pain management and behaviour change, supported by clinical champions, who are experienced clinical pharmacists and have completed the PROMPPT e-learning and received additional training in mentoring and supporting reflective practice. The online workshops incorporate role play, in simulated consultations, with feedback from the facilitators. In addition, practice pharmacists delivering PROMPPT reviews are mentored during the trial by one of the clinical champions.

Practice pharmacists are also provided with study-specific training including training on completion of study documentation, good clinical practice as applicable to research, and the maintenance of the study site file and study records. Reporting of serious adverse events and adverse events will also be covered.

Comparator - usual NHS primary care

MOPP study participants in control arm practices receive usual primary care arrangements for reviewing patients on long-term opioids for persistent pain, which are known to be variable¹⁰.

Such reviews may be conducted by the GP or by another appropriately qualified healthcare professional and may take place as a face-to-face consultation or as a virtual review with the patient's medication assessed from practice records without them being present.

Participating practices all have at least one practice pharmacist working in the practice at least some of the time. The roles adopted by practice pharmacists are variable, often including reviews for specific long-term conditions such as hypertension, diabetes and asthma, and Structured Medication Reviews (SMRs) for patients who may benefit from these, for example due to potentially problematic polypharmacy and / or use of potentially dependence forming medicines³⁶. Since the PROMPPT trial was conceived, reducing high-risk opioid prescribing has been included in NHS England's Medicines Safety Improvement Programme and, as a result, practice pharmacists may increasingly be conducting SMRs with patients who are prescribed opioids, but there is no specific training available regarding SMRs in this population and it remains unlikely that a practice pharmacist in a control practice would offer a structured medication review in the same way as a PROMPPT review without having received the PROMPPT training. Usual care arrangements are investigated as part of the process evaluation (described in detail below) to explore whether and how this affects outcomes.

Post-trial care

All trial participants receive usual care from their treating primary care clinician(s).

Data collection

There are three types of outcome data collection:

1. Individual participant data collected from baseline and follow-up (3, 6 and 12-month) questionnaires (online or postal).
2. Primary care electronic health record review.
3. Practice-level anonymised aggregated data of pain-related prescribing.

Individual participant data

Baseline and follow-up questionnaires. The baseline and follow-up questionnaires are designed to collect information on descriptive characteristics of the participants and primary and secondary outcome measures (see Table 3). Patients are informed in their study invitation that they have been invited to take part in the Management of Opioids & Persistent Pain (MOPP) Study because they have long term pain and have been regularly prescribed opioid medicines.

To maximise data collection at all follow-up timepoints, non-responders (online) receive a reminder by email (with text alert) after 1 week and a postal questionnaire after 2 weeks. Non-responders (postal) receive a reminder postcard after 2 weeks and a new paper questionnaire after 4 weeks. All non-responders to the reminders are contacted by telephone by a blinded trial administrator for minimum data collection

Table 3. Summary of participant questionnaire data collection.

Assessments	Number of items	Timepoint				Minimum data collection for non-responders
		Baseline	Follow-up			
			3-m	6-m	12-m	
Demographics						
Date of birth	1	X	X	X	X	X
Sex	1	X	X	X	X	X
Ethnicity	1	X				
Socioeconomic status (Index of Multiple Deprivation (IMD))	1	X				
Pain duration (years)	1	X				
Primary outcomes						
Brief Pain Inventory ³⁷ (BPI) (total score)	11	X	X	X	X	X
Opioid use (mean daily morphine equivalent dose (MED) ^a)		X	X	X	X	X
Secondary outcomes						
BPI ³⁷ pain severity	4	X	X	X	X	X
BPI ³⁷ pain Interference	7	X	X	X	X	X
Non-opioid pain medicines use (past week) ^b		X	X	X	X	X
Opioid-related side-effects (Checklist ^c)	10	X	X	X	X	
Depression (Patient Health Questionnaire (PHQ-8) ³⁸)	8	X	X	X	X	
Anxiety (Generalised Anxiety Disorder Questionnaire (GAD-7) ³⁹)	7	X	X	X	X	
Confidence to cope with pain (Pain Self-Efficacy Questionnaire ⁴⁰)	10	X	X	X	X	
Health-related quality of life (EQ-5D-5L) ⁴¹	5	X	X	X	X	X
Work (work status, occupation, time off work, presenteeism) ^{42,43}	5	X	X	X	X	
Healthcare resource use (NHS/private & out of pocket expenses) ^d	7		X	X	X	

^a Daily MED calculated from self-reported pain medicines use questionnaire, with any missing information regarding drug name/ strength obtained from the electronic health record (EHR).

^b Obtained from self-reported pain medicines use questionnaire, with any missing data on prescribed non-opioid pain medicines obtained from EHR.

^c Checklist of opioid-related side-effects (presence & severity) developed from existing measures⁴⁴⁻⁴⁶

^d Healthcare resource use questionnaire developed for this research and refined following a feasibility study²²

(MDC) after 6 weeks. A brief MDC questionnaire is sent by post to those who cannot be contacted after 3 telephone attempts (Amendment 4, Table 1). MDC collects primary and key secondary outcome data (opioid and non-opioid pain medicines use, Brief Pain Inventory (BPI) and EQ-5D-5L) along with date of birth and sex to ensure the data are provided by the intended participant. Participants opting to complete the questionnaire

online are advised, in the participant information leaflet, that they can stop completing the questionnaire at any time point, without giving a reason, but that answers entered up to that point are retained unless they contact the study team to opt out of this (Amendment 4, Table 1). Where there are ambiguous or incomplete questionnaire entries that interfere with calculation of daily opioid use, a member of Keele CTU staff attempts

to contact participants by telephone or in writing to obtain the missing data. Incomplete or ambiguous questionnaire entries regarding prescribed pain medicines can also be checked with the electronic health record, to obtain the missing data e.g. regarding drug strength, if necessary.

Medical Record Review (MRR). With participant consent, data is extracted from electronic practice health records to capture data on their prescriptions from baseline (defined as the period 90 days up to the date of their recruitment) up to the date of their 12-month follow-up to facilitate checking of ambiguous or incomplete questionnaire entries regarding pain medicines use if needed. MRR also captures information about PROMPT-related consultations.

