Protocol for Ethics

**RESPONSIBLE PRE-OPERATIVE OPIOID USE FOR HIP AND KNEE ARTHROPLASTY II (OPIOIDHALT II) STUDY**: Opioid tapering in patients prior to hip or knee arthroplasty.

**Funded via:** Commonwealth Government of Australia - 2022 MRFF Clinician Researchers - Nurses Midwives and Allied Health – MRF2022763.

**Grantee/Sponsor:** The University of Sydney.

**Table 1. PROJECT TEAM MEMBERS - ROLES AND RESPONSIBILITIES**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Name | | Position | Project Role/Responsibility | |
| Dr Jonathan Penm | | Senior Lecturer, Sydney Pharmacy School, University of Sydney, Pharmacist. | Chief Investigator Lead A (CIA), Lead OpioidHALT I pilot study, and medication safety expert. | |
| Professor Justine Naylor | | Conjoint Professor UNSW, and South Western Sydney Local Health District; Senior Principal Research Fellow, Ingham Institute of Applied Medical Research, Physiotherapist | Project co-lead (CIB), co-lead OpioidHALT I pilot study, expertise in clinical and patient-centred research outcomes associated with musculoskeletal conditions. | |
| Professor Asad Patanwala | | Professor, Sydney Pharmacy School, The University of Sydney | Design of the pilot trial that has provided the preliminary data for the project | |
| Professor Nicholas Lintzeris | | Professor, The University of Sydney and Director Drug and Alcohol Services, SESLHD | Development and evaluation of treatment interventions for individuals with substance use disorders, with expertise in evaluation of pharmacotherapies for opioids and cannabinoids. | |
| Professor Rebekah Moles | | Professor, Sydney Pharmacy School, The University of Sydney, Pharmacist | Pharmacy and medication safety expert. | |
| Associate Professor Betty Chaar | | Associate Professor, Sydney Pharmacy School, The University of Sydney, Pharmacist | Qualitative and quantitative methods expert and provide insight into the foundations of clinical practice in healthcare. | |
| Associate Professor Lei Si | | Associate Professor, Western Sydney University | Health Economics expert, extensive experience in cost-of-illness analysis, quality-of-life research, and health economic evaluation alongside clinical trials and model-based health economic evaluation. | |
| Associate Professor Claire O'Reilly | | Associate Professor, Sydney Pharmacy School, The University of Sydney | Focused on developing the skills of pharmacists in mental healthcare, and developing the evidence base for pharmacist-led mental health programs in practice. | |
| Associate Professor Sam Adie | | Associate Professor, St. George, and University of New South Wales. | Orthopaedic Surgeon and Co-lead in OpioidHALT I pilot study. | |
| Associate Professor Carl Schneider | | Associate Professor, Sydney Pharmacy School, The University of Sydney | Facilitate Patient Safety through Collaborative Care and Optimising the Use of Medicines. Expertise in scientific design and conduct of a complex collaborative medication safety. | |
| Mr Joseph Descallar | | Biostatistical Officer, Ingham Institute for Applied Medical Research | Statistical Expert, proficiency in SAS, R, and M-Plus programs. | |
| Associate Professor Jennifer Stevens | | Associate Professor, University of New South Wales. | Identifying the extent, nature and associations of perioperative opioid use and harms. | |
| Doctor Bernadette Brady | | Clinical Specialist Physiotherapist / Research Fellow, Liverpool Hospital, SWSLHD. | Expert in consumer engagement and co-design focused on chronic pain management. | |
| Doctor Kylie Bailey | | Senior Lecturer, School of Psychological Sciences, The University of Newcastle and Hunter Medical Research Institute | Expertise in comorbidity, which includes mental health, alcohol and other drug use, and more recently chronic pain. | |
| Ms Shania Liu | | PhD Candidate, The University of Sydney, Pharmacist | Co-Lead in OpioidHALT 1 Pilot Study, Implementation of the study. | |
| Doctor Michelle Penm | | General Practitioner, Redfern Station Medical Centre | General Practice, Medication safety, Pain, and Primary care expert | |
| Mr Frank Schaper | | Director and Company Secretary, Director and Company Secretary  Schlim Pty Ltd | Consumer representative, improve quality and safety of healthcare. | |
| Associate Professor Claire Ashton-James | | Associate Professor, Pain Management Research Institute, Northern Clinical School, The University of Sydney | Pain Management, evaluate and improve healthcare delivery for the benefit of both patients and clinicians (wellbeing and job satisfaction). | |
| Associate Professor Danijela Gnjidic | | Associate Professor, Sydney Pharmacy School, The University of Sydney. | Expert in clinical and geriatric pharmacology and the quality use of medicines. | |
| Doctor Kate Luckie | | Pharmacist,  The University of New South Wales | SPHERE Project Officer | |
| Dr Stephanie Mathieson | | Senior Research FellowSydney Musculoskeletal Health, Kolling Institute, The University of Sydney | Pain management, Reducing low-value care for musculoskeletal conditions. | |
| Doctor Furkan Genel | | PhD candidate, The University of New South Wales; Orthopaedic Registrar, St. George and Sutherland Clinical School | Expert in pain management, quality use of medicines. | |
| Professor Christine Lin | | Professor,Sydney School of Public Health, The University of Sydney | Expert in pain management, quality use of medicines. | |
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1. **SUMMARY**

