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Clinical Trial Protocol

CLINICAL TRIAL PROTOCOL

# Analgesia using intrathecal morphine to improve quality of recovery after minimally invasive major abdominal surgery (AIM Trial): study protocol for a multicentre randomised controlled trial

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## Abstract

**Background:** Evidence to support the effectiveness of intrathecal morphine in patients undergoing minimally invasive abdominal surgery is largely based on small, single-centre studies. We therefore designed a large, multi-centre clinical trial to investigate the effect of intrathecal morphine with local anaesthetic on patient postoperative quality of recovery. The primary objective is to compare quality of recovery on postoperative Day 1. The secondary objectives are to compare opioid consumption, pain scores, and opioid-related adverse events.
**Methods:** This multi-centre, prospective, randomised controlled trial will recruit 280 adult patients undergoing minimally invasive major abdominal surgery. The intervention group will receive 200 mcg of intrathecal morphine with local anaesthetic, as part of a multimodal analgesic strategy. Following safety analysis after the first 100 patients the dose of ITM will increase to 300 mcg. The control group will receive non-neuraxial multimodal analgesia.
**Conclusions:** This trial is expected to provide evidence on the effectiveness and the safety of two different ITM doses with local anaesthetic in major minimally invasive abdominal surgery.
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**Protocol version number and date:** 1.0, May 2, 2024.

**Keywords:** abdominal surgery; anaesthesia; analgesia; intrathecal morphine; laparoscopy; minimally invasive surgery; postoperative quality of recovery

Major abdominal surgery is common, encompassing a broad range of surgical subspecialities and patient populations.[1–3] It is associated with significant postoperative morbidity, including postoperative deconditioning from the catabolic surgical stress response, ileus, venous thromboembolism, and pulmonary complications.[4] Less invasive surgical techniques (laparoscopic, laparoscopic-assisted, or robotic-assisted) are increasingly utilised for major abdominal surgery to minimise the surgical stress response, reduce postoperative complications, and improve patient satisfaction.[5–7]

The incidence of postoperative complications can be reduced with effective analgesia.[8] Suboptimal postoperative pain management negatively affects functional recovery and is a risk factor for persistent postsurgical pain, long-term opioid use, and reduced quality of life.[9,10] Additionally, the requirement for high doses of opioids increases the risk of

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opioid dependence. Up to 10% of opioid-naive patients continue to use opioids beyond 90 days after a range of major and minor operations, with a substantial burden of morbidity and cost/risk to the community.[11–14] Opioid-sparing techniques in open and laparoscopic abdominal surgery are associated with early mobilisation, faster return of bowel function, fewer postoperative complications, and shorter hospital stay.[8] Strategies to minimise opioid use whilst optimising patient comfort and functional recovery are priorities in the perioperative setting given the worldwide opioid epidemic.[15–18]

A recent systematic review concluded that epidural analgesia, historically the gold standard for pain management, offers no clinical benefit within Enhanced Recovery After Surgery (ERAS)-based protocols in patients undergoing colorectal surgery.[19] Furthermore, the authors reported a potential favourable impact on clinical outcomes in laparoscopic surgery with the use of intrathecal opioids, an increasingly popular alternative analgesic option.[19,20] Performing a spinal procedure, to deliver intrathecal morphine, is commonly practiced by anaesthetists, and is technically easier than epidural placement, with a more definitive endpoint. A recent meta-analysis of intrathecal hydrophilic opioids in abdominal surgery reported a reduction in sedation, lower pain scores, and lower opioid consumption in the intrathecal opioid group, but at the expense of increased incidence of mild pruritus.[21] Subgroup analysis of those studies that evaluated intrathecal opioid use in laparoscopic surgery was consistent with the overall findings. Furthermore, at doses of intrathecal morphine $\leq$500 μg, the incidence of respiratory depression was comparable to the control group.

