STUDY PROTOCOL

REVISED Pharmacist-led DE-eSCALation of opioids post-surgical dischargE (DESCALE) – A multi-centre, non-randomised, feasibility study protocol

[version 3; peer review: 3 approved, 1 approved with reservations]

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Abstract

Background

Opioids are frequently prescribed for short-term acute pain following surgery. Used appropriately, opioids deliver extremely favourable pain relief. Used longer than 90-days, however, can result in health complications, including unintentional overdose and addiction. Globally, >40 million people are dependent on opioids and annually >100,000 die from opioid misuse. With >4.7 million surgical procedures occurring annually in the United Kingdom it is imperative that opioid-use is managed upon discharge. A declining General Practitioner (GP) workforce and increased patient numbers, however, means gaps in healthcare during transfer of care. Here we report a mixed-methods protocol to understand the feasibility, and acceptability of a clinical pharmacist (CP)-led early opioid deprescribing intervention for discharged surgical patients.

Methods

DESCALE is a multicentre, non-randomised, pragmatic feasibility study. Participants aged ≥18 years who have undergone a surgical procedure at a single NHS trust in Southeast England and discharged

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with opioids and without a history of long-term opioid use, cancer diagnosis or study contraindications will be offered a Medicines Use Review (MUR) within 7–10 days of discharge. The MUR will be delivered by CPs at participating GP practices. Feasibility outcomes will focus on recruitment, fidelity of CPs to deliver the MUR, and barriers within primary care that affect delivery of the intervention, with a maximum sample size of 100. Clinical outcomes will focus on the number of participants that reduce or stop opioid use within 91 days. Prescribing, medical, surgical, and demographic data for individual participants will be collected and analysed to inform future trial design. Qualitative interviews with participants and associated healthcare professionals will explore acceptability and implementation of the intervention.

Conclusion

Data collected with respect to opioid use post-surgery, feasibility and acceptability of the intervention, patient experience and outcome data will inform the design of future research and larger clinical trials.

Plain Language Summary

Opioids are very strong pain killers often given to help with severe pain, such as after having surgery. Used for a short time these drugs are very good at taking away pain. When used longer than the recommended 2-4 weeks, opioids can cause more pain and become addictive or even, the risk of early death. Despite the high side effects from using opioids, the numbers of people given these drugs has risen sharply. Whilst it's important that surgical pain is treated correctly, it is equally important that opioids are not continued for longer than is needed and is safe. Almost 5-million surgeries occur every year in the United Kingdom (UK), yet there are no national guidelines for healthcare professionals giving out opioids after surgery. This risks these sorts of drugs being used for too long by patients. In the UK, East Kent has been highlighted as a region with above average use of these drugs by patients and use for longer than is needed and safe.

This study is funded by the National Institute for Health Research, approved by the North-West Greater Manchester Central Research Ethics Committee, and designed with public and patient involvement groups. Learning from this study will help us understand if it is feasible for pharmacists based in GP surgeries to speak with, and support patients given opioid drugs after surgery, and ensure these drugs are used for only the amount of time needed. It will also show us what improvements need to be made before conducting a larger study.

We are working with all three hospitals within East Kent University Foundation Trust and six participating GP practices to recruit 100 patients to take part. Results will be shared in NHS websites/newsletters, in community magazines and in academic journals.

Keywords
Opioids, deprescribing, surgery, dependence, clinical pharmacists, Medicines Use Review, primary care, secondary care

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REVISED **Amendments from Version 2**

The manuscript has been amended to show that participants were offered a £25 shopping voucher to take part in an interview.

Any further responses from the reviewers can be found at the end of the article

Introduction

The opioid problem

Opioids are very strong painkillers that are frequently prescribed to treat short-term acute pain, such as after having a surgical procedure. Used for acute or end of life pain, these drugs deliver favourable analgesic pain-relief. Opioids can however cause serious health risks and side effects such as more pain (opioid-induced hyperalgesia), medication dependence and in some cases unintentional overdose or premature death from misuse if used for a long period of time (>90-days)[1,2]. In the United States (US), a White House commissioned report in 2017 into opioid misuse, found that it was responsible for the death of 64,000 people annually and the leading cause of death related to unintentional injury[3,4]. In the United Kingdom (UK), during the period 2020-2021, almost half (49.6%) of all drug-related deaths involved an opioid[5]. Despite the high potential for serious adverse events when using opioids, the global numbers of people using opioids, over the past two decades has risen dramatically, along with an associated increase in long-term dependency and mortality[6–10]. In 2017, it was estimated that 40.5 million people were classified as 'dependent' on opioids and 109,500 people had died from opioid overdose, worldwide[10]. The first few days of opioid therapy have been shown to be crucial in determining the likelihood of long-term opioid use. Patients receiving opioids for longer than a week, were found to double their risk of using opioids for more than a year, which doubled again if opioids were used for longer than a month[11,12]. Whilst another study has shown that the cumulative opioid dose dispensed in the first month was also strongly related to the probability of long-term use, with long-acting drugs being worse, than short-acting drugs[13].

Surgical opioid use

Opioids are routinely used pre-, intra-, and post-surgically for the treatment of acute pain and post-operatively for pain management and is a primary route to exposure to these types of medicines, often for the first time[14,15]. Evidence from the US and Canada has shown a clear link between post-surgical opioid prescribing for both minor and major surgery, and persistent long-term use in the community, beyond tissue healing. Inappropriate prescribing of opioids both peri- and post-operatively, accounts for 36.5% of all opioid prescribing in the US, with 3 – 10% of these patients transitioning to long-term use[11,14,16,17]. Patients undergoing surgery are almost four times more likely to be discharged with opioids than their non-surgical counterparts[18]. This is often with more opioid medication than is actually required to treat post-surgical pain[19–22]. Perhaps more alarmingly, almost half (45%) of these patients are given opioids even though they would not have been taking any opioids at point of discharge[23]. In the United States (US), a study showed that between 5.9 – 6.5% of all patients who underwent surgery (versus 0.4% of the non-surgical control) went on to become long-term opioid dependent, even if they had never taken opioids before[15].

It is becoming clear from the US, that postsurgical prescribing of opioids is a problematic, underexplored, new source of long-term opioid use[17]. Compared to the US and Canada, less is known in the UK about peri-operative opioid prescribing in hospitals and any link to long-term use. Two recent studies in the UK have identified long-term opioid use (>1 year) to be associated with older age (>75 years), being socio-economically disadvantaged, having a history of depression and/or alcoholism, prior gapapentinoid or psychotrophic use, and those initiated on >120 morphine milligram equivalents (MME) following major surgery[6,24]. There are over 5.6 million opioid prescriptions dispensed each year in the UK, corresponding to around 13% of the adult UK population[25] and over 4.7 million surgical procedures occurring each year[26] and nearly 8 million people on surgical waiting lists, with over 300,000 waiting more than 52 weeks for surgery[27]. This, along with no current national guidelines on peri-operative opioid prescribing, a declining GP workforce and increasing patient numbers[28], policy makers and professional bodies are rightly concerned. In 2020, the Faculty of Pain Medicine and Royal College of Anaesthetists established a working party to set out 'guiding principles' in opioid management in the peri-operative period[29]. In these guidelines, they acknowledge the critical role that surgery plays in the burgeoning opioid problem: "*We have a duty to act to minimise the role that anaesthesia, surgery and primary care may have in contributing to the "opioid load" in the community in the UK. It is imperative that all healthcare professionals involved in surgery and perioperative care, work collaboratively to ensure robust opioid stewardship"*[29,30]. Whilst, the National Health Service (NHS) England Medicines Optimisation Executive Group have made reducing opioid use in chronic non-cancer pain a priority of the integrated care boards for 2023/2024[31].

Opioid problem in East Kent

Prescribing of high-dose opioids in East Kent has long been a growing concern within the NHS Kent and Medway Integrated Care Board and Integrated Care System (previously known as the Clinical Commissioning Group (CCG)). A recent report from Public Health England (PHE) highlighted East Kent Health and Care Partnership as being one of the top 30 highest opioid prescribers in England, with an opioid spend of £422,000/year above the national average and prescribing rates 3 – 4 times above the Kent and Medway CCG average[25]. This has led to initiatives such as the East Kent High Dose Opioid Reduction project, a pharmacist-led intervention, established to tackle, high-dose long-term opioid users on >120 mg morphine milligram equivalent (MME) per day[32]. Despite the success of such projects to reduce harmful levels of opioid use in the East Kent community, they

do not allow us to understand the root source of the opioid problem from which these complex opioid users arise. Local prescribing and chronic pain clinical leads supporting this study are therefore keen to understand why these patterns of prescribing exist and what preventative opportunities might reduce prescribing and is where our study is based. Deprescribing opioids in a timely manner is important to minimise both the risk of any patient developing opioid tolerance and the possibility of any withdrawal symptoms or adverse events occurring.

Pharmacists and opioid management

Pharmacists are experts in medicines management and are trained to deliver high-risk Medicines Use Reviews (MURs), an activity that the public closely associate with the role of a pharmacist[33–35]. Indeed, in the UK, community pharmacists are contracted as part of the Community Pharmacy Contractual Framework[36] to deliver MURs to patients and by clinical pharmacists based in GP practices, as part of the additional role reimbursement scheme[37]. However, for community pharmacists, access to a patient's medical records and GP, can be a limiting factor[38]. particularly when deprescribing medications such as opioids. Thus, clinical pharmacists employed in GP practices with access to patient hospital discharge lists, medical records and onsite support from GPs are ideally positioned to initiate early opioid deprescribing in post-surgical patients discharged back into the community.

Aims, objectives and outcomes

The primary aim of this study is to evaluate a multi-centre, pharmacist-led, early opioid deprescribing intervention. This is designed for patients discharged following a surgical procedure with an opioid prescription from hospitals within a single NHS Trust in an area of high opioid prescribing, East Kent. It will determine whether this designed intervention is able to support early deprescribing of opioids in this particular healthcare setting and with this particular patient population and to inform a much larger, clinical trial. The primary outcome of the DESCALE study is to determine the feasibility of the designed intervention to support early deprescribing of opioids in this particular healthcare setting, using this particular healthcare personal and with this particular patient population, in order to inform a much larger, clinical trial. A summary of the aims, objectives and outcomes for this study are collated in Table 1.

Protocol

Patient and Public Involvement

The patient and public involvement and engagement team (PPIE) consists of 3 National Institute for Health and Care Research (NIHR) Research Champions from Kent Community Health Foundation National Health Service (NHS) Trust, who have reviewed and modified the protocol and informed the content of the study, to ensure a patient-centred approach. In addition, each Research Champion has undergone qualitative research training, assisted in designing the interview schedule and are involved in delivering qualitative interviews to patient participants of the study. Two members of the public, with experience of receiving post-surgical opioids, participated in practice training MURs with the clinical pharmacists and two additional public contributors joined the research team, participating in monthly project meetings, assisting, and embedding their support in the project as it progresses. On completion of data collection, we will continue to work with the PPIE team to develop lay-friendly summaries of the findings for dissemination to the participants and public.