|  |  |
| --- | --- |
| **Study Title** | **RESPONSIBLE PRE-OPERATIVE OPIOID USE FOR HIP AND KNEE ARTHROPLASTY II (OPIOIDHALT II) STUDY** |
|  |  |
|  |  |
| **Aims/Objectives** | Aim: The proposed Randomised Control Trial aims to determine the effectiveness and acceptability of pharmacist-led opioid tapering in patients awaiting total hip arthroplasty (THA) or total knee arthroplasty (TKA).   * Hypothesis 1: We hypothesise that people using opioids prior to THA or TKA who participate in a pharmacist-led opioid tapering program before surgery, compared to those who receive usual care, will: (i) be less likely to use opioids 3 months post-surgery; and (ii) report better pain and physical function 3 months post-surgery. We hypothesise this will be achieved through preoperative tapering of 50-100% of the preoperative opioid dose over a period of up to 3 months. * Hypothesis 2: We hypothesise that a pharmacist-led opioid tapering program before THA or TKA will be acceptable to patients and clinicians. |
| **Study design** | Randomised controlled clinical trial, followed by qualitative one-on-one semi-structured interviews with individuals who are part of the OpioidHALT II study. |
| **Planned sample size** | 314 participants in total (157 per group). |
| **Inclusion criteria** | Age ≥ 18 years, undergoing elective THA or TKA for osteoarthritis, speaks and reads English, uses opioid analgesics at least 4 days a week, has access to telephone or internet. |
| **Study procedures** | 1. Enrolment in the study: Research Officers (ROs) will identify potentially eligible patients from orthopaedic surgery waitlists at the participating hospitals. Those meeting the inclusion criteria will be invited to participate in the study and sent an information statement and consent form.  2. Informed consent: Patients who meet the inclusion criteria will be asked to read a participant information statement and sign a consent form if they agree to participate. Consent will include consent for access to online prescription monitoring program (Safe Script) and/or for ROs to contact participants’ pharmacies to validate data.  3. Randomisation: Participants will be randomised per site on a 1:1 basis to one of two arms: (1) pharmacist tele-health consultations to individualise pain management and opioid tapering plans; or (2) usual care.  4. Intervention: Pain management and opioid tapering training will be provided to pharmacists using an existing training package developed for the pilot RCT and revised on participant feedback. Data will be collected from participants at recruitment approximately 3 months prior to surgery (baseline), 1 to 3 days preoperatively (post-intervention) and 3 months after surgery by telephone call.  5. Follow-up interviews: At 3 months post-surgery, qualitative one-on-one semi-structured interviews will be conducted by experienced researchers with individuals (including patient-participants, research officers, and clinicians) involved in the opioid tapering program to determine their beliefs, attitudes and perceived acceptability, facilitators, and barriers to opioid tapering before the surgery.  6. Statistical analysis: A statistician, blinded to group allocation, will undertake the analysis. Post-intervention outcomes will be compared using intention to treat principles. A generalized estimating equation model will be used to model persistent opioid use from 1-3 days pre-surgery to 3 months post-surgery. A multilevel model will be used to model primary and secondary outcomes (WOMAC) from baseline to 3 months after surgery.  The interviews conducted at 3 months post-surgery will be transcribed and analysed using inductive thematic analysis. Interview questions and analysis will be iterative throughout the study to allow emerging themes to be examined in later interviews. |
| **Analysis considerations** | For each model, the participant will be specified as level 2 (i.e., clustering by participant), and the individual timepoint as level 1. Independent variables in the model will be group, time and an interaction between group and time. The primary and key outcome measures will be compared at the 3-month after surgery timepoint based on the models. Covariates between groups will be examined for potential imbalance and will be adjusted if necessary. Sensitivity analyses using per-protocol (defined as achieving a tapering dose > 50%) and as-treated (tapered 50% or more regardless of group allocation) analyses will also be conducted. |
| **Study duration** | 4 years |

**2. BACKGROUND AND RATIONALE**

Opioid analgesics are often used by patients with osteoarthritis awaiting total hip or knee arthroplasty (THA, TKA). In a previous study undertaken by our group involving five NSW hospitals, 38% of patients were using opioids before a THA or TKA.[1] A recent meta-analysis involving 9,283 patients awaiting TKA or THA revealed pain due to osteoarthritis was the most common justification for pre-operative opioid use,[2] even though there is little evidence to show opioids provide symptom relief and can cause harm.[2]

Opioid use in patients awaiting arthroplasty is problematic for several reasons. Firstly, our research and that of others demonstrated that preoperative opioid use is the strongest predictor of persistent opioid use after arthroplasty.[1] Importantly, even modest doses of short durations (e.g., 12 mg per day for three months pre-operatively) in chronic pre-operative users, have been shown to increase the risk of persistent opioid use post-arthroplasty 6-fold compared to opioid naïve patients.[3] Our findings also demonstrated that patients who were opioid-tolerant before TKA required significantly more opioids and experienced worse pain after surgery.[4] Persistent opioid use is undesirable because it is associated with opioid tolerance, dependence, and side effects, including sedation and falls. [5] Secondly, a meta-analysis of 7,356 patients demonstrated that pre-operative opioid use is associated with worse postoperative patient-reported outcomes when compared to those who did not use opioids pre-surgery (Standardized Mean Difference (SMD) -0.53, 95% CI -0.75 to -0.32).[6] Thirdly, pre-operative opioid use is associated with increased risk for some complications including revision surgery, periprosthetic infection and readmission. (10-15) Given these realities, **strategies to mitigate the harms associated with preoperative opioid use are warranted.**

**What we know about potential strategies:** A retrospective study showed that patients with a history of chronic opioid use who decreased their opioid dose (by at least 50%) before arthroplasty had significantly improved postoperative clinical outcomes compared to those who did not wean preoperatively (Western Ontario and McMaster Universities Arthritis Index [WOMAC] 43.7 vs. 17.8, p < 0.001).[7] As the study was a retrospective analysis of administrative data, the method of tapering employed by individuals could not be determined. Beyond this study, no clinical trial has been conducted on the effectiveness of opioid tapering prior to surgery.[8] Opioid tapering has been recommended in multidisciplinary chronic pain clinics.[9] However, demand for these services far exceeds supply, with a 2021 review of chronic pain services in Australia revealing lengthy waiting times of a median of 80 days and up to three years.[10] These findings highlight an unmet need for accessible, low-cost, and effective pain management and opioid tapering services for people awaiting surgery.

In Australia, pharmacists have been federally funded since 2001 to review patients' medications (Home Medicines Review). This pharmacist service has been shown to deprescribe on average, one medication per patient greater than a GP clinical audit. [11] For opioids in particular, a pharmacist-led intervention to taper opioids in the community was shown to successfully reduce opioid use by at least 50% of the original dose.[12] Thus, we plan to use a pharmacist-led deprescribing service for people awaiting THA or TKA to taper opioids.

**Our team’s contribution:** Our team’s systematic review published in 2022 found rates of persistent opioid use after hospital discharge in Australia were less than 10%.[13]. We then conducted another systematic review in 2022 and found this rate was more than double among patients receiving THA or TKA specifically.[14] Our systematic review found regular opioid use before surgery was a major risk factor for persistent opioid use after surgery.[14] Our research in Australia confirmed that persistent opioid use is higher in patients who use opioids regularly before THA or TKA, compared to those who are opioid-naïve (34% vs 9%).[15] Furthermore, another systematic review published in 2022 found regular opioid use before surgery increased the risk of opioid-related adverse drug events (such as constipation and respiratory depression) in hospitalised patients.[16]

In 2021, our team conducted a systematic review to identify prospective studies including RCTs and quasi-experimental studies examining the effectiveness of tapering interventions to reduce opioids for non-cancer pain before elective surgery (PROSPERO ID: CRD42020202221).[8] We found no studies had been published, despite recommendations in the literature for people to taper prior to surgery.[17,18]

To identify the best evidence to taper opioids, our team developed an evidence-based Clinical Practice Guideline for Deprescribing Opioid Analgesics that has undergone public consultation.[19] This guideline supports gradual opioid tapering, tailoring deprescribing plans to each patient, regular review while tapering opioids and using non-pharmacological pain management strategies to support opioid tapering.[19] These processes will be used in the opioid tapering intervention for this study. Critically, we have also conducted a pilot RCT to assess the acceptability and feasibility of a pharmacist-led opioid tapering intervention before THA or TKA (Table 1).