Intrathecal morphine is not devoid of limitations or adverse effects, and its use is supported only by relatively small, single-centre studies. There is no consensus on the dose of intrathecal morphine.[22] We therefore require a large definitive trial to inform best practice guidelines accessible to clinicians. We conducted a feasibility study comparing intrathecal morphine with non-neuraxial analgesia in patients undergoing laparoscopic, laparoscopic-assisted, or robotic-assisted major abdominal surgery to inform the design of this larger, definitive trial.[23] Fifty-one patients across two sites were randomly allocated to receive either intrathecal morphine (intervention group) or a sham subcutaneous injection of normal saline in the lumbar area (control group) immediately before the induction of general anaesthesia. The co-primary outcomes of patient recruitment (46%, ~1:2) and protocol adherence (>95%) were successfully achieved.

Secondary exploratory endpoints were consistent with the current literature: fewer patients in the intrathecal morphine group required opioids in the post-anaesthesia care unit (44% *vs* 77%; $P$=0.02), their postoperative pain scores at rest were lower across the four time points measured ($P$=0.007), although this was not statistically significant for dynamic pain scores ($P$=0.061). A non-statistically significant reduction in total oral morphine equivalents until postoperative Day 3 and improved quality of recovery were evident in the intrathecal morphine group. Pruritus was more common after intrathecal morphine (68% *vs* 23%; $P$=0.007). However, severe pruritus, defined as a score of 3 or more out of 10 on a numerical rating scale, was not different between the two groups. Excessive sedation occurred more frequently in the control group (9 *vs* 3; $P$=0.049). A non-significant increase in the incidence of hypotension requiring intervention was found in the intrathecal morphine group. There were no serious adverse events related to intrathecal morphine.

These findings support conducting a definitive clinical trial based on a refined version of the feasibility protocol incorporating knowledge gained from the conduct of that study. It is presented below as a multicentre, prospective, randomised, phase III trial.

We hypothesise that intrathecal morphine will be superior to systemic opioids in terms of quality of postoperative recovery, pain control, opioid consumption, and functional recovery in the context of similar or lower side-effects and thereby improve outcomes for patients having minimally invasive (laparoscopic, robotic-assisted) major abdominal surgery.

## Study design

We plan to conduct a pragmatic, adaptive, multicentre, randomised controlled trial comparing intrathecal morphine with local anaesthetic *vs* non-intrathecal analgesia in patients undergoing elective minimally invasive (laparoscopic or robotic-assisted) major (>2 h surgical time) abdominal surgery. Ethics approval has been obtained from Alfred Health, Australia (June 2024, HREC 103544). We are recruiting at several tertiary referral centres in Victoria and New South Wales, Australia. An updated list of study sites can be obtained from the authors. This protocol is based on the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines[24] and the SPIRIT checklist (Supplementary Appendix 1). The Consort 2010 Trial Flow diagram is outlined in Figure 1 and the schedule of trial procedures can be seen in Table 1.

## Randomisation, blinding, and treatment allocation

All adult patients undergoing elective major laparoscopic, laparoscopic-assisted or robotic-assisted abdominal surgery will be screened for eligibility. Before giving informed consent, they will receive written and verbal information. Each site investigator will be responsible for recruitment at their site. The consent form is provided in Supplementary Appendix 2.

### Assignment of interventions

Randomisation will be via computer-based simple randomisation software, REDCap, with a sequential study number allocated to one of the two groups with stratification per treatment site by a member of the research staff. After randomisation, the treating anaesthetist will follow the protocol to which each participant has been allocated. If an intrathecal injection is unsuccessful, the patient will remain in the study and follow-up continued.