Practice-level anonymised and aggregated data of pain-related prescribing

Each participating practice provides anonymised electronic prescribing data for registered adult patients, aged ≥ 18 years, who are not receiving palliative care for cancer (defined as patients without both a code for cancer and for palliative care). We will compare prescribing of opioids and non-opioid medicines commonly prescribed for patients with persistent pain (specifically paracetamol, topical pain treatments, non-steroidal anti-inflammatory drugs (NSAIDs), nefopam, gabapentinoids (gabapentin, pregabalin), antidepressants, benzodiazepines and Z-drug hypnotics (zopiclone, zolpidem) at baseline (defined as the period 90 days up to the date the first participant was recruited at that practice) and 12-month follow-up (defined as the period 90 days up to the date 12 months after the first participant was recruited at that practice).

Outcomes

Co-primary outcome measures

When evaluating interventions aimed at reducing opioid use it is recommended to also measure the impact on pain⁴⁷, therefore we chose two co-primary outcomes, measured at 12-month follow-up:

1. Reduction in opioid use (participant achieves at least a 25% reduction in daily morphine equivalent dose (MED) from their baseline (binary outcome, yes or no))

AND

2. Non-inferiority of the Brief Pain Inventory (BPI)³⁷ total score

Members of the research team calculate a daily MED from self-reported pain medicines use data in participant questionnaires using a calculator created in Microsoft Excel (2016) by lead author JA. The calculator uses published opioid conversion factors^{48–50} (see Table 4) and was refined following testing with members of the research team (SAH, TH, SW, RK) in a feasibility study²². As there is currently no accepted definition of a clinically meaningful reduction in opioid use^{47,51}, it was agreed with the study funder that, based on clinical experience, a 25% reduction in opioid use from their baseline reflects

Table 4. Morphine Equivalent Conversion Factors.

	Conversion factor*	Equivalent dose to 10mg morphine
Oral preparations (mg/day)		
Codeine	0.1	100mg
Dihydrocodeine	0.1	100mg
Dextropropoxyphene	0.23 [†]	43.5mg
Tramadol	0.1	100mg
Tapentadol	0.4	25mg
Oxycodone	1.5	6.6mg
Pethidine (Merperidine)	0.1 [†]	100mg
Hydromorphone	5.0	2mg
Methadone	3.0 [†]	
Sublingual preparations (mg/day)		
Buprenorphine	40 [‡]	0.25mg
Transdermal patches (micrograms / hour)		Morphine equivalent (mg/day)
Buprenorphine (5)	2.4	12
Buprenorphine (10)	2.4	24
Buprenorphine (20)	2.4	48
Fentanyl (12)	2.5	30
Fentanyl (25)	2.4	60
Fentanyl (50)	2.4	120
Fentanyl (75)	2.4	180
Fentanyl (100)	2.4	240

*Conversion factors are approximations of equianalgesic doses and there is some variation across different sources. The conversions factors used in this study are those accepted by the UK Faculty of Pain Medicine, Royal College of Anaesthetists (Opioid Aware⁴⁹), except for dextropropoxyphene, pethidine, methadone and sublingual buprenorphine, which are not included in the Opioid Aware list. The source of conversion factors for these drugs are below

[†]CONSORT morphine equivalent conversion factors⁴⁸ (dextropropoxyphene, pethidine, methadone)

[‡]Faculty of Pain Medicine, Australian and New Zealand College of Anaesthetists (ANZCA)⁵⁰ (sublingual buprenorphine)

a clinically reasonable minimum threshold across a range of opioids and doses.

Defining the non-inferiority margin for the BPI total score

The BPI is a composite measure of pain intensity and pain-related functional interference, recommended for use in chronic pain trials and validated in primary care populations with persistent pain^{52,53}. The total score reflects the multidimensional impact of pain and has comparable responsiveness to the BPI pain intensity and interference subscales in this population^{54,55}.

In defining the non-inferiority margin for the BPI total score we considered the following: (1) Feedback from patients that pain and pain-related interference does not noticeably increase as a result of reducing opioids and, (2) the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT)^{52,53} international consensus recommendations on interpreting the clinical importance of treatment outcomes in chronic pain trials. IMMPACT identified a 1-point change on the BPI pain intensity (0-10) scale as the smallest noticeable change in pain and a 1-point change on the BPI pain interference (0-10) scale as a clinically meaningful change⁵³. Therefore, our non-inferiority margin for the BPI total score needed to be less than 1.0. We chose 0.6 as a difference that is considered clinically non-inferior and aligns with the standard error of measurement of the BPI total score⁵⁴.

Our non-inferiority margin translates to an effect size of 0.3 (0.6/2) if a standard deviation for the BPI of 2⁵³ is assumed. We chose not to lower the non-inferiority margin further, for example to give a small effect size of 0.2 (based on effect size criteria from Cohen⁵⁶), as recent IMMPACT guidance on evaluating opioid reduction in clinical trials suggests that a somewhat larger non-inferiority margin can be considered for pain in 'opioid sparing' trials because of the potentially large benefits of reducing opioid use (e.g. reducing opioid-related adverse effects)⁴⁷.

Secondary outcome measures

To facilitate comparison and pooling of our results, our secondary outcomes are informed by IMMPACT recommendations for trials of interventions for persistent pain and opioid sparing^{47,52,53}. These include:

- Pain severity, assessed using the BPI³⁷ pain severity subscale.
- Pain-related interference, assessed using the BPI³⁷ interference subscale.
- Daily opioid use (mean daily MED calculated as described above).
- Non-opioid pain-related medicines use (yes or no) of paracetamol, topical pain treatments, NSAIDs, nefopam, gabapentinoids, antidepressants, benzodiazepines and z-drug hypnotics (zopiclone and zolpidem), assessed from the self-reported pain medicines questionnaire.
- Opioid-related side-effects (presence and severity) assessed from a self-reported side-effects checklist, developed for this research programme from existing measures⁴⁴⁻⁴⁶.
- Depressive symptoms assessed using the Patient Health Questionnaire Depression Scale (PHQ-8)³⁸, a validated 8-item questionnaire to assess depressive symptomatology over the past 2 weeks.
- Anxiety symptoms assessed using the Generalised Anxiety Assessment (GAD-7)³⁹, a validated 7-item questionnaire.

- Confidence to cope with pain (pain self-efficacy), assessed using the validated 10-item Pain Self-Efficacy Questionnaire (PSEQ)⁴⁰.
- Health-related quality of life assessed using the EQ-5D-5L⁴¹.

All outcome measures and data collection timepoints are presented in [Table 3](#).