**Table 1.** Data from OpioidHALT I Pilot Study in 8 hospitals (ACTRN12621000919819)

|  |  |  |
| --- | --- | --- |
| **Outcome** | | **Preliminary findings** |
| Participants recruited (n) | | 77 |
| Recruitment rate per month, n/month | | 18 |
| Eligibility rate, % (n) | | 20% (98/498) |
| Baseline (~3 months prior to surgery) daily morphine milligram equivalents dose, median (range) | | 27.9 (2-106) |
| Intervention group (n) | | 35 |
|  | Participants found intervention acceptable, % (n) | 97% (34) |
| Recruited participants that have had their surgery (n) | | 51 |
|  | Intervention group who tapered ³ 50% of opioid dose, % (n) | 93% (26/28) |
|  | Control group who tapered ³ 50% of opioid dose, % (n) | 17% (4/23) |
| Adverse events from opioid tapering in those that have had surgery | |  |
|  | Intervention group | 64% (18/28; nausea, muscle tension) |
|  | Control group | 57% (13/23) |
| 3-month post-operative follow-up (n) | | 37 |
|  | Intervention group: opioid use at 3-month follow-up, % (n) | 15% (3/20) |
|  | Control group: opioid use at 3-month follow-up, % (n) | 69% (11/17) |

Based on the recruitment rates (notably under pandemic conditions whereby surgeries were widely disrupted), eligibility rates, high acceptability and near 100% opioid tapering efficacy and acceptable adverse events, our pilot data supports the feasibility of a full-scale RCT.

Positive qualitative feedback has been received from all hospital sites, and from participants receiving the intervention. Preliminary findings from a qualitative study by AI Genel (PhD thesis) suggest patients awaiting THA or TKA are willing to taper their opioids before surgery with the support of a pharmacist. Therefore, data from our pilot RCT and qualitative exploration support the feasibility and acceptability of the proposed pharmacist-led opioid tapering program. To ensure this program is consumer-centred[20], a consumer (Mr AI Schaper) has been closely involved in its design. This research leverages existing funding from the NHMRC Postgraduate Research Scholarship and Avant Foundation Grant.

**Australian priority and engagement:** Improving the appropriate use of opioids has been identified as a priority in Australia.[21] Improving appropriate opioid use aligns with the Australian 2021 National Strategic Action Plan for Pain objective of “*Medication for pain management is used appropriately to minimise inappropriate reliance on pain medication*.” It is also supported by the Australian Commission On Safety And Quality In Health Care’s Opioid Analgesic Stewardship in Acute Pain Clinical Care Standard released in April 2022.[22] These standards aim to improve opioid use in hospitals and reduce persistent opioid use, but there is no mention of deprescribing opioids before surgery, highlighting the need for further work in this area. The Commission supports this study as a national priority. Australian dispensing data shows inappropriate opioid use also appears higher in regional and rural areas,[23] which our research further supports, as a higher proportion of patients (50%) in inner regional hospitals used opioids before THA or TKA. ([1] Thus, any research aimed at deprescribing opioids prior to surgery needs to be inclusive of both metropolitan and regional hospitals.

**3. STUDY AIMS/OBJECTIVES**

The proposed RCT aims to determine the effectiveness and acceptability of pharmacist-led opioid tapering in patients awaiting THA or TKA.

* Study 1 Hypothesis: We hypothesise that people using opioids prior to THA or TKA who participate in a pharmacist-led opioid tapering program before surgery, compared to those who receive usual care, will: (i) be less likely to use opioids 3 months post-surgery; and (ii) report better pain and physical function 3 months post-surgery. We hypothesise this will be achieved through preoperative tapering to less than 50% of the preoperative opioid dose over a period of up to 12 weeks (3 months).
* Study 2 Hypothesis: We hypothesise that a pharmacist-led opioid tapering program before THA or TKA will be acceptable to patients and clinicians.

**4. PARTICIPATING SITES**

**Table 2.** Participating sites

|  |  |  |
| --- | --- | --- |
| **Hospital Site** | **Local Health District** | **Named PI Site Lead** |
| Fairfield Hospital | South Western Sydney LHD | Shaniya Ogul |
| Nepean Hospital | Nepean Blue Mountain LHD | Yasser Khatib |
| Wyong Hospital | Central Coast LHD | Frances Page |
| Gosford Hospital | Central Coast LHD | Frances Page |
| Dubbo Base Hospital | Western NSW LHD | Andrew Sefton |
| Orange Health Service | Western NSW LHD | Anders Jansson |
| Shoalhaven District Memorial Hospital | Illawarra Shoalhaven LHD | Clare Eastment |
| The Wollongong Hospital | Illawarra Shoalhaven LHD | Karin Sylvester |
| Coffs Harbour Community Health | Mid North Coast LHD | Dave Gillespie |
| Prince of Wales Hospital | South Eastern LHD | Lisa Nealon |
| Launceston General Hospital | Tasmania | Jonathan Mulford |

**5. STUDY DESIGN**

**Phase 1: To determine the effectiveness of preoperative pharmacist-led opioid tapering to reduce persistent opioid use after arthroplasty.**

Design: Two-arm prospective, assessor-blind, randomised controlled trial.

Setting: Eleven public hospitals in NSW - Dubbo, Orange, Fairfield, Gosford, Wyong, Shoalhaven, Wollongong, Nepean, Prince of Wales, Coffs Harbour Public Hospitals and Launceston General Hospital will participate. A mix of urban, regional, and rural hospitals have been chosen to assist generalisability.

Screening, Recruitment and Consent: Research Officers (ROs) who are qualitifed researchers employed by the research team will identify potentially eligible patients from surgery waitlists at the study hospitals, where surgery wait times are approximately 8 to 15 months. Patients will be contacted 4 to 6 months (Figure 1) before surgery by telephone to determine eligibility. Those meeting the inclusion criteria (see below) will be invited to participate in the study and sent an information statement and consent form. Consent forms will include provision of access to an online prescription medication monitoring program (SafeScript) and/or for ROs to contact participants’ pharmacies to validate data. SafeScript is a software that allows general practitioners, medical specialists and pharmacists to access real-time information about patient’s prescription history for monitored medicines, such as opioids and benzodiazepines. Eligible participants will be included after written informed consent is obtained. The participant will receive a study enrolment number, and this will be recorded on all study documents pertaining to that participant.

