

PROTOCOL TITLE:

Intrathecal Morphine vs Intrathecal Morphine Combined with Clonidine for 1-2 Level Lumbar Fusion

PRINCIPAL INVESTIGATOR:

Parker Merrill, MD Department of Anesthesiology 207-232-8593

Parker.merrill@spectrumhcp.com

VERSION NUMBER/DATE:

Version 1.0 - 3/1/2026

Version 1.1 - 5/29/2026

Version 1.2 – 6/26/2026

Version 1.3 – 7/8/2026

Version 1.4 – 8/20/2026

Version 1.5 – 8/26/2026

REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
1.1	5/29/2026	Added a DSMB, the study is now planned to be fully blinded, additional details added regarding the consent process.	yes
1.2	6/29/2026	Aligned the reporting guidelines in the table and text	yes
1.3	7/8/2026	Additional details added RE: DSMB	no
1.4	8/20/2026	DSMB Charter and nursing info sheet	no
1.5	8/26/2026	Include additional vital signs in data collection	no

Table of Contents

1.0	Study Summary	3
2.0	Objectives	4
3.0	Background.....	4
4.0	Study Endpoints.....	6
5.0	Study Intervention/Investigational Agent.....	7
6.0	Procedures Involved	8
7.0	Data and Specimen Banking	13
8.0	Sharing of Results with Subjects	13
9.0	Study Timelines	13
10.0	Inclusion and Exclusion Criteria	13
11.0	Vulnerable Populations.....	14
12.0	Local Number of Subjects.....	14
13.0	Recruitment Methods.....	14
14.0	Withdrawal of Subjects	16
15.0	Risks to Subjects	16
16.0	Potential Benefits to Subjects	17
17.0	Data Management and Confidentiality	17
18.0	Provisions to Monitor the Data to Ensure the Safety of Subjects	18
19.0	Provisions to Protect the Privacy Interests of Subjects	19
20.0	HIPAA Authorization for Research.....	19
21.0	Compensation for Research-Related Injury	20
22.0	Economic Burden to Subjects.....	20
23.0	Consent Process	20
24.0	Process to Document Consent in Writing	21
25.0	Setting	22
26.0	Resources Available	23
27.0	Multi-Site Research	23

1.0 Study Summary

Protocol Information	Description
Study Title	Intrathecal Morphine vs Intrathecal Morphine Combined with Clonidine for 1-2 Level Lumbar Fusion
Study Design	Prospective Randomized Controlled Trial
Primary Objective	Postoperative opioid consumption measured as morphine milligram equivalents (MME) during the first 24 hours after surgery
Secondary Objective(s)	Pain level measured using a numeric rating scale (NRS) of 0 to 10 during the first 72 hours after surgery Postoperative opioid consumption measured as MME during the first 72 hours after surgery
Research Intervention(s)/ Investigational Agent(s)	Group A: The intrathecal morphine arm of the study will undergo an intrathecal injection of 150mcg preservative free morphine Group B: The ITM + clonidine arm will undergo intrathecal injection of 150mcg preservative free morphine with 75 mcg clonidine
IND/IDE #	n/a
Study Population	Adult patients undergoing scheduled 1-2 level lumbar fusion at Maine Medical Center (MMC), Bramhall Campus
Sample Size	70 patients (35 patients per group)
Study Duration for individual participants	72 hours post-procedure
Study Specific Abbreviations/ Definitions	ITM – Intrathecal Morphine MME – morphine milligram equivalents NRS – Numeric rating scale (Pain level) Modified POSS – Modified Pasero opioid-induced sedation scale

2.0 Objectives

2.1 To recruit and enroll 70 patients into a randomized trial that compares the efficacy of intrathecal morphine (ITM) compared to ITM and clonidine in improving clinical and analgesic outcomes after lumbar fusion. We will assess efficacy using the following outcome metrics:

- Postoperative opioid consumption measured as morphine milligram equivalents (MME) during the first 24 hours after surgery (primary outcome)
- Pain level measured using a numeric rating scale (NRS) of 0 to 10 during the first 72 hours after surgery (secondary outcome)
- Postoperative opioid consumption measured as MME during the first 72 hours after surgery (secondary outcome)
- Length of stay
- Side effects such as respiratory depression, post-operative hypotension, PONV, pruritis requiring treatment, and excessive sedation (Modified Pasero Opioid-induced sedation scale, POSS)
- Intraoperative bradycardia and/or hypotension following administration of study drug.

2.2 In this study, we hypothesize that there will be significant differences in postoperative opioid consumption and pain scores between patients receiving ITM compared to those receiving ITM and clonidine following lumbar fusion.

3.0 Background

3.1 Patients undergoing spinal fusion surgery are at high risk of acute and persistent postoperative pain in a population that already has a high incidence of chronic pain.[1] Post-operative pain in these patients can lead to high doses of opioid pain medications and lead to difficulty in mobilization and recovery. Treatments for post-operative pain following spinal fusion has been an ongoing topic of investigation for both spine surgeons and anesthesiologists, and several multimodal pain strategies have been

developed to address this problem.[2] While perioperative medications have developed into robust multi-modal regimens, the mainstay of treatment for post-surgical pain remains IV and PO opioids. Multiple strategies have been employed to improve patient pain scores, including administration of long-acting opioids such as intrathecal morphine. Literature from several surgical populations including obstetrical, cardiac, and orthopedic patients also shows potential benefit to intrathecal clonidine regarding post-operative pain relief. To address the desire for continued improvement of available pain relief treatments, we propose to study the co-administration of ITM with intrathecal clonidine to determine if combination therapy provides a benefit to spine surgery patients in their post-operative recovery.

