Protocol Elements Checklist for:

Single-dose Intraoperative Methadone for Early Ambulation and Sustained Pain Control in Spinal Fusion Surgery Patients

1) Background/Significance

Methadone is a synthetic opioid analgesic with agonist properties at the μ-opioid receptor binding site that has long been used as an alternative to morphine and hydromorphone in patients with severe pain.[1] It has a diffuse bioavailability and is highly efficacious through its oral form, yet its bioavailability is heavily dependent on variability in cytochrome P450 3A4 activity, and is quite variable amongst individuals. Methadone reaches peak plasma concentrations in 2.5 to 4 hours after oral administration, has a rapid onset, has a half-life is between 20-35 hours (range 5-130 hours), and analgesia may be reported for up to 108 hours after a single dose.[1,2] Repeated dosing during this interval may result in drug accumulation and an increased risk of adverse reactions.

Methadone has an asymmetric carbon skeleton with two carbon side chains which allow for two enantiomeric forms, the D- and L-isomers, and while the racemic mixture is administered, only the L-isoform seems to have clinical activity.[1,2] The binding of the D-isomer, while not implicated in pain control may influence opioid potentiation and tolerance by binding to the NMDA receptor. Methadone's NMDA receptor site antagonism acts to inhibit enzymes such as adenyl cyclase and their downstream production of secondary signaling molecules like cyclic AMP.[1] This activity may attenuate opioid tolerance and opioid abstinence syndrome as NMDA receptor agonism has been implicated in the development of hyperalgesia, acute and chronic tolerance, and chronic pain states.[3] Its antagonisms may explain the low rate of dependence seen with methadone.

Methadone excretion occurs by demethylation primarily by cytochrome P450 3A4 and is renally removed from the body, yet urine PH and autoinduction may influence its rate of excretion.[2] Its metabolism is also influenced by previous narcotic used as half-life significantly drops with chronic use of narcotics, and a steady state may take longer to reach in these patients due to autoinduction of CYP3A4. CYP3A4 inducers such as rifampin, rifabutin, carbamazepine, phenytoin, phenobarbital, abacavir, and St. John's Wort will increase methadone metabolism and decrease it concentration in the blood stream, while CYP3A4 inhibitors such as fluconazole, fluvoxamine, fluoxetine, paroxetine, HIV-1 protease inhibitors, erythromycin, ketoconazole, and grapefruit juice will increase serum levels of methadone.[2]

Methadone use has long been studied and bolstered by its low cost, long half-life, convenient dosing schedule, excellent oral bioavailability, and slow onset to withdrawal.[2] Despite its positives, methadone, as other narcotics, may be dangerous when abused, yet by minimizing dosing, these risks may be abated.

IV dosing typically ranges from 2.5mg to 10mg every 8-12 hours, with PO forms dosed at 5-20mg every 6-8 hours. Patient with renal failure should be dosed no more frequently than every 6 hours and with more severe disease, no more than 8-12 hours. Cirrhotic patients with liver failure do not need to have their doses altered. Due to the factors listed above, the literature demonstrates up to a 17-fold inter-individual variation in methadone blood concentrations for a given dosage.

In a series of women undergoing caesarean delivery, methadone administration was associated with lower pain scores and 40% lower overall opioid consumption than control subjects undergoing the same procedure who received iv morphine or fentanyl post-operatively.[11] Over sedation of the respiratory system occurred in one of 25 patients in the methadone group and three of 50 in the control sample. The authors comment on the concern for QT interval prolongation with methadone use, but cite that this is reported only with chronic use, not with single operative dose administration.

In another series, three groups of methadone vs. morphine vs. placebo for the treatment of pain in cardiac surgery patients were used, and the methadone group had equivalent anesthetic times, required lower narcotic doses, had longer latencies to fist analgesic dose, had better pain control, and had lower incidences of nausea and vomiting compared to all other groups.[10] The authors speculated that the decreased nausea and vomiting was due to the overall lower narcotic doses post-operatively. Methadone patients required fewer additional post-operative analgesic administrations, on average less than 1 additional dose, and morphine and control patients required significantly more.

In a series of 156 cardiopulmonary bypass patients randomized to receive either fentanyl of methadone, the quality of pain management was rated better by the patients in the methadone group and there was no greater opioid-related adverse events compared to controls.[6] Patients used smaller equivalent narcotic doses in the methadone group (40% less in the first 24 hours) and had nearly twice as long times to first rescue dose. Of the few patients in this series who required no additional narcotic dosing (5), they were all in the methadone group.