, completing tasks, understanding, remembering, or following instructions).

Randomisation, Allocation Concealment and Blinding: Participants will be randomised in a 1:1 ratio in permuted blocks of 2 and 4 to: (1) pharmacist tele-health consultation to individualise pain management and opioid tapering plans; or (2) usual care. Randomisation will be conducted using a centralised randomisation service to ensure allocation concealment. Randomisation will be stratified

Diagram

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Inclusion criteria: Aged 18 years or older, undergoing elective THA or TKA, speaks and reads English, uses prescription opioid analgesics at least 4 days a week, has access to internet or telephone.

As a safeguard, we will perform a mental health screening of those who consent to identify those at risk of psychological harm from tapering. Psychological distress and suicidality will be screened using the 6-item Kessler Psychological Distress Scale (K6)[24] and the 3-item Patient Safety Screener (PSS).[25] Patients with: (i) a K6 score of 19 or greater AND PSS criteria 1 (feeling down, depressed or hopeless over past two weeks); OR (ii) PSS criteria 2 (thoughts of killing yourself over past two weeks); OR (iii) PSS criteria 3 (ever attempted to kill yourself) AND report suicidality in the past 6 months will be referred to their GP to confirm whether participation in the trial is appropriate and for further follow up for mental health care if required. We note that no patient in the pilot study developed or expressed psychological harm.

Exclusion criteria: Patients undergoing planned surgeries within 6 months using opioids for cancer, palliative care or substance use disorder; previously or already undergoing an opioid tapering program or active medication review or have major cognitive impairment (e.g., having trouble concentrating by hospital site.

Description of Study Intervention: Pain management and opioid tapering training will be provided to pharmacists using an existing training package developed for the pilot RCT and revised on participant feedback.

As depicted in Figure 2, prior to opioid tapering, a pharmacist (employed by the research team) will contact the participant’s GP to outline the intervention and address any concerns. The pharmacist will engage in shared decision-making with participants to develop an individualized biopsychosocial pain management plan and an opioid weaning plan. [26] The NPS Medicinewise opioid weaning plan [27] will be used to guide rates of opioid tapering. Participants will receive the intervention for approximately 3 months. The opioid tapering target of ≤50% of the baseline opioid dose was chosen as this has been shown to improve post-surgical outcomes similar to opioid-naïve participants.[7] If this target is reached before the participant is due for surgery, the participant will continue to be followed up until the day of surgery.

The intervention employs key components of the Behaviour Change Wheel [28] to target participant behaviour change by leveraging:

1. capability (by improving participants’ confidence and knowledge of effective pain management and opioid tapering),
2. opportunity (by providing an individualized pain management and opioid tapering service that is more accessible than traditional pain clinics) and
3. motivation (by engaging with participants through the shared decision making and encouraging active involvement in participants’ own health).

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| **Figure 2.** Study Intervention Procedures |

Description of Control Arm: Usual care will serve as the control arm. This involves review by the hospital preadmission clinic multidisciplinary team to assess medical, physical and psychological health prior to surgery. Participants will be provided education for preoperative and postoperative care that does not involve an active opioid tapering program.

Data collection: Data will be collected from participants at recruitment approximately 3 months prior to surgery (baseline), 1 to 3 days preoperatively (post-intervention) and 3 months after surgery by telephone call using a standard Data Collection Form (shown below). Telephone calls were shown in the pilot study to be an acceptable mode of data collection for participants. We will also collect information related to hospital stay from the hospital medical records. Data on analgesic and benzodiazepine use will be verified using SafeScript and/or calling the participant’s pharmacy.

The following baseline data will be collected: demographics (sex, age, body mass index, comorbidities, postcode, treating surgeon, treating GP, surgery type (THA or TKA), pain catastrophising using the Pain Catastrophising Scale[29]), stiffness, pain and function (using WOMAC[30]), pain intensity measured using the Brief Pain Inventory,[31] analgesic use (including non-opioid analgesia, opioid use in daily oral morphine milligram equivalents [MME][32]), benzodiazepine use in equivalent daily diazepam milligram dose,[33] substance use (including alcohol, cannabis, tobacco and non-prescribed opioid use) using the Australian Treatment Outcomes Profile (ATOP),[34] opioid dependency, anxiety and depression using the Mini-International Neuropsychiatric Interview (MINI),[35] opioid withdrawal using the Short Opiate Withdrawal Scale,[36] pain self-efficacy using the Pain Self-Efficacy Questionnaire,[37] potentially aberrant behaviours using the Opioid Risk Assessment Tool,[38] psychological distress using the Kessler 6-item (K6) Scale,[24] and health-related quality of life using the EQ-5D-5L tool.[39]

Outcomes: Trial outcomes and timepoints for measurement are described in Table 3. Our primary outcome is the incidence of persistent opioid use at 3 months postoperatively. Our key secondary outcome is WOMAC score at 3 months postoperatively. WOMAC scores[30] evaluate joint pain, stiffness and physical function and are shown to be highly predictive for treatment success.[40] Other secondary outcome measures include pain intensity, whether opioids are tapered by at least 50% before surgery, analgesic and other substance use, length of acute hospital stay, discharge destination (home, inpatient rehabilitation, other acute hospital, death), 30-day readmission, 90-day joint related readmission and post-operative complications (combined as a composite outcome), incidence of opioid-related adverse events, which may include: constipation, nausea and vomiting, heartburn, diarrhoea, abdominal pain, somnolence, dizziness, headache, hallucinations, sleep disturbances, respiratory depression, urinary retention, pruritis, dry mouth, or falls, opioid withdrawal symptoms, pain self-efficacy, psychological distress, health-related quality of life, cost-effectiveness and surgical complications. [5]

