TITLE

Proactive clinical Review of patients taking Opioid Medicines long-term for persistent Pain led by clinical Pharmacists in primary care Teams (PROMPPT). A non-randomised Feasibility Study with mixed methods process evaluation.

SHORT STUDY TITLE

PROMPPT Feasibility Study

ACRONYM

PROMPPT-FS: **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 non-randomised **F**easibility **S**tudy with mixed methods process evaluation.

PATIENT-FACING NAME

Management of Opioids and Persistent Pain **(MOPP)** Study

PROTOCOL VERSION NUMBER AND DATE

Version 1.0 30 Apr 2020

This protocol has regard for the HRA guidance and order of content

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SIGNATURE PAGE

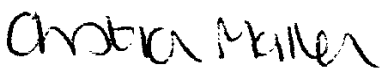
For Keele University sponsored studies, the sponsor will confirm approval of the protocol by signing the IRAS form and therefore a signature on the protocol is not required. The sponsor must be notified of all amendments to the protocol, both substantial and non-substantial. Review of amendments by the sponsor will act as the confirmation that the sponsor confirms approval of the amended protocol.

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol, GCP guidelines, the Sponsor's SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

Chief Investigator:

Signature: 

Date:

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Name (please print):

Professor Christian Mallen

Sponsor statement:

Where Keele University takes on the sponsor role for protocol development oversight, the signing of the IRAS form by the sponsor will serve as confirmation of approval of this protocol.

LIST of CONTENTS

LIST OF ABBREVIATIONS

AE	Adverse Event
AI	Associate Investigator
BPI	Brief Pain Inventory
BNF	British National Formulary
CI	Chief Investigator
CRF	Case Report Form
CRN	Clinical Research Network
CTU	Clinical Trials Unit
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GP	General Practitioner
ID	Identification Detail number
IP	Intellectual Property
HRA	Health Research Authority
HSCR	Health and Social Care Research Policy
ISRCTN	International Standard Randomised Controlled Trials Number
MED	Morphine Equivalent Dose
MRR	Medical Record Review
NPT	Normalisation Process Theory
PAG	Patient Advisory Group
PCN	Primary Care Network
PIL	Participant Information Leaflet
PPIE	Patient and Public Involvement and Engagement
PSC	Programme Steering Committee
RCT	Randomised Control Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SMF	Study Master File
SMG	Study Management Group
SOP	Standard Operating Procedure
TDF	Theoretical Domains Framework
TFA	Theoretical Framework of Acceptability

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STUDY SUMMARY

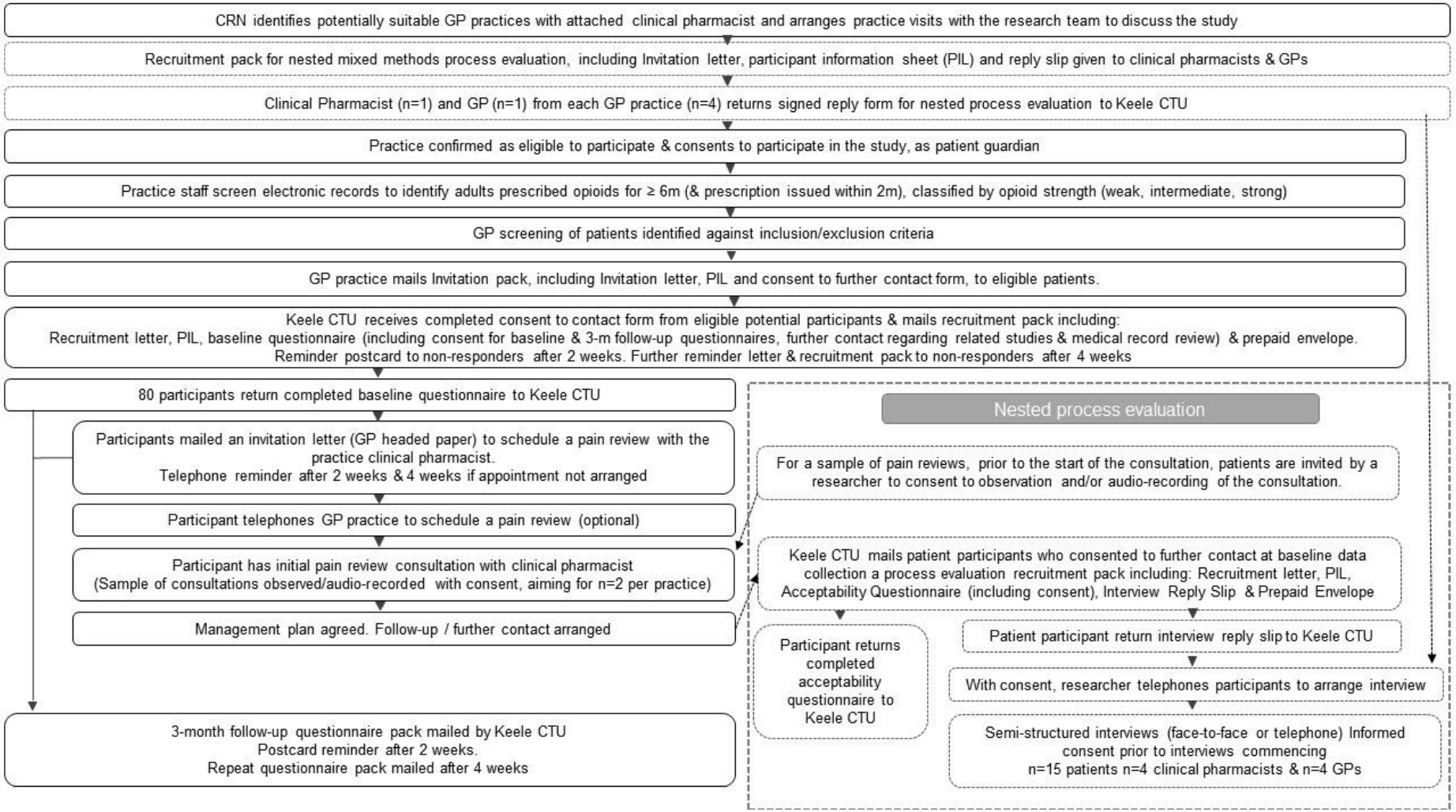
Study Title	**P**roactive clinical **R**eview of patients taking **O**pioid **M**edicines long-term for persistent **P**ain led by clinical **P**harmacists in primary care **T**eams (PROMPPT). A non-randomised Feasibility Study with mixed methods process evaluation.
Internal Ref. Number (or short title)	PROMPPT FS
Patient facing title / ACRONYM	Management of Opioids and Persistent Pain **(MOPP)** Study
Study Design	Single arm, non-randomised feasibility study with mixed methods process evaluation
Intervention	Proactive clinical pharmacist-led review of patients taking opioid medicines for persistent pain incorporating, where appropriate, support to reduce opioids and to self-manage persistent pain.
Study Participants	Adults aged ≥ 18 years regularly prescribed any opioid-containing analgesic for persistent pain for ≥ 6 months with a prescription dispensed within the previous 2 months
Planned Sample Size	4 GP practices 80 patient participants <u>Process evaluation (**MOPP 2** study)</u> 8 consultations audio-recorded across the participating practices (aiming for 2 per participating practice) 15 patient participants interviewed 4 clinical pharmacists interviewed (1 per participating practice) 4 GPs interviewed (1 per participating practice)
Treatment duration	Initial clinical pharmacist consultation will last around 30 minutes Follow-up arranged according to clinical need
Follow up duration	3 months
Planned Study Period	16 months

Primary Objectives To determine:	**Outcome Measures**
1. Availability and recruitment of eligible patients, the proportion scheduling and attending clinical pharmacist appointments and retention to 3-month follow-up.	• Proportion of patients eligible (out of all GP registered patients) to be mailed a study invitation.