Health economics outcome data

Questions on additional persistent pain-related NHS and private practice health care appointments are included in the 3, 6 and 12-month follow-up questionnaires. The health care resource use questionnaire was developed for this research programme, tested in the feasibility study²² and refined considering the findings. Resource use information is obtained on primary care visits, (e.g. general practitioners, practice nurses, and physiotherapy), visits to other health care professionals (e.g. osteopath, chiropractor, psychologist / counsellor), pain medicines (prescribed and non-prescribed) including opioids, non-opioid analgesics and drugs to manage opioid-related side-effects e.g. laxatives and antihistamines, tests and investigations, non-drug treatments (e.g. acupuncture, injections), secondary care consultations, inpatient stays, and surgery during the previous 6 months. Given the nature of persistent pain, broader costs related to both out of pocket costs (e.g. over the counter medicines such as laxatives) and productivity losses (e.g. time-off work related to pain and reduced work performance (presenteeism)) are also included. Information on time off work, occupation, typical work activities and the nature of their employment (full time or part time) is requested, and the Single-Item Presenteeism Question from the Work Productivity and Activity Impairment Questionnaire^{42,43} is used to estimate productivity losses relating to presenteeism. The average wage for each respondent will be identified using UK Standard Occupational Classification coding and annual earnings data for each job type. The outcome of interest for the economic analysis is the quality-adjusted life years (QALYs) and these will be calculated using EQ-5D-5L⁴¹ responses obtained at baseline, 3, 6, and 12-months follow-up.

Adverse events

The clinical management recommendations given to participating practice pharmacists and GPs in intervention arm practices represent evidence-based best practice and have strong clinical community endorsement and credibility. Therefore, the potential harms of this study are minimal.

A Serious Adverse Event (SAE) is defined by the Health Research Authority (HRA) as an untoward occurrence that: results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, consists of a congenital anomaly or birth defect; or is otherwise considered medically significant by the investigator. All SAEs, either confirmed or suspected, are communicated to Keele CTU within 24 hours. The Chief Investigator (CI) or Associated Investigator (AI) is responsible for conducting a causality assessment. Suspected or confirmed

SAEs are reviewed by the Data Monitoring Committee and reported to the Trial Steering Committee. SAE's that are assessed as related to the trial and unexpected are reported to the Research Ethics Committee.

Sample size

Our first co-primary outcome is opioid (daily MED) reduction, by at least a 25% (yes/no), between baseline and 12 months. We judged from our clinical experience that a 20% difference between the intervention and control arms in the proportion of patients reporting $\geq 25\%$ reduction in opioid use represents a meaningful difference. Therefore, assuming 40% of the control arm and 60% of the intervention arm reduce opioid use according to that definition over 12 months, we estimated that a total sample size of 260 would be needed for a non-cluster RCT (power 90%, two-tailed statistical significance 5%). Our assumption that 40% in the control arm would reduce opioids was based on our previous (unpublished) analysis of opioid prescribing data from the Clinical Practice Research Datalink (CPRD) indicating that approximately 20% of patients who have been prescribed opioids for 6 months or longer stop taking opioids completely without any intervention and our assumption, based on clinical experience, that a further 20% of the control arm, whilst not stopping completely, would reduce their opioid use according to our definition.

For the second co-primary outcome (total BPI), as explained above, we assumed a 0.6-point non-inferiority margin and a standard deviation of 2. We estimated the standard deviation from published literature^{54,57} and from our feasibility study²². With power 90%, one-tailed statistical significance 2.5%, a sample size of 468 would be needed for a non-cluster RCT.

Given the co-primary study hypotheses, we considered that power for our study may not be persevered at 90%. However, given that sample size differs considerably between the two hypotheses the impact on study power is lessened. Conservatively assuming that the two co-primary outcomes are not correlated, using the intersection-union test^{58,59}, the overall power for the study is 0.89. As 0.89 is close to 0.9, the sample size was not adjusted to account for the loss of power from testing a co-primary hypothesis.

Given the cluster design, our sample size was inflated to account for clustering. Assuming (i) an intra-cluster correlation coefficient 0.01 (estimated from our POST trial and other similar trials in primary care⁶⁰⁻⁶²), (ii) a coefficient of variation 0.40 (estimated to be slightly lower than other estimates in primary care trials⁶³ to reflect that our study design caps the number of patients invited per practice), and (iii) an average of 30 patients recruited per practice (estimated from our feasibility study²²), this translated to a design effect of 1.34⁶⁴. Given a 20% loss to follow-up at 3 months in our feasibility study, we conservatively assumed a 30% loss to questionnaire follow-up at the later 12-month follow-up and therefore the sample size for the individually randomised RCT was inflated by 1.91 and we planned to recruit 896 patients (448 per arm).

Based on our feasibility study²², we estimated that, on average, 2.5% of patients on a practice list would be eligible for our study, and that from a practice with 8000 patients, 200 would be invited to participate in the study and 15% ($n=30$) would consent and return a baseline questionnaire. Therefore, we initially planned to recruit 30 general practices, with a plan to review our recruitment assumptions following the internal pilot study. The 3-month follow-up rate in the internal pilot was slightly lower than the 70% we had assumed at 12 months. To mitigate this, we increased the number of GP practices included in the study (from 30 to 38) to maintain the desired level of power for the study at 90%.

Data analysis & statistical plan

A priori data analysis plans will be agreed with the independent TSC and DMC prior to database lock and will form the definitive analysis plan for the trial. An outline of the planned statistical analysis is given below:

Baseline data and flow of patients

A CONSORT flow diagram will be produced to document the flow of clusters and participants through the trial and will include reasons for withdrawal if given. Descriptive statistics will be used to describe key patient and practice-level baseline variables overall, by treatment arm (to explore balance of characteristics across randomised treatment arms) and by whether participants returned a 12-month follow-up questionnaire (to explore the impact of loss to follow-up).

Co-primary outcome analysis

Primary analysis will use multilevel linear (BPI) and logistic (opioid reduction) regression to account for the clustering in the data and will compare the effectiveness of providing the PROMPT intervention with usual primary care arrangements for review of patients prescribed opioids for persistent pain at 12 months, adjusting for baseline BPI score (for the BPI outcome) and baseline daily MED (for the opioid reduction outcome). The superiority and non-inferiority hypotheses will be assessed simultaneously; superiority will be concluded if the 95% two-sided confidence interval for the opioid reduction treatment effect does not contain one and non-inferiority concluded if the upper limit of the 95% two-sided confidence interval for the mean difference in BPI score is <0.6 .