**Table 3.** Outcomes and timepoints for measurement

|  |  |  |  |
| --- | --- | --- | --- |
| **Measure** | **Baseline (3 months before surgery)** | **1-3 days before surgery** | **3 months after surgery** |
| Demographics | x |  |  |
| Pain, stiffness and function (WOMAC score) | x | x | x |
| Pain intensity (Brief Pain Inventory) | x | x | x |
| Non-opioid analgesic use (self-report) | x | x | x |
| Analgesic and benzodiazepine use (self-report + SafeScript) | x | x | x |
| Substance use (Australian Treatment Outcomes Profile) | x | x | x |
| Length of hospital stay (hospital records) |  |  | x |
| Discharge destination (patient report and hospital records) |  |  | x |
| 30-day hospital readmission rate (patient report and hospital records) |  |  | x |
| Opioid-related adverse events (self-report) | x | x | x |
| Opioid withdrawal symptoms (Short Opioid Withdrawal Scale) | x | x |  |
| Pain self-efficacy (Pain Self-Efficacy Questionnaire) | x | x |  |
| Health-related quality of life (EQ-5D-5L tool) | x | x | x |
| Surgical complications (hospital records & self-report) |  |  | x |
| Psychological distress (Kessler 6-item Scale) | x | x | x |

WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index

**Data Collection Form at 3 months prior to surgery**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Patient ID | Sex | Age | Body mass Index | Comorbidities | Postcode | Treating surgeon | Treating GP | Surgery type (total hip or knee arthroplasty) | Pain intensity (using Brief Pain Inventory) | Analgesic use |
|  |  |  |  |  |  |  |  |  |  |  |
| Pain catastrophising (using PCS tool) | Benzodiazepine use | Substance use (using Australian Treatment Outcomes Profile) | Opioid Dependency | Anxiety and depression (using Mini-International Neuropsychiatric Interview) | Opioid withdrawal (using SOWS tool) | Potentially aberrant behaviours (using Opioid Risk Assessment Tool) | Psychological Distress (using Kessler 6-item scale) | Health-related quality of life (using EuroQol 5 Dimensions) | Pain, stiffness, function (using WOMAC) |  |
|  |  |  |  |  |  |  |  |  |  |  |

PCS = Pain Catastrophising Scale; SOWS = Short Opiate Withdrawal Scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

**Data Collection Form at 1 to 3 days prior to surgery**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Patient ID | Pain intensity (using Brief Pain Inventory) | Analgesic use | Pain catastrophising (using PCS tool) | Benzodiazepine use | Substance use (using Australian Treatment Outcomes Profile) | Opioid Dependency | Anxiety and depression (using Mini-International Neuropsychiatric Interview) | Opioid withdrawal (using SOWS tool) |
|  |  |  |  |  |  |  |  |  |
| Potentially aberrant behaviours (using Opioid Risk Assessment Tool) | Psychological Distress (using Kessler 6-item scale) | Health-related quality of life (using EuroQol 5 Dimensions) | Pain, stiffness, function (using WOMAC) |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |

PCS = Pain Catastrophising Scale; SOWS = Short Opiate Withdrawal Scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

**Data Collection Form at 3 months after surgery**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Patient ID | Pain intensity (using Brief Pain Inventory) | Analgesic use | Pain catastrophising (using PCS tool) | Benzodiazepine use | Substance use (using Australian Treatment Outcomes Profile) | Opioid Dependency | Anxiety and depression (using Mini-International Neuropsychiatric Interview) | Opioid withdrawal (using SOWS tool) |
|  |  |  |  |  |  |  |  |  |
| Potentially aberrant behaviours (using Opioid Risk Assessment Tool) | Psychological Distress (using Kessler 6-item scale) | Health-related quality of life (using EuroQol 5 Dimensions) | Pain, stiffness, function (using WOMAC) | Length of hospital stay | Discharge destination | 30-day hospital readmission | 90-day hospital readmission | Postoperative complications |
|  |  |  |  |  |  |  |  |  |

PCS = Pain Catastrophising Scale; SOWS = Short Opiate Withdrawal Scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

Sample Size: We plan to power the study to detect clinically meaningful differences in both our primary (persistent opioid use) and key secondary (WOMAC total) outcomes. Our previous work [15] indicated that rates of persistent use at 3-months post-surgery amongst regular opioid users pre-operatively and opioid naive patients were 34% and 10%, respectively. That is an absolute difference of 24%. For this study, we will power the study to be able to detect a more conservative absolute difference of 19% (34% amongst regular pre-operative opioid users exposed to usual care and 15% amongst regular opioid users exposed to the tapering intervention). Using an alpha of 0.025 in a two-sided test and 90% power, 250 participants in total will be required for the primary outcome. Previous literature shows the mean total WOMAC score at 6 months after surgery of patients taking opioids preoperatively was 65.3 (standard deviation [SD] 35.1) compared to 83.1 (SD 35.1) among patients who were opioid naïve pre-surgery,[6]; a difference exceeding the Minimal clinically important differences (MCID) for total WOMAC score for people following TKA.[41] Here we will aim to detect a similar difference (absolute difference of 18). Using an alpha of 0.025 in a two-sided test and 90% power, 196 participants will be required. Considering both outcomes and taking the more conservative power calculation and accounting for a potential drop-out rate of 20%, we aim to recruit 314 participants in total (157 per group).

Participant withdrawal: Data from participants who decide to withdraw from the study will be included until the point of withdrawal.

Safety Monitoring: ROs conducting eligibility screening and pharmacists will be trained in Mental Health First Aid. Safety will be monitored for all intervention-group participants during follow-up appointments with the pharmacist, including psychological distress using the K6 scale where a score ≥ 19 will warrant GP review.[24] The intervention was developed in consultation with CIs Lintzeris and Chaar who have extensive expertise in drug & alcohol and CIs O’Reilly and Bailey who have extensive expertise in mental health. Opioid tapering plans where baseline opioid dose is ≥50 MME [42] will be reviewed by our pain specialist CI Stevens for safety, and participants will be offered take-home naloxone to reduce the risk of opioid overdose and receive twice-weekly follow-up during opioid tapering. Further details are available in the Risk Management Plan as shown below.

Independent Data Safety Monitoring Board: Study risks and safety will be reported and monitored via standard clinical trial reporting procedures involving a data safety monitoring board (DSMB). The DSMB will consist of at least 3 members who are independent of the study, including pharmacist/s, pain specialist/s and a biostatistician. Members of DSMB will meet 6-monthly to review reported adverse events and make recommendations as required concerning the ongoing conduct and safety of the trial. Two formal interim analyses will be planned to review data relating to treatment efficacy, participant safety and trial conduct, including recruitment, participant retention rate and completion of study intervention. Prior to the first interim analysis a detailed statistical analysis plan (SAP) will be developed to describe analysis methodology, data handling conventions and procedures to be used to account for missing data.  The SAP will inform both interim analyses.  A description of trial metrics required for review will be included.