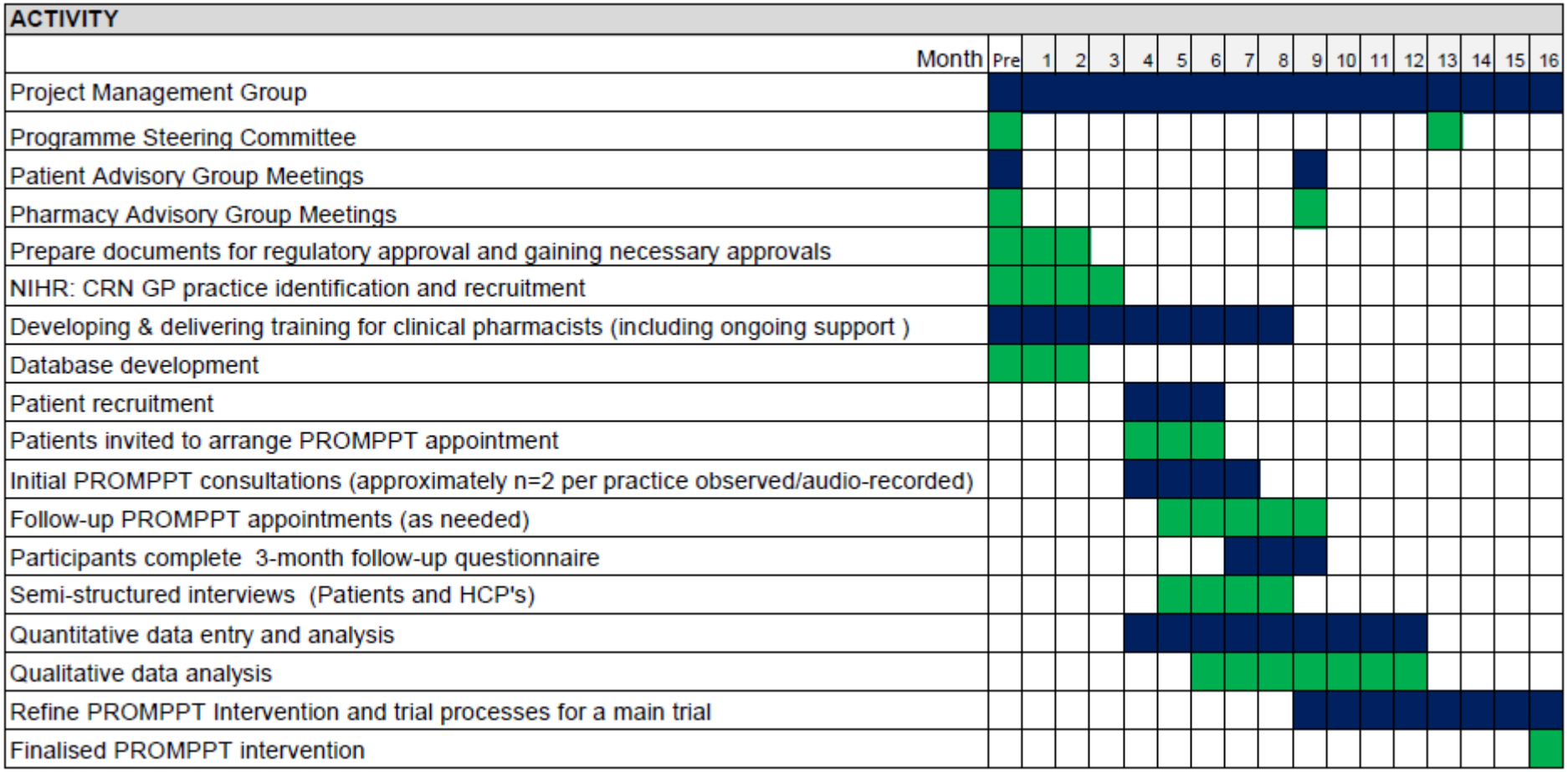
	• Proportion of patients returning a baseline questionnaire (out of those mailed a study invitation). • Proportion of participants attending the initial PROMPPT consultation with the clinical pharmacist (out of those who returned the baseline questionnaire). • Proportion of participants who have at least one follow-up appointment scheduled (out of those who attend the initial consultation). • Proportion of participants who fail to attend one or more scheduled follow-up appointments (out of those who are scheduled a follow-up following the initial consultation). • Proportion of participants returning a 3-month follow-up questionnaire (out of those consenting to complete questionnaires at baseline).
2. Completeness of data collection.	• Missing data rates will be calculated for each outcome measure in the baseline and follow-up self-report questionnaires at each data collection time-point (baseline and 3-month).
3. Fidelity of intervention delivery per protocol.	• Proportion of times that use of each intervention component is recorded in intervention case report forms (CRFs). • Proportion of patients being treated per-protocol (out of all patients who attended the initial clinical pharmacist appointment). • Findings from qualitative analysis of observed/audio-recorded consultations.
4. Suitability of a self-reported pain medicines use questionnaire to calculate mean daily morphine equivalent dose.	• Completeness of response to pain medicines use questionnaire. • Comparison of average daily morphine equivalent dose (MED) calculated using data from self-report questionnaires with MED calculated using prescription data from electronic medical records at baseline and 3-month follow-up.
5. Suitability of the health resource use questionnaire for use in a future health economic evaluation.	• Rate and completeness of response to healthcare resource use and productivity questionnaire.
6. Barriers to and facilitators of successful delivery of the intervention.	• Findings from observed/audio-recorded consultations. • Findings from interviews with patients, clinical pharmacists and GPs.

7. The acceptability and credibility of the intervention to patients.	• Responses to the Acceptability Questionnaire. • Findings from interviews with patients.
8. Acceptability of the intervention and training to clinical pharmacists and GPs, and the feasibility of delivering the intervention in general practice.	• Findings from interviews with clinical pharmacists and GPs.

STUDY FLOW CHART



STUDY GANTT CHART



1. BACKGROUND

Persistent pain, defined as long-term pain not caused by cancer, affects almost half the UK adult population, with 10-14% (around 8 million adults) reporting that persistent pain causes moderate or severe interference with life.[1] Two-thirds of people with persistent pain are treated with prescribed analgesics and, of these, 62% are prescribed opioid (morphine-like) analgesics.[2] Opioid prescribing for persistent pain has increased, with a trend towards prescribing stronger long-acting opioids and earlier escalation from 'weak' (e.g. codeine) to 'strong' opioids (e.g. morphine).[3] In UK primary care, prescribing almost doubled for 'weak' opioids and rose almost six-fold for 'strong' opioids between 2005-2012, with much of this prescribing being for patients with unspecified non-cancer pain.[4] Prescribing of the most commonly used 'strong' opioids (morphine, oxycodone, fentanyl, buprenorphine) increased by 466% between 2001 and 2010, with most (87.8%) prescribed for non-cancer pain.[5]

Evidence for long-term effectiveness of opioids for people with persistent pain is limited.[6-8] The majority of people living with persistent pain do not obtain useful pain relief from opioids[9] and they are frequently associated with side-effects which can worsen quality of life, including constipation, nausea, dizziness, sedation and confusion.[6,7,10] People with persistent pain who take opioids are more likely to report worse pain, poorer self-rated health, and lower quality of life than people with persistent pain who do not take opioids.[11,12] These data suggest that, for many people with persistent pain, opioid therapy does not fulfil the key goals of treatment, namely pain relief, improved functioning and improved quality of life and. Opioid therapy is also associated with increased risk of serious harm including overdose, addiction, fractures and myocardial infarction.[13-15] Furthermore, studies of gradual reduction of long-term opioids in the context of multidisciplinary pain management programmes report that, overall, patients do not experience worse pain and may notice improved function and quality of life.[16]

It seems, therefore, that opioids are prescribed more often and for longer than would be expected given the evidence for their effectiveness for persistent pain[9,17]. Most long-term opioid prescribing occurs in primary care, where most persistent pain is managed. GPs report low satisfaction with care they provide for patients with persistent pain[17,18] and, whilst 75% report concerns about opioid-related harm, 50% of GPs perceive no alternative to prescribing opioids for some patients.[19,20]

2. RATIONALE

Best practice guidelines[21,22] recommend that opioids should be reviewed within four weeks of starting opioid treatment. Once a stable opioid regimen is reached, it is recommended that opioids should be reviewed face to face at least 6 monthly, and more often if there are concerns. Structured review is recommended, taking into account evidence of effectiveness, including functional improvement / progress towards treatment goals, side-effects and evidence of problematic use[16]. Supporting patients to taper and stop opioids is recommended if treatment goals are not met[21-23]. However, implementation of opioid guideline recommendations is low.[24,25] Lack of time and resources are potential barriers to guideline-concordant care,[24,25] and the available time in routine GP appointments offers limited opportunity to undertake a comprehensive face-to-face review.

To address challenges facing primary care, a recent report recommends adopting a multidisciplinary model and increasing the role of clinical pharmacists working within GP practices in managing patients on long-term medicines.[26] An expansion in the clinical pharmacist workforce in UK primary care is underway, with clinical practice pharmacists being a key component of the evolving Primary Care Networks (PCNs).[27,28] These practice clinical pharmacists will see patients in face-to-face consultations in GP surgeries and will be trained as independent prescribers. Practice pharmacists do not dispense medicines and patients will still collect their medicines from the community pharmacy in the usual way. There is considerable variation in the roles adopted by clinical pharmacists in GP practices and research is needed to determine the most clinically and cost-effective ways to utilise this new primary care resource. One emerging role for clinical practice pharmacists is reviewing patients with polypharmacy and complex medicines regimens. Given that increasing polypharmacy is associated with incremental increases in long-term and stronger opioid prescribing, [29] clinical practice pharmacists are ideally placed to take a proactive role in reviewing and managing patients on long-term opioids, but there is currently no evidence about how they should do this or whether it would be clinically or cost-effective.

Evidence supporting interventions to reduce opioid use is sparse.[30-32] Recent Cochrane reviews found the need for further, larger, RCTs of theoretically grounded behaviour-change interventions focussing on reducing opioids in the context of persistent pain.[32]

This study is part of a 5-year research programme comprising three linked workstreams to develop and test a clinical pharmacist-led primary care intervention (PROMPPT) and an associated clinical pharmacist training package which aim to reduce opioid use for people with persistent pain (where appropriate) and support self-management for those with persistent pain in primary care.

In workstream 1 (WS1), we used a person-based approach,[33] combined with best practice guidance, theory (on behaviour change and normalisation of health care interventions) and stakeholder engagement, to develop the PROMPPT pain management review and clinical pharmacist training package.

This protocol describes workstream 2 (WS2), a non-randomised feasibility study and nested mixed methods process evaluation, which will inform refinement of the PROMPPT pain management review, training package and the design of the proposed main trial design. In workstream 3 a multicentre cluster randomised controlled trial (cluster RCT) will test the clinical and cost-effectiveness of providing the PROMPPT pain management review in reducing prescribed opioid use, without increasing pain/pain –related interference, when compared with usual primary care review of patients prescribed long-term opioids.

3. OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

The overall aim is to investigate the viability, credibility and acceptability (to patients, clinical pharmacists and GPs), and the fidelity of clinical pharmacists delivering the PROMPPT intervention to patients with persistent pain prescribed long-term opioids in primary care, and the feasibility of conducting a future cluster randomised controlled trial (cluster RCT) to determine clinical and cost-effectiveness.

3.1 Primary objectives

1. Determine the availability and recruitment of eligible patients, the proportion scheduling and attending clinical pharmacist appointments and rates of retention at 3-month follow-up;
2. Determine the completeness of data collection;
3. Determine the fidelity of intervention delivery per protocol;
4. Determine the suitability of a self-reported pain medicines questionnaire and electronic medical records to calculate mean daily morphine equivalent dose;
5. Determine the suitability of the health resource use questionnaire for use in a future health economic evaluation;
6. Determine the potential barriers to and facilitators of successful delivery of the intervention;
7. Determine the acceptability and credibility of the intervention to patients;
8. Determine the acceptability of the intervention and training to Clinical Pharmacists and GPs, and the feasibility of delivering the intervention in general practice.

3.2 Secondary objectives

To use the study findings to:

1. Refine and optimise the PROMPPT intervention and associated clinical pharmacist training package;
2. Refine sample size estimates for the main cluster randomised controlled trial (cluster RCT);
3. Refine and optimise the study design and processes, including self-reported patient questionnaires, for use in the main cluster RCT.

4 STUDY DESIGN AND SETTING

4.1 Study design

This study is a non-randomised feasibility study. We have chosen a non-randomised design for this feasibility study because the design of the proposed main trial in the final workstream of the PROMPPT research programme is a cluster RCT of a similar design to previous cluster RCTs[34-36] conducted successfully by School of Primary, Community and Social Care, Keele University in a wide range of patients with musculoskeletal pain. Patient recruitment to these studies resulted in participation rates in the region of 40% of eligible patients with similar retention rates at both short term (greater than 75%) and 12 months follow-up (around 70%) in both intervention and control practices, and there was no evidence of selection bias. Therefore, we are confident in our ability to recruit and retain patients to a similar extent in both intervention and control arms of studies using this design and have included only an

intervention arm and not a control arm in this feasibility study. We will however monitor recruitment and retention rates in both intervention and control arms in an internal pilot within a main trial if this study demonstrates that progressing to a main trial is feasible.

The study design employs a theoretically informed mixed methods approach to meet the study objectives outlined in section 3. A nested mixed methods process evaluation will collect data regarding process outcomes from observations/audio-recordings of PROMPPT consultations, a patient self-reported acceptability questionnaire and semi-structured interviews with participating patients and clinicians. Data collection and analysis will be informed by the Theoretical Domains Framework (TDF)[74] which identifies 14 related domains of influence on behaviour including knowledge, beliefs about capabilities, skills, motivation and goals. This will identify potential barriers and enablers for patients and clinical pharmacists to undertake behaviour change in relation to PROMPPT. The Theoretical Framework of Acceptability (TFA)[58] will be used as an overarching framework to explore the acceptability of PROMPPT to clinical pharmacists, GPs and patients. Normalisation Process Theory (NPT)[75,76] will be used to investigate the dynamics of implementing, embedding, and integrating PROMPPT, in order to identify potential process problems related to implementing PROMPPT.

4.2 Study Setting

PROMPPT-FS will be delivered from two general practices in the National Institute for Health Research (NIHR) Clinical Research Networks (CRN) West Midlands (CRN: WM) and two general practices in CRN: East Midlands (CRN: EM). Practices will invite patients to participate in the MOPP study. All MOPP study participants will be invited to a PROMPPT consultation.

4.3 Eligibility criteria

4.3.1 GP practices

Average sized (≥5,000 list size) GP practices will be eligible to participate if:

- The practice has a clinical pharmacist working in the practice for at least one session per week;
- The clinical pharmacist sees patients for face-to-face consultations in the practice;
- The clinical pharmacist is an independent prescriber;
- The clinical pharmacist consents to participate in the nested process evaluation including observation/audio-recording of a sample of PROMPPT consultations and an interview;
- One GP from the practice consents to an interview.

4.3.2 Individual patient participants

Inclusion criteria

(1) Adult patients aged ≥18 years who are:
(2) 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)[37] for chronic non-cancer pain continuously for ≥6 months, with a prescription issued within the previous 2 months.

Exclusion criteria

(1) Patients with acute pain, cancer pain and/or terminal illness (life expectancy <6m);
(2) Vulnerable patients (e.g. severe mental illness, learning difficulties, dementia);
(3) Patients currently receiving treatment for substance misuse;
(4) Patients who are unable to understand English.

4.4 Intervention

4.4.1 The PROMPPT intervention

PROMPPT is a clinical pharmacist-led intervention incorporating proactive review for patients who have been taking opioids regularly for at least 6 months and aims to reduce opioids, where appropriate, and to support self-management of persistent pain.

Best practice guidelines recommend review of patients taking opioids for persistent pain at least 6-monthly and gradual tapering of opioids where treatment goals are not met or when any modest benefit is outweighed by harm[21,22,38]. In primary care, such reviews may be conducted by the GP or by another appropriately qualified healthcare professional, such as a clinical pharmacist.

PROMPPT was developed in line with guidance on development and evaluation of complex interventions[39,40] using a person based approach[33] combined with best practice guidance with theory (on behaviour change and normalisation of health care interventions) and stakeholder engagement during workstream one of this research programme. Extensive intervention development work included qualitative interviews with patients, clinical pharmacists and GPs, an online qualitative study (research discussion forum for people with experience of persistent pain and use of opioid medicines) and in-practice testing of prototype PROMPPT consultations in 3 GP practices with a clinical pharmacist. Findings have informed the study processes, intervention components and content of the training programme for clinical pharmacists. Specifically, findings identified that patients prioritise feeling respected and listened to and receiving individualised care, including relevant information resources and further support (e.g. referral or follow-up appointments), where appropriate. These findings also confirmed that the training programme needs to focus on developing clinical pharmacists' communication skills that support patient autonomy (e.g. respectful, values patient input, supports patient ownership of healthcare), understanding of pain conditions, knowledge of pain management and appropriate signposting and referral options.

Patients with persistent pain who have been prescribed opioids regularly for at least 6 months will be invited to schedule a PROMPPT pain review with the clinical pharmacist working at their GP practice. The clinical pharmacists will be independent prescribers and will complete specific training to deliver the PROMPPT intervention.

The invitation letter will be accompanied by a Pain Concerns Form. The Pain Concerns Form was developed from the Pain Concern Pain Navigator Tool[41] with stakeholder engagement (including patients and a range of healthcare professionals) and in conjunction with a patient advisory (PPIE) group. The Pain Concerns Form is designed to help focus the consultation on the things that are most important to the patient. Patients are asked to complete the form, prior to their appointment, by reading a list of statements that represent concerns commonly

reported by patients with persistent pain, ticking those statements they agree with and adding any further concerns in a free text box.

The first consultation, (approximately 30 min) may be conducted face-to-face or remotely by video or telephone, depending on the impact of COVID-19 on service provision and any ongoing social distancing measures, and will begin with a holistic assessment of the patient's persistent pain including the impact of pain, followed by a personalised discussion to explore the patient's own experience of the effects (wanted/unwanted, useful/bothersome) of opioids, using information provided in the Pain Concerns Form where appropriate. Motivational interviewing techniques will be used to explore patient's reasons for considering changing their opioid medicines, their readiness to change and any ambivalence, before agreeing an individualised management plan.

Management plans will arise from shared decision making. The plan may include opioid tapering but this will not be mandatory, for example if the patient obtains continued useful benefit from moderate dose opioids, without experiencing troublesome side-effects. Where changes to medicines are agreed, SMART (specific, measurable, achievable, realistic, time-related) goal setting will be used to facilitate translation of intensions into action. Important barriers to reducing opioids specific to the individual, such as fear of pain worsening and/or withdrawal symptoms following opioid reduction will be addressed.

Management plans may also include advice and goals relating to self-management, signposting to information resources, signposting or referral to appropriate community services (for example physiotherapy, exercise classes and community psychology services) and, for more complex cases, discussion/collaboration with the GP and/or referral to specialist services if needed.

Follow-up will be arranged according to clinical need. Patients will also be provided with a clear plan for how to contact the clinical pharmacist between appointments if needed. Follow-up appointments may be conducted face-to-face or remotely by video or telephone, according to clinical need and patient preference, and are anticipated to be shorter in duration (no longer than 15 minutes).

4.4.2 The PROMPPT training package

The PROMPPT training package for clinical pharmacists will involve up to four training sessions. This training will cover communication skills, communication of risk and benefit in personalised discussions about opioids, motivational interviewing techniques, negotiating treatment plans, creating opioid tapering plans, optimising non-opioid pain management, supporting self-management for persistent pain, signposting to patient information resources and when to seek help (e.g. from GP). Training will also include self-care strategies to help clinical pharmacists manage any emotional impact of conducting pain reviews. A training manual will be supplemented by online training resources, for example videos of good and bad consultations, podcasts and written materials. In addition, clinical pharmacists delivering PROMPPT will be provided with regular mentoring by a multi-professional group of clinical champions.