The primary analysis will be conducted using data from all clusters and patients randomised into the trial. A secondary analysis will be conducted to compare the effectiveness of accessing the PROMPT intervention compared to usual primary care in participants who attended a PROMPT review.

Secondary outcome analysis

Secondary (longitudinal) multilevel analyses, based on self-report questionnaire data, will explore whether change in the BPI total score (the co-primary outcome measure) and the secondary outcomes (BPI pain, BPI pain interference, daily MED, non-opioid pain medicine use, depression, anxiety, pain self-efficacy and treatment side effects) differ by treatment arm over

time (i.e. using data from all time-points). The models will include a term to account for clustering by general practice and a time by treatment interaction. The beta coefficient and 95% confidence interval for the interaction term will be reported and graphical methods used to display the nature of any interactions found in the data. The continuous outcome, percentage change in daily MED (baseline to 12-month follow-up), will also be analysed using multilevel linear models, but as the data will be a single observation per participant, this model will not include a term for “time” in the multilevel model.

Descriptive statistics and 95% confidence intervals will be used to describe the aggregate data from the pseudonymised electronic health records at baseline and 12-months, to include a comparison of opioid and non-opioid analgesic use by treatment arm and to explore within-practice changes in between baseline (defined as the period 90 days up to the date the first participant was recruited at that practice) and 12-month follow-up (defined as the period 90 days up to the date 12 months after the first participant was recruited at that practice).

Subgroup analyses

Subgroup analyses will explore whether the conclusions of the primary analysis for opioid reduction depends on baseline levels of pain self-efficacy and baseline daily MED. This will be explored by including an interaction term in the primary model between treatment and the subgroup covariate of interest, and by running separate models for each covariate.

Adjusted analysis

The primary analysis will be adjusted for key a priori covariates specified in the analysis plan but are likely to include (1) stratification factors included in the randomisation process and (2) key patient-level variables likely to impact on outcome e.g. deprivation, age and sex.

Missing data

Missing data will be handled by using multi-level models as the analysis method or by multiple imputation of missing data as appropriate.

Health economics

An incremental cost-utility analysis will be undertaken from a base-case NHS/Personal Social Services (PSS) perspective to estimate the cost per quality adjusted life year (QALY) over 12 months follow-up, using patient level data on costs and trial outcomes. Alternative perspectives will include a health care and societal perspectives, taking into account private expenditures and out of pocket cost and productivity losses due to time off work.

The outcome of interest for the economic analysis is quality-adjusted life years (QALYs) and these will be calculated using EQ-5D-5L responses obtained in at baseline, 3, 6, and 12-months follow-up.

In line with updated NICE recommendations, individual EQ-5D-5L responses will be converted into index scores using

a mapping algorithm developed by the Decision Support Unit. The ‘EEPRU dataset’ will be employed to convert EQ-5D-5L questionnaire responses onto the EQ-5D-3L utility scores⁶⁵.

Cost data is likely to have a skewed distribution and therefore a non-parametric comparison of means (e.g., bootstrapping) will be undertaken to estimate 95% confidence intervals around costs. Multilevel modelling statistical techniques, taking into consideration clustering and correlation in the cost and effect data will be considered in line with standard literature. QALYs will be calculated from EQ-5D-5L responses, using the “area under the curve” approach. Unit costs will be applied to all health care resource use items, and mean resource use (for each health care use category) and mean total costs will be calculated for all trial participants. Analysis of productivity losses will use the human capital approach. Multiple imputation will be used to impute all missing values for the EQ-5D-5L and total cost estimates for non-responders to ensure all participants are included in the analysis.

A cost-consequence analysis will initially be reported, describing all the important results relating to costs and consequences (across the full range of clinical and cost outcomes). Subsequently, incremental cost-utility analysis will be undertaken to estimate the incremental cost per QALY gained, adjusting for baseline covariates in line with the primary clinical evaluation. The analysis will be conducted on an intention to treat basis, and in accordance with current cRCT guidelines⁶⁶. This analysis will involve adopting multilevel modelling statistical techniques taking into consideration clustering in the cost and effect data⁶⁷. Separate generalised equation models, controlling for clustering will be used to estimate the mean incremental costs and QALYs for the intervention relative to the control.

The robustness of the results will be explored using sensitivity analysis. This will explore uncertainties in the methods employed to analyse the data (for example, a complete-case analysis as an alternative to using a multiple-imputed data set, and in estimation of costs), and any assumptions made in the analysis. Cost-effectiveness acceptability curves will be generated to reflect the probability the intervention will be cost effective at different cost per QALY willingness to pay thresholds. If the intervention is shown to be clinically and cost-effective within the trial, a simple budget impact analysis will be undertaken to calculate the potential overall cost for a typical primary care practice, in terms of delivering the intervention and potential cost savings from reduced opioid prescribing.

Decision modelling, using a Markov model will also be undertaken to estimate the potential longer-term cost-effectiveness of the intervention. The model-based analysis will be performed from an NHS perspective with appropriate discounting of costs and outcomes at 3.5%. The model will assess the impact of the intervention on quality of life, continued opioid use, escalation of opioid medication, and the potential for opioid-related serious adverse events. The model will be populated using the trial data, literature review of previously published relevant

models, routine datasets and where appropriate consultation with clinical experts and Patient and Public Involvement (PPI). The model will be subject to deterministic sensitivity analysis by changing individual parameter values, broadening the perspective and changing model assumptions. Model parameters will be inputted as distributions and probabilistic sensitivity analysis will be undertaken to simultaneously incorporate all parameter uncertainty. Cost-effectiveness planes and cost-effectiveness acceptability curves will be presented to show the probability the intervention is cost-effective at different cost/QALY thresholds. Full details of the decision model methods, time horizon, structure and parameters will be detailed in the final health economics publication.

Linked mixed methods process evaluation (MOPP-2 study)

To provide greater confidence in conclusions about effectiveness of the PROMPPT intervention and the generalisability of the results, a process evaluation using a mixed methods approach⁶⁸ is being conducted. In line with MRC guidance on the evaluation of complex interventions⁶⁹, the objectives, aligned to the key domains of implementation, mechanisms of impact and contextual factors, are:

1. To assess how PROMPPT is implemented in and adopted by clusters and assess the processes by which practice pharmacists and GPs integrate and adopt PROMPPT related work into existing systems and everyday work.
2. To investigate intervention fidelity by observing what is delivered in each intervention cluster and what practice pharmacists do because of PROMPPT. This will highlight how closely the delivery of PROMPPT matches what was intended.
3. To investigate how patients with persistent pain respond to and engage with PROMPPT and what mechanisms of impact lead to change.