Methods

Study design and setting. This is a prospective multi-centre, non-randomised, pragmatic feasibility sub-study, within the larger DESCALE study. The study involves clinical pharmacists based in GP practices in East Kent, initiating an early opioid MUR to support pain management and initiate opioid de-escalation, for surgical patients discharged from a hospital belonging to East Kent Hospitals University NHS Foundation Trust (EKHUFT). The study identifies potential participants from surgical discharge letters by practice staff, before an initial eligibility check, and consent to take part. A baseline MUR is conducted within 7 – 10 days of hospital discharge and continued monitoring and follow up MURs conducted as per the study design (see Study Flow Chart – Figure 1) until opioids have been discontinued or the participant is 3-months post-discharge[39]. Recruitment of GP sites and participants, commenced in January 2024 and will continue until December 2024. We have currently recruited six primary care GP practices from East Kent to participate in the study.

Trial registration

ClinicalTrials.gov: NCT06396663 (02/05/2024)

Accessed at: https://clinicaltrials.gov/study/NCT06396663

Protocol version

Protocol Version 11, approval date 03.05.2024

Eligibility criteria

Inclusion criteria

- Adults aged ≥18 years
- Undergone a major or minor surgical procedure (see surgical exclusions below) in a hospital belonging to EKHUFT, either as an in- or outpatient, who were discharged with opioid medication ≤120 mg MME/day and registered at a participating East Kent, GP practice.

Exclusion criteria

- Aged ≤18
- Unable to provide written informed consent
- On a dose of opioids >120 mg MME/day
- Taken opioids for >90 days prior to having surgery
- Taking opioids for malignant pain

Table 1. Summary of study aims, objectives and outcomes.

Aims/questions	Objectives	Data collected/Outcomes
Test the feasibility of delivering an early opioid deprescribing intervention in primary care, led by trained clinical pharmacists.	Ascertain stakeholder acceptability of the intervention	• Qualitative interviews with pharmacists and stakeholders - identify perceptions of the intervention and barriers/enablers for delivery • Research team notes on barriers and facilitators when delivering the study within GP practices
	Determination of the fidelity of an early opioid deprescribing intervention led by trained clinical pharmacists in primary care and its potential role in wider medicine's optimisation	Assess the capabilities of trained clinical pharmacists to deliver an early opioid medication review through: • Completion of intervention delivery training with the Clinical Lead • Observational competency checks by Clinical Lead at regular weekly drop-in support sessions • Completed medication review case reports reviewed by the research staff at GP surgery and by study team for accuracy • The percentage of participants successfully de-escalated by the pharmacists delivering the intervention. Measured as the mean difference in morphine milligram equivalent (MME) dose at baseline and at end of intervention (<91 days)
	Ascertain participant acceptability of the intervention	• Number and baseline characteristic (age, gender, surgical procedure) of participants that are eligible for the study versus those that are approached and subsequently enrol in the study Number of participants that decline or withdrawal from the study Adherence to pharmacist medication recommendations based on the completed CRF • Participant satisfaction questionnaire avalable at https://osf.io/yv2cj/ • Themes derived from participant interviews –participants experience, support and thoughts on the intervention including barriers/enablers that affect the delivery of the intervention from patient perspective
	Apply a micro-costing approach to estimate the intervention costs	• opioid medication costs per patient • staff and equipment costs to deliver intervention (pharmacist, practice staff and training)
To understand post-surgical opioid prescribing experiences including opioid use, long-term opioid use, participant pain and quality of life in the 3-month period post-surgery when discharged with an opioid prescription	To ascertain factors involved in post-surgical opioid prescribing and use and to relate this information for a future trial	• Medication opioid use data at baseline (day 0) and at all follow-up appointments (≤91 days) • Opioid prescribing (type, dose, amount) at baseline (day 0) for each surgical specialty and hospital • Pain scores at baseline (day 0) and final appointment • Measurement of risk factors in the participant population that have been previously linked to long-term opioid use Baseline demographics (age, sex, BMI, ethnicity, social deprivation scores, smoking and alcohol consumption) • Medical (comorbidities, healthcare use), prescription (prior opioid, gabapentinoid and psychotropic use, other medication use) and surgical (surgery type, hospital, ward, opioid – type, strength, duration, average pain score) histories • Quality-Of-Life questionnaire (EQ5D-5L) responses at baseline and final appointment (≤91 days post-surgery) to assess health status before and after the intervention. Scores will be related to opioid-use and pain scores at each data collection point

Aims/questions	Objectives	Data collected/Outcomes
To ascertain per protocol feasibility to inform a future study or adoption of the protocol in the existing healthcare system	Determination of the integrity, robustness, and transferability of the protocol for future trial or adoption by the NHS	Measurements of: • Screening and recruiting participants as recorded in the recruitment log • Perspectives on adaptability of the intervention between primary care settings • Availability of pharmacists available to deliver the intervention • Time taken from hospital discharge to receiving first MUR. • Average time taken for each appointment • Average time taken to successfully deescalate opioids in surgical patients • Number of participants that are successfully deprescribed opioids within 3 months • Number of patients that require additional appointments with the pharmacist • Number of participants that require additional support post-90 days • Themes derived from participant and stakeholder interviews

- Follow-on surgery planned in the next 3 months
- Undergone a caesarean section
- Pregnant
- A history of using methadone or injecting opioids
- In the opinion of the recruiting clinician the participant is considered vulnerable (e.g., severe dementia, severe co-existing or terminal medical condition).

Recruitment

Participants: Participants will be identified through GP practice database search using criteria as per the inclusion criteria i.e. as having had surgery and discharged with opioids (<120 mg) within the last 7 days. In some cases, local processes may require a manual review of discharge letters as time taken to process the discharge letters and code patients to make them searchable, can vary. Searches will be undertaken on a weekly/bi-monthly basis where possible. Potential participants identified via searches or discharge letters, will also be screened against the exclusion criteria. Participating sites will then contact potential participants by either an email or text, inviting them to participate in the study and providing a link to the patient information leaflet (PIL). Invited participants will then be contacted once by the practice using a consecutive sampling approach via telephone within 48 hours of the invite being sent, asking if they would like to take part in the study, answering any questions and confirming their eligibility. For patients that agree to participate, an MUR appointment (online, telephone or in person) will be arranged with the pharmacist and a link to an online consent form sent to the participate to complete. For participants that decline to participate, baseline characteristics collected during database searches (age, gender, surgical procedure and opioid prescribed) will be analysed against those that choose to participate to determine any factors that may influence participation, so to inform feasibility and future intervention design. At the last MUR appointment, patients will then be invited to a follow up interview to ask about their experiences of the intervention. Consent will be taken by the research assistant for those that agree to participate, and the interviews will be carried out by a public research champion allowing peer-to-peer interaction.

Sample size: A sample size of 80 – 100 participants will be recruited. Statistically, sensitivity power analyses have confirmed that the proposed number is able to detect significant differences of the expected effect size and is in line with the recommended sample size of 70 to estimate key parameters, bench-marked from external pilot randomised controlled trials[40] and will allow for participant loss, to follow-up. To maximise recruitment all participants will be invited to take part in the follow up interview, with the aim to achieve 20% of the sample size, giving 16–20 interviews.

GP practices: By utilising networks locally an Expressions of Interest document was circulated to GP practices in Kent. Further to this, research active practices in East Kent and South Kent were approached directly and capacity and capability assessed. Moreover, the project's Clinical Lead contacted clinical pharmacists who had interest in, or experience in research of opioids or pain, to invite them to express interest in recruiting via their practice(s).

Clinical pharmacists: GP practice-based clinical pharmacists with experience of delivering MURs and opioid deprescribing will be recruited from participating practices. The clinical pharmacist/s will receive detailed information about the

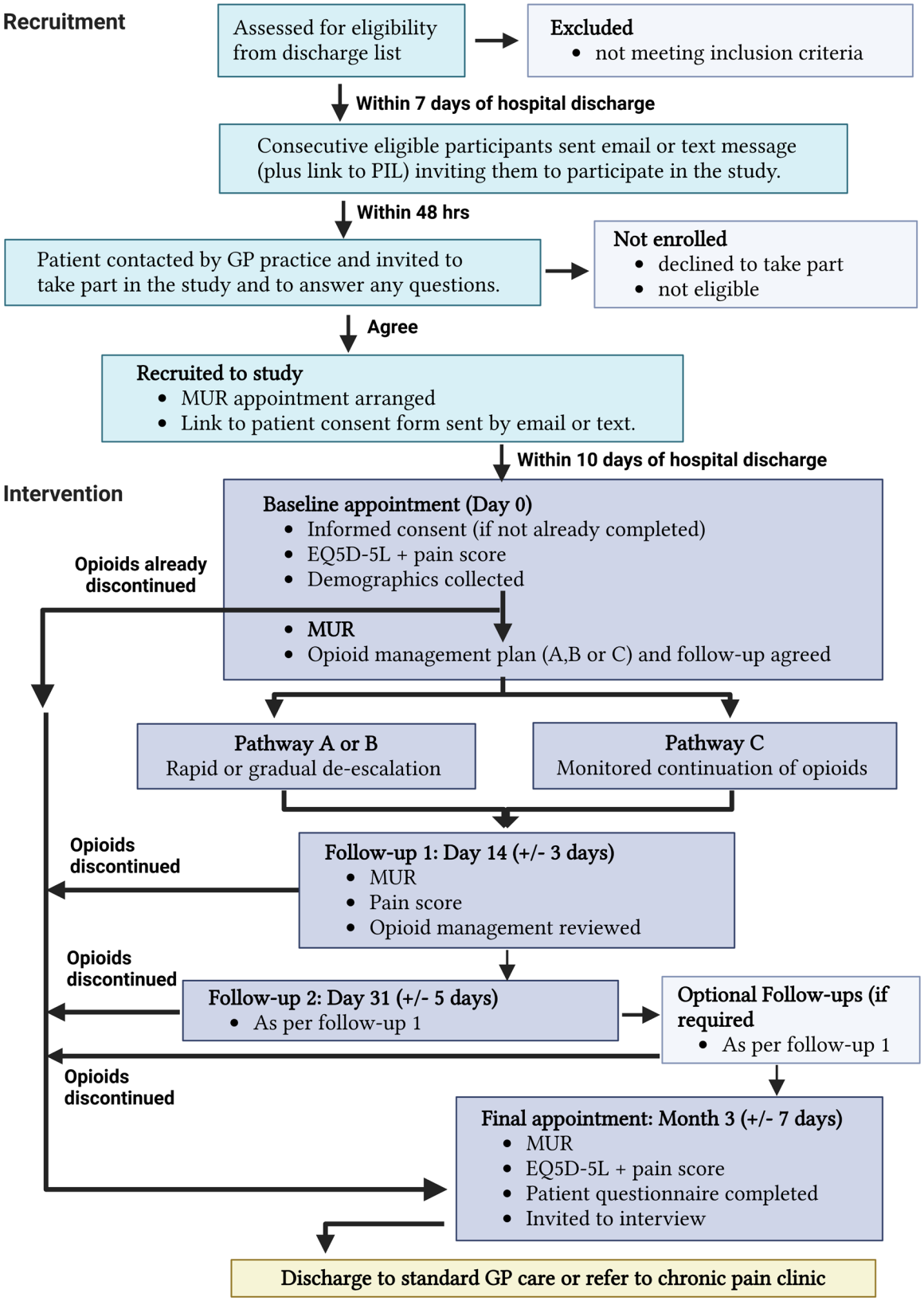

Figure 1. DESCALE Study Flow Chart. Abbreviations: PIL – patient information leaflet; hrs – hours; GP – general practitioner; MUR – medicines use review; EQ5D-5L – European Quality of Life 5 Dimension 5 Level survey. Image created with BioRender.com.

study, undergo some training with the study Clinical Lead and will be asked to provide written informed consent.