Clinical pharmacists will also be 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.

Training will be provided by experts in pain management, primary care clinicians, behaviour change experts and medical/pharmacy educationalists.

Education/advice about the study will be provided for GPs in the participating practices to facilitate practice-wide engagement with the intervention and effective collaboration and ongoing support of clinical pharmacists.

5 STUDY PROCEDURES

5.1 Recruitment

5.1.1 Identification, recruitment and consent of GP practices (PROMPPT-FS)

The NIHR CRN: WM and CRN: EM will identify eligible general practices for the PROMPPT-FS as outlined in section 4.3.1. As part of the site identification process, a feasibility audit will be conducted by the CRNs to review the practice coding habits, to ensure that eligible patients can be identified and to ensure that the practice identified can meet the study requirements to deliver.

The study team will accompany CRN Research Facilitators to visit the identified practices to fully explain the study and describe the study requirements. Informed consent for practices to participate will be provided by the senior GP partner in each practice acting as 'guardian' for patients in their care, following agreement with their team clarifying willingness to undertake the PROMPPT intervention (see 5.1.3). GP practice consent to participate in the PROMPPT-FS will be formalised through written agreements. Eligible patients consenting to participate in the nested research evaluation (MOPP study) will receive the care which their practice is currently delivering for the PROMPPT-FS.

5.1.2 Identification and recruitment of participants (MOPP Study)

The PROMPPT-FS Health Informatic Specialist will design a search and report compatible with the participating practice GP System of Choice (GPSoC), to identify eligible participants as outlined in section 4.3.2. The search and report will be provided to the practice, to screen their electronic patient records to systematically identify adults prescribed opioid-containing pain medicines for 6 months or longer (with a prescription dispensed in the last two months), and grouped according to the strength of opioid medicine (weak, intermediate, strong). Grouping will be based on a published categorisation for prescribed analgesics in primary care[42]. GPs will be asked to screen the patients identified according to the study inclusion and exclusion criteria, excluding ineligible patients.

Each patient identified will be assigned an individual study ID and their details will be mail-merged into a Consent to Contact invitation pack (to include an Invitation letter, a Participant Information Leaflet (PIL), a Consent to Contact form and reply paid envelope) inviting them to receive further information about the MOPP study. The Consent to Contact invitation pack will be sent via Docmail from the practice. Docmail is a standards-compliant hybrid mail service, providing document management and ISO 27001 secure mailings. Non-identifiable

sample demographic data (including age and sex, and opioid strength grouping) will be provided to the research team. This will allow any evidence of selection bias to be assessed.

Response rates to mail-outs will be monitored and, if needed, a further Consent to Contact invitation pack will be sent from the practice to non-responders after 2 weeks.

On receipt of a Consent to Contact invitation pack, the potential participant will complete the Consent to Contact form and return this in the pre-paid envelope provide to Keele Clinical Trials Unit (CTU), Keele University. Consent for Keele CTU to contact the potential participant providing them with further information regarding the MOPP Study will be obtained, in line with the definition outlined in Article 4(11) of the GDPR guidance, "any freely given, specific, informed and unambiguous indication of the data subject's wishes by which he or she, by a statement or by a clear affirmative action, signifies agreement to the processing of personal data relating to him or her" (European Union, 2016). Consent to be contacted with a MOPP Study invitation pack will therefore be implied by return of a completed Consent to Contact form.

On receipt of a completed Consent to Contact form, Keele CTU will mail potential participants a MOPP Study recruitment pack (to include; an invitation letter, Patient Information Leaflet, Baseline Questionnaire including consent form, and a prepaid envelope). A reminder postcard will be sent to non-responders after 2 weeks. A further reminder letter & recruitment pack will be mailed to non-responders after 4 weeks. A letter will be sent to participants where data is missing from consent forms in order to check that they are happy to take part in the study and that all required information is collected.

Consent to participate

Consent to participate in the MOPP Study is provided by the potential participant in their completion and return of the MOPP Study Baseline Questionnaire and included consent form. Consent is requested for;

- Taking part in the MOPP Study (Read and understood the MOPP PIL, voluntary participation, completion of baseline and 3-month follow-up questionnaires).
- Depersonalised access to electronic medical records.
- Contact about future related research studies.

5.1.3 Identification and recruitment of participants (MOPP-2 Study)

Clinicians (GPs and clinical pharmacists) working at the identified practices, will be invited to participate in the nested process evaluation (MOPP-2 study). Participant Information Leaflet and reply forms will be provided. The Clinical pharmacist from each participating practice will be asked to consent to observation/audio-recording of a sample of PROMPPT consultations (with patient consent) and to an interview. GPs at each practice will be asked to consent to an interview. When Keele CTU has received signed interview reply forms from one clinical pharmacist and from one GP working in an identified GP practice, eligibility of that practice is confirmed and the CRN will complete recruitment of the practice.

<u>Observation /audio-recording of consultations</u>

The research team will work with participating practices to identify and approach patients who are suitable to take part in the pain review observation/audio recording study.

A member of the research team will attend participating GP practices for a sample of consultations and will invite patients to consent to observation and/or audio-recording of the consultation, with the aim of observing and/or audio-recording two consultations per practice.

Informed, written consent to observe or audio-record the consultation will be obtained from patients attending for face-face consultations and confirmed with clinical pharmacists prior to the start of the consultation. For remote consultations by video or telephone, an information leaflet will be sent in advance of the consultation, and the researcher will read through and complete the consent form with the participant over the telephone; this will be undertaken verbally and recorded prior to the remote consultation commencing. The research team will inform clinical pharmacists which participants have agreed. The participant will then send back a signed consent form on completion of the consultation.

If patients consent to this, consultations will be audio-recorded using a digital audio-recorder, which will be switched on by a researcher or the clinical pharmacist prior to the start of the consultation. Following the consultation, the researcher or clinical pharmacist will securely send the audio recording to Keele CTU for analysis.

Acceptability Questionnaire

Following the initial consultation with the practice clinical pharmacist, participants who gave consent to future contact about related studies, will be mailed a MOPP-2 recruitment pack by Keele CTU. The MOPP-2 Recruitment pack will include an invitation letter, Participant Information Leaflet, Acceptability Questionnaire (including consent form), an Interview Reply Slip and a prepaid envelope. Participants may choose to consent to any, all or none of these options.

Patient Interviews

Patient participants who return the Interview Reply Slip consenting to further contact for an interview, will be contacted by a researcher to arrange a mutually convenient time and location for this. Interviews may be conducted face-to-face or by telephone. Face-to-face interviews are likely to take place in the participants' own home. When interviews take place in a person's home, they will be conducted in accordance to Keele University's lone working guidelines. The qualitative researcher(s) and a nominated contact will follow standard procedures regarding contact before and after the interview.

An interview confirmation letter will be sent specifying the date, time and location (or telephone number). A letter will be sent to the participant's GPs informing them that their patient is taking part in an interview. Once the target sample size of 15 participants has been reached, all subsequent participants who return their interview reply form will be sent a letter thanking them for their interest and informing them that we will not be inviting them to take part on this occasion.

Fully informed consent will be obtained prior to all interviews commencing.

For telephone interviews, the researcher will read through and complete the consent form with the participant over the phone; this will be undertaken verbally and recorded prior to the interview commencing. The participant will then send back a signed consent form on completion of the interview.

Clinician Interviews

Clinical pharmacists and GPs who consent to being interviewed will be contacted by a researcher, after the majority of initial reviews in their practice have been completed, to schedule a mutually convenient appointment. The interviews may be conducted face-to-face or by telephone. Face-to-face interviews will be arranged at a location convenient for the interviewee, likely to be their clinical practice setting. An interview confirmation letter will be sent to the clinician specifying the date, time and location (or telephone number) of the interview.

Fully informed consent will be obtained prior to all interviews commencing.

For telephone interviews, the researcher will read through and complete the consent form with the participant over the phone; this will be undertaken verbally and recorded prior to the interview commencing. The participant will then send back a signed consent form on completion of the interview.

5.2 PROMPPT Intervention

Following receipt of a completed baseline questionnaire, MOPP participants will be mailed an invitation letter (GP headed paper) asking them to schedule, at their earliest convenience, a pain review with the clinical pharmacist working at their practice. Telephone reminders will be made by the practice after 2 weeks and 4 weeks if appointments have not been arranged.

Patients who do not have a pain review with the clinical pharmacist will continue with usual GP care.

5.3 Outcome data collection

This feasibility study will report on both process and research outcomes and data will be collected via participant self-reported questionnaires, clinical pharmacist-completed CRFs, audio-recordings of the PROMPPT consultations and semi-structured interviews with patients and clinicians. These methods of data collection will enable the acceptability and feasibility of training the clinical pharmacists delivering the PROMPPT intervention and delivering a larger randomised cluster RCT to be fully assessed. Table 1 (below) summarises the outcome measures and their respective time-points of data collection.

5.3.1 Self-reported questionnaires

All participants will be asked to complete self-report questionnaires at 2 time points:

- At baseline
- At 3 months from receipt of the completed baseline questionnaire.

Participants will return the questionnaires to Keele CTU in pre-paid envelopes. To maximise response rates to the questionnaires, participants will be sent a reminder postcard at 2 weeks and a reminder letter and further recruitment pack after 4 weeks.