In a series of 31 children who were administered single-dose intraoperative methadone for scoliosis repair, doses of up to 20mg were tolerated well and pharmacokinetic profiles were followed for 96 hours.[4] Pharmacokinetics in children were similar to those for methadone in adults. There was no difference between methadone patients and control patients receiving equivalent doses of morphine, hydromorphone, fentanyl, sufetanil and oxycodone in regards to adverse events including respiratory depression, decreased oxygen saturation, or altered mental status. Post-operative PCA use was lower in the methadone group, however this difference did not reach statistical significance, possibly because, as the authors speculate, the dose of methadone being small compared to the overall narcotic dose. Children in the methadone group also reported overall greater comfort in the recovery room as compared to their cohort controls.

In another series of spinal fusion patients administered 20mg methadone intra-operatively and 5mg doses as needed post-operatively in the recovery room (1-3 doses), there was little variability in methadone blood concentration in patients with adequate pain control, suggesting a dose-dependent effect.[8] Mean half-life was 21±13hours with a range of 5-48 hours, with a VAS rating of 1.5±1.3 with adequate pain control. A repeat dose of methadone (i.e. 2.5, 5, or 10 mg iv) in the recovery room provided sufficient pain control for the remainder of the hospitalization for some patients in this cohort. The 2.5mg dose was associated with an average additional 7.4h of pain control, while the 5 and 10mg doses were associated with 9.6h of pain control. In another study cited in this report, 40% of surgical patients required no additional post-operative pain control after a single 20mg iv methadone dose intra-operatively, and the 35% that did require a single additional dose required it on average 18.4±6.6 hours post-operatively. The remainder received additional non-narcotic pain medications post-operatively which were sufficient to control pain to tolerable levels.

In one of the first series of methadone use in patients undergoing lumbar fusion surgeries, 22 patients were divided into two treatment arms with one group of patients receiving methadone only and the other receiving methadone plus ketamine.[5] While there was no difference in pain rating post-operatively, the ketamine plus methadone group used significantly less methadone (70%) than the other control groups. This finding suggests that intra-operative co-administration of ketamine may potentiate the effects of methadone. To keep consistent with this data and to demonstrate a narcotic minimizing plan that sufficiently controls patients' pain, ketamine will included in this proposed protocol, as it is already a medication used for the analgesia of patients undergoing this surgical procedure.

In the most relevant study in the literature, a series of 29 patients undergoing multilevel thoracolumbar spine surgeries with instrumentation and fusion and were randomized to receive either methadone (0.2mg/kg) or sufentanil infusion of 0.25µg/kg/h after a load of 0.75 µg/kg.[9] Post-operative pain control was delivered by patient-controlled analgesia and patients were assessed by visual analogue scale for pain, opioid dose, and side effected at 1, 2, and 3 days post-operatively. Patients reported less pain in the methadone group 48 hours post-operatively, as well as used less cumulative narcotic dose than the

remifentanil control group. Side effects were not significantly different between the two groups. This study however, did not evaluate post-operative functional status, ambulation, and time to discharge.
The literature comparing methadone to more commonly used post-operative narcotics demonstrates that it manages pain better, decreases narcotic requirement, results in no additional adverse events, and is safe, even in children. Since the standard of care is narcotic usage to manage the significant pain of complex spinal surgery cases, it is understandable that methadone could be a desirable therapy to promote sustained pain control and early ambulation in these patients.

2) Study Design

- **Describe the study design, e.g. clinical trial (phase I, II, III); observational cohort study; case-control study.**

Our study is a prospective, positive-control, double-blinded study

- **State study objectives, and if applicable, specific hypotheses**

Since the standard of care is narcotic usage to manage the significant pain that complex spinal surgery causes, it is understandable that methadone could be a desirable therapy to promote sustained pain control and early ambulation in these patients. It is our hypothesis that methadone use intraoperatively will result in earlier time to ambulate post op and better ability to participate with post-operative PT evaluation, lower narcotic usage, earlier discharge, and improved scores on clinical outcome scales including the Oswestry Low Back Pain Disability Questionnaire and the Short Form 36 Health Survery. It is also foreseeable that since methadone would be administered while the patient was sedated intraoperatively, it could prevent the association between the analgesia and euphoria that may result from self- or nurse-administered narcotics, such as with a PCA, which could promote early tolerance or reliance. Randomization of patients between methadone administration and standard intra-operative narcotic administration allows for controlled and accurate investigation of subjects compared to the current standard of care.