Consent process

Consent to participate in the study will be sought from all eligible patients that have undergone a surgical procedure and are discharged with an opioid prescription from the participating East Kent hospital sites and participating GP practices. Consent will only be sought after a full explanation and/or the PIL has been offered with time allowed for questions and proper consideration. Individuals willing to take part and for whom an MUR appointment has been made will be asked to complete a Participant Consent Form. A Consent form will be sent to those with digital capabilities prior to the MUR or completed together with the pharmacist at the first appointment. A typewritten signature or tick box declaration option, in accordance with the UK eIDAS Regulations (SI 2016/696) will be used for all digital consent forms. All consent forms will be checked and countersigned by the pharmacist prior to the commencement of the medication review. A copy of the consent form will be added to the participants medical records, and another retained in the study site folder, stored at the practice and a copy sent to the participant. Additional consent will be sort from any participants that agree to participate in a post-study interview.

Study interventions

Following recruitment and consent of eligible participants, a timely appointment (within ten days of hospital discharge) will be arranged with the pharmacist for an opioid MUR and biopsychosocial assessment. A detailed schedule of events can be found in Table 2.

Study MUR and biopsychosocial assessment protocol

During the intervention the clinical pharmacist will complete an online baseline data collection, case report form (CRF) where they will record:

- Surgical procedure undergone (hospital, ward, date, and length of stay)
- Opioid (drug name, dose per tablet (milligram (mg)), number of tablets/patches prescribed per day (24 hrs), total number of tablets prescribed)
- Opioid use prior to surgery (drug name, dose per tablet (mg), number of tablets/patches prescribed per day (8 am to 8 am), total number of tablets prescribed), length of time on opioids
- Calculate the combined morphine equivalent dose (MME, using Faculty of Pain Medicine guidelines)[29]

Table 2. Participant timeline and schedule of events.

			Follow-up			
Study activity	**Pre-intervention**	**Baseline (Day 0)**	**Day 14 (± 3 days)**	**Day 31 (± 5 days)**	**Month 3 (± 7 days)**	**Post-intervention**
Eligibility check by Health Care Professional	☑	☑				
Informed consent	☑	☑				
Demographics		☑				
EQ5D-5L		☑	☑[a]	☑[a]	☑[a]	
Pain Score		☑	☑	☑	☑	
MUR		☑[b]	☑[b]	☑[b]	☑	
De-escalation pathway agreed		☑	☑	☑	☑	
Medication change form and prescription if required.		☑	☑	☑	☑	
Data Collection		☑	☑	☑	☑	
Participant experience questionnaire			☑[a]	☑[a]	☑[a]	
Participant interview invite			☑[a]	☑[a]	☑[a]	
Handover /discharge to standard care or pain clinic					☑	
Participant interview						☑

[a]Activities occurring at participants final appointment as determined by their individual de-escalation plans. [b]Optional follow-up appointments may be agreed depending on de-escalation plan and individual needs. Abbreviations: EQ5D-5L - European Quality of Life 5 Dimension 5 Level; MUR – medicines use review.

- ➢ Record use of other analgesics including paracetamol, Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and other adjuvants – (drug name, dose per day)
- ➢ Determine if medically treated for depression or anxiety (if yes, drug name and dose) – taken from patient or retrieved from medical records, where applicable.
- ➢ Patient pain intensity in the last 24 hrs, measured using the Verbal Pain Rating Scale (No pain = 0; mild pain = 1; moderate pain = 2; severe pain = 3; very severe pain = 4)
- ➢ Record any coexisting morbidities and their effect on pain
- ➢ Record alcohol weekly consumption (1 – 7, 8 – 14, or >14 units*)
- ➢ Smoker (yes/no)

*One unit of alcohol is equivalent to 10 mL or 8 g of pure alcohol. E.g., 1 glass of wine (175 mL) = 2.1 units.

Following the MUR and biopsychosocial assessment, the clinical pharmacist will then decide with the patient which one of the three opioid de-escalation pathways (A, B or C) developed using various sources, American Pain Society[41], Veteran Affairs/Department of Defence[42], see also Kral *et al.*, 2015[43] they will follow (Figure 2). Due to a paucity of guidelines available for reference for dosage reduction or discontinuation of opioids particularly following surgery, guidance was adapted from the CDC Guideline for Prescribing Opioids for chronic pain[44]; from the Veterans Health Administration Practice Guideline for Opioid Therapy in Chronic Pain[45]; from the US Department of Health and Human Services Guide for Clinicians[46]; and in collaboration with the local Community Chronic Pain Service.

Pathway A – Rapid opioid de-escalation

For this pathway the clinical pharmacist may recommend immediate discontinuation of opioids if any of the following apply:

- ➢ Patient has been taking opioids for less than 7 days post-discharge and combined MME is less than < 30 mg/day (see Table 1).
- ➢ Opioids were not being used prior to surgery.
- ➢ Patient has no history of alcohol or substance abuse.
- ➢ The acute pain condition following surgery has resolved.
- ➢ The patient requests discontinuation of opioids.
- ➢ The patient has developed intolerable side effects from taking opioids.
- ➢ *The patient is at risk of a serious adverse event (SAE), such as overdose (refer to specialist service).
- ➢ *There is evidence of opioid diversion (refer to specialist service).

*Specialist services are required to manage these complex patients and will be referred to the Clinical Lead for guidance and recommendation.

Pathway B – Gradual de-escalation of opioids

For this pathway the clinical pharmacist may recommend 'gradual' discontinuation of opioids if any of the following apply:

- ➢ Patient has been taking opioids for more than 7 days and/or the combined MME is more than > 30 mg – 120 mg/day or ≥12 μg/hr transdermal Fentanyl patches or ≥15 microgram (mcg)/hr Buprenorphine patches
- ➢ The medication is not providing useful pain relief and function has not improved
- ➢ Patient was taking opioids prior to surgery to treat pain related to their condition.
- ➢ Presents with other co-morbidities including mental health disorders
- ➢ Patient has a history of alcohol or substance abuse
- ➢ Patient is taking other medications (e.g., benzodiazepines, gabapentin, pregabalin or muscle relaxants) or medical conditions (lung disease, sleep apnoea, liver disease, kidney disease, fall risk, advanced age) that could increase the risk of adverse events (AEs)
- ➢ Patient requests a dosage reduction of their opioids
- ➢ The pharmacist feels it is safer to start with a gradual de-escalation of opioids

Pathway C – Continuation of opioids

In some instances, such as following major surgery or in cases where the patient is in considerable discomfort reflected in their pain scores the clinical pharmacist will recommend that the patient should continue taking their prescribed opioids, which is reviewed again after one week, if:

- ➢ Benefits of taking opioids outweigh the risk of discontinuing opioid therapy – participants are still enduring considerable pain from the surgery as measured by their pain scores
- ➢ Prior opioid use was for another condition not related to the surgical procedure
- ➢ Patient does not want to discontinue their opioids

Pathway's will not be exclusive to allow for patient variability in opioid withdrawal coping, and ongoing pain management and thus possible that patients will transition between pathway A and B, and from pathway C to B or A. We anticipate that for most participants, where opioids are being used primarily for the treatment of post-surgical pain or acute injury, pain which should normally subside after 3 – 4 days, and receiving opioids for the first time, will not require complex de-escalation protocols and psychological support. For those participants who have required prior (≤90 days) opioid use to manage their condition prior to surgery, or opioids for an unrelated condition, or on a higher dose, a more gradual discontinuation of opioids or referral to a specialist pain service, may be required.