## Study population

### Eligibility criteria

*A patient must meet the following criteria to be included in the study:*

- Age 18 yr or over, undergoing elective major laparoscopic, laparoscopic-assisted or robotic-assisted abdominal surgery, and
- Major surgery is defined as a planned operative time of at least 2 h

*A patient will be excluded from the study should they meet any of the following criteria:*

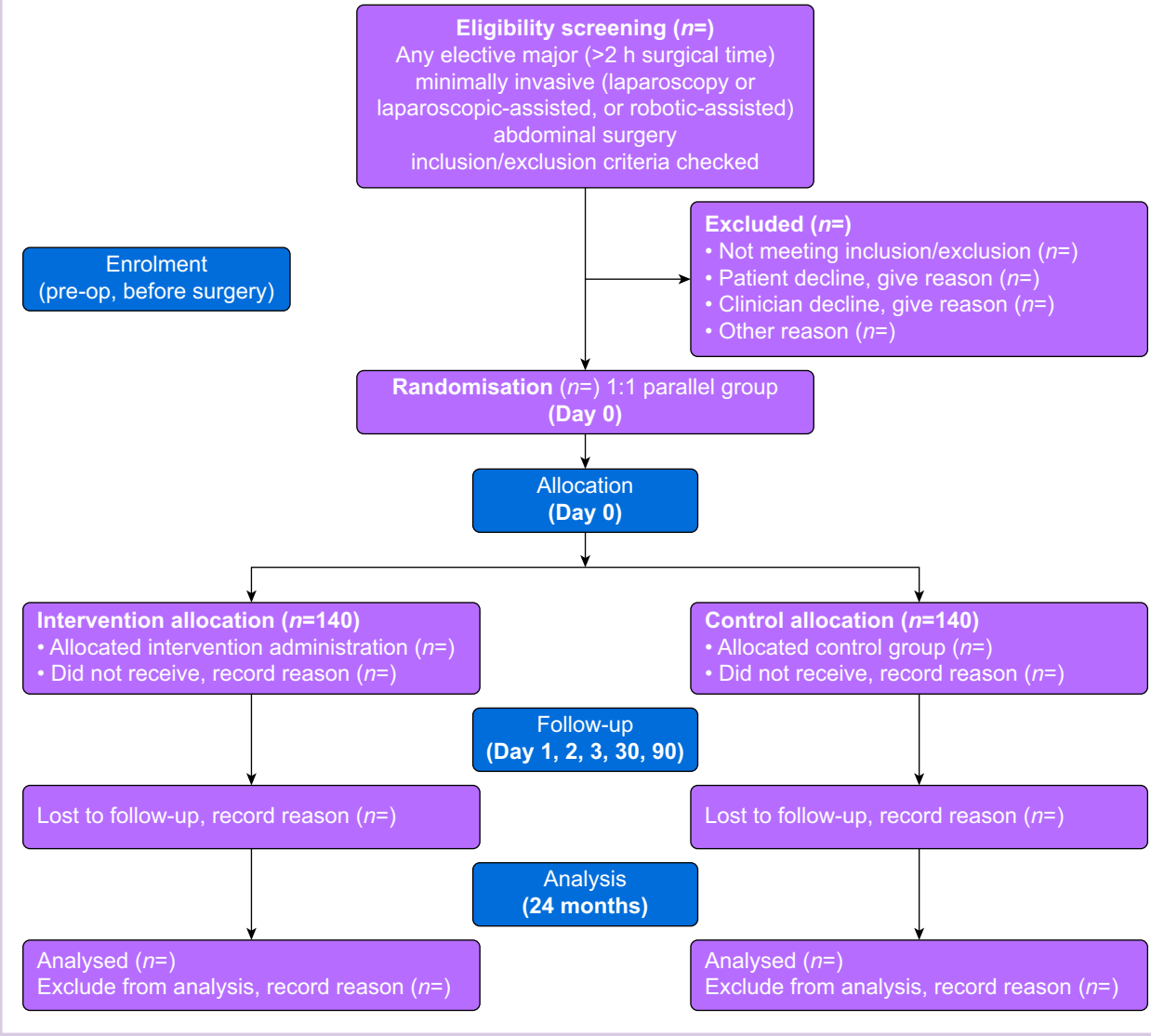


Fig 1. CONSORT trial flow diagram.
CONSORT, Consolidated Standards of Reporting Trials.