Statistical Analysis: Post-intervention outcomes will be compared using intention to treat principles. A generalized estimating equation model will be used to model persistent opioid use from 1-3 days pre-surgery to 3 months post-surgery. A multilevel model will be used to model the key secondary outcome (WOMAC) from baseline to 3 months after surgery. For each model, the participant will be specified as level 2 (i.e., clustering by the participant), and the individual timepoint as level 1. Independent variables in the model will be group, time, and an interaction between group and time. The primary and key outcome measures will be compared at the 3-month after surgery timepoint based on the models. Covariates between groups will be examined for potential imbalance and will be adjusted if necessary. Sensitivity analyses using per-protocol (defined as achieving a tapering dose > 50%) and as-treated (tapered 50% or more regardless of group allocation) analyses will also be conducted. To account for a potential loss to follow-up of 25%, we will recruit 80 participants (40 per group).

Data Management and Integrity: All data (re-identifiable) will be stored in a password-protected cloud-based software, OneDrive on the University of Sydney Platform. Data will be stored for 15 years according to the University of Sydney’s Research Code of Conduct 2019. Random checks of 10% of data will be conducted for quality assurance.

Potential Confounding Considerations: Participants in the comparison arm will receive usual care. The detail of this will vary by site in response to the participants’ individual characteristics and clinicians’ interpretation of this. Randomisation at the participant level should achieve similar distribution of variables in both arms. As the trial progresses, it is possible that an increasing focus on opioid tapering may occur within the sites in the usual care arm, which may diminish the ability to identify differences in outcomes between intervention and comparison arms. To detect such phenomena, all participants’ preoperative clinic notes will be examined to detect if there was an increased emphasis on opioid tapering as the trial progresses. Furthermore, the as-treated analysis will take this into account.

Intervention Treatment Fidelity: Participant adherence will be assessed by the number of telehealth interactions between participants and pharmacists. Participating GPs’ fidelity to the weaning plans will be assessed by evidence of opioid reduction. Safe script will also be used to verify opioid use in the participants. If participants adhere to the program and between-group differences in opioid reduction are observed, we can reliably attribute this to the program.

Therapeutic Validity: The intervention arm is guided by known principles of behaviour change, and well supported by relatively intensive but manageable pharmacist input and permits involvement of other disciplines typically included in pain management/opioid tapering programs. Further, proof of concept and thus therapeutic validity, are provided by the pilot study.

Economic Evaluation: A within-trial cost-effectiveness analysis will be conducted from the health system perspective, accounting for intervention costs (pharmacist time and training), cost offsets from the reduction in health resources utilisation (length of stay in hospital, complications acutely and up to 3 months) and effectiveness (opioid use) at 3 months postoperatively. We will collect individual data related to health resources uses, including GP visits, hospital visits, analgesics used, and other visits to health professionals for pain management by the patients. The trial audit will be used to estimate the intervention costs. The primary effectiveness measure will be in line with the primary outcome of the trial, i.e., the incidence of persistent opioid use at 3 months postoperatively.

We will also include quality-adjusted life years (QALYs) as an effectiveness measure for a cost-utility analysis. The QALYs will be calculated from the EQ-5D responses of the study participants and their duration in the trial period.

The incremental cost-effectiveness ratio (ICER) will be calculated by the difference in healthcare costs divided by the differences in outcomes (i.e., opioid use and QALYs). The pharmacist-led opioid tapering intervention will be considered cost-effective in either of the following two scenarios:

1. The overall healthcare cost is lower, where the mean QALYs are higher in the intervention group compared to standard care.
2. Both the overall healthcare cost and QALYs are higher in the intervention group, the ICER is no greater than $50,000 per QALY gained.

Where necessary, costs will be converted to 2023 prices using the Australian Institute of Health and Welfare health price index. A number of one-way sensitivity analyses and scenario analyses will be performed to test the robustness of the cost-effectiveness result. Non-parametric bootstrapping will be conducted to estimate the distribution and the confidence interval of ICER. A cost-effectiveness acceptability curve will be provided to estimate the probabilities of the intervention being cost-effective at a range of willingness-to-pay thresholds.

Process Evaluation: To assess the factors affecting trial implementation, we plan to evaluate the following:

* Internal fidelity – random observational audits will be conducted to assess the degree to which the pharmacist-led interventions are delivered as intended.
* Relationship between intervention implementation and trial outcomes – potential factors affecting trial outcomes will be identified, such as surgery performed at a public or private hospital.
* Mechanisms, barriers, and facilitators for successful implementation of the pharmacist-led interventions.

Consumer Involvement: We have developed a Consumer Advisory Group (CAG; AI Schaper and consumer-representative partner organisations) to ensure the intervention is consumer centred. CIs Penm, Naylor, Adie, Brady & Schneider and AIs Lin & Genel (PhD thesis) have conducted research exploring consumers’ and GPs’ views on opioid tapering.[20,43] We identified that improved communication between healthcare professionals and consumers regarding expectations of opioid tapering, as well as providing more opportunities for shared decision making would improve the success of opioid tapering.[20] Therefore, from the outset of our pilot RCT and writing this proposal we have had a consumer (AI Schaper) closely involved in the trial design.

**Phase 2: To explore the acceptability of preoperative pharmacist-led opioid tapering**

At 3 months post-surgery, qualitative one-on-one semi-structured interviews ranging from 30-60 minutes will be conducted with stakeholders (including participants, clinicians, and research assistants) involved in the opioid tapering program to determine their beliefs, attitudes and perceived acceptability, facilitators and barriers to opioid tapering before THA or TKA. Interviews will be conducted by investigators who possess training in qualitative research methods using telephone or telehealth. Interviews will be conducted until saturation of themes is identified. It is estimated that this will be 60 interviews (30 participants and 30 clinicians/research assistants) based on previous studies. [44] The interview guide will be based on the consolidated framework for implementation research (CFIR). [45] In addition, the qualitative interviews will explore how factors affecting the implementation of the study intervention relate to elements within the Behaviour Change Wheel [28] including (i) patient/clinician capability to manage pain, (ii) opportunity to discuss pain management, and (iii) motivations to taper opioid before surgery. This model is known as the ‘COM-B system’. [28] The CFIR and COM-B models have been used extensively to evaluate the implementation of an intervention to explain success or failure.

Interviews will be transcribed and analysed using inductive thematic analysis. Interview questions and analysis will be iterative throughout the study to allow emerging themes to be examined in later interviews. Data analyses will follow the methodology proposed by Bernard and Ryan. [46] Concordant processes of memo-ing on codes will enable clustering of related codes into categories. Two independent researchers will use comparative analysis to refine codes and categories. [46] Any disagreements will be discussed with a third researcher to reach consensus.