3.2 Morphine is an extensively studied mu-opioid receptor agonist used for perioperative analgesia. Its analgesic effect stems from its direct action on the substantia gelatinosa of the posterior spinal cord.[3] It is unique among opioids in that its hydrophobic nature results in prolonged duration of action when administered intrathecally, between 18 and 24 hours.[4] This specific feature of morphine makes it an attractive analgesic for surgeries associated with an expected and relatively consistent level of post-operative pain. The beneficial effects of intrathecal morphine have been extensively studied and include a reduction in opioid requirements intraoperatively and up to 48 hours after operation, as well as improved pain scores at 4-, 12-, and 24-hour timepoints. These effects are most pronounced in patients undergoing intra-abdominal surgery but extend to other surgery types as well.[5]

While the hydrophobic nature of morphine is responsible for its long duration of action, it is also the reason for the greatest concern regarding ITM use, which is delayed respiratory depression.[6] Early studies suggested an incidence of 0.09–3% for respiratory depression in patients receiving ITM, although the larger doses used at that time may not be relevant to current clinical practice.[7] Two more recent meta-analyses determined the incidence of respiratory depression in patients receiving low-dose (<0.2 and 0.2–0.3 mg) ITM to be 0–1.2%.[5,8] Incidence of respiratory depression following neuraxial morphine has been shown to be dose-dependent. At the current doses used in clinical practice, studies indicate that the incidence of respiratory depression is not greater with neuraxial compared with systemic administration of morphine.[7]

Another promising intrathecal analgesic is clonidine, which is often used as a pain adjuvant in addition to spinal anesthetics. A meta-analysis exploring the efficacy of neuraxial morphine with clonidine showed an enhancement in several surgical populations including obstetrical, cardiac, urologic, and orthopedic patients. In these studies, peri-operative opioid use was reduced with notable side effect of intra-operative hypotension, although this can be easily mitigated by modest use of standard vasopressor medications. Reductions in heart- rate were also noted, but non-clinically significant. It is our hope that the benefits of increased time to first opiate medication and decrease in overall opiate consumption can be extended to our population of patients receiving spinal fusion through the co-administration of ITM and clonidine.[9]

In this prospective trial, we aim to investigate the analgesic efficacy of ITM versus ITM including clonidine for lumbar fusions. There is significant departmental desire to improve postoperative pain outcomes in patients undergoing lumbar fusion. It is possible that intrathecal clonidine in addition to ITM may help improve these measures. ITM is an established option for analgesia in 1-2 level spinal fusion surgery with multiple studies on efficacy, however none to-date have studied the addition of intrathecal clonidine.[10] Although there is substantial evidence in the obstetric literature that clonidine enhances opioid based intrathecal analgesia, no study to date has investigated its use intrathecally in lumbar fusions.

4.0 Study Endpoints

4.1 Our primary outcome measure will be opioid consumption during the first twenty-four hours after lumbar fusion. Our secondary outcomes will be pain scores at 24, 48 and 72 hours post procedure, along with opioid consumption up to 72 hours post-procedure. We anticipate that this study will inform strategies for improving analgesic outcomes among patients requiring lumbar fusion.

4.2 Data and Safety Monitoring Board

Our study will use a data safety monitoring board (DSMB) that will be scheduled to meet once the study reaches 50% enrollment and in response to any major adverse event. The DSMB will review the progress of the study, monitor data, identify any

inconsistencies or errors in data collection, and review patient safety. Any errors in data collection that are identified will be reconciled immediately to ensure the validity of our findings. The DSMB will also ensure that this study will not continue to enroll patients if one treatment modality shows early and significant superiority. Below is a table of major and minor adverse outcomes (AEs) that will be reported to the DSMB during the study period. Any unanticipated problems (UPs) will be reported to the MaineHealth IRB according to their requirements (SAEs within 5 business days and UP within 10 business days).

Primary Safety endpoints include statistically significant increased risk of the following:

1. Respiratory depression requiring mechanical intervention or chemical reversal with naloxone.
2. Severe bradycardia (HR < 50 BPM with evidence of hypotension) or hypotension (MAP < 65 mmHg for > 10 minutes) that is refractory to standard pharmacologic interventions (ie. Phenylephrine, ephedrine, norepinephrine, glycopyrolate). This includes any event requiring the administration of epinephrine, or CPR.

Each of the above events will be reported to the DSMB immediately, and to the IRB within 5 days

Secondary Safety endpoints – statistically significant increased risk of the following:

1. Hospital discharge delay due to poor pain control with hospital stay of greater than 9 days (95th percentile based on historical data from 2023-2026. Median length of stay 3 days).
2. Escalation to ICU level of care for monitoring of sedation or respiratory depression

Each of the above events will be reported to the DSMB within 30 days, and the DSMB to the IRB within 7 days.

Please refer to the Data Safety Monitoring Plan document for additional details regarding the DSMB and Charter. This includes definitions of major adverse events and stop rules.

5.0 Study Intervention/Investigational Agent

5.1 Group A: The ITM arm of the study will undergo an intrathecal injection of 150 mcg preservative free morphine.

Group B: The ITM+clonidine arm will undergo intrathecal injection of 150 mcg preservative free morphine with 75 mcg clonidine.

The 150 mcg dose of intrathecal morphine was chosen due to its well-balanced clinical efficacy and safety profile. At doses in this range, studies indicate that the incidence of respiratory depression is not greater with neuraxial than with systemic administration of morphine.[7] This dose is also consistent with pre-existing ITM use at our institution for Obstetrics and lumbar fusions.

The 75 mcg dose of intrathecal clonidine was selected for the ITM+clonidine arm based upon data available from previous studies which found similar analgesic efficacy with minimal side effects.[12] In a dose finding analysis conducted by Peach et al where patients were given ITM and clonidine, clonidine doses of 60-150 had similar postoperative analgesic effects without increased incidence of hypotension.[13] Doses of clonidine greater than 150 mcg are not recommended due to the increased risk of cardiovascular complications and deeper level of sedation.[14] We elected to use 75 mcg of intrathecal clonidine as it is slightly above the minimum effective dose of 60 mcg determined by Paech et al but half the maximum recommended dose of 150 mcg.

5.2 Preservative-free morphine is readily available via our standard pharmacy pyxis system. As clonidine is generally a low-use, low-stock medication at our institution, a dedicated stock of clonidine vials will be purchased with research funding. This stock will be labeled as research only and stored in our pharmacy's secured storage area.

After the intervention is determined via randomization, the study medication (saline or clonidine) is prepared by pharmacy per standard sterile intrathecal medication preparation protocol in a blinded syringe. This syringe is subsequently delivered to the operating room by hand to ensure medication security. The study medications are then administered as detailed below in section 6.2. Prior to administration, the study medication is mixed with morphine and administered as one injection. Morphine and clonidine are stable when mixed together in solution, so precipitation is not anticipated (Hildebrand et. Al.)