- Patient declines enrolment or does not have capacity to consent
- Contraindication to intrathecal morphine or local anaesthetic
- Contraindication to a neuraxial injection, including; injection site concerns, coagulopathy, administration of anticoagulant not meeting the ASRA guidelines for safe neuraxial analagesia,[25] or untreated sepsis
- Cognitive impairment or language proficiency leading to inability to complete Quality of Recovery 15 (QoR-15) questionnaire or understand the pain scores
- Chronic pain defined as operative site-related pain over the preceding 90 days
- Opioid tolerance defined as >60 mg oral morphine equivalent dose (OMED) in the 7 days before surgery[26]

## Sample size calculation

In previous studies the QoR-15 response within each subject group was normally distributed, with a standard deviation of ~15.[27,28] If the minimally clinically important difference of QoR-15 is six[28] we will need to study 132 experimental subjects and 132 control subjects to be able to reject the null hypothesis that the population means of the experimental and control groups are equal, with probability (power) 0.9. The type I error

Table 1 Schedule of trial procedures from screening to the end of the study follow-up.

| Procedure | Screening | Baseline (before randomisation) | Day of surgery (preoperative) | Day of surgery (intraoperative) | Day of surgery (postoperative) | Day 1 after surgery | Day 2 after surgery | Day 3 after surgery | Day 30 after surgery | Day 90 after surgery |
|---|---|---|---|---|---|---|---|---|---|---|
| Review inclusion/ exclusion criteria | x | | | | | | | | | |
| Written informed consent | x | | x | | | | | | | |
| Patient characteristics | | x | x | | | | | | | |
| Medical/medication history | | x | x | | | | | | | |
| Height and weight | | x | | | | | | | | |
| Randomise | | | x | | | | | | | |
| Intraoperative data | | | | x | | | | | | |
| Opioid side-effects | | | | | x | x | x | x | | |
| Functional recovery (i.e. move, eat, bowels, IDC) | | | | | | x | x | x | | |
| QoR-15 | | x | | | | x | x | x | | |
| Patient subjective experience of analgesia | | | | | | x | x | x/before discharge | | |
| PACU nurse subjective experience of analgesia | | | | | x | | | | | |
| Rest and dynamic pain | | | | | x | x | x | x | | |
| Pruritus distress scores | | | | | x | x | x | x | | |
| Pruritus score | | | | | x | x | x | x | | |
| Sedation score | | | | | x | x | x | x | | |
| Total opioid consumption | | | | | x | x | x | x | | |
| Post-discharge telephone call | | | | | | | | | x | x |
| Adverse events (as per Clavien–Dindo and CCI) | | | | | | | | | x | |
| Review length of hospital stay | | | | | | | | | x | |
| Review ongoing opioid use | | | | | | | | | x | |
| Review pain control and ongoing opioid use | | | | | | | | | | x |
| Mortality at postoperative Day 90 | | | | | | | | | | x |

CCI, Comprehensive Complication Index; IDC, In-Dwelling Catheter; ITM, intrathecal morphine; QoR-15, quality of recovery 15.

probability associated with the test of this null hypothesis is 0.05. Therefore, we plan to recruit 280 patients, accounting for up to 5% loss to follow-up amongst recruited patients.

## Patient management

### Investigational medicinal product

Morphine sulphate for intrathecal injection that is supplied as 200 μg or 500 μg in 1 ml will be used. The local anaesthetic will be bupivacaine 0.5% or ropivacaine 0.75%, chosen by the treating anaesthesiologist.

### Study drug preparation

Intrathecal morphine 200 μg will be drawn up by the treating anaesthesiologist using a sterile technique using a 1 ml syringe and added to plain bupivacaine 0.5%, 2–4 ml or ropivacaine 0.75% (volume determined by attending anaesthesiologist, according to patient age, height/weight, and extent of surgery) and injected intrathecally, immediately before the induction of general anaesthesia.