**6. MILESTONES AND PERFORMANCE INDICATORS**

The following Gantt Chart outlines the project milestones and performance indicators.

**Table 4.** Gantt Chart of milestones and performance indicators

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Task** | **2023** | | | **2024** | | | **2025** | | | **2026** | | |
| **T1** | **T2** | **T3** | **T1** | **T2** | **T3** | **T1** | **T2** | **T3** | **T1** | **T2** | **T3** |
| Steering group meeting |  |  |  |  |  |  |  |  |  |  |  |  |
| Data safety monitoring meeting |  |  |  |  |  |  |  |  |  |  |  |  |
| Project advisory group meeting |  |  |  |  |  |  |  |  |  |  |  |  |
| Recruitment of staff |  |  |  |  |  |  |  |  |  |  |  |  |
| ***Aim 1:*** |  |  |  |  |  |  |  |  |  |  |  |  |
| Compile data forms |  |  |  |  |  |  |  |  |  |  |  |  |
| Obtain ethics approval |  |  |  |  |  |  |  |  |  |  |  |  |
| Training of pharmacists |  |  |  |  |  |  |  |  |  |  |  |  |
| Database development |  |  |  |  |  |  |  |  |  |  |  |  |
| Recruitment of participants (n=13 per month) |  |  |  |  |  |  |  |  |  |  |  |  |
| Collect baseline data |  |  |  |  |  |  |  |  |  |  |  |  |
| Collect preoperative data |  |  |  |  |  |  |  |  |  |  |  |  |
| Collect postoperative data |  |  |  |  |  |  |  |  |  |  |  |  |
| Reporting to Site HRECs |  |  |  |  |  |  |  |  |  |  |  |  |
| Study close-out |  |  |  |  |  |  |  |  |  |  |  |  |
| Data analysis |  |  |  |  |  |  |  |  |  |  |  |  |
| Economic evaluation |  |  |  |  |  |  |  |  |  |  |  |  |
| Report writing |  |  |  |  |  |  |  |  |  |  |  |  |
| ***Aim 2:*** |  |  |  |  |  |  |  |  |  |  |  |  |
| Obtain ethics approval |  |  |  |  |  |  |  |  |  |  |  |  |
| Recruitment of participants |  |  |  |  |  |  |  |  |  |  |  |  |
| Conduct interviews and write transcripts |  |  |  |  |  |  |  |  |  |  |  |  |
| Study close-out |  |  |  |  |  |  |  |  |  |  |  |  |
| Data analysis |  |  |  |  |  |  |  |  |  |  |  |  |
| Report writing |  |  |  |  |  |  |  |  |  |  |  |  |

HREC, Human Research Ethics Committee.

**Potential COVID-19 impacts on milestones and timelines:**

Several strategies have been employed to ensure potential disruptions due to COVID-19 restrictions are accounted for. First, CI and stakeholder meetings, Personnel recruitment and training of the opioid tapering pharmacists will be conducted via teleconference to minimise the impact of COVID-19 lockdowns on these milestones. Recruitment of participants will occur by screening arthroplasty waitlists, which can be done remotely. The opioid tapering intervention and data collection are conducted via telephone or teleconference to mitigate the risk of COVID-19 exposure. Based on pilot data, a 6-month leeway in time to recruit participants has been allocated to accommodate potential recruitment disruptions due to COVID-19 and/or ongoing surgical disruptions consequent to staffing and bed availability problems created by the pandemic.

**7. RISK MANAGEMENT PLAN**

**Step 1: Key risks and management**

|  |  |  |
| --- | --- | --- |
| **Risk theme** | **Risk** | **How risk is managed/mitigated** |
| People (Personnel) | Recruitment of Project Personnel is delayed, which may delay project planning and implementation. | The project will be managed by CIs Penm and Liu (under the mentorship of CI Naylor and Patanwala) until Project Personnel are recruited. Delays in recruitment for all personnel is unlikely and employment at 0.2 to 0.5 FTE for most staff would allow us to adjust employee hours as required while hiring key staff members.  Likelihood: Possible; Consequence: Minor; Acceptability: Acceptable. |
| Delivery (Resources, Budget) | Project requires more resources, which may cause the budget to be exceeded. | The project plan will be strictly monitored by the project team to ensure adherence to the budget.  Likelihood: Unlikely; Consequence: Moderate; Acceptability: Acceptable. |
| Regulatory (Ethics) | Ethics approval delay, which may delay recruitment and lead to further costs if timeline is extended. | The research team involves several experts with prior experience in applying for clinical trials ethics approval at the University of Sydney. Site Ethics committees meet monthly. The pilot protocol has been approved by the HRECs thus we do not foresee problems with approval given the definitive trial is based on the pilot protocol. Ample time allocated in timeline for ethics approvals to ensure that any delays have a minimal impact on our ability to deliver the intervention within the grant period.  Likelihood: Possible; Consequence: Moderate; Acceptability: Acceptable. |
| People (People capability) | Training of opioid tapering pharmacists may be delayed, which may delay commencement of interventions. | Pharmacists will be trained using existing materials used in the pilot trial led by several CIs listed on this grant. These materials will be provided to pharmacists with ample time for training. Ample time allocated in timeline for pharmacist training using existing materials. Team meetings with CIs will be held to address any questions raised.  Likelihood: Unlikely; Consequence: Moderate; Acceptability: Acceptable. |
| People (Recruitment) | Inadequate number of patients recruited which may lead to issues with evaluating impact of intervention. | We have set realistic recruitment targets based off pilot data. Conservative estimates of effect size have been made. Increasing the effect size would allow for a smaller sample if required. A 6-month leeway in patient recruitment has been allocated to provide a buffer. Pilot data have been used to inform recruitment rates.  Likelihood: Possible; Consequence: Moderate; Acceptability: Acceptable. |
| Information (Data collection) | Difficulty/delays in data collection from patients leading to delayed or missing baseline, post-intervention and follow-up data. | Patients will be required to consent at the outset of the study to allow for the project team to collect data via telephone. Participants will be reimbursed $30 for their time for each call. Several communication strategies can be used. Home/mobile telephone, email and postage details will be obtained at consent, including caregiver details if appropriate. These facilitate social distancing for COVID-19. Analgesic and benzodiazepine use will be validated using SafeScript and/or calling participants’ pharmacies to improve accuracy with participants’ consent. As per the pilot RCT, if participants’ surgeries are delayed, the intervention or usual care will continue until surgery.  Likelihood: Possible; Consequence: Moderate; Acceptability: Acceptable. |
| People (Stakeholders) | Patients’ GPs may not wish their patient to participate in study. | Pilot trial data suggests 100% intervention acceptability among GPs. The intervention is supported by CI Anaesthetist/Pain Specialist Dr Jennifer Stevens who will liaise with GP. The CI Pain Specialist Stevens will contact any GPs who are unwilling to taper patients’ opioids to discuss benefits/risks of opioid tapering and address questions.  Likelihood: Unlikely; Consequence: Moderate; Acceptability: Acceptable. |
| People (Safety) | Patients may experience opioid withdrawal symptoms when tapering opioids | Pilot trial data shows very low incidence of opioid withdrawal symptoms given slow rates of opioid tapering. The pain management plan will include instructions on how to safely manage opioid withdrawal symptoms, including non-opioid analgesics and non-pharmacological pain management techniques based on Australia’s NPS MedicineWise materials. These have also been reviewed by our CIs experienced in mental health, drug and alcohol and pain who are pharmacists, physiotherapists, specialists and clinical psychologists to ensure it meets the needs of our cohort. Opioid tapering plans where baseline opioid dose is above 50 MME are reviewed by CI Pain Specialist Stevens for safety. In the event of adverse effects, participants can call the intervention pharmacist during work hours. The pharmacist will provide advice on pain management techniques or will refer patients to their treating physician for review. CI Lintzeris (Additional Medicine Specialist) is available for providing clinical advice to pharmacists. For after-hours assistance, contact details for Lifeline will be available. For serious or potentially life-threatening adverse events, patients will be instructed to call 000 immediately. A Data Safety Monitoring Board will also be established with independent members to review accumulating trial data every 3 months.  Likelihood: Unlikely; Consequence: Moderate; Acceptability: Acceptable. |