Morphine will be withdrawn from the OR pyxis per standard operating procedure by anesthesia. This will be handed to the circulating nurse to be sterilely passed onto the field at time of medication delivery. Excess morphine will be accounted for and wasted according to our facility's controlled medications policy. Our standard medication waste policy is included as Appendix 1.

6.0 Procedures Involved

6.1 After the confirmation that the informed consent process is complete, participants will be randomized to one of the two arms of the study in a 1:1 ratio as follows:

Group A: The ITM arm of the study will undergo an intrathecal injection of 150 mcg preservative free morphine.

Group B: The ITM+ clonidine arm will undergo intrathecal injection of 150 mcg preservative free morphine with 75 mcg clonidine.

Full blinding will be achieved via the following methods: The randomization scheme will be developed by the CIPHR analyst team using a block randomization scheme with permuted blocks. The analyst will provide the research coordinator with randomization assignments in sequentially numbered opaque envelopes. Prior to surgery, the envelope will be delivered by the study coordinator to the preparing pharmacist who will prepare the appropriate study medication (clonidine or preservative-free saline) in a blinded syringe. This syringe will then be delivered to the intra-operative team (Anesthesia providers, surgeon, circulating nurse) who will remain blinded to the assignment. The study medication will be administered to the patient as described in Section 6.2. Administration of the medication will be documented by the anesthesia team in EPIC and will be recorded as "ITMC Clonidine/placebo 75mcg in PF sodium chloride 0.9% Intrathecal 0.75mL". This will allow for post-operative care members (PACU nursing, floor nursing, post-operative neurosurgery team) to remain blinded as well. Additionally, team members collecting and entering data will be masked regarding the patient's assignment. The REDCap database will have randomization assignments in an instrument separate from the study data collection instruments, allowing for data entry without seeing which group the subject is in.

In the rare event of unexplained severe allergic reaction or cardiovascular collapse, the study medication may be emergently unblinded to the clinical team to facilitate timely and appropriate care to the patient.

Per spinal fusion ERAS protocol, preoperatively all patients (without allergies to these medications) will receive 1000 mg acetaminophen PO x1 (dose adjusted to liver function) and Aprepitant 40 mg PO x1. Intraoperatively after induction, patients will receive dexamethasone 8 mg IV x1, ondansetron 4 mg IV x1, and ketamine bolus of 0.2 mg/kg x1 on induction. IV fentanyl may be used intra-operatively at the discretion of the anesthesiologist. Postoperatively, all patients will receive 1000 mg acetaminophen every 6 hours for up to 72 hours. Patients with allergies to these medications will not be excluded from the study and the reason for not receiving these medications will be documented in REDCap. In addition to education by study staff, the documents in Appendix 2 will be available in OR and post-operative areas to ensure compliance with study protocols.

In the event of poorly controlled pain at any point during the study, we will provide the participants with appropriate analgesic rescue agents to ensure that postop pain is adequately controlled. As is current standard practice, opioid medications to treat postsurgical pain will be administered based on patient's pain score. Patients will be able to receive immediate-release oxycodone or hydromorphone, administered every 4 hours as needed. Per standard protocol, oral opioid analgesics may be administered if it has been greater than 8 hours since ITM administration, patient is alert, respiratory rate is greater than 12 breaths per minute, and analgesia is inadequate. Gabapentin use will be allowed at any point of the study and its use will be documented in REDCap.

Default fluid management will be goal-directed, with default goal of 1-2 liters of Lactated Ringers solution by case end. Treatment of intra-operative hypotension after administration of intrathecal medication will be treated initially with incremental doses of IV phenylephrine or ephedrine, and bradycardia with incremental doses of IV ephedrine or glycopyrrolate at discretion of anesthesiologist.

6.2 Intraoperative intrathecal morphine (ITM) injection by neurosurgery:

The protocol for study medication administration is as follows:

Pharmacy will deliver the blinded study medication (either clonidine or preservative-free saline) to the operating room either by hand or via coordinated tube delivery. The circulating nurse will retrieve the study medication and bring to the operating room. The anesthesia team will separately obtain a preservative-free morphine vial from the OR pyxis and deliver this to the circulating nurse. The circulating nurse will verify medication labels, concentrations, and 'preservative-free' annotation before sterilely delivering both the morphine and the study medication on the surgical field. The medications will be mixed together in a single syringe prior to administration, which occurs after initial surgical exposure but prior to spinal decompression. The surgeon will directly administer the study medications to an adjacent segment of dura to the surgical site via single intrathecal injection with a fine 27g needle. This small gauge allows for maintenance of integrity of the dura, which minimizes the risk of dural injury. The circulating nurse and anesthesia team member will then properly dispose of and document any remaining morphine, including what was initially provided to the surgical field but not administered to the patient as discussed in Section 6.1. Administration of intrathecal morphine will prompt the anesthesia team to place the appropriate ITM monitoring order-set in EPIC per our institutional policy.

6.3 Variables that will be recorded will include: intraoperative bradycardia and/or hypotension following administration of study drug; postoperative bradycardia and/or hypotension; postoperative nausea; vomiting; pruritis; respiratory depression; sedation; vasopressor use based on a potency of 81.2 between phenylephrine and ephedrine;[15] PACU length of stay; hospital length of stay; pain scores; opioid consumption; non-opioid analgesics. A list of the variables that will be recorded is included in Table 1. Vital signs (respiratory rate, heart rate, and blood pressure) will be recorded every 4 hours, any irregular vital signs recorded will be noted in the data collection tool. Pain scores and will be recorded in the electronic medical record by nursing personnel every 4 hours using an order set designed for a previous study (IRBNet# 1807862-15). Sedation scores will be monitored every 2 hours for 24 hours per Society for Obstetric Anesthesia and Perinatology Consensus guidelines, with stipulation to increase monitoring to every 1 hour if additional breakthrough opiate medication is required per our ERAS protocol.[16] Sedation level is scored based on the Modified Pasero Opioid-induced sedation scale (POSS), with notification to providers initiated for levels of moderate sedation or greater. The variables of

interest will be manually extracted from the electronic medical record by study staff and entered into a REDCap database. A complete list of variables collected can be found in Table 1.