The baseline questionnaire will collect information on participant characteristics (age, sex, and duration of pain) and will include the proposed primary and secondary outcome measures for a main cluster RCT, as described below.

Clinical outcome measures

The Brief Pain Inventory is a composite self-report measure comprising a pain intensity subscale (4 items; current, least, worst, and average pain rated on 0-10 scale) and a pain-related functional interference subscale (7 items assessing interference with general activity, walking, sleep, work, mood, enjoyment of life and relationships rated on 0-10 scale).[43] The BPI is a recommended outcome measure in chronic pain trials and is validated in primary care populations.[44-46]

BPI total score and opioid use, expressed as daily morphine equivalent dose, are proposed as the co-primary outcomes for a future main trial. This reflects the importance to patients, confirmed by PPIE, that pain and pain-related interference does not increase when reducing opioids.

In this study we will explore the feasibility of calculating average daily morphine equivalent dose (MED) using participant self-reported data about opioid use over the preceding 4 weeks, and using prescribing data from electronic medical records. A pain medicines use questionnaire will collect data on dose, dosing regimen (regular or as required) and frequency of use for each opioid and non-opioid pain medicine used. Morphine equivalent doses will be calculated for each opioid medicine prescribed using published conversion factors.[47,48]

A medication-related side-effects checklist will collect information about common opioid-related side-effects (constipation, itching, daytime sleepiness, dry mouth, nausea, vomiting, dizziness, headache, confusion, difficulty concentrating)[49] and their severity on a 5-point scale.[50,51]

Pain-related self-efficacy will be measured using the Pain Self-Efficacy Questionnaire[52] (PSEQ), a 10-item questionnaire, assessing the confidence of people with any type of chronic pain to cope with pain in general, to perform a range of specific activities despite pain and their confidence to cope with pain without medication. Each item is rated on a 0- 6 scale, with higher scores reflecting stronger self-efficacy beliefs.

Health economic evaluation

The EQ-5D-5L[53] is a generic measure of health related quality of life that provides a single index value for health status that will allow calculation of Quality-Adjusted Life Years (QALYs) in the health economic evaluation nested in a proposed future main trial. Respondents rate their degree of impairment in five health domains (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) on a 5-point scale (no problems, slight problems, moderate problems, severe problems and extreme problems).

A patient self-report questionnaire (developed for the study) will be used to collect relevant healthcare resource use data, including the use of NHS and private health care, over the counter purchases and information on both time off work and presenteeism. The focus will be on persistent pain-related healthcare resource use and healthcare resource use due to opioid-related side effects. Questions will request information regarding primary care visits, visits to other health care professionals, tests and investigations, opioid prescriptions, treatment (e.g. injections), secondary care consultations, inpatient stays and surgery during the previous 3

months. Data on broader health care costs will also be collected, related to out of pocket costs (e.g. over the counter medications such as laxatives) and private health care. Information on time off work, occupation, typical work activities and the nature of their employment (full time or part time) will also be requested and the Single-Item Presenteeism Question from the Work Productivity and Activity Impairment Questionnaire[54,55] will be used to estimate presenteeism.

Preliminary resource use data will also be collected regarding delivery of the PROMPPT intervention, including clinical pharmacist appointments (face to face and telephone) and GP input, to refine data collection processes in a future main trial. Opioid prescription information will also be available through medical record review (see 5.3.3).

5.3.2 Nested Process Evaluation

Observed Consultations

A sample of approximately 10% of consultations[56] (aiming for n=2 per practice) will be observed (by a researcher and/or digitally audio-recorded) with clinical pharmacist and participant consent. Data from these observed consultations will be collected to allow assessment of key aspects of intervention delivery[56]: treatment differentiation, (Did the clinical pharmacists only deliver PROMPPT and not other treatments?), treatment competency (Did Clinical Pharmacists maintain the skills learned in training?), and treatment delivery (Were PROMPPT components delivered as intended?).

Case report forms (CRF)

The clinical pharmacists will be required to complete a CRF for each participant. An e-CRF will be embedded within the practice electronic medical record. Following completion this can be embedded into the individual participants' medical record. The CRF will collect information on what happened during the PROMPPT interventions (e.g. discussion of the Pain Concerns Form, discussion of the patient perspective on making changes to opioid medicine, developing a personalised management plan using a shared decision making approach, signposting to relevant self-management/self-care information resources). The eCRFs will be analysed at the end of the study to assess engagement with the intervention, intervention uptake, delivery, and to identify any further training requirements ahead of a main cluster RCT.

Acceptability Questionnaire

All participants who attended the clinical pharmacist appointment will be mailed a short survey (known as the Acceptability Questionnaire) about their experiences of the consultation, which will supplement the qualitative data. This short survey will have a total of 12 questions from two existing measures: a modified version of the treatment acceptability and credibility measure[57] and the Theoretical Framework of Acceptability (TFA) questionnaire[58]. The modified acceptability and credibility measure has been used in previous similar studies[59, 60]. The measure includes 4 items, (scored on a 0-10 scale) and will assess (1) how logical the PROMPPT Intervention 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 questionnaire comprises 8 items (scored on a 0-5 scale) [58] . The first is a global acceptability question and the remaining 7 (items 2-8) represent key constructs of

acceptability relating to healthcare interventions (affective attitude, burden, intervention coherence, ethicality, perceived expectations, opportunity cost, and self-efficacy).

Semi-structured interviews

Patient participants will be interviewed after attending at least one appointment with the clinical pharmacist. The interviews will be based on semi-structured topic guides developed in association with our PPIE group and will include questions informed by our programme theories regarding behaviour change, implementation and acceptability[39,40,33]. Topic guides will be refined during data collection to allow any emerging issues to be explored. A similar process will be followed for the clinician participants whereby they will be interviewed once they have experience of PROMPPT intervention delivery.

We expect that up to 15 patients (sampled from across the 4 participating practices) and approximately 8 clinicians, n=4 GPs and n=4 clinical pharmacists (one of each from each participating practice) will be sufficient to attain rich data. We will cover similar topics with all interviewees to ensure we can compare their responses, while at the same time enabling them to reflect on their specific expectations, understandings and experiences. All interviews will be conducted by an experienced qualitative researcher. With the participants' consent, interviews will be audio recorded. The interviews will be securely sent to a professional transcription company (The Transcription Company UK) who operate under the terms of a confidentiality agreement and who have an existing contract with Keele CTU. Transcripts will be transcribed verbatim. Transcripts will be anonymised by members of the research team ahead of analysis.

5.3.3 Medical Record Review (MRR)

Full general practice medical records of consenting participants will be accessed and extracted and securely transferred to the study team to obtain information on consultations, prescriptions and associated aspects in the medical record, for the duration of the study requirements.

Table 1. Schedule of Data Collection

Table 1. Schedule of Data Collection				
	Time point			
Outcome measure	Baseline	PROMPPT consultation	Post PROMPPT consultation	Follow-up 3 months from baseline
Self-reported questionnaires				
Demographics (sex, date of birth)	☑			☑
Chronic pain duration (in years, single question)	☑			
Pain severity: Brief Pain Inventory (BPI) pain subscale[43]	☑			☑
Pain-related interference: BPI pain interference subscale[43]	☑			☑
Opioid medicines use, expressed as average daily morphine equivalent dose (MED)	☑			☑
Opioid-related pain medication side-effects checklist	☑			☑
Other (non-opioid) pain medicines use (drug name(s), dose(s), frequency)	☑			☑
Pain Self-Efficacy Questionnaire (PSEQ)[52]	☑			☑
Health-related quality of life (EQ-5D-5L)[53]	☑			☑
Healthcare resource use (chronic pain and opioid side-effect related)				☑
Work (work status, occupation, time off work, Single-Item Presenteeism Question from the Work Productivity and Activity Impairment Questionnaire[54,55])				☑
Process measures				
PROMPPT intervention case report form		☑		
Fidelity checklist using observed/audio-recorded consultations		☑		
Acceptability Questionnaire [57,58]			☑	
Semi-structured interviews with patient participants			☑	
Semi-structured interviews with clinical pharmacists			☑	
Semi-structured interviews with GPs			☑	

5.4 Withdrawal Criteria

Participants are free to withdraw from the study at any time. Keele CTU will make every effort to ensure that the specific wishes of any participant who wishes to withdraw consent for further involvement in the study are defined and documented.

Participants who wish to withdraw from the study will have the option to still attend for initial and/or follow-up PROMPPT consultations with the practice clinical pharmacist if they wish.

5.5 End of Study

The end of the study is defined as the point at which data collection is complete and the study database is locked. All CRFs, audio files and transcripts will have been received by the data management team at Keele CTU and any data queries will have been resolved. The Chief Investigator will notify the REC of the end of the study within 90 days of study completion.

6 STATISTICS AND DATA ANALYSIS

6.1. Sample size

Based on data from our regional anonymised primary care database (Consultations in Primary Care Archive (CiPCA)), we expect to identify around 270 patients with persistent pain prescribed long-term opioids per average sized practice of around 5000-6000 patients. Assuming GPs exclude 30% of patients identified according to study exclusion criteria and assuming that a minimum of 25% of those contacted consent to participate and return a baseline questionnaire, we estimate a mean of at least 47 eligible patients per practice will consent to participate.