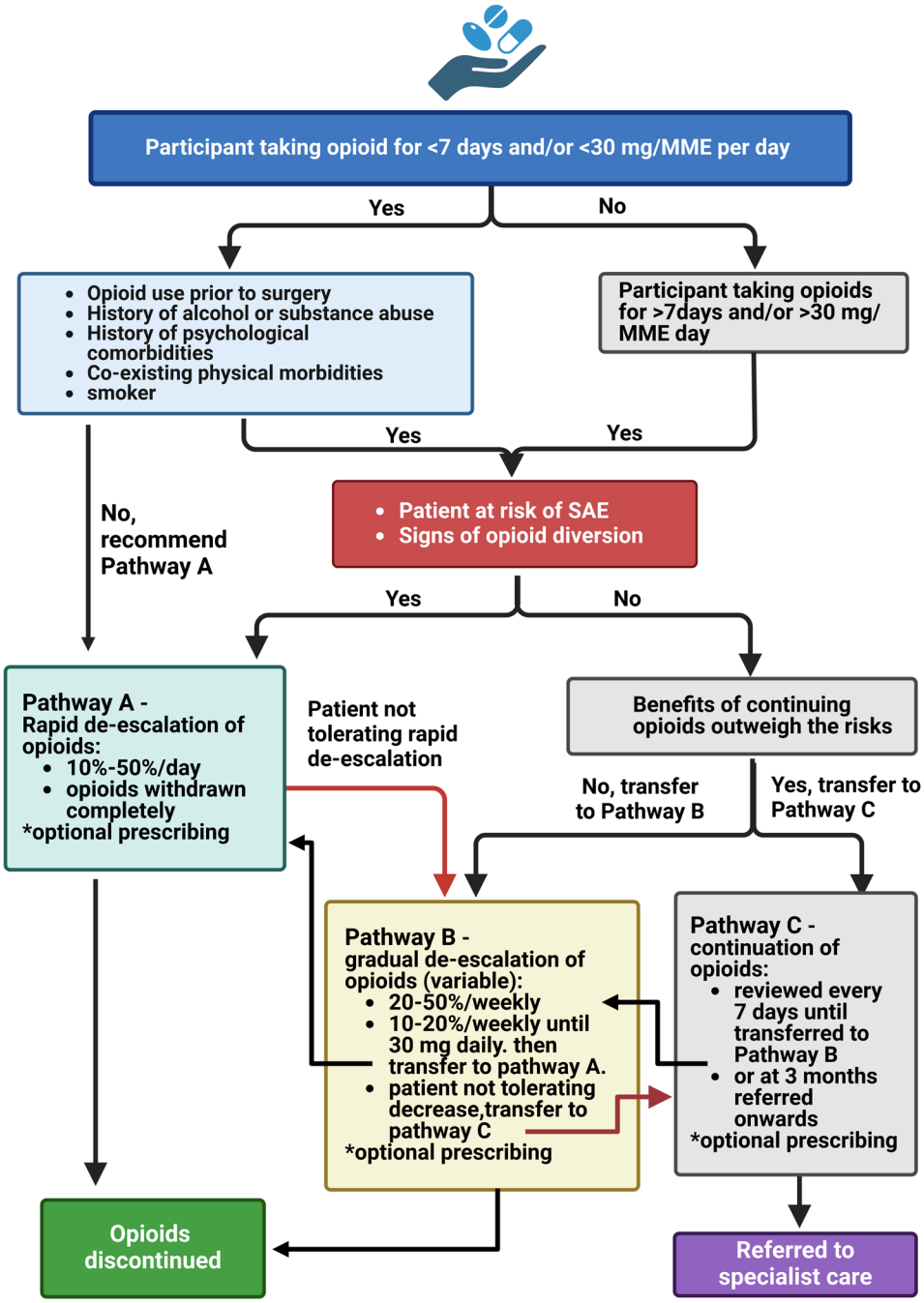

Figure 2. Intervention pathways and guidelines flow chart. N.B. These are just guidelines and subject to adjustment by the participating practices and pharmacists. *The pharmacist may also prescribe/recommend other pharmacological approaches to deal with: aches/pains – NSAIDs: Ibuprofen, 400mg/3X/daily or paracetamol, 1000 mg, every 6 hours; diarrhoea – Loperamide 2-4 mg as needed (up to 16 mg/day); constipation – laxative, as and when needed. Abbreviations: MME – morphine milligram equivalent; SAE – serious adverse event; hr – hour; mcg – microgram; NSAIDs – non-steroidal anti-inflammatory drugs. Image created by Biorender.com.

GP notification and medication change recommendations

The clinical pharmacist will record all medication changes and recommendations on the participants medical records. In cases where alternative medication or additional prescriptions are required this will be handled as per normal GP practice procedure.

Withdrawal symptoms and adverse events

Due to the design of the intervention, we anticipate that withdrawal symptoms and adverse events that may occur as a result of opioid de-escalation will be minimal, and it at all will occur only in the first few hours or days. Any withdrawal symptoms or adverse events that are considered associated with opioid withdrawal will be recorded by the

clinical pharmacist on the CRF. Any untoward medical occurrence or hospital readmission that could be related to the study intervention will be recorded and reported to the study coordinator within 24 hrs. The Clinical Lead will review causality and if required report it to the sponsor (University of Kent) who will inform the NHS ethics committee.

End of intervention

The end of the intervention is defined as when the participant has either discontinued their opioids and all final paperwork has been completed or after 3 months, where any participants still taking opioids at 91 days, and where pain will be considered chronic[39], will be referred on to specialist care. All participants will be invited to fill in an online participant satisfaction questionnaire (15 – 20 mins) about their experience of the intervention they received. In addition, all participants will be invited to take part in an online or telephone interview with a member of the study team. Interviews are expected to take 30 – 45 minutes, will be semi-structured using a topic guide and cover a knowledge of opioids and their potential risks, experiences of taking part in the intervention, including pain management support and experience of advice received and uptake of the clinical pharmacist's medication recommendations. All participant interviews will be delivered by trained members of our PPIE team.

Healthcare professional feedback

Feedback will also be sought from those trained individuals implementing the intervention including facilitators of the intervention. These would include the clinical pharmacists delivering the intervention, as well as relevant primary and secondary healthcare professionals who may be facilitating the study, such as hospital research nurses, clinicians, GPs and members of the ICB. The interviews will be delivered by a member of the research team using the theoretical framework of acceptability, either online or by telephone and expected to take 30 – 45 minutes. Participants will be offered a £25 shopping voucher for taking part in an interview.

Data collection

Data variables collected pre-intervention or on day 0 will include baseline demographics, pain scores, EQ5D-5L (Quality of Life Questionnaire), and a number of key confounders that have been reported in the literature, and linked to long-term opioid use:

- Baseline demographics (age, sex, body mass index (BMI), ethnicity, social deprivation scores, smoking and alcohol consumption).
- Surgical history (surgery type, hospital, ward, opioid – type, strength, duration, average pain score).
- Medical history (prior opioid use, prior gabapentinoid and psychotropic use, other medication use, comorbidities, healthcare use).

At each additional follow-up appointment data variables collected will include pain scores, further medication changes, symptom management and for final appointments only, EQ5D-5L and Participant Satisfaction Questionnaire data. The aim of this questionnaire is to ascertain their experience of the deprescribing intervention, their views, and opinions on the process. In addition, all participants will be invited to take part in an online or telephone interview after their final follow-up with the pharmacist. Participants will be offered a £25 shopping voucher for taking part in an interview.

Data confidentiality

All data recorded from participants will be de-identified to the research study team in line with NHS governance (Unique Reference Number (URN) and date of birth) and transmitted to a secure server which is confidentiality/privacy standard compliant. Access to the de-identified data will be accessible via a password-protected website, by authorised members of the research team. All participants in the study will be assigned a URN at the first MUR with the clinical pharmacist. This URN which will consist of GP practice initials followed by sequential number (double digits) and their date of birth will act as a medical identifier for each participant. All data collected from participants will be de-identified to the research study team using the URN.

Data management

Submitted data will be collected, reviewed for completeness, analysed, and stored in compliance with the Data Protection Act of 2018[47] by the University of Kent (UoK) research team members and public contributors where appropriate. All data will be entered onto a secure, database and accessible only to authorised members of the team. All participants recorded details will be anonymised and de-identified to the university's research team by means of a unique research number, allocated during participant consent, by the clinical pharmacist. The handling of personal information by the research team will be clearly stated in the participant information sheet. All saved electronic data will be stored on password protected computers/laptops for a maximum of 5 years, post-project publication. All paper documentation, participant questionnaires, demographics data etc. will be stored in locked filing cabinets at the UoK (Medway School of Pharmacy). Paper documentation will be destroyed (shredded) five years post project publication. Similarly, all recorded interviews and transcripts will be deleted 5 years post-publication. Identifiable data (e.g., consent form) will be stored on secure UoK networks and destroyed 3 – 6 months after the study has ended.

Statistical analysis

For the quantitative measures descriptive statistics (proportions, means, standard deviations, medians and interquartile ranges) will be used to describe the intervention population including patient demographic variables, deprivation scores, comorbidities for each surgical type, medication prescribed (including type, dose, amount, duration and long or short-acting), pain scores and history of opioid use. We will consider sub-group analysis for quality of life and pain scores by pathway (A, B or C) and at each timepoint. Descriptive statistics will also be used to assess de-escalation success rates and proportion of long-term users. Similarly, descriptive statistics will be used to determine

attrition rates at various stages and the different reasons provided. Means difference analyses will be performed via corrected repeated measures *t*-test/Wilcoxon's tests or mixed ANOVAs (depending on data distribution and number of participants) to test the difference of MME taken at discharge and 91-days post discharge in each of the three pathways. A number of demographic variables information collected at baseline will be used as covariates to control for and address issues of health inequalities. The allocation to pathway C or not will be treated as a dichotomous outcome variable in a set of logistic regression models to determine the significance of a number of predictors as risk factors. Chi-square analyses will be used to compare the proportion of patients who accepted or declined the intervention. For the health economic analysis, a micro-costing approach will be used to estimate the intervention costs (e.g., equipment required, space, staff time delivering the intervention), opioid and other analgesic medication costs, and relevant participant health resource use in community, primary and secondary care. For the qualitative data analysis: Closed questions from participant satisfaction questionnaires will be analysed using SPSS (version 25). Whilst responses to open-ended questions will be imported into NVivo v11 and analysed using content analysis. Words will be coded and frequency of occurrence recorded, for grouping into themes. These themes will then by compared with responses to the questionnaires closed questions. All interviews will be transcribed verbatim, entered into qualitative data analysis software (NVivo v11) or Microsoft Excel 2021. The transcripts will be coded and subjected to thematic analysis[48]. Transcription and coding accuracy will be verified independently by another researcher. Themes will be reviewed and refined again, to identify any themes that may not have been previously recognised. Deviant case analysis will be used to refine the analysis so that perspectives that diverged from dominant trends are not overlooked. Notes collected at each medication assessment meeting will be reviewed and analyses for themes related to recommendations for the intervention and the role of clinical pharmacists in deprescribing opioids post-surgery. Where feasible quantitative and qualitative data will be triangulated by comparing and contrasting themes identified from the patient satisfaction questionnaire with interview data depending on data available.

Ethics and amendments

The DESCALE feasibility study was granted ethical approval by the North-West Greater Manchester Central Research Ethics Committee on 19th September 2023, reference number 23/NW/0241. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 (World Medical Association, 2013[49], and later revisions) and the UK Policy Framework for Health and Social Care Research, 2022[50]. All data will be stored securely, and confidentiality of participants held in accordance with the Data Protection Act of 2018[47]. Any substantial amendments to the protocol or other study documents may require review and approval by the Research Ethics Committee (REC) before the changes can be implemented to the study. Where amendments are required, NHS Health Research Authority and REC procedures will be followed.

Sponsorship and indemnity

This project is sponsored by the University of Kent (Reference: ResGov 470) who provide appropriate indemnity arrangements to cover research staff working on the project. NHS indemnity covers the procedures carried out according to the prospective protocol at all NHS study GP sites.

Audits

The study may be subject to audit by the University of Kent under their remit as sponsor and other regulatory bodies to ensure adherence to the UK Policy Framework for Health and Social Care Research.

Sources of bias

All potential eligible participants will be approached using emails or SMS text and followed up by telephone and the intervention delivered mainly by video or telephone. This will introduce selection bias towards those participants who are technologically adept. In addition, by restricting eligibility to participants that are taking opioids less than 120 mg/MME day, we are biasing our selection towards potentially less medically complex patients.

Study dissemination

The research findings will be disseminated as an accessible online report summarising key findings and recommendations, that will be distributed to all stakeholders and public groups supporting the study. Results will also be disseminated via an open access peer reviewed journal. Members of the research team may also disseminate findings through Stakeholder/University Twitter and LinkedIn accounts and at relevant third sector conferences.