Table 1: Variables Collected

Variables
Master List
Study ID
MRN
DOS
Demographics (all extracted from EHR by study staff)
Sex
Age
Race
Ethnicity
Randomization Assignment
ITM or ITM+clonidine
Intraoperative Data
Anesthesia Type
Anesthesia start and stop times
Time of intrathecal injection
Lowest mean arterial pressure before intrathecal injection (mmHg)
Lowest mean arterial pressure after intrathecal injection (mmHg)
Lowest heart rate before intrathecal injection (BPM)
Lowest heart rate after intrathecal injection (BPM)
Total intraoperative phenylephrine dose (mcg)
Total intraoperative Ephedrine dose (mg)
Total intraoperative Glycopyrrolate dose (mg)

Total intraoperative atropine dose (mg)
Total intraoperative epinephrine dose (mcg)
Total intraoperative norepinephrine dose (mcg)
Total fluid administration (L)
Analgesic medications (intraoperative, PACU, and POD0, POD1, POD 2)
Fentanyl
IV hydromorphone
IV morphine
PO oxycodone
PO hydromorphone
PO morphine
IV Tylenol
PO Tylenol
Gabapentin
Ketamine (dose, including infusions and bolus)
PACU
Was there Bradycardia requiring intervention? Yes/no
Was there hypotension requiring intervention? Yes/no
Pruritus requiring nalbuphine or other medication? Yes/no
Post-Operative Nausea? Yes/no
Post-Operative Vomiting? Yes/no
PACU length of stay – Minutes
Pain Scores (NRS) (recorded every 4 hours)
Sedation Scores (POSS) (recorded every 2 hours for 24 hours, every 1 hour if additional opiates are given)
Respiratory rate (breaths/min, recorded every 4 hours)
Heart rate (noted at same interval as respiratory rate)
Blood pressure (note as same interval as respiratory rate)
POD0, POD1, POD2

Pain Scores (NRS) (recorded every 4 hours)
Sedation Scores (POSS) (recorded every 2 hours for 24 hours, every 1 hour if additional opiates are given)
Respiratory rate (breaths/min, recorded every 4 hours)
Heart rate (noted at same interval as respiratory rate)
Blood pressure (note as same interval as respiratory rate)

7.0 Data and Specimen Banking

No specimens will be banked. All study data will be deleted 6 years after study completion.

8.0 Sharing of Results with Subjects

There is no plan to contact study participants to share the results but they will be publicly available on clinicaltrials.gov once the study is complete.

9.0 Study Timelines

Individuals study subject participation will extend for 72 hours post-procedure. For patients who remain inpatient for 72 hours, all data points will be collected by nursing staff during routine pain score assessments. For patients that are discharged prior to 72 hours, research staff will collect remaining assessments via phone call to the final 72 hour point.

Given that an average of 160-170 one- or two-level lumbar fusions are performed yearly at MMC, factoring in our exclusion criteria, we anticipate it will take 8-12 months to complete recruitment for this study. It will take one month to complete data analysis and one month to produce a manuscript for publication.

10.0 Inclusion and Exclusion Criteria

10.1 Patients will be screened for study eligibility during their pre-operative visit.

10.2 The inclusion criteria include patients (1) aged 18-70 (hypotension risk), (2) who have the capacity to provide informed consent, (3) scheduled for 1-2 level lumbar fusions, (4) with an expected inpatient stay of at least 24 hours (5) ASA I-III (6) English speaking (98.7% of our spine surgical population is English speaking since 2019).

The exclusion criteria include patients with (1) substance use disorder diagnosis, (2) chronic pain by evidence of opiate use exceeding 90 MME daily prior to surgery (3) BMI > 40 (4) allergies to clonidine or morphine (5) emergent surgery (6) coagulopathy/INR >1.5 (7) platelet count <80, (8) significant cardiovascular disease (9) baseline SBP <100 systolic, (10) patients already on clonidine (11) revision surgery

10.3 Special patient populations listed below will be excluded due to ethical considerations which is not expected to impact our study design or recruitment.

- Adults unable to consent
- Individuals who are not yet adults (infants, children, teenagers)
- Pregnant women
- Prisoners

11.0 Vulnerable Populations

Vulnerable populations such as children/neonates, prisoners, and pregnant women will be excluded from this study.

12.0 Local Number of Subjects

12.1 Our sample size calculation was based on a prospective trial conducted by Paech et al where participants were randomized to receive intrathecal morphine compared to intrathecal morphine and clonidine combined. The authors identified a 5.8 MME reduction with the addition of clonidine which translated to a 29% reduction in opioid utilization with clonidine. A sample size of 30 in each group will have 90% power to detect a difference in means of 0.294 (the difference between a Group 1 mean, μ_1 , of 1.47 and a Group 2 mean, μ_2 , of 1.176) assuming that the common standard deviation is 0.34 using a two group t-test with a 5% two-sided significance level.

12.2 To allow for dropouts and missing data, we aim to recruit 35 patients per group.

13.0 Recruitment Methods

13.1 Study participants will be recruited among patients undergoing scheduled 1-2 level lumbar fusion at Maine Medical Center (MMC), Bramhall Campus. Participants will be recruited from the following Neurosurgical office: MaineHealth Neurosurgery and

Spine, 92 Campus Dr. Suite A, Scarborough, ME 04074. The neurosurgical attendings, residents, Physician Assistants, inpatient and outpatient nurses will be briefed on the study, its objectives and goals, including the inclusion and exclusion criteria.

A member of the study team will introduce the study to patients that appear to meet inclusion criteria to determine baseline interest and to provide the patient with contact information for the study team. In addition to being introduced to the study directly, flyers describing the study will be posted in the clinic and visible to patients. Contact information, including PI's and research coordinator's phone number, will be listed on the flyer for patients to contact if they are interested in enrollment. Interested patients will have the option of being given a copy of the consent form at this time, as well. If a patient expresses interest in enrolling in the study during their neurosurgical office visit, they will have the opportunity to sign the consent form at that time with a member of the neurosurgical department's study staff.