A sample of 80 eligible participants from across 4 practices in 2 regional centres is therefore feasible and will allow us to estimate the overall consent rate with precision of at least ±10%. Similarly, if the 3-month follow-up rate is around 75%, this estimate will have precision of around ±10%.

6.2 Quantitative data analysis

Analysis of the quantitative data from the study will be exploratory and used to inform the design of a future main trial

6.2.1 Recruitment and retention rates

A CONSORT flow diagram will be produced and used to estimate the following proportions:

- % (out of all GP registered patients) identified to be screened by GP
- % eligible (out of all GP registered patients) to be mailed a study invitation
- % returning a baseline questionnaire (out of those mailed a study invitation)
- % of participants attending the initial PROMPPT consultation with the clinical pharmacist (out of those who returned the baseline questionnaire)
- % of participants who have at least one follow-up appointment scheduled (out of those who attend the initial consultation)

- % of participants who fail to attend one or more scheduled follow-up appointments (out of those who are scheduled a follow-up following the initial consultation)
- % of participants returning a 3-month follow-up questionnaire (out of those consenting to complete questionnaires at baseline)

These estimates will be used to review the feasibility of recruitment and follow-up for a main trial.

6.2.2 Baseline and follow-up questionnaire completion

Missing data rates will be calculated for each outcome measure in the baseline and follow-up self-report questionnaires at each data collection time-point (baseline and 3-month). Outcomes with a poor completion rate will be identified and used to inform if any changes are needed to the outcome measures used as data collection tools in a main trial design.

6.2.3 Participant characteristics

Participants baseline characteristics will be described (using means, standard deviations, medians, interquartile range, numbers and percentages as appropriate) to characterise the sample and also highlight any potential areas of selection bias that could be minimised in a main trial design. Participants' baseline characteristics will be explored in the following subgroups, however, between-group differences will not be tested for statistical significance due to small sample size:

- Eligible patients mailed a study invitation (date of birth, sex and postcode deprivation only)
- Eligible patients consenting to participate and returning a baseline questionnaire
- Participants returning a 3-month follow-up questionnaire

6.2.4 Intervention delivery template

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 per-protocol and whether the patient attended all scheduled follow-up appointments. The proportion of patients being treated per-protocol will then be calculated out of all participants who attended the first appointment with the clinical pharmacist.

6.2.5 Feasibility of primary outcome data collection for a main trial

The proposed co-primary outcomes for a main trial are Brief Pain Inventory (total score combining pain severity and pain interference subscales) and opioid use, expressed as average daily morphine equivalent dose.

Average daily morphine equivalent dose (MED) will be calculated at baseline and 3-month follow-up using data from the self-report questionnaires and prescribing data from linked medical records. Correspondence in MED between the two data sources will be explored by calculating individual differences in MED between self-report and MRR data at each time point and plotting the resulting distributions.

6.2.6 Health economic evaluation

A formal health economic evaluation will not be conducted in this feasibility study.

To assess the feasibility of the proposed health economic evaluation for the main trial, we will assess the level of completion of the EQ-5D-5L questionnaire at baseline and 3 months, and the level of completion and suitability of the patient resource use questionnaire at 3 months.

Overall response rates for each questionnaire will be calculated. Within questionnaire completion rates will also be calculated in order to assess the level of completion of specific questions. Assessment of appropriateness of completion will also be undertaken, with questions to be refined as necessary.

Data on opioid prescriptions and use will be available from patient self-report questionnaires and medical record review. This will allow comparison of the two data sources to determine the final method of data collection on opioids for the economic evaluation within the definitive trial.

6.2.7 Sample size estimate for a main trial

The following parameters will be calculated, along with a 95% confidence interval, to inform the sample size calculation for a main trial, however our interpretation will be cautious and will focus on the 95% confidence interval (rather than the point estimate) given the small number of clusters and sample size in the feasibility study.[61]

- Intra-cluster correlation coefficient (ICC)
- Coefficient of variation (CV)
- Standard deviation (SD) of the BPI total score at baseline

6.2.8 Acceptability questionnaire data

The mean and standard deviation (SD) as well as the median and interquartile range (IQR) 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. These data will be considered alongside qualitative data as part of decision making regarding progression to a main trial. A mean score of ≥ 5/10 for each of items 9-12 will be considered the threshold for acceptability/credibility, as in the previous trials using this measure.[59,60]

6.3 Qualitative data analysis

Audio-recorded consultations and interviews will be professionally transcribed ad verbatim. The Framework approach[62] to analysis will be used as this starts deductively from pre-set aims and objectives, and will enable a focused and efficient analysis within the timeframe of this study,[63-66] and can be used within a multidisciplinary research team setting.[67] Analysis will involve familiarisation, identification of a framework (including study aims, TDF[74] , TFA[58] and NPT[75,76]) indexing, charting and mapping, and interpretation.[62] Coding of transcripts will be undertaken by members of the research team from different professional backgrounds (including GPs and clinical pharmacists) to increase trustworthiness of the analysis.[68] Continuous team analysis of data will help to challenge interpretations and coding will be refined and agreed through ongoing discussion. The approach described will allow for both

a-priori (TDF, TFA, NPT) and emergent codes to be identified.[69] The data analysis will be facilitated using qualitative data-analysis software QSR NVivo.[70]

6.4 Integrated analysis

When analysis of the quantitative and qualitative data is complete, a triangulation protocol[71,72] will be used. This technique enables integration of data in order to investigate completeness, convergence, and dissonance of key themes across datasets[73]. 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 and inform decisions about changes to trial processes or intervention components ahead of a full-scale trial. Feasibility of the proposed main trial design will be assessed from recruitment and retention rates to the research evaluation in patients taking up the PROMPPT intervention and uptake of PROMPPT by patients who do not participate in the research evaluation. Intervention acceptability/feasibility will be assessed by integrating findings from the process evaluation with rates of intervention uptake, attendance at follow-up appointments and acceptability/credibility scores.

6.5 Progression criteria

The findings will determine the extent of modification needed to the intervention, clinical pharmacist training and/or trial processes before proceeding to the main trial.

Criteria to progress to a main trial with no more than minor modifications are:

- Recruitment rate to MOPP: is ≥20% of eligible patients consent to participate
- >50% of MOPP participants attend at least one PROMPPT consultation
- ≥ 70% of MOPP participants complete 3-month follow-up questionnaires.
- Mean acceptability/credibility score (items 9-12 of the Acceptability Questionnaire) ≥ 5
- Evidence from interviews about intervention acceptability is in line with the TFA (e.g. PROMPPT is understandable/has coherence, is ethical, perceived as likely to achieve its purpose, does not place excess burden on participants and participants can and want to take part).

If these criteria are not met, discussions will follow in collaboration with the Programme Steering Committee to determine which elements of the intervention, training and/or trial processes need modification and these will be refined accordingly before proceeding to a main trial.

7 DATA HANDLING

7.1 Data collection tools and source document identification

Self-report questionnaires, clinical data collected on study specific case report forms (CRFs) audio-recordings (of consultations and interviews) and prescribing data from linked medical records will form the basis of the data collection. A dedicated study database will be

developed and maintained on a secure password protected network environment at Keele University Clinical Trials Unit (registered with UK Clinical Research Collaboration) and managed by a Senior Data Manager and will be the final repository for the data collection.

Each person will be allocated a unique study number on mailing of the baseline questionnaire, so that only anonymised data are used for analysis. The unique study numbers will be generated from the study database and provided to each practice for use when mailing. The number will be made up of site ID followed by a sequence of unique numbers. The study number will be for use on CRFs, other study documents and the electronic database. The documents will also use participants' initials (of first and last names separated by a hyphen) and date of birth (dd/mm/yy).

Questionnaires will include the participant's Study ID plus date of birth and gender to confirm the correct participant's study ID has been provided. Study data will be recorded on CRFs by clinicians or local research staff who are taking part in the study and will be trained in accordance with the protocol on completing CRFs. The study site is responsible for redacting all other personal identifiable data prior to CRFs and any other reports being sent to Keele CTU, where appropriate. Following receipt, Keele CTU will contact the site to resolve any missing or discrepant data queries relating to clinical data in accordance with Keele CTU procedures.

Medical records of participant's who consent to this part of the study, will be extracted and de-personalised at their GP surgery before being securely transferred to Keele Clinical Trials Unit. De-personalised medical records will be linked to the participant's Study ID and to other study data attributed to each participant.

Consultations and interviews will be electronically audio-recorded using a dictaphone provided by Keele University and the audio files will be securely transferred from study sites into Keele's Secure Network. We will be using audio devices commonly used for research purposes. Although the devices are not password protected, the device will not be left unattended at any point until the data is transferred to Keele University's password protected secure network. The recording will be kept on the device only whilst the researcher is travelling back to Keele University, and will be removed from the device as soon as possible.

7.2 Data handling and record keeping

Data management is by Keele CTU. A Data Manager based at the Keele University CTU will oversee all responsibilities delegated to the CTU for data management and data entered to the study database.

Completed self-report questionnaires will be returned to Keele CTU in pre-paid envelopes provided to participants. Questionnaires will be date stamped on receipt at Keele CTU. CRFs will be sent to the Keele CTU either electronically or in pre-paid envelopes provided to each centre. The CTU data administrator will enter questionnaire and CRF data on to the study database around the time that they are received. Following receipt of associated consent forms, audio files will be securely transferred from study sites into Keele CTU's Secure Network and then will be securely transferred from Keele CTU to a professional transcription company, who are contracted under strict terms of confidentiality, via a secure portal.