Study status

As of 23rd July 2024, three sites are currently active and have recruited 18 participants so far and one qualitative participant interview conducted.

Strengths and limitations of this study

- This study will inform our understanding of patients' experience of post-surgical opioid prescribing, surgical related pain and potentially identify individuals who require more support for opioid de-prescribing.
- This study will test the feasibility of an intervention designed to support patient and system outcomes in routine health settings, led by pharmacists.
- Patient data collected will provide a snapshot of real-world post-surgical prescribing in a single NHS trust, and highlight patient, medical and social factors that may influence long-term opioid dependence.

- This study will provide important information about current prescribing and deprescribing practices, however the small sample size (80–100) will limit the confidence in the statistical significance of these findings.
- Results on post-surgical opioid de-prescribing might not be generalisable to other- healthcare settings, professionals, or patient populations due to the localised study population.

Discussion

Together with the local Chronic Pain Service, academics from the University of Kent, healthcare professionals from Kent Community Health NHS Foundation Trust and East Kent Hospital University Foundation Trust have come together to test an early deprescribing intervention working at the interface between secondary and primary care to determine whether the intervention is feasible and if it has the potential to prevent post-surgical patients transitioning from acute to long-term opioid persistent use. In addition, this study, combined with data collected as part of a parallel retrospective study looking at surgical prescribing data from the same trust, will provide information on perioperative opioid prescribing and the role it may play in contributing to opioid overuse in the community, for which there is a paucity of data in the UK.

List of abbreviations

AE: Adverse Event

ANOVA: Analysis of Variance

BMI: Body Mass Index

CRF: Case Report Form

CCG: Clinical Commissioning Group

DESCALE: DE-eSCALation of opioid post-surgical discharge

EKHUFT: East Kent Hospitals University NHS Foundation Trust

EQ5D-5L: European Quality of Life 5 Dimension 5 Level

GP: General Practitioner

hr: hour

HRA: Health Research Authority

mg: milligram

mcg: microgram

MME: Morphine Milligram Equivalent

MUR: Medicines Use Review

NHS: National Health Service

NIHR: National Institute for Health and Care Research

NSAID: Non-Steroidal Anti-Inflammatory Drug

PHE: Public Health England

PIL: Patient Information Leaflet

REC: Research Ethics Committee

SAE: Serious Adverse Event

SMS: Standard Messaging Service

SPIRIT: Standard Protocol Items: Recommendation for International Trials

UK: United Kingdom

UoK: University of Kent

URN: Unique Reference Number

US: United States

Ethics and consent

The DESCALE feasibility study was granted ethical approval by the North-West Greater Manchester Central Research Ethics Committee on 19th September 2023, reference number 23/NW/0241. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 (World Medical Association, 2013[49], and later revisions) and the UK Policy Framework for Health and Social Care Research, 2022[50]. All data will be stored securely, and confidentiality of participants held in accordance with the Data Protection Act of 2018[47]. Any substantial amendments to the protocol or other study documents may require review and approval by the Research Ethics Committee (REC) before the changes can be implemented to the study. Where amendments are required, NHS Health Research Authority and REC procedures will be followed.

Consent to participate in the study will be sought from all eligible patients that have undergone a surgical procedure and are discharged with an opioid prescription from the participating East Kent hospital sites and participating GP practices. Consent will only be sought after a full explanation and/or the PIL has been offered with time allowed for questions and proper consideration. Individuals willing to take part and for whom an MUR appointment has been made will be asked to complete a Participant Consent Form. A Consent form will be sent to those with digital capabilities prior to the MUR or completed together with the pharmacist at the first appointment. A typewritten signature or tick box declaration option, in accordance with the UK eIDAS Regulations (SI 2016/696) will be used for all digital consent forms. All consent forms will be checked and countersigned by the pharmacist prior to the commencement of the medication review. A copy of the consent form will be added to the participants medical records, and another retained in the study site folder, stored at the practice and a copy sent to the participant.

Data availability

Underlying data

Only the study team will have access to the full dataset throughout the study. A summary of findings will be reported to the participating research sites on completion of the study.

Data sharing represents an efficient use of public money and supports more timely scientific discovery. Anonymised data will be made available after completion of this study to researchers at universities, NHS organisations or other healthcare providers where the sharing of data has a clearly defined purpose, and its use will be of benefit to wider society (Medical Research Council Policy and Guidance on Sharing of Research Data). **There are currently no data associated with this feasibility study.**

Extended data

Open Science Framework Data Repository: Pharmacist-led DE-eSCALation of opioids post-surgical dischargE (DESCALE), DOI 10.17605/OSF.IO/YV2CJ[51]; URL: https://osf.io/yv2cj/

This project contains the following underlying data:

- Participant Consent Form - V3 - 05.09.2023.pdf
- Participant Information Leaflet - V3 - 05.09.2023.pdf
- Participant Satisfaction Questionnaire - V2 -11.05.2023.pdf
- SPIRIT_Fillable-checklist-15-Aug-2013 - 08.08.2024.doc

Software availability

NVivo is a proprietary software, free alternatives such as Microsoft Excel (https://www.microsoft.com/en-us/microsoft-365/excel) could be used.

Acknowledgements

We would like to acknowledge members of the NIHR Research Champions (Kent Community Health NHS Foundation Trust) and Claire Manning (NHS Kent & Medway ICB) who provided their thoughts and insights on the protocol, intervention and the study and ethics documentation. Also, to Mr Adrian Bawtree and Mrs Lyn Gallimore who took part in practice opioid MURs as part of the clinical pharmacists training and testing of protocols. We would like to also thank our two public contributors, Miss Jade Davies, and Mr Mike Latter for their ongoing support with the research study. Continued thanks to Professor Alistair Mathie for ongoing support with the project and comments on the manuscript.

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Open Peer Review

Current Peer Review Status: ✔ ? ✔ ✔

Version 2

Reviewer Report 04 March 2025

https://doi.org/10.3310/nihropenres.15070.r34493

✔ **Deepika Rao**
[1] Dartmouth College, Hanover, NH, USA
[2] Dartmouth College, Hanover, NH, USA

The protocol describes the feasibility and acceptability testing of an intervention to reduce opioid use among post-surgical patients. I have no major recommendations.
The only question I had was regarding patient compensation or incentive payments for participation. Considering the protocol requires multiple points of patient participation apart from the MUR appointment itself such as the survey and interview, incentive amounts may be necessary to reach recruitment goals. Please include this information in the methods.

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?
Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Opioid safety interventions in pharmacy settings

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.

Author Response 18 Mar 2025

Emma Veale

Thank you for reading the manuscript and your helpful comments. In response to your question; we did not offer any payment to participate in the study, as is standard in these types of trials. However after low response rate we amended our protocol to offer a £25 shopping for any participants taking part in a post-intervention interview. We have amended the protocol to reflect this.

Competing Interests: There are no competing interests to declare.

Reviewer Report 28 January 2025

https://doi.org/10.3310/nihropenres.15070.r34399

Judy Mullan
[1] University of Wollongong, Wollongong, New South Wales, Australia
[2] University of Wollongong, Wollongong, New South Wales, Australia

I am satisfied that the authors have addressed each of my comments in this revised version of the manuscript.

Is the rationale for, and objectives of, the study clearly described?
Not applicable

Is the study design appropriate for the research question?
Not applicable

Are sufficient details of the methods provided to allow replication by others?
Not applicable

Are the datasets clearly presented in a useable and accessible format?
Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Quality Use of Medicines

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.

Reviewer Report 23 January 2025

https://doi.org/10.3310/nihropenres.15070.r34398

Liz Shaw
[1] University of Exeter, Exeter, England, UK
[2] University of Exeter, Exeter, England, UK

I can confirm that I'm happy with how the authors have responded to my comments and am happy for the protocol to proceed to indexing.

Is the rationale for, and objectives of, the study clearly described?
Not applicable

Is the study design appropriate for the research question?
Not applicable

Are sufficient details of the methods provided to allow replication by others?
Not applicable

Are the datasets clearly presented in a useable and accessible format?
Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Systematic reviewer; expertise in qualitative synthesis

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.

Version 1

Reviewer Report 31 October 2024

https://doi.org/10.3310/nihropenres.14892.r33042

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Liz Shaw
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This protocol outlines a pharmacist-led programme to promote deprescribing of opioids post surgery. The methods propose a mixed-methods study.

The protocol indicates that data collection has already commenced and I am uneasy about the retrospective publication of this protocol. It limits the potential utility of my comments and the ability of the study authors to address comments relevant to improving the conduct of the study and somewhat undermines the peer-review process. I hope the queries and comments below are helpful to the authors in refining their reporting of their methods.

Further details regarding methods:

Intervention Population:
1) Further rationale for the study population would be useful. Is it appropriate to implement the intervention at same time point for different surgery populations? i.e. do recovery timeframes differ? Are there some operations where it may be realistically expected for recovery to be longer? Will some age groups be expected to have longer recovery/need opiates for longer? This may be covered by the exclusion criteria stating max. opioid dose and Pathway C but could be made more explicit.

Recruitment:
2) My comments here pertain mainly to study methods. Patients may be more able/willing to consent if contacted prior to recruitment. Could imagine some would be most unwilling after a hospital admission to consider a surprise research participation request after being discharged home. Online consent form will not be accessible to some populations (Lower SES, older people, not technologically literate). Consent form in person with Pharmacist may place some under pressure to participate. How can potential participants be given a longer time to consider if they wish to participate and identify questions they may have?

Data Collection
3) For qualitative interviews - Why only patient participants? This intervention has implications for family, carers, pharmacists and other healthcare professionals (in both primary and secondary care). To fully assess feasibility and acceptability, rich qualitative data from these groups would also be extremely beneficial.

4) Further detail regarding qualitative interviews required - Interview schedule, Where will they be conducted? Duration?

Outcomes
5) It is not clear which outcome measures will be used to measure which outcomes at which timepoints. Further clarity here would be useful.
6) Will long term PROMS/PREMS be collected post 3-month discharge (see point 11 below)? This may enable triangulation with qualitative data.

7) How will authors consider impact of potential health inequities in their data collection and analyses (e.g. those posited by PROGRESS-PLUS criteria)
8) Will hospital readmissions (both under and over 30 days post discharge) be assessed alongside use of primary care services to see if intervention has any unintended negative consequences for service use?
9) For the outcomes in Table 3: How will these be measured?
10) Should a measure of anxiety/depression e.g. PHQ-9 or HADS be used to confirm MH diagnosis and patient current level of symptomology (and allow baseline-post intervention comparisons)? Should patient self-harm/suicide risk be monitored and how will this be dealt with should concerns arise?