If a patient reaches out after seeing the flyer, a member of the study team will tell them more about the study over the phone (a phone script will be included in IRB submission) and will send the consent form, either by mail or via DocuSign, for the patient to review. The patient will be given contact information to reach out to Research Coordinator or PI with questions after receiving the consent form.

13.2 Outpatient subjects will be recruited via standard referral networks of participating neurosurgeons at MaineHealth Neurosurgery and Spine. Inpatient subjects at Maine Medical Center may also be recruited if an operation would occur during their admission.

13.3 Registered nurses and Neurosurgical physicians will introduce the study to patients that appear to meet inclusion criteria to determine baseline interest and to provide the patient with contact information for the study team.

For inpatient recruitment, patients that require surgery during their admission to Maine Medical Center will be identified by the surgeon's office at the time their surgery is scheduled. At least one day prior to surgery, study staff will approach identified patients to introduce them to the study and answer any questions. Informed consent forms for

inpatients will be presented by these study staff and signed by subjects in person per standard processes.

13.4 There is a study flyer that will be on display in the neurosurgery office briefly outlining the study and providing contact information for the study team. A copy of that flyer, and an accompanying phone script is included in this submission.

13.5 Upon completion of data collection (72 hours post-op) participants will receive a \$40 stipend. Patient stipends will be distributed via the Advarra Participant Payment system. Participants will be able to select if they want a physical card or check mailed to them or if they would like the amount direct deposited into a bank account.

14.0 Withdrawal of Subjects

14.1 Subjects may be withdrawn from the research without their consent in certain rare circumstances. These include but are not limited to: discovery of allergic reaction to study medications prior to surgery, changes to your surgical plan to no longer include 1-2 level fusion, new changes to your medication list or medical history that would limit your inclusion, or other possible unanticipated circumstances that would affect the validity of the study.

14.2 Contact information for the PI and the research coordinator is included in the consent form should a patient wish to withdraw from the study.

14.3 If a patient wishes to withdraw from the study, data collection will cease. Any data collected to that point may still be used unless the patient requests otherwise.

15.0 Risks to Subjects

Intrathecal use of morphine and clonidine are currently approved for use at MMC for the management of acute surgical pain. ITM is routinely used for postoperative analgesia for cesarean delivery at our institution, as well as for multi-level spinal fusions. The addition of clonidine intrathecally is performed at provider discretion for various procedures outside of cesarean delivery, including pediatric surgical procedures and total knee and hip replacements. Given that there is no clinical basis to believe that intrathecal clonidine would exhibit a different safety profile in adults undergoing lumbar fusion compared to other surgical procedures such as prostatectomy, total hip replacement, CABG, or cesarean

section, we have decided against conducting a pilot study to assess safety and feasibility.[9,16-18] Patients will be informed of the potential risks and complications of intrathecal procedures, per standard clinical practice. These include bleeding, infection, and nerve injury. These risks are inherent to any person undergoing intrathecal anesthesia for surgery. Intrathecal anesthesia is commonly used for various surgical procedures, including total hip and knee arthroplasty and cesarean delivery. The CITI trained Neurosurgeon (Dr. Christopher Neal) who is part of the study team will perform the intrathecal procedure during the operation.

Rare risks of respiratory depression and hemodynamic collapse will be reviewed, as well as the possibility of increased length of stay. The risk of allergic reaction to study medications will also be reviewed.

16.0 Potential Benefits to Subjects

The primary potential benefit to individual study participants would be an improvement in their post-operative pain. This may also be accompanied by improvement in nausea or other common opiate side effects, improved ability to mobilize for physical therapy, and possibly leave the hospital sooner than they otherwise would. In a prior prospective trial conducted by Paech et al where participants undergoing cesarean delivery were randomized to receive intrathecal morphine compared to intrathecal morphine and clonidine combined, the authors identified a 5.8 MME reduction with the addition of clonidine which translated to a 29% reduction in opioid utilization with clonidine.[13] We are hopeful that participants in this study may benefit from this potential improvement in post-operative pain outcomes.

17.0 Data Management and Confidentiality

17.1 We will summarize data using descriptive statistics, after stratification by randomization group. Continuous data will be shown as mean $\pm$ standardization or as median [interquartile range], as appropriate, and categorical data will be shown as n (%). As participants will be randomly assigned to the two study arms, formal analyses to compare differences in participant characteristics between the groups will not be necessary and we will not adjust differences in outcomes for potential covariates. Continuous variables will be logarithmically transformed as needed to approximate a

normal distribution. Differences in outcome measures between the two groups will be explored in univariate analyses, using t test or Mann Whitney U test, as appropriate, for continuous variables and chi square or Fisher's exact test for categorical variables. We will estimate the relative risk for binary adverse events (respiratory depression, post-operative hypotension, PONV, pruritis requiring excessive sedation, intraoperative bradycardia and/or hypotension) using generalized linear regression with a Poisson distribution, a log linking function and a robust covariance structure, with Group A (intrathecal morphine only) as the reference group. Significance will be accepted at $p < 0.049$ after adjusting for interim analysis (see section 4.2)[11]; the study is powered to detect differences in postoperative opioid consumption during the first 24 hours after surgery and differences in other outcomes will be interpreted in the context of exploratory analyses. Analyses will be performed using SPSS Statistical Software version 30 (IBM SPSS Inc., Armonk, NY).

17.2 Study data will be entered by trained study staff into a secure, HIPAA-compliant REDCap database that only members of the study team will have access to. Identifiers will be entered into a separate tool in REDCap and data extracted from the medical record will be linked with a study ID. Once data collection is complete, the master list linking the study ID to patient identifiers will be deleted from REDCap.

17.3 All members of the study team will be trained by the research coordinator or a physician investigator prior to extracting data to ensure consistency throughout the study. The study staff extracting and entering data from the electronic health record will be blinded to the randomization assignments-these will be recorded in a separate instrument in REDCap. The randomization instrument will not need to be accessed to obtain the information needed to open charts or to record any additional data. All study personnel doing data entry will be instructed not to access this instrument.

17.4 As stated in section above, the master list linking patient identifiers to study IDs will be deleted once data collection is complete. All data will be deleted from REDCap six years after study completion.