Transcripts will be password encrypted when being returned by the transcription company via email to Keele CTU and will then be securely uploaded back onto Keele's Secure Network and the email version deleted.

All data collected during the course of the study will be kept strictly confidential and will be handled and stored in line with the local NHS and Keele CTU Data Security procedures and Keele University's Health and Social Care Quality Management System's Standard Operating Procedures (HSCR SOPs), which are in accordance with the relevant Data Protection regulations and good practice guidelines.

Audit of data entry is undertaken for questionnaires and CRFs by Keele CTU following HSCR SOPs and the verification checks supported by the research team. For details on data protection systems, see Section 9.7.

7.3 Access to Data

Direct access to study-specific data only will be given to authorised representatives of the Sponsor to permit study monitoring and audit.

7.4 Data Sharing Agreements

Prior to the start of recruitment, a signed Organisation Information Document and model non-commercial study agreement (mNCA) will be in place between each site, and Keele University to ensure the safe and lawful process of data sharing across organisations, as required by the Health Research Authority (HRA). Audio files containing qualitative data will be securely shared with a professional UK based transcription company under the terms of a confidentiality and data sharing agreement.

The EQ-5D-5L will be used with permission from EuroQol under the terms of its Non-Commercial Research Licence. Similarly, the BPI will be used with permission from the developers. The Pain Self Efficacy Questionnaire is a free to use questionnaire that does not require permission from the developers.

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 University's SOP on data sharing.

7.5 Archiving

At the end of the study, data will be securely archived in line with the Sponsor's (Keele University) HSCR 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. Archiving will be in accordance with Keele University.

8 MONITORING & AUDIT

8.1 Study Management

Sponsor

Keele University as the sponsor is responsible for initiation, operationalisation and financial management of the study. These functions are devolved to Keele CTU as will be detailed in the Delegation of Sponsorship Functions agreement, as follows:

Chief Investigator (CI)

The CI (CDM) has overall responsibility for the scientific quality and delivery of the study. The CI will also be responsible for safety reporting and escalation of reportable adverse events.

Associate Investigator (AI)

The Associate Investigator (JA) will support the CI in the day-to-day conduct, co-ordination and management of the study, ensuring the study is delivered in line with this protocol.

Keele CTU

The Study Sponsor, Keele University, delegates the management of the study to Keele CTU. Keele CTU will provide set-up and monitoring of study conduct to Keele University HSCR SOPs, and GCP, database and web application development and maintenance, protocol development, CRF design, study design, monitoring schedule and statistical analysis for the study. In addition, Keele CTU will support obtaining research ethics and governance approvals and site set-up, ongoing management including training, monitoring reports and promotion of the study. In association with the CI and AI, Keele CTU will be responsible for the day-to-day running of the study including study management and administration, database administrative functions, data management, safety reporting and all statistical analyses. Regular monitoring of study recruitment will be performed and intervention eCRFs will be monitored, against the study protocol for compliance.

NIHR Clinical Research Networks

NIHR CRNs will co-ordinate CRN support across the general practice sites and will provide funding or staff resource to secure the additional clinical time associated with service support to embed the study into the sites to allow identification of potentially eligible participants.

Study Management Group (SMG)

The SMG, convened by the CI, will comprise members of the research team and Keele CTU and will have overall responsibility for the clinical set-up, promotion, ongoing management and monitoring of the study, and for analysis and interpretation of results. The AI (JA) will chair the SMG to oversee; obtaining regulatory approvals from the HRA and general practices; monitoring and managing funding; CRF development; protocol delivery; monitoring of recruitment, intervention delivery and follow-up procedures; data collection and database development; completion of regulatory reporting requirements; reporting of unexpected events to the REC, Programme Steering Committee (PSC) and Sponsor; and completing funder reporting requirements. The SMG will meet on a regular basis throughout the study.

Programme Steering Committee (PSC)

This study forms part of a 5-year research programme. An independent PSC has been appointed according to the funder's (NIHR) requirements and has been approved by the NIHR. The PSC will provide overall supervision of the research programme according to agreed timelines. The PSC includes an Independent Chair (Professor of Primary Care and GP) and three additional independent members including; a statistician, a pharmacist, and a representative of patients and the public. The PSC will meet at agreed time points, at least annually, for the duration of the 5-year programme. The CI and AI will attend the PSC meetings to report on progress, together with other members of the research team, including the Lead Statistician and Lead Qualitative Researcher, as appropriate. Since this is a feasibility study with no planned interim statistical analysis, a data monitoring committee has not been formed and the PSC will take responsibility for monitoring study progress, adherence to protocol, participant safety and consideration of new information relevant to the research question and study design.

8.2 Monitoring arrangements

Monitoring will be conducted according to a Study Monitoring Plan developed by the SMG based on the study risk assessment and in accordance with Keele CTU and Sponsor SOPs, and agreed by the PSC. Monitoring will also be undertaken by the approving Research Ethics Committee (REC) in the format of annual progress reports, and the funder in the format of progress reports as required by the NIHR Programme Grants for Applied Research funding stream.

8.3 Safety Reporting

Adverse events

A Serious Adverse Event (SAE) is defined by the Health Research Authority (HRA) as an untoward occurrence that:

(a) results in death;

(b) is life-threatening;

(c) requires hospitalisation or prolongation of existing hospitalisation;

(d) results in persistent or significant disability or incapacity;

(e) consists of a congenital anomaly or birth defect; or

(f) is otherwise considered medically significant by the investigator.

A SAE occurring to a research participant must be reported to the REC where in the opinion of the CI the event was: "Related" that is, it resulted from administration of any of the research procedures, and "Unexpected" that is, the type of event that is not an expected occurrence as a result of the intervention provided.

The potential harms of this feasibility study are considered to be minimal. The clinical management recommendations given to participating clinical pharmacists and GPs in participating practices are considered not only to be evidence-based best practice but also have strong clinical community endorsement and credibility.

Safety Reporting Exceptions

The following expected adverse events will not be collected; transient increase in pain and /or withdrawal symptoms following opioid dose reduction that the participant feels able to manage without requirement for healthcare consultation.

Safety Reporting Process

In addition to participant self-report, we will ask study clinicians (mainly clinical pharmacists) to report related and/or unexpected adverse events and SAEs if they become aware of them during the study. Similarly, if the participant's GP becomes aware that a SAE has occurred we will request that this is reported, as detailed in the letter informing them that their patient is participating in the study. Reporting procedures will be made clear during the protocol study training and will be contained in site files for all clinicians involved in the study.

Clinicians in participating practices will be asked to record events or concerns about the safety of subjects that arise as a result of the study, even if these events or concerns do not meet the definition of a serious adverse event requiring notification to the regulatory authorities.

All SAEs occurring from the point at which participants consent to participation in the MOPP study must be notified to the study Sponsor:

- via telephone +44 (0)1782 732950 within 24 hours of the study clinicians becoming aware of the event AND
- via email sch-tr.studypromppt@nhs.net

The Study CI or AI will be asked to assess SAE causality.

Any follow-up information should be sent to the Sponsor via the Study Team as it is available, and where appropriate. Events will be followed up until the event has been resolved or a final.

Once a SAE is identified and reported, this information is to be passed to the Study Manager who will ensure that the necessary paperwork is completed and will inform the CI. In line with Keele University's HSCR SOPs the reporting clinician will give their assessment and the CI will assess whether the event is related to or resulted from any of the study procedures or interventions and expectedness, according to the process laid out in Keele University's HSCR SOPs. Any SAE considered to be related to the study procedures will be reported to the REC and the PSC Chair by the CI within 15 calendar days of becoming aware of the event. All related or unexpected SAEs will also be reported to the study sponsor.

Responsibilities for safety reporting

Chief Investigator (CI,) delegate or independent reviewer

- Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk/benefit.

- Using medical judgement in assigning seriousness and causality where it has not been possible to obtain local medical assessment.

- Review of all SAEs as detailed in the study monitoring plan.

Sponsor

- Expedited reporting of Related Unexpected SAEs to the main REC.

- Reporting of confirmed related and unexpected SAEs to the Health Research Oversight Committee (HROC) in accordance with their requirements.

8.5 Study timeline

See Study Gantt Chart (p11)

9. ETHICAL AND REGULATORY CONSIDERATIONS

9.1 Research Ethics Committee (REC) review & reports

The study will be submitted to and approved by the HRA (which includes REC) to gain the appropriate NHS Permissions prior to recruiting participants into the study. Keele CTU will provide the final protocol, participant information leaflets, consent forms and all other relevant study documentation as part of the ethical approval process.

Following initial approval from the REC, they will continually be informed of all substantial changes to the management of the study. Routine reporting will take place in line with REC requirements.

All correspondence with the REC will be retained in the Study Master File (SMF). Study Site Files including details of the original REC approval will be updated with any REC approval letters acknowledging a substantial change.

The Chief Investigator will be responsible for producing the annual reports as required and will:

- Notify the REC of the end of the study;
- Notify the REC if the study is ended prematurely, including the reasons for the premature termination and;
- Submit a final report with the results, including any publications/abstracts, to the REC within one year after the end of the study.

9.2 Peer review

This study is part of a programme of research that has obtained independent peer review, prior to award of funding, by NIHR Research Design Service (West Midlands) and through the NIHR Programme Grants for Applied Research funding application process. Further review has been undertaken within Keele CTU to ensure additional quality checks and compliance with standard operating procedures.