### Adaptive design; dosage modification

After confirmation of safety from the first 100 patients recruited, the dose of intrathecal morphine will increase to 300 μg. If significant clinical safety concerns are reported by the safety committee the decision to proceed (or not) with the proposed dose increase will be made by the trial steering committee.

### Perioperative management

To keep the trial as pragmatic as possible, all other aspects of anaesthesia care for all patients in the study will be determined by the treating anaesthesiologist with adherence to principles of multimodal analgesia. Guiding principles include:

- Intravenous ondansetron and vasoconstrictors (e.g. ephedrine, metaraminol) to reduce pruritus, hypotension, and the Bezold–Jarish reflex.[29,30]
- Short-acting opioids (e.g. alfentanil, fentanyl, or remifentanil) will be administered during induction and maintenance of anaesthesia, with incremental doses added if the heart rate or blood pressure increase by >20% in comparison to a stable phase during surgery
- **NO** methadone is to be given in either group
- Intraoperatively, dexamethasone 8 mg
- Perioperative multimodal analgesia, including: NSAIDs (e.g. parecoxib 40 mg intraoperatively and celecoxib for 3 days postoperatively—unless contraindicated), paracetamol 1 g (regular for 48 h)
- Local anaesthetic infiltration or regional block by surgeon/anaesthesiologist can be utilised according to local practice (we will collect these data)

*Neither group* will have drugs administered into the epidural space.

After operation, all patients will have i.v. fentanyl administered as patient-controlled analgesia (PCA) for the first 24 h after induction of anaesthesia (fentanyl 10 μg with 5 min lockout). Oral opioids can be commenced once the PCA is ceased. Regular (if no contraindication) non-steroidal anti-inflammatory drug and paracetamol will be prescribed. First-line treatment for mild pruritus will be ondansetron, for moderate pruritus add cyclizine, and for severe pruritus/vomiting add naloxone (40 μg).

To ensure patient safety from the delayed effects of intrathecal morphine on sedation and respiration, for the first 12 postoperative hours, patients will be monitored hourly (sedation score, ventilation frequency, oximetry measurement). Two-hourly observations will continue for at least the first 24 h or for the duration that the PCA is prescribed. No additional opioids or sedatives can be administered during this period.

### Outcomes

#### *Primary outcome*

- Quality of recovery on postoperative Day 1 using QoR-15.[27] Measured ~24 h after wound closure by trial personnel trained in the administration of this questionnaire

#### *Secondary outcomes*

- Quality of recovery on postoperative Days 2 and 3 using QoR-15[27]
- Postoperative opioid consumption (mg), using OMED, abstracted from the medical record. Time points at which OMED will be calculated include: intraoperatively, recovery unit, at 24 h, 48 h, and 72 h after operation
- Rest and dynamic pain scores as assessed by numerical rating score (0–10). Time points include: in the recovery unit, and daily whilst an inpatient through to postoperative Day 3, unless discharged earlier. The worst score at the measured time points will be recorded
- Pain distress, using the Brief Assessment of Distress about Pain (BADP) distress scale.[31] Time points include: in the recovery unit and once per day whilst an inpatient through to postoperative Day 3, unless discharged earlier
- Time to return of bowel function as assessed by the time from surgery ending to the first passage of flatus

#### *Tertiary outcomes*

- Nausea or vomiting requiring antiemetic therapy
- Pruritus as assessed by numerical rating score (0–10)
- Pruritus distress as assessed using a numerical rating scale (0–10)
- Intraoperative hypotension as assessed by amount (mg) of vasopressor infused and total volume of i.v. fluids administered
- Hypotension as assessed by need for fluid bolus or vasopressor use. Time point—any time point during hospital admission after operation
- Urinary catheter duration as assessed by time of insertion to removal
- Time to mobilise, as assessed by time from end of surgery to first movement out of bed
- Time to commencement of oral diet, as assessed by time from end of surgery to first retaining oral food/fluid (not clear fluids alone)
- Sedation, as assessed by sedation score
- Respiratory depression, as assessed by a ventilatory frequency of <8 bpm, $Spo_2$<92%, or requirement for airway intervention including use of oropharyngeal/nasopharyngeal airways or requiring naloxone administration
- Time until the patient is fit for discharge from the PACU as recorded by PACU staff