18.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

As outlined in section 4.2 this study will utilize a DSMB. Data will be collected daily for study patients during their inpatient stay by manually extracting data points (Table 1) from

the electronic medical record. Patients discharged prior to 72 hours post-surgery will be contacted on the first business day after the 72-hour mark. Participants will be provided with contact information should any urgent issues develop.

Study data will be reviewed by the PI at 25%, 50%, and 75% of the enrollment target of 70 participants. Because there are no greater risks than the standard of care, there is no plan to use formal statistical analysis for these interim data reviews.

The study will be immediately suspended if a data review suggests harm in the intervention, at the request of the DSMB, or if an institutional policy changes that renders the continuation of the study unfeasible.

19.0 Provisions to Protect the Privacy Interests of Subjects

19.1 Patients will be assured that participation in this research is completely voluntary and that every person interacting with their personal information has been properly trained to protect their privacy and confidentiality.

19.2 The data collection for this study is largely done via the electronic medical record, using routinely collected information. If at any time, a patient is unable to or unwilling to answer questions about their pain scores, we will address the missing variables during the statistical analysis process. Any participants discharged from the hospital prior to 72 hours after surgery can decline to answer the follow-up phone call—their inpatient data will still be included in the primary outcome analysis, but they will be ineligible for the study stipend.

19.3 The research team will be permitted to review charts for eligibility, access the medical record for data collection, and to review any potential adverse events. Other access of the participants' information will be restricted to purposes of patient care.

20.0 HIPAA Authorization for Research

20.1 We are seeking a partial waiver of HIPAA authorization for screening and recruitment purposes. We will be screening patients for eligibility prior to consenting.

All patient data will be completely deidentified once data collection is complete (the master list will be deleted from REDCap) and all study data and documentation will be destroyed 6 years after study completion.

Medical information may be discussed over the phone with patients or via secure Epic chat with study team members prior to participant consent.

20.2 The research could not be conducted without this partial waiver because study staff need to ensure subjects are eligible.

To evaluate an individual's eligibility for a research study, the inclusion and exclusion criteria for the study must be reviewed. The research could not practicably be conducted without accessing and using PHI prior to full written HIPAA authorization, as the research team would not know who may be eligible or who they could determine is ineligible and should not be considered for the study.

Screening logs will be maintained in a secure REDCap database that only study staff has access to and that uses a "Master List" to keep PHI separate from other data.

All screening logs will be permanently deleted after recruitment for this study has ended.

20.3 No identifiable data will be released outside of MaineHealth.

• ***Check this box to confirm*** ☒

21.0 Compensation for Research-Related Injury

There is no compensation available for any research related injury.

22.0 Economic Burden to Subjects

Economic burden to study participants will be minimal. Morphine administration during surgery is common and low-cost as it is within the standard of care. The addition of clonidine will cause no increase in billing due to all vials being purchased with research funding. No cost of data collection will be passed on to patients.

23.0 Consent Process

23.1 We will be obtaining full written consent from all participants. Most of the consenting will occur at the MaineHealth Neurosurgery and Spine Clinic. With additional consenting occurring on inpatient floors and via DocuSign. There is no waiting period between informing the subject and obtaining consent, but we will obtain consent at least 1 day prior to surgery. There is contact information available should a participant wish to withdraw, but there is no formal process to ensure ongoing consent.

23.2 All study staff who will be obtaining consent are included in this IRB application and have completed all the required training. The study staff who will obtain consent include anesthesiologists, neurosurgeons, and research coordinators.

23.3 Patients will be allowed as much time as they need to review the consent form and ask questions. They will be assured that their participation is completely voluntary and that opting not to enroll in the study will in no way negatively impact their care. Patients will be asked some questions to ensure their full understanding of the study.

Non-English Speaking Subjects

Only English-speaking patients will be recruited for this study (98.7% of our spine surgical population is English speaking since 2019).

24.0 Process to Document Consent in Writing

24.1 Participants will either sign a consent form in person, and be given a copy to bring home, or complete the process through DocuSign, where they will also be sent a copy of the signed form for their records.

24.2 For patients who wish to use DocuSign to complete the consent process the procedure is as follows:

- A DocuSign link for an electronic consent is sent to the subject's email address
- Research staff contact the subject by telephone or videophone to have the informed consent conversation. *This step confirms subject's identity.*
- The information for the informed consent discussion will be made using the IRB-approved consent form which is written in a language

comprehensible to the potential participant. The information presented in the consent form and by the research staff will detail the nature of the trial and what is expected of participants, including any potential risks or benefits of taking part. It will be clearly stated that the participant is free to withdraw from the trial at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

- After allowing the potential participant time to read the informed consent document, research staff will answer any additional questions.
- If the patient agrees, they will be given instructions for how to sign electronically. A signed and dated copy of the consent will be provided to subject's email address via DocuSign.
- A complete electronically signed and dated copy will be printed and scanned into subject's electronic medical record
- A complete electronically signed and dated copy will be kept with study records.

Patients who do not wish to use DocuSign but wish to participate will have the opportunity to sign the consent form when they present for surgery (prior to receiving any anxiolytics or other medications that might interfere with their ability to provide consent). There, CITI trained anesthesiologists or Neurosurgical team members that are on study staff will consent these patients that do not wish to use DocuSign, as above.

24.3 The consent form is included in this submission.

25.0 Setting

The majority of the participants will be recruited and consented at the MaineHealth Neurosurgery and Spine Clinic. Patients will be informed about the study during a pre-operative visit and will be able to review the consent and sign if they would like to participate. Those who are interested in participating but wish for more time to consider, may opt to sign the consent document electronically as described in section 24.2. The

neurosurgery team will also alert study staff to any inpatients who get scheduled for a 1-2 level fusion, these patients will have a study team member go to their room to discuss the study and complete the consent process if they would like to participate.

Aside from consenting, all research procedures will occur at MH MMC Portland, 22 Bramhall St.

There is no community advisory board for this study.

26.0 Resources Available

In the past several years, there have been 160-195 lumbar fusions a year at Maine Medical Center. Considering our inclusion and exclusion criteria, we feel like our recruitment timeline of 8-12 months is reasonable for the goal of 70 participants.