Additionally, given the rapidly changing landscape in primary care, in particular relating to the role of practice pharmacists in medicines optimisation, we recognised the importance of examining current usual care regarding review of patients prescribed opioids for persistent pain and the evolving role of practice pharmacists with clinicians from clusters in both trial arms, and topic guides evolved accordingly.

Identification and recruitment of participants

Patient participants. Participants from intervention arm clusters who provide written consent to being contacted about a future related research study and subsequently attend a PROMPPT review are invited to participate in the MOPP-2 study. Participants are invited to complete an acceptability questionnaire (described below) and/or take part in an interview (up to n=20) and may choose to consent to any, all or none of these options. Additionally, all participants who do not take up the PROMPPT review are invited to participate in an interview

to explore their reasons for declining. Written consent is obtained from all participants in the process evaluation.

Clinicians (GPs and practice pharmacists). All practice pharmacists from intervention arm practices are asked to consent to audio-recording of a sample of PROMPPT consultations and to an interview. A sample of GPs from intervention arm practices (up to n=15) and practice pharmacists and GPs from control arm practices (up to n=12) are also invited to take part in an interview.

PROMPPT clinical champions. All PROMPPT Clinical Champions are interviewed to explore their experiences of mentoring practice pharmacists during the delivery of PROMPPT.

Data collection

Audio-recorded consultations. A sample of approximately 10% of PROMPPT consultations are digitally audio-recorded to allow assessment of key aspects of intervention delivery⁷⁰: treatment differentiation (Did the practice pharmacists only deliver PROMPPT and not other treatments?), treatment competency (Did practice pharmacists maintain the skills learned in training?), and treatment delivery (Were PROMPPT components delivered as intended?).

The research team work with participating practices to identify and approach suitable participants who have scheduled a PROMPPT consultation. Informed, written consent to audio-record the consultation is obtained from patient participants by a researcher prior to the consultation and confirmed with practice pharmacists prior to the start of the consultation. This process was used successfully in the feasibility study²². Audio-recording files are securely sent to Keele CTU for analysis.

Case-report forms. Practice pharmacists in the intervention clusters are required to complete an electronic case report form (eCRF) following each PROMPPT consultation. The eCRF collects information on what happened during the PROMPPT consultation (e.g. discussing the patient's pain story and the impact of their pain, discussion of the patient perspective on making changes to opioid medicine, developing a personalised pain action plan) and will be used to assess intervention fidelity (i.e. Was PROMPPT delivered as intended?) and dose (How much was delivered?).

Semi-structured interviews. Consenting participants in the intervention arm are interviewed after attending at least one PROMPPT consultation. The interviews are based on semi-structured topic guides developed with our PPI group and include questions informed by our programme theories regarding behaviour change (Theoretical Domains Framework (TDF))⁷¹, implementation (Normalisation Process Theory (NTP))^{72,73} and acceptability (Theoretical Framework of Acceptability (TFA))⁷⁴. Consenting participants who decline a PROMPPT review, and accept an invitation to speak to a researcher, are interviewed using a semi-structured topic guide that will explore reasons for declining. A similar process is followed for the

clinicians, whereby they are interviewed once they have experience of PROMPPT intervention delivery. Topic guides are refined, as needed, during data collection to allow any emerging issues to be explored.

The sample sizes outlined above are expected to be sufficient to achieve information power⁷⁵, providing appropriate range and depth of insights, whilst being achievable within the scope of the project. Similar topics are covered with all interviewees to ensure comparisons between their responses, while at the same time enabling them to reflect on their specific expectations, understandings and experiences.

Informed consent is obtained prior to all interviews commencing. All interviews are conducted remotely via telephone by an experienced qualitative researcher, and audio-recorded with participants' consent. The interviews are securely sent to a professional transcription company to be transcribed verbatim. Transcripts are checked for accuracy and anonymised by members of the research team ahead of analysis.

Acceptability questionnaire. All participants who attended the initial PROMPPT review are sent a short survey (known as the Acceptability Questionnaire) about their experiences of the consultation. The Acceptability Questionnaire comprises 12 questions from two existing measures: a modified version of the treatment acceptability and credibility measure⁷⁶ and the Theoretical Framework of Acceptability (TFA) questionnaire⁷⁴.

The modified acceptability and credibility measure, which has been used in previous similar studies^{77,78}, includes 4 items (scored on a 0-10 scale) and will assess (1) how logical the PROMPPT review seems to participants, (2) how confident participants are that it will be successful in helping them, (3) how confident participants would be in recommending it to a friend, and (4) how satisfied they were with the intervention overall.

The TFA questionnaire⁷⁴ comprises 8 items (scored on a 0-5 scale). The first is a global acceptability question and the remainder represent key constructs of acceptability relating to healthcare interventions (affective attitude, burden, intervention coherence, ethicality, perceived effectiveness, opportunity costs, and self-efficacy).

Practice profile form. A practice profile form is completed by all participating GP practices at multiple time points across the trial, including at the beginning and towards the end. It collects information about current practice activity relating to persistent pain management, practice pharmacist workload and responsibilities within the practice, and practice size and organisational characteristics. These data will facilitate assessment of practice context and effects of any variation in context.

Data analysis

Audio-recorded consultations. Researchers from the process evaluation team will examine the audio-recordings from the PROMPPT consultations and use a previously developed tick

box score sheet to assess whether components of the consultation intended to be included, and focused on during training, were demonstrated by the practice pharmacists.

eCRFs. The intervention delivery template will be reviewed for each participant and the proportion of times that each component of the intervention was used will be reported. A judgement will also be made as to whether the patient received the intervention as intended, in line with the training, and whether the patient attended all scheduled follow-up appointments. The proportion of patients being treated in line with the training will then be calculated out of all participants who attended the first appointment with the practice pharmacist. For audio-recorded consultations, corresponding eCRFs will be triangulated with the audio-recordings to assess fidelity of the training and intervention.

Semi-structured interviews. The Framework approach⁷⁹ to analysis will be used starting deductively from pre-set aims and objectives, will enable a focused and efficient analysis within the timeframe of this study⁸⁰, and can be used within a multidisciplinary research team setting⁷⁹. Analysis will involve familiarisation, identification of an analytical framework (e.g. study aims, TDF⁷¹, TFA⁷⁴ and NPT^{72,73,81}), indexing, charting and mapping, and interpretation⁸². Analysis will include members of the research team from different professional backgrounds (e.g. GPs and pharmacists) to increase trustworthiness⁸³. Continuous team analysis of data will help to challenge interpretations, and coding will be refined and agreed through ongoing discussion⁸⁴. The data analysis will be facilitated using qualitative data-analysis software (NVivo: Qualitative Data Analysis Software Version 14⁸⁵).