- **Clearly state target population and recruitment methods**

We would screen the first 200 consecutive patients to determine whether inclusion criteria are met, with an end goal of 120 patients who will complete the study and 60 control subjects who receive the current standard of care in a 1:1 randomized fashion. Patient will be recruited in office at time of consent for surgery by the principal investigator.

- **State inclusion/exclusion criteria clearly**
  - **Inclusion criteria:**

Patients undergoing elective lumbar transforaminal interbody fusion or lumbar laminectomy and posterolateral fusion will be enrolled in the study and consented for intraoperative single-dose methadone administration or standard narcotic regimen administration in a 1:1 block randomization plan. Patient may undergo one or two spinal level fusions and in blocks of 5, will be assigned to intervention or control groups in a manner that will be blinded to both the clinical team and the patients.

  - **Exclusion criteria:**

Age <21 or >80, renal failure requiring dialysis or serum creatinine greater than 2.0, significant hepatic dysfunction (liver function tests greater than twice the upper limit), hepatic cirrhosis, pulmonary disease requiring home oxygen therapy, obstructive sleep apnea, severe heart disease, allergy to methadone, morphine, ketamine or fentanyl, **recent or distant history of opioid abuse,** opioid use equal to or greater that the equivalent of 10mg morphine per day, poorly managed psychiatric illness, a known history of alcohol abuse, morbid **obesity (for the purposes of this study body mass index > 50 kg/m2),** treatment with other NMDA receptor antagonists, HIV-1 protease inhibitors, erythromycin or ketoconazole, prolonged QTc on pre-operative EKG, and the refusal or inability to sign the consent form to agree to participate in this study,.

- **State primary and secondary outcome(s)**

The primary outcomes for the study include total narcotic dose post-operative, frequency of narcotic use, the time to first ambulation after surgery with PT, length of stay, disposition (i.e. level of rehabilitative care), and improvement on clinical questionnaires in the intervention group as compared to the control group. Secondary outcomes include better subjective pain control, need for post-operative course of

dexamethasone for post-operative/post-fusion radiculopathy or neurapraxia/neuropathy and fusion at 3-6 months.

- **For Randomized clinical trials**
  - **Indicate whether a parallel or crossover study, and the number of treatment groups**

The study will take the form of a parallel, 2 arm analysis of a methadone treatment group or a group receiving the current standard of care without intra-operative methadone administration.

- **Describe randomization and blinding procedures**

The patients will be randomized with 1:1 ratio of intervention and control groups, in blinded blocks of 5, randomly assigned by software used on www.randomizer.org to create 60 study patients and 60 control patients. Envelopes will be used to assign the patients in blocks of 5. Therefore in the first group is to be a control group, the first 5 patients will be controls, then the next group of 5 will be randomly assigned to control or intervention group based on a randomized protocol listed on a study envelope. Overall the blocks of 5 will create even groups of control and intervention patients overall to reach the 120 patient goal. One member of the study team, not involved in the surgical procedure and post-operative pain evaluation will be designated unblended and will communicate with the anesthesiology team pre-operatively to determine whether the patient is to receive methadone or not. The anesthesia team will be responsible for allocation and administration of the methadone, in addition to the standard fentanyl and ketamine, from the Montefiore pharmacy which is already available for intra-operative use as an alternate narcotic regimen. Post-operatively, blinded team members will collect pain data, as well as time to ambulation and discharge data. The pain measures will be patient derived, and time to event data will be part of the patient's chart.

Describe what safety outcomes will be monitored

Safety outcomes to be measured as stated in the adverse events section of this protocol include risks of using any opioid narcotic, which include overdose leading to respiratory depression, dependence and QTc prolongation. Psychological risks include obtunded, lethargic state or altered mental status due to long half-life and opioid effects post-operatively and any resultant mental distress, especially in opioid-naïve patients

Include a data safety monitoring plan

A data safety monitoring plan is included in section 7, under the subheading "Describe methods for interim analyses or early stopping, if applicable"

- **For Observational studies**
  - **Describe predictors of interest along with potential confounders and effect modifiers**

Predictors of interest include drug abuse history and/or behavior, as well as anticipated benefit from history of medication usage in the literature. Potential confounders include previous narcotic use history, narcotic tolerance/dependence in patients not otherwise excluded during recruitment, variable pain thresholds and tolerance amongst different patients, duration and complexity of surgeries, as well as variable renal clearance. Many of these are also effect modifiers.

- **Describe matching criteria, if applicable**

Matching criteria will not be used at this study will be structured as a randomized control trial.