The department of anesthesia has protected time available for staff who are conducting research and this project was also awarded a Mentored Research Grant.

Prior to the start of recruitment, the PI and the anesthesia department research coordinator will meet with the entire study team to review all study procedures. Additional time will be spent with study staff who will be doing data extraction from the electronic medical record to ensure consistency. We will have sign off logs to track that the study team has all been informed of and acknowledges their duties and responsibilities.

27.0 Multi-Site Research

Not applicable

Appendix 1

Maine Medical Center Pharmacy Standard Operating Procedure:

 x **Maine Medical Center (MMC)**

Maine Medical Partners (MMP)

Contact Position/Dept.: Pharmacy

Controlled Substance: Anesthesia Waste and Disposal

Summary:

The purpose of this document is to provide a consistent approach to pharmacy team members for education, training, and tools to process and safely dispose of anesthesia-controlled substance waste.

Definitions:

- **ADC-** Automated dispensing cabinet aka Pyxis
- **Black Minibin-** Solid RCRA hazardous waste container designated for controlled substance waste.
- **Drop Box-** Freestanding mailbox type structure located in the Anesthesia Pain Management Service (APMS) workroom, Bean 2 OR, Surg2 Pharmacy office, CFT 2 Anesthesia workroom, SSC, ACCU and RADCU.
- **Operating Room (OR) Pharmacy Team Member-** A member of the pharmacy team licensed by the Board of Pharmacy and deemed qualified through training and education to process operating room waste.
- **Return Bin-** External, physical bin attached directly to an Anesthesia Pyxis station. Similar to the ones currently in use in P4 ENDO.
- **Super Sandi-Cloth Germicidal Disposable Wipe-** “purple top wipes” suitable for equipment requiring alcohol-based products, bactericidal, tuberculocidal, virucidal in 2 minute.s
- **Vault-** The secure room where controlled substance safe is located.

Procedures:

Waste Disposal

- OR pharmacy team members collect controlled substance waste from drop boxes and return bins located in procedural areas) each weekday.
- Collection will occur by two team members wearing appropriate PPE . Box/Bin contents shall be placed into a tamper evident bag. Each bag will be sealed and labeled with location name, date/time and team member initials.

- Collection and transportation of the controlled substance waste shall be completed using a solid and intact container as approved by Infection Control and Safety. The OR waste will be placed in the Surg2_OR Satellite Pharmacy Workroom
 -
- Upon receipt of the waste, the OR Pharmacy team member shall prepare an area free from medications and other clean materials. The OR Pharmacy team member shall don gloves prior to handling the contents within the tamper evident bag bag.
- Visibly bloodied syringes or vials shall not be used to test, and a safety report shall be submitted
-
- All syringes shall be matched against a report of all ADC waste transactions
 - Syringes must fall within 10% of documented waste volume to be considered a match
 - Enter a safety report for any unmatched syringes or waste transactions
- Waste syringe contents into a black mini-bin and discard syringes into a red sharps container
- Return unopened/intact vials to the CII safe from the location they were picked up from. 1
- Reconciled report shall be signed by two OR Pharmacy team members
- Super Sandi-Cloth Germicidal Disposable Wipes “Purple Top Wipes” shall be used to disinfect the workspace, any items that came into contact with the waste syringes or packaging and the un-used/intact vials being returned to the C2 Safe.
- Mask and gloves shall be removed and hands washed.
- Reconciled matching reports shall be filed in the vault

Testing

-
- Test a minimum of 10 randomly selected waste syringes daily 4 from SSC and 10 from Bramhall
- Refer to the Refractometer Testing Standard Operating Procedure for testing procedures

Discrepancy

-
- Enter a safety report for all discrepancies ,rSafety Repots are entered for unresolved discrepancies

References:

- Refractometer Testing Standard Operating Procedure

Appendix 2: Nursing Education Handouts

CLINICAL TRIAL PROTOCOL: INTRATHECAL MORPHINE VS. INTRATHECAL MORPHINE COMBINED WITH CLONIDINE FOR 1-2 LEVEL LUMBAR FUSION

Please follow this protocol for patients that have enrolled in the above study. Please confirm that study consent has been signed prior to Anesthesia Start time. The blinded study medication (either 75mcg clonidine or preservative-free saline) will be ordered by research staff prior to patient arrival and should be delivered by pharmacy to OR staff either by hand or via coordinated tube delivery.

Preoperative Medications

1. Acetaminophen 1000 mg PO x 1 (dose adjusted for hepatic function)
2. Aprepitant 40 mg PO x1
3. Mechanical DVT prophylaxis perioperatively (no heparin)

Intrathecal Morphine (ITM) with Study Medication Injection by Surgeon

The anesthesia team will obtain a preservative-free morphine vial from the OR pyxis and deliver this to the circulating nurse. The circulating nurse will verify medication labels, concentrations, and 'preservative-free' annotation before sterilely delivering both 0.15 mL (0.15mg) morphine and 0.75 mL of study medication on the surgical field. The medications will be combined (0.85mL total) in a single syringe prior to administration, which occurs after initial surgical exposure but prior to spinal decompression. The surgeon will directly administer the study medications to an adjacent segment of dura to the surgical site via single intrathecal injection with a fine 27g needle. The circulating nurse and anesthesia team member will then properly dispose of and document any remaining morphine.

- Anesthesia will document the administration of 0.15mg IT morphine in EPIC. Please document study medication in EPIC as **ITMC Clonidine/placebo 75mcg in PF sodium chloride 0.9% Intrathecal 0.75mL**

Intraoperative Management:

1. General Anesthesia. Induction and maintenance per personal standard of care.
2. Fentanyl or remifentanyl may be used for induction and intra-operatively at provider's discretion.
3. No long-acting opioids (hydromorphone/morphine).
4. Dexamethasone 8 mg IV after induction.
5. Ketamine 0.3 mg/kg IV bolus x 1 prior to incision.
6. Maintain FiO₂ ≥ 50% during case to reduce postoperative infection risk;
7. Goal directed fluid management using traditional vital sign monitoring and clinical judgement, with a default fluid target of 1-2 Liters peri-operatively unless otherwise indicated.
8. Maintain MAP > 65 with phenylephrine/ephedrine as needed
9. Maintain HR > 50 with ephedrine/glycopyrrolate/atropine as needed.
10. No peripheral nerve/plane blocks. Local infiltration by surgeon 10-15 mL lidocaine with epinephrine 1:200,000 at start of case, and bupivacaine 0.25% 20 mL with 10mL liposomal bupivacaine (Exparel).