Study timelines:
11) Is it feasible to conduct longer term follow up? Patient reported outcome measures and patient reported experience measures post-hospital discharge are rarely assessed in the long-term, as is the case here, which limits conclusions that can be drawn re: safety/efficacy/acceptability of an intervention.

Analysis
12) How will authors take into account influence of different populations/procedures and consider impact of possible health inequities (e.g. those detailed by PROGRESS-PLUS criteria) across analysis of both quant and qual data.
13) Further detail on rationale for analysis methods chosen and methods would be helpful. Why is thematic analysis of interview data most suited method?
How will you reduce risk of bias in your analysis e.g. double coding, checking arising themes with PPI/HCP stakeholders?
Will the questions you ask interviewees remain fixed throughout study, or will the interview schedule evolve - informed by the content/analysis of previous interviews (a more Grounded Theory Approach)
Will you make any attempts to integrate quantitative and qualitative findings? If so, how?
14) I am not best placed to comment on methods used to calculate costs, but I think further details are required re: calculating your cost data. E.g. What factors are you you considering? What sources for costs are you using?

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?

No

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

No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Systematic reviewer; expertise in qualitative synthesis

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.

Author Response 07 Jan 2025

Emma Veale

Reviewer Comments:
This protocol outlines a pharmacist-led programme to promote deprescribing of opioids post-surgery. The methods propose a mixed-methods study.

The protocol indicates that data collection has already commenced and I am uneasy about the retrospective publication of this protocol. It limits the potential utility of my comments and the ability of the study authors to address comments relevant to improving the conduct of the study and somewhat undermines the peer-review process. I hope the queries and comments below are helpful to the authors in refining their reporting of their methods.

Author Response:
Dear Dr Shaw, thank you for reviewing our protocol and for your helpful comments and suggestions. We have responded to your comments below in bold and in the manuscript.

It is not uncommon when publishing protocol papers of this type that the study has already commenced. The only requirement is that it is not submitted once data collection has finished. A protocol of this type will already have undergone multiple rounds of funding external peer review and then additional rounds of review by NHS ethics, including an interview, prior to the intervention commencing and additionally any amendments to the protocol approved via NHS ethics committee, as the study commences. The data we subsequently collect will allow us to report on whether this protocol is feasible or not, how it can be improved, so that it can be adopted in the field or equally, any pitfalls we uncover can be avoided by others.

Reviewer Comments:
Further details regarding methods:

Intervention Population:
1) Further rationale for the study population would be useful. Is it appropriate to implement the intervention at same time point for different surgery populations? i.e. do recovery timeframes differ? Are there some operations where it may be realistically expected for recovery to be longer? Will some age groups be expected to have longer recovery/need opiates for longer? This may be covered by the exclusion criteria stating max. opioid dose and Pathway C but could be made more explicit.

Author Response:
These are very good points and the type of things we hope to determine from the data collected during the feasibility study. We have offered 3 pathways (rapid, slower, no

change) which we hope will allow flexibility for just these points you have raised. We have added more description to pathway C to reflect this.

Reviewer Comments:
Recruitment:
2) My comments here pertain mainly to study methods. Patients may be more able/willing to consent if contacted prior to recruitment. Could imagine some would be most unwilling after a hospital admission to consider a surprise research participation request after being discharged home. Online consent form will not be accessible to some populations (Lower SES, older people, not technologically literate). Consent form in person with Pharmacist may place some under pressure to participate. How can potential participants be given a longer time to consider if they wish to participate and identify questions they may have?

Author Response:
Yes, we totally agree. Our initial hope was to recruit directly from surgical wards; and use a team of study pharmacists to deliver the intervention. However, we realised quite early on as we designed the protocol that pharmacists would need to be affiliated to a GP practice in order to access medical records and screening patients on a hospital ward or from a hospital pharmacy would be untenable for the staff involved. We considered that patients receiving an email or text message directly from their GP surgery would be something that they are accustomed to, rather than a surprise.

We totally accept that online consent is only accessible to those with digital capabilities, although we can offer to take them through a consent form over the telephone and we do offer telephone MURs. Unfortunately, due to the timeframe which we want to deliver these MURS we were unable to offer postal options. We accept that this is a limitation of the study, and we noted this in the sources of bias section of the manuscript. A consent form is only completed with the patient and appointment made with the pharmacist if they agree to take part after consideration. No patient is coerced into taking part by the practice staff.

Reviewer Comments:
Data Collection
3) For qualitative interviews - Why only patient participants? This intervention has implications for family, carers, pharmacists and other healthcare professionals (in both primary and secondary care). To fully assess feasibility and acceptability, rich qualitative data from these groups would also be extremely beneficial.

Author Response:
Thank you for pointing this out. Qualitative interviews are intended for all those that participated, including HCPs. We also intend to interview key stakeholders from the ICB and from EKHUFT. We have amended the text to make this clear and added a section on HCP feedback that was inadvertently missing.

Reviewer Comments:
4) Further detail regarding qualitative interviews required - Interview schedule, Where will they be conducted? Duration?

Author Response:
Thank you for highlighting this. We have amended the text to provide more detail about these interviews.

Reviewer Comments:
Outcomes
5) It is not clear which outcome measures will be used to measure which outcomes at which timepoints. Further clarity here would be useful.

Author Response:
We have combined the outcomes with the aims and objectives table (1) so that this is clearer to the reader.

Reviewer Comments:
6) Will long term PROMS/PREMS be collected post 3-month discharge (see point 11 below)? This may enable triangulation with qualitative data.

Author Response:
Due to the budget and timeframe, we are regrettably unable to collect long term PROMS/PREMS data for this study. Should we be able to conduct a larger study, then this is something that we would want to do.

Reviewer Comments:
7) How will authors consider impact of potential health inequities in their data collection and analyses (e.g. those posited by PROGRESS-PLUS criteria)

Author Response:
We are collecting and will report socioeconomic factors of participants in this study. However, the small sample size will make any inferences of this data limited.

Reviewer Comments:
8) Will hospital readmissions (both under and over 30 days post discharge) be assessed alongside use of primary care services to see if intervention has any unintended negative consequences for service use?

Author Response:
Any adverse events whether related to the intervention or not must be reported by the practice to the study team. Due to this intervention designed to target mostly opioid naïve participants on **≤120 mg MME/day we anticipate few if any unintended negative consequences to occur.**

Reviewer Comments:
9) For the outcomes in Table 3: How will these be measured?

Author Response:
We have recombined these with the aims and objectives (Table 1), so that this is clearer to

the reader.

Reviewer Comments:
10) Should a measure of anxiety/depression e.g. PHQ-9 or HADS be used to confirm MH diagnosis and patient current level of symptomology (and allow baseline-post intervention comparisons)? Should patient self-harm/suicide risk be monitored and how will this be dealt with should concerns arise?

Author Response:
As for question 8, the intervention targets patients that are early on in an opioid journey and do not have a previous history of long-term opioid or drug abuse. Therefore, we do not anticipate any serious adverse events relating to opioid deescalation. The CRF however captures all medication use by the participant and any red flags should be recognised by the pharmacists who are trained to deliver high risk MURs and reported to the clinical lead who has also vast experience of working with long-term opioid dependent patients.

Reviewer Comments:
Study timelines:
11) Is it feasible to conduct longer term follow up? Patient reported outcome measures and patient reported experience measures post-hospital discharge are rarely assessed in the long-term, as is the case here, which limits conclusions that can be drawn re: safety/efficacy/acceptability of an intervention.

Author Response:
We agree with you completely, but for this small project it has not been possible. We would hope to address this in a larger study. The purpose of this study is to determine whether it is feasible, what needs to improve and what type of patient we should target or not target, with this type of intervention.

Reviewer Comments:
Analysis
12) How will authors take into account influence of different populations/procedures and consider impact of possible health inequities (e.g. those detailed by PROGRESS-PLUS criteria) across analysis of both quant and qual data.
13) Further detail on rationale for analysis methods chosen and methods would be helpful.
Why is thematic analysis of interview data most suited method?
How will you reduce risk of bias in your analysis e.g. double coding, checking arising themes with PPI/HCP stakeholders?
Will the questions you ask interviewees remain fixed throughout study, or will the interview schedule evolve - informed by the content/analysis of previous interviews (a more Grounded Theory Approach)
Will you make any attempts to integrate quantitative and qualitative findings? If so, how?
14) I am not best placed to comment on methods used to calculate costs, but I think further details are required re: calculating your cost data. E.g. What factors are you you considering? What sources for costs are you using?

Author Response:

We have added more detail around the methods and statistical analysis in the manuscript to address your comments in questions 12, 13 and 14 and to provide more clarity.

Competing Interests: The authors have no competing interests to declare.

Reviewer Report 25 October 2024

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Neetu Bansal
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Thank you for the opportunity to review this submission, which addresses the important issue of problematic long-term opioid use in post-surgical patients. The mixed-methods approach employed in this feasibility study is well thought out and pragmatic, making it suitable for exploring the practicalities of early opioid de-escalation in primary care settings.
There are several strengths in the study's aims and objectives, particularly in addressing a key public health issue. However, there are also a few areas that would benefit from further clarification and refinement to enhance the study's overall impact and feasibility. Below are some points for consideration:

1. Some objectives, such as "ascertain stakeholder acceptability of the intervention" and "ascertain participant acceptability of the intervention," are somewhat broad and vague. These could be more clearly defined by specifying the exact dimensions of acceptability that will be measured, such as willingness to participate, perceived effectiveness, or identification of barriers to implementation.
   - While stakeholder interviews are mentioned, there is no clear identification of who the stakeholders are (e.g., GPs, surgeons, pharmacists, patients). Clarifying the stakeholder groups and how their perspectives will be incorporated into the analysis would strengthen the study. It would also be helpful to describe how the results from these interviews will influence the development or adaptation of the intervention
   - The objective to "Measure the capabilities of trained clinical pharmacists" references "observational competency checks by the Clinical Lead," but there is no information on how these checks will be standardised across different pharmacists or validated. Providing more detail on how competency will be measured (e.g., using competency frameworks or objective performance metrics) would enhance the robustness of this objective. Additional information on the training modules used to assess pharmacist capabilities would also be useful.
   - The use of EQ-5D-5L for measuring quality of life and pain scores is appropriate, but there is

no mention of how changes in these metrics will be analysed in relation to opioid de-escalation. Outlining a plan for analysing pain and quality of life data in relation to opioid use (e.g., through subgroup analyses) would strengthen the interpretation of outcomes
- There is no clear plan for managing participants who do not respond to the intervention or who drop out before completion. Including an objective or process for handling non-responders would provide valuable insights into barriers to intervention effectiveness and inform the design of future studies.