Acceptability questionnaire. The mean and standard deviation, as well as the median and interquartile range, for the TFA questions and the acceptability/credibility questions will be calculated from items 1-8 and items 9-12 of the Acceptability Questionnaire respectively. A mean score of $\geq 5/10$ for each of items 9-12 will be considered the threshold for acceptability/credibility, as in previous trials using this measure^{77,78}.

Practice profile form. A narrative review of practice profile form responses from participating practices will be undertaken. Responses from multiple time points across the trial will be examined and descriptive summaries produced to facilitate assessment of practice context and effects of variation in context.

Integrated analysis. When analysis of the quantitative and qualitative data is complete, a triangulation protocol^{68,86} will be used. This technique enables integration of data in order to investigate completeness, convergence, and dissonance of key themes across datasets⁸⁷. Methods include following a thread and development of a convergence coding matrix. The matrix allows findings from different study components to be displayed side by side. Integration will aid interpretation of findings on implementation, acceptability, fidelity, mechanisms of impact and context.

Trial management, oversight and monitoring

The PROMPPT Trial Management Group (TMG), comprising members of the research team and Keele CTU, has overall responsibility for the set-up, promotion, ongoing management and monitoring of the trial, and for the analysis and interpretation of results. The TMG meets regularly to monitor protocol compliance of recruitment, intervention delivery and follow-up procedures; data collection and database development; completion of regulatory and funder reporting requirements and appropriate reporting of adverse events. All data collection, database design, data input and cleaning, as well as trial oversight procedures, are managed in accordance with Keele University's Health and Social Care Research (HSCR) Quality Management System (QMS) and Keele CTU's QMS. An independent Trial Steering Committee (TSC) was established to provide independent oversight of the trial. The TSC is chaired by a Professor of Primary Care and includes a statistician, a pharmacist, and a patient representative. The TSC was consulted during protocol development and met to approve the final protocol prior to submission for ethical approval, and at agreed intervals over the course of the trial. An independent Data Monitoring Committee (DMC), comprising a statistician and academics with clinical expertise in pharmacy and general practice, was also convened and is responsible for scrutinising trial data, with oversight responsibility for the safety of participants. Detailed reports, focusing on recruitment, retention, protocol compliance, protocol amendments and adverse events are prepared for the TSC and DMC by Keele CTU and members of the research team.

All data collection, database design, data input and cleaning, as well as trial oversight procedures, are in line with Keele University's HSCR QMS and Keele CTU QMS and the conditions of the funding body. Data will be centrally monitored for quality and completeness by Keele CTU.

Data confidentiality and archiving

All data collected during the trial are kept strictly confidential and are handled and stored in line with Keele University and Keele CTU Data Security procedures, Keele University's HSCR QMS and Keele CTU QMS, which are in accordance with the Data Protection Act (2018) and UK General Data Protection Regulation (GDPR). If a participant withdraws consent for further data collection, their data up to that point remains on file and will be included in the final analysis.

At the end of the study, data will be securely archived in line with Keele University HSCR and Keele CTU Standard Operating Procedures (SOPs) for 10 years after submission of the End of Study Declaration. Data held by Keele CTU will be archived in the designated Keele CTU archive facility and site data and documents will be archived at the participating sites. Following a retention review, if the archived material is agreed to be destroyed, arrangements for confidential destruction will then be made.

Any requests for access to the data from anyone outside of the research team (e.g. collaboration, joint publication, and

data sharing requests from publishers) will follow the Keele CTU SOP on data sharing.

Progress of the trial

Recruitment of general practices commenced on 20 May 2022 and participant recruitment started on 21 June 2022.

Internal pilot study

An internal pilot study analysed recruitment, intervention uptake and fidelity of intervention delivery against pre-specified progression criteria between 20 May 2022 and 22 December 2022 from participants in the first batch of GP practices recruited and assessed retention at 3-month follow-up. Recruitment exceeded the pre-specified targets with 14 practices (target 12) and 388 participants (target 350, 50 per month on average) recruited. Fidelity of intervention (PROMPPT review) delivery was good with 89% of pain reviews delivered in line with the training (target 80%) based on the intervention delivery template. Intervention uptake was slightly lower at 62% than the pre-specified target of 70%. However, the first practice to invite participants sent all the invitations at once and had particularly low uptake (32%) which lowered the overall rate. Subsequently, practices were advised to send the review invitations in batches, according to pharmacist availability, which made it easier for practices to monitor uptake and send reminders. Rates of retention at 3-month follow-up were lower than expected, with 106 out of 174 (61%) of participants with sufficient time (8 weeks) to respond returning the 3-month follow-up questionnaire, whilst the sample size estimate assumed 70% retention at 12-month follow-up. These findings were reported to the DMC and TSC (March 2023). Both were satisfied that the trial should continue, and a range of measures were agreed and implemented to improve retention at follow-up and maximise primary outcome data collection at 12 months (See Amendment 4. [Table 1](#)). To mitigate any impact of lower follow-up rates on study power we also increased the number of general practices in the trial from 30 to 38 (Amendment 7. [Table 1](#)).

Dissemination

Dissemination of the results of the PROMPPT trial will be supported by Keele University's Impact Acceleration Unit. The findings will be made widely and freely available to all stakeholders in ways that are easy to access at no cost. Our PPI Group will advise on how to translate these into easily understandable messages and on how best to disseminate the results to the wider public. In addition to publications in open-access peer-reviewed journals and conference presentations, we will use our website, NHS networks, links to professional bodies and social media to support dissemination of the findings to all stakeholders.