- Length of hospital stay as measured by time from end of surgery until discharge from acute hospital care
- Persistent opioid use as assessed by ongoing opioid consumption because of surgically-related pain at 90 days after surgery
- Number of days at home within the first 30 days after surgery ($DAH_{30}$)[32,33]
- Patient satisfaction (patient- and healthcare worker-reported) in the PACU as analysed through survey of participants.

### *Other outcome variables*

Baseline values which will be collected including ASA physical status classification, age, sex at birth, body mass index, presence of comorbidities, type of surgery.

## Data management

### *Data collection*

Data will be collected and stored onto a REDCap database (GCP compliant) by the study investigators. Data integrity will be assessed at study completion by two independent observers.

The chief investigator and co-investigators alone will have access to the full dataset before the main publication. Data will be available upon reasonable request thereafter.

## Statistics methods

### *Summary of baseline data*

Data will be expressed as number (%), mean (standard deviation [SD]), median (interquartile range [IQR]), or both based on whether the data are parametric or nonparametric. Group comparisons will be described by point estimates with 95% confidence intervals. All patients that are enrolled in the trial and undergo induction of anaesthesia and surgical incision will be considered as comprising the intention-to-treat population for all primary, secondary, and safety analyses. Baseline characteristics of the two randomised groups will be tabulated using appropriate summary statistics.

The primary endpoint (QoR-15) will be analysed using linear regression, adjusting for the baseline (preoperative) QoR-15. Other continuous data will be compared using unpaired Student's *t*-test (two tailed) or Wilcoxon rank sum test, as appropriate. Categorical data will be analysed using $\chi^2$ with Yates' correction (or Fisher's exact test, as appropriate). All statistical analyses will be performed using SPSS for Windows V30.0 (SPSS Australasia, Sydney, NSW, Australia). A *P*-value $<0.05$ will be considered significant; no correction will be made for multiple comparisons. Analyses of pe-defined subgroups based on the type of surgical procedure will be conducted.

There will be no substitution of missing data.

### *Interim analysis*

The safety committee will consist of three perioperative physicians independent of the trial and approved by the Alfred Health Ethics Committee. After recruitment of the first 100 patients, any adverse events that have been reported will be reviewed by the safety committee to provide an opinion on whether a dose increase of intrathecal morphine from 200 to 300 μg can be safely implemented. A final decision to proceed (or not) with the proposed dose increase will be made by the trial steering committee.

### *Protocol amendments*

Any proposed amendment will be submitted to the sponsor for classification and authorisation. Important protocol changes will be communicated to the recruiting sites via the trial newsletter.

## Dissemination plan

Data will be analysed and disseminated through peer-reviewed open-access journals. The study will be reported using the Consolidated Standards of Reporting Trials (CONSORT) guidelines. Findings will be made available through the ANZCTR website, and prepared for presentations at relevant anaesthetic scientific meetings.

The authorship of the study is planned to include the writing committee of the study, with acknowledgements to site investigators and external statisticians. Changes to the authorship may occur, pending the unanimous approval of the writing committee.

# Authors' contributions

Study conception: KP, PSM, BR
Study protocol design: KP, PSM, BR
Obtaining funds: KP, PSM, BR, WB, NW, ET
Development of protocol: KP, PSM, BR, NW, ET
Statistical expertise for the protocol: PSM
Drafting of article: KP
Critical review of protocol: all authors
Substantial review of article: all authors
Approval of final article: all authors

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# Declarations of interest

The authors declare that they have no conflicts of interest.

# Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bjao.2025.100386.

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