Additional Considerations:
- **Introduction**: The statement that opioids cause "more pain" needs clarification. It would be helpful to explicitly reference opioid-induced hyperalgesia to clarify that you are referring to increased sensitivity to pain as a potential side effect of long-term opioid use.
- **Methods**:
  - It is unclear how often the discharge list will be generated and what the process will be for identifying patients. Providing more detail on how discharge lists will be compiled and reviewed would improve the transparency of participant identification.
  - What is the level of buy-in from clinical pharmacists? Will the same pharmacist consistently see each patient during follow-up? Consistency in pharmacist-patient interaction could influence outcomes, so it would be helpful to clarify this aspect.
  - Clarification is needed regarding the types of surgical procedures included in the study. Will both minor and major surgeries be included, and will day-case procedures also be part of the intervention?
  - Exclusion criteria - how will you decide on 'severe' co-existing medical condition (using standardised co-morbidity scoring systems for example)
  - Pathway C - refer to non-pharmacological options as an option?
  - Pathway C - Continuation of opioids, benefits of taking opioids outweigh the risk of discontinuing opioid therapy - can you give examples of such situations as this appears vague
  - Recruitment period Jan to September 2014. States 17 participants recruited. Does this refer to the patients? As per protocol sample size to aim for is around 100 participants.

In summary, this is a well-constructed study that addresses an important topic. Strengthening the clarity and detail in the areas highlighted above would enhance the study's feasibility and robustness, ensuring it provides actionable insights into the effectiveness of early opioid de-escalation.

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

Yes

Is the study design appropriate for the research question?

Partly

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: Pain management in surgical patients and medicines optimisation

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.

Author Response 07 Jan 2025

Emma Veale

Thank you for the opportunity to review this submission, which addresses the important issue of problematic long-term opioid use in post-surgical patients. The mixed-methods approach employed in this feasibility study is well thought out and pragmatic, making it suitable for exploring the practicalities of early opioid de-escalation in primary care settings.

Dear Dr Bansal, thank you for reviewing the manuscript, for your positive comments and recommendations to improve it. We realise that in an attempt to be concise we have missed some important details. We have responded to your queries below in bold and in the edited manuscript.

There are several strengths in the study's aims and objectives, particularly in addressing a key public health issue. However, there are also a few areas that would benefit from further clarification and refinement to enhance the study's overall impact and feasibility. Below are some points for consideration:

1. Some objectives, such as "ascertain stakeholder acceptability of the intervention" and "ascertain participant acceptability of the intervention," are somewhat broad and vague. These could be more clearly defined by specifying the exact dimensions of acceptability that will be measured, such as willingness to participate, perceived effectiveness, or identification of barriers to implementation.
   - While stakeholder interviews are mentioned, there is no clear identification of who the stakeholders are (e.g., GPs, surgeons, pharmacists, patients). Clarifying the stakeholder groups and how their perspectives will be incorporated into the analysis would strengthen the study. It would also be helpful to describe how the results from these interviews will influence the development or adaptation of the intervention

We agree, these objectives are vague and concede that we have inadvertently oversimplified Table1 in an attempt to be concise. We have clarified the stakeholder groups that will be approached and added more detail around what information will be collected to inform the design of a future intervention in Table 1 and in the manuscript.

   - The objective to "Measure the capabilities of trained clinical pharmacists" references "observational competency checks by the Clinical Lead," but there is no information on how these checks will be standardised across different pharmacists or validated. Providing more detail on how competency will be measured (e.g., using competency

frameworks or objective performance metrics) would enhance the robustness of this objective. Additional information on the training modules used to assess pharmacist capabilities would also be useful.

Response: We determined that this type of MUR being delivered was standard procedure for the pharmacists participating in the study (most had been involved in a high-use opioid study previously with the clinical lead), and patients recruited deemed low-risk compared to long-term users of opioids. Therefore, the competency would be as expected in undertaking a standard MUR. However, all pharmacists received additional training by the Clinical Lead to conduct the MUR for the purpose of the study. For this they received an hour-long opioid lecture at the start, with signposting to multiple learning resources and regular individual contact with Dr Theron on each patient's reduction programme. For this feasibility study, we designed broad reduction pathways options (A, B, C,) for the pharmacists to follow and weekly drop-in sessions with the Clinical Lead for pharmacists to discuss any clinical queries that may have arisen. Each pharmacist also has a responsible GP to check their prescriptions as part of the partaking surgeries' agreement. Fidelity checks of the filled CRFs are performed by the research team and during the Clinical Lead's drop-in sessions for the pharmacists. We have replaced the word measure with assess. It is possible that more in-depth training in the form of modules may be a finding of our qualitative interviews with participating pharmacists.

- The use of EQ-5D-5L for measuring quality of life and pain scores is appropriate, but there is no mention of how changes in these metrics will be analysed in relation to opioid de-escalation. Outlining a plan for analysing pain and quality of life data in relation to opioid use (e.g., through subgroup analyses) would strengthen the interpretation of outcomes

Thank you for pointing this out. We have added a bit more information as to how we will use this data in the analysis section.

- There is no clear plan for managing participants who do not respond to the intervention or who drop out before completion. Including an objective or process for handling non-responders would provide valuable insights into barriers to intervention effectiveness and inform the design of future studies.

The practices collect baseline data (age, gender and surgical procedure) of all participants eligible for the intervention on the recruitment log. This data will be used to determine whether these factors influence non/participation in the study. We have tried to make this clearer in the objectives and participant recruitment section. Unfortunately, due to the short time frame between identifying participants and inviting them to the study, we can only approach eligible participants once.

Additional Considerations:

- **Introduction**: The statement that opioids cause "more pain" needs clarification. It would be helpful to explicitly reference opioid-induced hyperalgesia to clarify that you are referring to increased sensitivity to pain as a potential side effect of long-term opioid use.

Thank you for pointing this out. It had slipped in from previous lay summaries of the research. We have amended this.

- **Methods**:
  - It is unclear how often the discharge list will be generated and what the

process will be for identifying patients. Providing more detail on how discharge lists will be compiled and reviewed would improve the transparency of participant identification.

We had written under recruitment, that searches would be undertaken on a weekly basis, however this would be at the discretion and capacity of the practice and pharmacists to do this. I have adjusted to say weekly/bi-monthly as this is more realistic of what we are experiencing. I agree that the method used to search for eligible patients is lacking. This is because individual GP practices have had to develop searches based on the systems that they use and the way in which they handle the discharge lists. No practice has been the same and will be reported as one of the barriers!

- What is the level of buy-in from clinical pharmacists? Will the same pharmacist consistently see each patient during follow-up? Consistency in pharmacist-patient interaction could influence outcomes, so it would be helpful to clarify this aspect.

We will capture the level of buy-in from pharmacists through the interview process. We intend to interview pharmacists that engaged and those that didn't engage at practices which had undergone site-initiation. Time permitting, we will also approach pharmacists from other practices that had initially expressed an interest but did not participate. I have added this to the objectives.

We did not stipulate that the same pharmacist must complete follow-up reviews with the same participate. We have left this decision to the discretion of the practice. However, as the pharmacist books the next appointment with the patient at the MUR and most practices only have one pharmacist participating this has occurred spontaneously.

- Clarification is needed regarding the types of surgical procedures included in the study. Will both minor and major surgeries be included, and will day-case procedures also be part of the intervention?

We include all types of surgical procedure (inpatient and outpatient), with the exclusion of caesarean sections and cancer patients. We have amended the inclusion criteria to be clearer.

- Exclusion criteria - how will you decide on 'severe' co-existing medical condition (using standardised co-morbidity scoring systems for example)

No scoring is done, the rationale used will be the same as in any other clinic situation. Where there is uncertainty about a participant's suitability, this is discussed directly with the Clinical Lead who is the lead Clinician of a Chronic Pain service. If during the time of the project that assessing the severity of a medical condition is proving difficult for pharmacists, then we would report this as a barrier and use this information to adapt the intervention going forward. We have amended the exclusion criteria to reflect this.

- Pathway C - refer to non-pharmacological options as an option?

This is not an option of this pathway or the project and would relate more to patients that are suffering from chronic pain (>91 days) conditions or those that continue with opioids past 90 days and who are transferred back into the system for support.

- Pathway C - Continuation of opioids, benefits of taking opioids outweigh the risk of discontinuing opioid therapy - can you give examples of such situations

as this appears vague

This relates to the pain scores, where the patient is still suffering from severe pain at the time of the MUR which would warrant a continuation of opioids and in some circumstances potentially an increase in dose or a change in medication. We have amended the text to reflect this.

- Recruitment period Jan to September 2014. States 17 participants recruited. Does this refer to the patients? As per protocol sample size to aim for is around 100 participants.

Yes, this related to the number of patients recruited at the time of submission of the manuscript. However, it should read 2024, not 2014!

In summary, this is a well-constructed study that addresses an important topic. Strengthening the clarity and detail in the areas highlighted above would enhance the study's feasibility and robustness, ensuring it provides actionable insights into the effectiveness of early opioid de-escalation.

Thank you!

Competing Interests: The authors have no competing interests to declare.

Reviewer Report 16 September 2024

https://doi.org/10.3310/nihropenres.14892.r32791

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Judy Mullan
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Thank you for the opportunity to review this submission, which addresses the critical issue of long-term opioid use. The rationale for the study is clearly articulated, emphasising that while opioids can be prescribed for short-term pain management after surgery, their long-term use can lead to dependence, overdose, and even death in severe cases. This is a significant public health concern worldwide. Reducing long-term opioid use among post-surgical patients would therefore help address an important global public health issue.
The study aims to fill a gap in the current literature by identifying an effective, evidence-based strategy using trained clinical pharmacists in GP practices to reduce long-term opioid use in post-surgical patients. Additionally, it seeks to assess the feasibility of the pharmacist-led intervention. Evaluating the feasibility of this intervention—including ease of implementation, acceptance by healthcare providers and patients, and establishing its effectiveness—can provide valuable insights for implementation on a much broader scale and would also help to inform policy and

future practice.

The study design, a prospective multi-centre, non-randomised pragmatic feasibility sub-study within the DESCALE study is appropriate to answer the research questions and the methods provided allow for replication by others. However, there are some points which need to be clarified regarding some of the objectives and data collection points for the different aims in Table 1(Summary of Aims and Objectives):
For example:
Aim/question 1: To test the feasibility of delivering an early opioid deprescribing intervention in primary care, lead by trained clinical pharmacist
-To ascertain stakeholder acceptability – it is not clear where the detailed records of any barriers or enablers in response to setting up and whilst delivering the intervention will be drawn from. It is also not clear which stakeholders and how many will be interviewed
In addition, more clarity is needed regarding the modules which will be used to measure the capabilities of the trained clinical pharmacists. Have they already been developed or are they going to be developed as part of the study?
In addition to measuring acceptability of the intervention by measuring patient participant engagement would it also be worthwhile to measure health practitioner engagement?