Abbreviations

BPI	Brief Pain Inventory
CI	Chief Investigator
CRN	Clinical Research Network

CTU	Clinical Trials Unit
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
EHR	Electronic Health Record
GDPR	General Data Protection Regulation
GP	General Practitioner
HSCR	Health and Social Care Research
IMD	Indices of Multiple Deprivation
IMMPACT	Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials
MDC	Minimum Data Collection
MED	Morphine Equivalent Dose
MOPP	Management of Opioids and Persistent Pain
MRR	Medical Record Review
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NSAID	Non-steroidal anti-inflammatory drug
PPI	Patient and Public Involvement
PROMPPT	Proactive clinical Review of patients taking Opioid Medicines long-term for persistent Pain led by clinical Pharmacists in primary care Teams
QMS	Quality Management System
RCT	Randomised Controlled Trial
REC	Research Ethics Committee

SMR	Structured Medication Review
TSC	Trial Steering Committee
SOP	Standard Operating Procedure
TMG	Trial Management Group
TFA	Theoretical Framework of Acceptability
UK	United Kingdom

Data availability

No data are associated with this study protocol.

Keele Data Repository: The SPIRIT checklist for ‘Evaluating a primary care pharmacist-led intervention to reduce opioid use for persistent non-cancer pain: the PROMPPT cluster randomised controlled trial protocol’ available at <https://doi.org/10.21252/7m5x-0j51>⁸⁸.

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Benjamin Lai

Mayo Clinic Cancer Center, Rochester, Minnesota, USA

This work is much needed, as it addresses an important and increasingly prevalent issue of patients prescribed opioids long-term for chronic, non-cancer pain. As the authors nicely stated, the evidence for chronic opioid therapy is poor while the evidence of potential harm is well established.

The protocol will integrate the pharmacist into primary care that takes the pressure off the primary care physician while simultaneously makes the most optimal use of the pharmacist's scope of practice. Patients are likely to benefit with having more time and counseling with the pharmacist.

The described study design is sound, although I am somewhat disappointed to see the relatively lower-than-expected uptake and follow-up response rates in the initial pilot phase of the study.

Several important considerations:

1) The authors name a number of secondary outcome measures - all of which are important. However, one important consideration is to have some sort of screening tool for opioid use disorder (OUD). Prior studies demonstrate that at least a proportion of patients prescribed chronic opioids misuse their prescriptions, or even meet the diagnostic criteria for OUD. Treatment for OUD is not tapering, but rather a comprehensive approach - including transitioning a patient from traditional chronic opioids to a medication indicated to treat OUD, e.g. methadone, buprenorphine or naltrexone. Please consider adding some form of OUD screening tool in your protocol. An example might be: the EMPOWER OUD Screening tool, [Reference 1].

2) As there is a higher prevalence of chronic pain in patients with alcohol use disorder (e.g.[Reference 2]), it may be a good idea to consider gathering information about alcohol consumption before, during and after your intervention. Doing so will be helpful to determine if patients have instead turned to alcohol (increasing consumption) to treat any chronic pain, or anxiety associated with tapering.

3) There is increasing evidence associating opioid tapering with destabilization of mental health

conditions and suicidal ideation. It would, therefore, be important to acknowledge these associations. This is likely another reason why at least some primary care providers are hesitant to taper. Example: [Reference 3] and [Reference 4]. There is also evidence to suggest decreased adherence to hypertension & diabetes treatment, [Reference 5]. It would be important to acknowledge this prior work in your background. Moreover, please consider what your team would do should patients report increased symptoms of depression/anxiety or if they express suicidal thoughts/ideation in your protocol (e.g. when they complete the follow-up PHQ & GAD questionnaires).

Additionally, please see further comments by section below:

Abstract:

Background

*it may be a good idea to clarify that this intervention is targeted toward patients with chronic non-cancer pain (or, if chronic cancer-related pain is also included, to clarify this as well in the abstract)

Methods Patient and Public Involvement (PPI)

*the subtitle is missing a space between "Methods" and "Patient"

*Design and setting: since one of the main outcomes measure is patient self-reported opioid use, this could be subjected to Response Bias (e.g. social desirability bias". Have the study group thought about using pharmacy data, e.g. prescription fill data frequency, in addition to patient self-report? This will provide a more objective measurement.

Background and rationale

*The first sentence of the second paragraph is very long and run-on. This impacts its readability. Please consider splitting the sentence into 2 shorter ones, *"Systematic reviews have found limited evidence, often of low methodological quality, supporting interventions to reduce long-term opioid use and recommended further, larger randomised controlled trials (RCTs) of theoretically grounded behaviour change interventions to support opioid deprescribing in the context of persistent pain, which measure long-term follow-up and include a health economic evaluation^{11-13."}*

Objectives

*Secondary objectives, #3: it is unclear to me exactly what the authors mean by "other potentially sedating medicines commonly prescribed for patients with persistent pain...". Does this include neuropathic medications (e.g. gabapentinoids and TCAs), muscle relaxants (including benzodiazepines for spasms), SNRI/SSRI, etc? Please specify.

*Figure 1 (at least on my end) seems blurred, even when expanded. Please consider getting a clearer image in the final version of this manuscript.

*it is well established that a proportion of patients prescribed chronic opioids likely meet the diagnostic criteria for opioid use disorder, or may have problematic opioid use pattern. In this study, it does not appear the pharmacists have asked or conducted screenings for problematic opioid use patterns or possible opioid use disorder. This might be a beneficial extension to this study. If patients have OUD, then opioid tapering could potentially lead to de-stabilization, increased cravings, and lead the patient to seek opioids outside of medical settings – all of which could lead to significant negative consequences. In this study, what happens if OUD is suspected? Were efforts made to connect the patient with the GP and specialists/behavioral health/social work, etc?

*Exclusion criteria: it is not clear what 'severe mental illness' means exactly. What if a patient scores a very high score in PHQ & GAD questionnaires at baseline? Or, if there is a significant worsening in these symptoms during the study. Will these patients be excluded from the study and be referred back to primary care?

Intervention

*the authors describe the initial 30-minute and subsequent (likely 15-minute) follow up with the pharmacist. Various data will be collected. However, based on the description, it is still not clear exactly what the pharmacist will do or say to the patient to prompt the patient to want to taper. For example, will the pharmacist be reviewing potential side effects (short and long-term) with patients about chronic opioid use? Or, will the pharmacist review with the patient on current best practices and lack of good evidence for continued opioid use? Will the pharmacist be helping the patient in coming up with individualized tapers? How will the GP be engaged following these consultations? Presumably, if patients require fewer opioids, the opioid prescriptions will need to be changed/adjusted by the GP, so how will this be communicated? What happens if the patients experience worsening pain after the initial taper? How will GPs be notified? Are patients instructed to contact the pharmacist or the GP first with worsening pain or with any acute injuries/unexpected surgeries that require additional opioids? Please consider adding these details.