**Step 2: Risk monitoring and reporting:**

Personnel recruitment will be monitored weekly. Ethics applications, pharmacist training progress, participant recruitment, and data collection will be audited fortnightly. Delays of >1 month for these tasks will be monitored by CI Penm and Liu and reported to the Steering Group (monthly).

Monthly budget evaluation will be conducted by CI Liu and reported to the Steering Group. If the trajectory of trial operations appears to be heading towards exceeding the budget, the Steering Group will critically assess trial procedures to ensure adherence to the budget.

GP approval rate will be audited fortnightly by CI Liu. Number of GPs who disagree to opioid tapering will be reported to Project Advisory Group (6 monthly) and in the annual progress report.

Potential opioid withdrawal symptoms will be followed closely by intervention-pharmacists weekly and will be reported to CI Penm.

Details of opioid withdrawal experience and the management will be reviewed by Data Safety Monitoring Board (3 monthly) and reported in annual progress reports.

**8. ETHICAL CONSIDERATIONS**

Study procedure benefits: Participants may benefit by receiving a pharmacist tele-consultation or GP consultation and structured pain management and opioid weaning plan. This may lead to improved clinical outcomes such as reduced pain and improved function after surgery compared to patients who don’t taper opioids before surgery.

On a broader scale, the project will fill a research gap on effective strategies to reduce opioid use before elective surgery. Once identified, these strategies may provide the basis for future preoperative opioid tapering programs to be implemented in hospitals to reduce opioid related harms and healthcare costs.

Study procedure risks: Upon tapering opioid analgesics, there is a risk of patients experiencing opioid withdrawal symptoms. However, opioid doses will be weaned very gradually (by 10-25% per week or per month) to reduce this risk.

Patients may experience increased pain upon tapering opioid analgesics. However, adjunct analgesics such as paracetamol or non-steroidal anti-inflammatory drugs (if clinically appropriate) and pain management techniques will be detailed in the pain management plan to minimise this. The pain management plan will include instructions given to patient on when to hold the current opioid dose or increase the opioid dose depending on levels of pain or opioid withdrawal symptoms. The intervention pharmacist will develop individualised pain management plans after considering the patient’s clinical and medication history.

In the event of any adverse effects of opioid weaning, participants can call the principal study investigator during work hours (9am to 5pm on Mondays to Fridays). The study investigator will then provide advice on pain management techniques or will refer patients to their treating physician for review. For after-hours assistance, contact details for Lifeline will be available. If any serious or potentially life-threatening adverse events are reported, patients will be instructed to call 000 immediately.

The qualitative interviews carry minimal risk as they are an evaluation of patients’ thoughts and experience on the pharmacist-led management of their pain and opioids. In the event, that the participant experiences any distress during the interview, they will be advised to contact the following support services for assistance.

Other Ethical Considerations:

* Voluntary participation: Participant involvement is voluntary and informed written consent is required.
* Ethical care: We contest the proposed intervention is ethical as it offers care above that of ‘usual care’.
* Ethical care: We contest the random allocation to ‘usual care’ is ethical as tapering programs are not routinely provided.
* Harm minimization: We contest we have endeavoured to minimise harm by including GP and anaesthetist oversight of the tapering plan if needed.
* Privacy and confidentiality: We will protect participant privacy and confidentiality by maintaining and storing study records in a secure database (Redcap TM, cloud-based storage) and paper-based records will be kept in locked research filing cabinets.
* Data integrity: We will adopt best practice for managing data including audit of data entry at regular intervals. All investigators will be required to have current certification of ‘Good Clinical Practice, GCP’ training prior to commencement.
* Scientific robustness: The research design is rigorous which is also an ethical consideration as it represents value for money in the context of limited research dollars.

**9. DATA STORAGE AND RECORD RETENTION**

Re-identifiable data will be stored in a password-protected cloud-based software. No data will be stored on personal computers. Data will be stored for 15 years according to the University of Sydney’s Research Code of Conduct 2019. After this period has elapsed, the research data will be destroyed permanently. Random checks of 10% of data will be conducted for quality assurance.

# 10. Early Termination (IF APPLICABLE)

In the event this study needs to be ceased prematurely for any reason, participants and HREC will be informed by study researchers, and a final study report will be compiled and submitted to HREC.

# 11. BLINDING AND UNBLINDING

Due to the nature of the intervention, it is not possible to blind participants or health care professionals to treatment group.

**12. CONFLICT OF INTEREST**

There are no actual or perceive conflicts of interest of any of the investigators.

**13. FUNDING**

Commonwealth Government of Australia - 2022 MRFF Clinician Researchers - Nurses Midwives and Allied Health – MRF2022763

**14. RESEARCH OUTCOMES**

We will disseminate the results of this study through presentations at scientific conferences, meetings with key stakeholders, and peer-reviewed publications. At this stage, data will be retained in a central repository, follow-up research or secondary use of data are anticipated.

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