Aim/question: To understand post-surgical opioid prescribing experiences including opioid use, long-term opioid use, participant pain and quality of life in the 3-month period post-surgery when discharged with an opioid prescription
It is not clear what the research team means by “Responses during participant interviews.” Does this mean that it is the intention to interview all study participants or a subset of the study participants?

Aim/questions: To ascertain the feasibility of delivering the intervention as per the protocol to inform a future study or adoption of the protocol?
The protocol suggests that measurements will include a number of process and outcome measures which are indeed important. However, to better understand the feasibility of conducting an intervention the following questions would also need to be addressed:

- Acceptability -from the perspective of the patients and the healthcare providers
- what are the required resources (time, personnel, equipment) for implementing the protocol.
- What are the barriers and facilitators to implementation of the intervention and is it practical.
- How easily can the intervention be integrated in the existing health care system
- Will the intervention need to be adapted for different primary care/clinical settings
- What are the potential challenges in scaling the intervention and what resources are required to sustain the intervention in the long-term?

While the outcome measures are identified in Table 3 (Summary of study outcomes) it is not clear in the submitted protocol how the data for some of these outcomes will be collected and measured.
In particular

- Determination of the barriers/enablers that affect the delivery of the intervention from the perspective of the NHS stakeholders
- Determination of the barriers/enablers that affect the delivery of the intervention from the

perspective of the
- Determination of the integrity, robustness, and transferability of the protocol for future adoption by the NHS

Thank you for the opportunity to review this submission, which addresses the critical issue of long-term opioid use. The rationale for the study is clearly articulated, emphasising that while opioids can be prescribed for short-term pain management after surgery, their long-term use can lead to dependence, overdose, and even death in severe cases. This is a significant public health concern worldwide. Reducing long-term opioid use among post-surgical patients would therefore help address an important global public health issue.
The study aims to fill a gap in the current literature by identifying an effective, evidence-based strategy using trained clinical pharmacists in GP practices to reduce long-term opioid use in post-surgical patients. Additionally, it seeks to assess the feasibility of the pharmacist-led intervention. Evaluating the feasibility of this intervention—including ease of implementation, acceptance by healthcare providers and patients, and establishing its effectiveness—can provide valuable insights for implementation on a much broader scale and would also help to inform policy and future practice.

The study design, a prospective multi-centre, non-randomised pragmatic feasibility sub-study within the DESCALE study is appropriate to answer the research questions and the methods provided allow for replication by others. However, there are some minor points which could be clarified regarding some of the objectives and data collection points for the different aims in Table 1(Summary of Aims and Objectives):
Aim/question 1: To test the feasibility of delivering an early opioid deprescribing intervention in primary care, lead by trained clinical pharmacist
-To ascertain stakeholder acceptability – it is not clear where the detailed records of any barriers or enablers in response to setting up the intervention and whilst delivering the intervention will be drawn from. It is also not clear which stakeholders and how many will be interviewed
It is also not clear if the modules to measure the capabilities of trained clinical pharmacists have already been developed or are to be developed as part of the study
In addition to measuring participant acceptability of the intervention by measuring patient participant engagement would it also be worthwhile to measure health practitioner engagement?

Aim/ question: To understand post-surgical opioid prescribing experiences including opioid use, long-term opioid use, participant pain and quality of life in the 3-month period post-surgery when discharged with an opioid prescription
It is not clear what the research team means by “Responses during participant interviews.” Does this mean that it is the intention to interview all study participants or a subset of the study participants?

Aim/questions: To ascertain the feasibility of delivering the intervention as per the protocol to inform a future study or adoption of the protocol?
The protocol suggest that measurements will include a number of process measurements and outcome measures which are indeed important. However, to better understand the feasibility of conducting an intervention the following questions would also need to be addressed:
- Acceptability -from the perspective of the patients and the healthcare providers
- what are the required resources (time, personnel, equipment) for implementing the protocol.

- What are the barriers and facilitators to implementation of the intervention and is it practical.
- How easily can the intervention be integrated in the existing health care system
- Will the intervention need to be adapted for different primary care/clinical settings
- What are the potential challenges in scaling the intervention and what resources are required to sustain the intervention in the long-term?

While the outcome measures are clearly identified in Table 3 (Summary of study outcomes) it is not clear in the submitted protocol how the data for some of these outcomes will be collected and measured.
In particular

- Determination of the barriers/enablers that affect the delivery of the intervention from the perspective of the NHS stakeholders
- Determination of the barriers/enablers that affect the delivery of the intervention from the perspective of the
- Determination of the integrity, robustness, and transferability of the protocol for future adoption by the NHS

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

Is the study design appropriate for the research question?
Partly

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: Quality Use of Medicines

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.

Author Response 07 Jan 2025

Emma Veale

Reviewer 1 – Judy Mullan

Dear Dr Mullan, thank you for reviewing the manuscript, for your positive comments and recommendations to improve it. We have responded to your comments below and amended the manuscript accordingly. Best wishes, DESCALE team.

Thank you for the opportunity to review this submission, which addresses the critical issue of long-term opioid use. The rationale for the study is clearly articulated, emphasising that while opioids can be prescribed for short-term pain management after surgery, their long-term use can lead to dependence, overdose, and even death in severe cases. This is a significant public health concern worldwide. Reducing long-term opioid use among post-surgical patients would therefore help address an important global public health issue.

The study aims to fill a gap in the current literature by identifying an effective, evidence-based strategy using trained clinical pharmacists in GP practices to reduce long-term opioid use in post-surgical patients. Additionally, it seeks to assess the feasibility of the pharmacist-led intervention. Evaluating the feasibility of this intervention—including ease of implementation, acceptance by healthcare providers and patients, and establishing its effectiveness—can provide valuable insights for implementation on a much broader scale and would also help to inform policy and future practice.

The study design, a prospective multi-centre, non-randomised pragmatic feasibility sub-study within the DESCALE study is appropriate to answer the research questions and the methods provided allow for replication by others. However, there are some points which need to be clarified regarding some of the objectives and data collection points for the different aims in Table 1(Summary of Aims and Objectives):
For example:
Aim/question 1: To test the feasibility of delivering an early opioid deprescribing intervention in primary care, lead by trained clinical pharmacist
-To ascertain stakeholder acceptability – it is not clear where the detailed records of any barriers or enablers in response to setting up and whilst delivering the intervention will be drawn from.

Regarding your query around barriers and enablers. We anticipate that these will arise from all aspects of the study delivered – from recruitment, participation, delivery of the MURs, clinical drop-in sessions, stakeholder queries, to the collection of the data and from the interviews. All of these are being recorded as the study progresses.

It is also not clear which stakeholders and how many will be interviewed

Thank you for highlighting that this was missing from the manuscript. We are indeed interviewing stakeholders and have adding in the information that was missing to the manuscript.

In addition, more clarity is needed regarding the modules which will be used to measure the capabilities of the trained clinical pharmacists. Have they already been developed or are they going to be developed as part of the study?

R***esponse: We determined that this type of MUR being delivered was standard procedure for the pharmacists participating in the study (most had been involved in a high-use opioid study previously with the clinical lead), and patients recruited deemed low-risk compared to long-term users of opioids. Therefore, the competency would be as expected in undertaking a standard MUR. However, all pharmacists received additional training by the***

Clinical Lead to conduct the MUR for the purpose of the study. For this they received an hour-long opioid lecture at the start, with signposting to multiple learning resources and regular individual contact with Dr Theron on each patient's reduction programme. For this feasibility study, we designed broad reduction pathways options (A, B, C,) for the pharmacists to follow and weekly drop-in sessions with the Clinical Lead for pharmacists to discuss any clinical queries that may have arisen. Each pharmacist also has a responsible GP to check their prescriptions as part of the partaking surgeries' agreement. Fidelity checks of the filled CRFs are performed by the research team and during the Clinical Lead's drop-in sessions for the pharmacists. We have added in more information to the text and replaced the word measure with assess. It is possible that more in-depth training in the form of modules may be a finding of our qualitative interviews with participating pharmacists.

In addition to measuring acceptability of the intervention by measuring patient participant engagement would it also be worthwhile to measure health practitioner engagement?

Response: This is an excellent suggestion. We have been recording this type of data and aim to find out more detailed information from HCP interviews.

Aim/question: To understand post-surgical opioid prescribing experiences including opioid use, long-term opioid use, participant pain and quality of life in the 3-month period post-surgery when discharged with an opioid prescription
It is not clear what the research team means by "Responses during participant interviews." Does this mean that it is the intention to interview all study participants or a subset of the study participants?

Response: The interview is optional and so we expect only a small subset of participants will agree to take part in an interview. We have improved the text around the interview process to make this much clearer.

Aim/questions: To ascertain the feasibility of delivering the intervention as per the protocol to inform a future study or adoption of the protocol?

The protocol suggests that measurements will include a number of process and outcome measures which are indeed important. However, to better understand the feasibility of conducting an intervention the following questions would also need to be addressed:

- Acceptability -from the perspective of the patients and the healthcare providers

We are capturing this data from participant satisfaction questionnaires and participant interviews and from interviews with key healthcare providers. We have amended the text to make this clearer.

- what are the required resources (time, personnel, equipment) for implementing the protocol.

***This* will be captured in the economic analysis and again we have expanded the text to make this clearer.**

- What are the barriers and facilitators to implementation of the intervention and is it practical.

This data is being captured as the study progresses via communication with the practices and via drop-in clinical sessions with the clinical lead. Additionally, data will be captured during interviews with HCPs. We plan to interview both, practice sites that engaged and sites that were interested but then did not then proceed to recruit participants.

- How easily can the intervention be integrated in the existing health care system

This data is collected under "to ascertain the feasibility of delivering the intervention as per the protocol to inform a future study or adoption of the protocol" I have edited text to say "or adoption of the protocol in the exiting healthcare system"

- Will the intervention need to be adapted for different primary care/clinical settings

We collect this data from communication with each of the practices and during site-initiation. I have added this into the objectives.

- What are the potential challenges in scaling the intervention and what resources are required to sustain the intervention in the long-term?

The answer to these questions, we hope to determine during the delivery of the study and from the data collected. From a participants' perspective we will gather important feasibility, randomisation and attrition information. One of the challenges being participants' recruitment and us being in a good position to understand participants' response to the study. From a resource perspective, data gathered from day-to-day communication with the sites, the economic analysis and interviews with HCPs should feed into this understanding of potential challenges.

While the outcome measures are identified in Table 3 (Summary of study outcomes) it is not clear in the submitted protocol how the data for some of these outcomes will be collected and measured.
In particular

- Determination of the barriers/enablers that affect the delivery of the intervention from the perspective of the NHS stakeholders
- Determination of the barriers/enablers that affect the delivery of the intervention from the perspective of the
- Determination of the integrity, robustness, and transferability of the protocol for future adoption by the NHS

We have combined the outcome measures with the aims and objectives in Table 1. We hope that this is now clearer.

Competing Interests: No competing interest to declare