Data collection

*Authors mentioned collecting MMED information, but was there an attempt to determine if patients take opioids daily (versus intermittently) and the exact type of opioids prescribed long-term? Patients taking opioids daily may be more difficult to taper (e.g. tapering rate may need to be slower compared to those who only take opioids 1-2 times per week).

*In the secondary outcomes measures, is there a reason why other non-benzodiazepine muscle relaxants (e.g. cyclobenzaprine or baclofen) and SNRI (e.g. duloxetine) are not included in this measure? At least in the US, these medications are frequent adjuncts.

*Will there attempts to formally evaluate the use of non-pharmacologic modalities and reporting this as a secondary outcome measure? For example, physical therapy, interventional measures (e.g. injections), massage/acupuncture, app-based CBT? It is possible that during the opioid tapering, patients are more likely to opt for non-pharmacologic modalities. The authors mentioned factoring in these modalities in the economic analysis, but it may be important (and interesting) to determine if a reduction in opioids lead to a concurrent rise in non-pharmacologic modalities.

Internal Pilot study:

*It is interesting to note that the first site only had a 32% uptake. Will the authors plan to assess practice characteristics/patient population to determine if there are co-morbidity, and/or potentially socio-demographic differences between practices with higher percentage of uptake versus those with lower uptake?

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Is the rationale for, and objectives of, the study clearly described?

Yes

Is the study design appropriate for the research question?

Yes

Are sufficient details of the methods provided to allow replication by others?

Partly

Are the datasets clearly presented in a useable and accessible format?

Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Chronic pain and chronic opioid manage in primary care. Opioid use disorder & medications for opioid use disorder, especially in primary care.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 20 August 2025

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Stephen E. Nadeau

University of Florida College of Medicine, Gainesville, Florida, USA

The investigators propose to carry out a cluster randomized controlled trial to test the value of a pharmacy-based intervention in reducing opioid use among patients with chronic pain. The study will include an economic analysis.

This is a well-designed, well-organized, well-written proposal that reflects vast effort on the part of the investigators. The proposed methodology, albeit complex, appears to be sound. There is a

high likelihood of successful trial completion.

Unfortunately, the proposal is founded on a number of assumptions that are not supported by scientific evidence and the goal is to reduce opioid use, as if that were well-established as a desirable outcome, as opposed to improvement in quality of care and relief of suffering. A number of specific details can be cited:

1. The proposal is transparently premised upon the Center for Disease Control and Prevention (CDC) guideline documents of 2016 and 2022. The authors of these two documents studiously avoided the now vast scientific literature, which strongly contradicts all of the conclusions in these documents (1). The CDC even disregarded its own data, which also contradicted the central premise of the guidelines, namely that the opioid crisis was caused by and continues to be sustained by excessive opioid prescribing by conscientious clinicians. It is now well-established that the two Guidelines are strictly political documents and the pathway to their authorship is also well established. Most particularly, there is no scientific evidence that reduction in opioid dosage is a desirable outcome. In fact, although the CDC guidelines resulted in a dramatic reduction in opioid prescriptions, the consequence has been that, in America, there are now 25 million people who are suffering severely, many committing suicide, some crossing over to the illicit market, which inevitably means fentanyl, hence eventual death.
2. If the goal is to reduce opioid use in the general population and substantially resolve the opioid crisis, then the target should be illicit drug users (mostly addicts). These have accounted for up to 85% of opioid-associated deaths. In America, there has recently been a decline in fentanyl-associated deaths but the reasons are many, complex, and ill-defined and in no way can this salutary outcome be credited to any public health policies adopted by the United States. There is now a large scientific literature bearing on rehabilitation approaches (2), some remarkably successful.
3. "Opioids do not help people..." This statement is not based upon solid scientific evidence (see 3)). There have been over 100 RCTs of opioids, none of which have provided compelling evidence of efficacy. This is clearly a reflection of inadequate trial design (4).
4. The alleged harms of opioid treatment have reflected studies that fail to separate the effects of opioids per se from the effects of chronic pain, which is usually associated with depression and severe stress.
5. In the United States, pharmacies have emerged as one of the major enforcers of limits on opioid dosage. This history can be traced back to 2008 or earlier. I do not know if this is also the case in Great Britain. If it is, and this study is successful in meeting its objectives, then it will effectively grant new power to the foxes guarding the hen houses — a highly undesirable outcome indeed..
6. Health economics analysis. Will this analysis include the cost of various interventional pain methods (epidural injections, lateral branch blocks, spinal cord stimulators, back or neck surgery, etc)? In the US, all of these procedures are quite expensive, even as their beneficial effects, if they occur at all, are overwhelmingly short-lived at best. The extreme limitations placed upon opioid prescriptions in the US have been a bonanza for interventionists and spine surgeons.

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Is the rationale for, and objectives of, the study clearly described?

Yes

Is the study design appropriate for the research question?

Yes

Are sufficient details of the methods provided to allow replication by others?

Yes

Are the datasets clearly presented in a useable and accessible format?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: I trained in behavioral neurology but for years practiced as a general neurologist caring for a large population of patients with chronic pain. Thus, I have vast clinical experience. Over the past 5 years, I have published a number of scientifically skeptical critical analyses of the opioid literature (most in collaboration with Richard Lawhern), first focused on the validity of the CDC guideline documents; subsequently focused on a methodological approach to successfully conducting randomized controlled trials of opioids for chronic pain; a comprehensive guideline for management of pain of all types; the origins for the two opioid crises (one in the clinics, entirely wrought by the CDC) and one in the streets; the literature on rehabilitation of opioid addiction; the different goals desired by the various populations using opioids, and the implications of these goals; and risks associated with use of both benzodiazepines and opioids. These publications, together, reference approaching 1000 scientific studies.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Author Response 21 Aug 2025

Julie Ashworth

The authors thank the reviewer for their positive comments about the quality and design of

the trial but respectfully disagree with the criticism that the protocol is based on unsupported assumptions. They wish to clarify that their approach aligns with international guidelines recommending regular review of long-term opioid use for chronic non-cancer pain. The authors also wish to correct a misunderstanding about the intervention's setting, explaining that it is led by clinical pharmacists embedded in general practice—not community pharmacies. The intervention focuses on shared decision-making about opioid use, not mandatory reduction, and aims to support patients in making informed choices without increasing pain. The authors also wish to emphasise their team's extensive clinical experience in chronic pain management, in both primary care and specialist settings, and the trial's relevance to prescribed, not illicit, opioid use.

Competing Interests: No competing interests were disclosed.