9.3 Public and Patient Involvement

A group of patients with experience of persistent pain and prescribed opioids was convened from Keele's Research Users' Group (RUG), to support the development of the PROMPPT research programme and the NIHR funding application. The group met 3 times prior to funding, helping to define the research questions and influencing research design by:

- Confirming that pain reviews by clinical pharmacists are acceptable if the pharmacists are part of the primary care team, the reviews are done in the GP practice with access to the medical records, and the pharmacist is an independent prescriber.
- Identifying potential advantages of a pharmacist review that would make it more attractive to patients including greater availability of appointments, longer consultations, the opportunity for telephone access to the pharmacist between appointments, and greater access to support and information.
- Highlighting valued aspects of a pain review including opportunities to address concerns about medicines, detect problems early, provide education and self-management advice or refer on to specialist services if needed.

Members of this group, including our lay co-applicant (C Sillitto) have subsequently been invited to form a Patient Advisory Group (PAG) to support delivery of the PROMPPT research programme, including this study.

The PAG will meet face-to-face at specified times over the course of the 5-year programme.

Over the course of four meetings during the intervention development work that preceded this study the PAG advised on:

- Wording of the patient-facing documents, including participant information leaflets, the invitation letter to attend a clinical pharmacist review and the development of a pre-consultation 'Pain Concerns Form'.
- How best to support discussions between patients with persistent pain and clinical pharmacists about the use of opioids for persistent pain.

In addition 2 patients were members of the stakeholder group that, over 3 stakeholder workshops, helped co-design the PROMPPT intervention and liaised with the PAG to seek feedback on the intervention design at each stage.

During this feasibility study the PAG will during two face-to-face meetings:

- Advise on the practicalities of delivering the study and data collection procedures from a patient perspective.
- Help interpret study findings from a patient perspective, including providing their perspective on emerging themes from the qualitative data analysis.
- Advise on considerations for the main trial in light of feasibility study findings.

The patient perspective will be embedded within study management and oversight. The lay co-applicant will be invited to study management group meetings and there is an independent lay members of the Programme Steering Committee representing the interests of patients and the public.

Keele University has a national and international reputation for good practice in PPIE and has strong PPIE infrastructure. The NIHR INVOLVE "jargon buster" will be used for participant information. Patients will be supported by a dedicated PPIE coordinator and user support worker. Patients have an induction, receive a plain English glossary of research terms and have access to training resources (e.g. contributing assertively to meetings). Feedback is provided

after meetings on how discussions impact on the research. Payment will be offered according to INVOLVE guidelines.

9.4 Regulatory Compliance

The study will be conducted in accordance with the principles of Good Clinical Practice (GCP) in research studies, the UK Policy Framework for Health and Social Care Research. Keele University as the Sponsor has a quality management system in place containing standard operating procedures which will be adhered to in the conduct of the study. Studies run by Keele CTU may be subject to an audit by Keele University as the Sponsor for quality assurance.

9.5 Protocol compliance

The Study Management Group will monitor protocol compliance of recruitment, treatment and follow-up procedures during conduct of this study and this will be discussed at monthly SMG meetings.

Technical deviations from protocol that do not result in harm to the study participants, do not compromise data integrity or significantly affect the scientific value of the reported results of the study will be documented and appropriate corrective and preventative actions will be taken by the research team with the CI being responsible for these with agreement from the study management group. Deviations which are found to frequently recur are not acceptable and will require consideration from the CI, sponsor and agreement from the study management as to whether they are to be classified as a serious breach.

9.6 Notification of Serious Breaches to GCP and/or the protocol

A “serious breach” is defined as a breach of the protocol or of the conditions or principles of Good Clinical Practice which is likely to affect to a significant degree the safety or physical or mental integrity of the study subjects, or the scientific value of the research.

Keele CTU has systems in place to ensure serious breaches of GCP of the study protocol are identified and reported.

In the event of doubt, or for further information or guidance, the investigator should contact the Study Manager or CI at Keele CTU. All protocol deviations and breaches of GCP will be recorded and reported to the Sponsor, REC and PSC according to the applicable HSCR SOP.

The Sponsor will be notified immediately of any case where the above definition applies during the study conduct phase. The sponsor will notify the REC in writing of any serious breach of

a. the conditions and principles of GCP in connection with that study; or

b. the protocol relating to that study, within 7 days of becoming aware of that breach.

9.7 Data protection and patient confidentiality

The standard data protection procedures operating in Keele CTU will be employed to protect confidentiality and anonymity. Each participant is allocated a unique study identification (ID)

number, so that only anonymised data are used for analysis. At the end of the study, database anonymisation and locking will be carried out in accordance with HSCR SOPs. Transcriptions from interviews will be checked for accuracy against the audio recording and fully anonymised (names of people or places removed, labelled with unique study ID numbers).

Keele CTU has robust data security systems and procedures in place, which are regularly reviewed, and which achieve the legal obligations set by the Data Protection Act (2018) and the General Data Protection Regulation (GDPR) and follow GMC Caldicott Guardian and British Computer Society standards and guidelines. Information about Keele University's Privacy Notice will be included in the Patient Information Leaflet.

All participant data will be housed in the CTU Infrastructure, which is a secure virtual network requiring two factor authentication (2FA) in order to access the data stored within. Permissions are applied to users within the network to restrict access to study data as required. Only authorised members of staff will have access to the study data.

The CTU Secure Infrastructure has been independently audited and achieved level one of the Government backed Cyber Essentials Scheme. All hard copy information will be stored securely in locked cabinets in accordance with HSCR SOPs. Data used for analysis will be kept separate from consent forms containing participant identifiable information.

All confidentiality arrangements adhere to relevant regulations and guidelines and the CI and study statisticians (Data Custodian) have responsibility to ensure the integrity of the data and that all confidentiality procedures are followed.

9.8 Financial and other competing interests

The chief investigator, associate investigator, study management committee members and independent steering committee members have no financial or other competing interests to declare

9.9 Indemnity

The study is sponsored by Keele University. The University carries Professional Liability and Medical Malpractice insurance to indemnify it, subject to the terms and conditions of the policy, for its legal liability for claims or damages arising out of any bodily injury, mental injury, illness, disease or death of any patient caused by negligent act, error or omission committed by the University in the course of its business.

The NHS has a duty of care to patients whether or not they are taking part in research. The NHS organisations remain liable for clinical negligence and other negligent harm to patients under their duty of care.

9.10 Amendments

The detailed protocol will be updated in response to approved amendments, as required.

9.11 Post study care

All participants in the study will continue to receive usual care from their treating clinician(s).

9.12 Access to the final trial dataset

At the end of the study, archiving of essential study documents at Keele University will be authorised by the sponsor following submission of end of study reports which will be for ten years after the end of the study. Destruction of essential documents requires authorisation from the Sponsor.

A record of consent will be held in the local investigator site file. All other data will be held by Keele CTU and will be archived in the designated Keele CTU archive facility. Following authorisation from the Sponsor, arrangements for the destruction of all confidential data will be made.

Any subsequent requests for access to the data from anyone outside of Keele CTU (e.g. collaboration, joint publication, data sharing requests from publishers) will follow Keele University's standard operating procedure.

The anonymised datasets generated during and/or analysed during the current study will be available upon request from primarycare.datasharing@keele.ac.uk. A data request form is required to be completed and must outline the type of data to be obtained, the reason for obtaining this data (research question / objective), the timing for when the data is required to be available (start date/end date). Checks will be performed by a Data Custodian and Academic Proposals (DCAP) committee at Keele to ensure that the data set requested is appropriately suited to answer the research question/objective and that the request fits with the original ethical approval and participant consent and adheres to funder and legal restrictions. Only de-identified data are available for request in aggregated format or at the level of the individual participant.

10 DISSEMINIATION POLICY

10.1 Dissemination policy

All foreground intellectual property (IP) arising from this study will be managed by Keele University. A consortium agreement between North Staffordshire CCG and Keele University assigns all foreground IP to Keele University and provides the legal framework for identification, management, protection and exploitation of IP. The copyright of all materials will belong to Keele University.

On completion of the study the data will be analysed and a final study report prepared. This report will be included in the annual report submitted to NIHR in accordance with the conditions of the grant award. All publications, presentations, correspondence and advertisements arising or related to the grant must acknowledge NIHR as the study's funding source. When acknowledging NIHR UK support, the grant reference number must be quoted.

The results of this study will be made widely and freely available to all stakeholders in ways that are easy to access at no cost. Our Patient Advisory Group will advise on how to translate these into easily understandable messages and on how best to disseminate the results to the wider public. We will feedback a summary of the results to participating GP practices by letter and publish these on the PROMPPT research programme website (www.promppt.co.uk) and on the Keele University School of Primary, Community and Social

Care website (https://www.keele.ac.uk/pchs/). In addition to publications in open-access peer-reviewed journals, we will use our website, NHS networks and links to professional bodies to support dissemination of the findings to all stakeholders and will use social media to promote the findings via our dedicated Twitter and Facebook feeds.

10.2 Authorship

Authorship for the final report of this study will be the PROMPPT study team, protocol contributors and individuals involved in study management. Authorship on any publication resulting from the work described in this protocol will follow the criteria of The International Committee of Medical Journal Editors has defined authorship criteria for manuscripts submitted for publication.

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