Postoperative Care:

1. Place Orders: Anes ITM/Clonidine Clinical Trial [3954] order set
 - a. Modify order set to specify time of IT morphine administration
2. Place standard PACU orders with IV analgesic rescue medications (Fentanyl, hydromorphone/morphine).
3. Avoid oral opioids until 8 hours after time of IT morphine administration
4. Avoid NSAIDs
5. Continue Acetaminophen IV/PO 1000mg Q6H

Nursing handout for ITM and Clonidine trial

Your patient is enrolled in a clinical trial!

Title: Intrathecal Morphine vs Intrathecal Morphine Combined with Clonidine for 1-2 Level Lumbar Fusion

What did they receive?

- They received intrathecal morphine during surgery
- They received intrathecal clonidine vs. placebo

What are we looking at post-operatively?

- Patient pain scores
- Patient sedation levels
- Patient vital signs (HR, BP, RR)
- Opioid medication usage

What help do we need from nursing staff?

- Continue your normal excellent post-operative care!
- Continue your normal administration and documentation of pain medications.
- Make sure to document patient vital signs and pain scores in Epic, every 4 hours unless sleeping.

If you have concerns about patient sedation, hemodynamics, or other safety issues, please immediately contact primary team **and** study principal investigator listed below.

Principal Investigator (PI):

Parker H. Merrill, MD

Department of Anesthesiology

Parker.merrill@spectrumhcp.com | Epic chat | (617) 221-3028

References

1. Mathiesen O, Dahl B, Thomsen BA, et al.: A comprehensive multimodal pain treatment reduces opioid consumption after multilevel spine surgery. *Eur Spine J.* 2013, 22:2089–2096. 10.1007/s00586-013-2826-1
2. Geisler A, Zachodnik J, Køppen K, Chakari R, Bech-Azeddine R: Postoperative pain treatment after spinal fusion surgery: a systematic review with meta-analyses and trial sequential analyses. *Pain Rep.* 2022, 7:e1005. 10.1097/pr9.0000000000001005
3. Stoelting RK: Intrathecal morphine--an underused combination for postoperative pain management. *Anesth Analg.* 1989, 68:707–709.
4. Pope JE, Deer TR, Amirdelfan K, McRoberts WP, Azeem N: The Pharmacology of Spinal Opioids and Ziconotide for the Treatment of Non-Cancer Pain. *Curr Neuropharmacol.* 2017, 15:206–216. 10.2174/1570159x14666160210142339
5. Meylan N, Elia N, Lysakowski C, Tramèr MR: Benefit and risk of intrathecal morphine without local anaesthetic in patients undergoing major surgery: meta-analysis of randomized trials. *Br J Anaesth.* 2009, 102:156–167. 10.1093/bja/aen368
6. Etches RC, Sandler AN, Daley MD: Respiratory depression and spinal opioids. *Can J Anaesth.* 1989, 36:165–185. 10.1007/bf03011441
7. Sultan P, Gutierrez MC, Carvalho B: Neuraxial morphine and respiratory depression: finding the right balance. *Drugs.* 2011, 71:1807–1819. 10.2165/11596250-000000000-00000
8. Gehling M, Tryba M: Risks and side-effects of intrathecal morphine combined with spinal anaesthesia: a meta-analysis. *Anaesthesia.* 2009, 64:643–651. 10.1111/j.1365-2044.2008.05817.x
9. Engelman E, Marsala C: Efficacy of adding clonidine to intrathecal morphine in acute postoperative pain: meta-analysis. *Br J Anaesth.* 2013, 110:21–27. 10.1093/bja/aes344
10. Lena P, Balarac N, Arnulf JJ, Teboul J, Bonnet F: Intrathecal morphine and clonidine for coronary artery bypass grafting. *Br J Anaesth.* 2003, 90:300–303. 10.1093/bja/aeg070
11. O'Brien PC, Fleming TR: A multiple testing procedure for clinical trials. *Biometrics.* 1979, 35:549–556.
12. Allen TK, Mishriky BM, Klinger RY, Habib AS: The impact of neuraxial clonidine on postoperative analgesia and perioperative adverse effects in women having elective Caesarean section-a systematic review and meta-analysis. *Br J Anaesth.* 2018, 120:228–240. 10.1016/j.bja.2017.11.085
13. Paech MJ, Pavy TJ, Orlikowski CE, et al.: Postcaesarean analgesia with spinal morphine, clonidine, or their combination. *Anesth Analg.* 2004, 98:1460–1466, table of contents. 10.1213/01.ane.0000111208.08867.3c
14. Filos KS, Goudas LC, Patroni O, Polyzou V: Hemodynamic and analgesic profile after intrathecal clonidine in humans. A dose-response study. *Anesthesiology.* 1994, 81:591–601; discussion 527A–528A. 10.1097/00000542-199409000-00011
15. Saravanan S, Kocarev M, Wilson RC, Watkins E, Columb MO, Lyons G: Equivalent dose of ephedrine and phenylephrine in the prevention of post-spinal hypotension in Caesarean section. *Br J Anaesth.* 2006, 96:95–99. 10.1093/bja/aei265
16. Baxter SN, Brennan JC, Johnson AH, et al.: The Effect of Preoperative, Low-Dose Intrathecal Morphine on Patient Outcomes Following Lumbar Fusion Surgery: Can We Teach an Old Dog New Tricks? *Int J Spine Surg.* 2023, 17:721–727. 10.14444/8532
17. Andrieu G, Roth B, Ousmane L, et al.: The efficacy of intrathecal morphine with or without clonidine for postoperative analgesia after radical prostatectomy. *Anesth Analg.* 2009, 108:1954–1957. 10.1213/ane.0b013e3181a30182
18. DeSousa KC, R: Intrathecal morphine for postoperative analgesia: Current trends. *World J Anesthesiol.* 2014, 3:191–202. 10.5313/wja.v3.i3.191