- **Describe duration of follow-up, and timing of data collection**

Post-operative imaging will be reviewed to determine successful decompression and instrumentation. Data collection will be done during patient's hospital stay. Patients will be asked about their post-operative pain at 4 hour intervals, and data regarding their overall narcotic usage and their time to ambulation will be recorded from the medical record. Follow-up will then consist of: 1 week for phone call by spine NP, 2 week evaluation as is standard for all post-operative patients.

- **Describe the planned interventions and their timing.**

A study participant will be randomized ahead of time to be administered methadone or the current standard of care in blocks of 5 blinded to clinical personnel. If the patient is assigned to the methadone group, the anesthesiology team will be given this information and the anesthesiologist assigned to the

case and will administer a 0.2 mg/kg single-dose administration of methadone on incision (not to exceed 20 mg, as used in the literature) with a ketamine infusion of 4 µg/kg/min and a remifentanil infusion starting at 0.1 µg/kg/min and titrating to effect or sufentanil infusion starting with a dose of 0.3 µg/kg/hr and titrating to effect. These standard doses have been well documented and studied in the literature as demonstrated above and will be overseen and have been approved by board certified anesthesiologist. For lengthier procedures, there will not be re-dosing of narcotics toward the end of the procedure. The operative procedure will not be altered in any way for the purposes of this study, and is beyond the scope of this protocol, yet can be detailed as requested. The patient will be taken to the recovery room post-operative and will be put on a standard post-operative morphine PCA as used in our department at a rate of 1mg per 6 minute lock-out period. This standard dose and therapy has been used in nearly all post-operative lumbar fusion patients to date. Patient's narcotic usage and pain rating will be recorded at the intervals listed above and when stable from a cardiovascular standpoint, will be transition to the neurosurgery floor. Once able to bare weight, the patient will be encouraged to work with physical and occupational therapy as per standard post-operative protocol. One the patient uses the PCA at a rate of less that once an hour, and can be managed with oral pain medications, the PCA will be removed. The remainder of their post-operative care will be according to the standard departmental protocol, and when milestones such as ambulation, voiding, and pain control are met, they will be discharged either to home, an acute care facility, or a subacute rehabilitation center. Per standard of care, the patients will return to the clinic at 2 weeks and 3 months as part of their routine clinical care. Any adverse events/reactions will be recorded and managed as normally they would be, and naloxone will be available for suspicion of narcotic overdose. Patient assigned to the control group will be monitored in the manner post-operatively, as is the standard of care for all of our patients.

Define the outcome measures pertaining to each aim.

The outcome measures, will serve to compare to the standard narcotic regimen controls by demonstrating the effect of methadone on postoperative pain use, rehabilitation time, and validated clinical measures. Control patients will have undergone the same 1 or 2 level lumbar fusions for lumbar stenosis with administration of standard narcotic regimen intra-operatively and post-operative patient controlled analgesia usage. We anticipate that with 60 patients per group, the randomization will create similar groups of patients with which we can accurately compare our outcome measures. Other than intra-operative narcotic administration, all other portions of the intra-operative and post-operative care will remain the same for control and intervention patients.

3) Study Population

- **Describe the study population: number, age range; health status or other characteristics pertinent to the study**

The study population will consist of 120 patients between the ages of 21 and 80 who will be undergoing lumbar fusion surgery. The patients will be either ASA grades I-III and will meet the inclusion criteria as listed above. They will be required to have no significant narcotic abuse or significant use (>10mg equivalents of morphine per day) in the past and should not be on medications that may induce or inhibit the metabolism of methadone. They must not meet any of the exclusion criteria stated above.

- **Describe how the sample size and power of the study were determined, including the statistical approach and any assumptions on which the calculations are based.**

The sample size was determined using the Gottschalk study listed in the reference section which used methadone vs. sufentanil in 29 patients undergoing lumbar fusion surgery and the measures for pain level and total narcotic usage at 48 hours to determine an 'n' for the total study population, using a power of 0.80. The details of the calculations is listed in the data analysis section (7a) below and calculated with the suggestion of the statistician on the IRB. The assumptions with which the outcomes are hypothesized are the result of previously published data using similar populations. Two sample t-tests are appropriate to determine statistical significance between mean pain scores between different patients in the control and study groups for each individual time point as there will be no censoring of the study data. Ranked T-test may also be used if outliers are present, however patients with unusual post-operative courses may be excluded if their reason for prolonged hospitalization is unrelated to immediate post-operative pain

control. The large sample size plans to take into account possible outliers that may not be included in final analysis, despite their mention in study write-up to determine why their post-operative hospitalization was prolonged. Additionally, data about patients' mean time to ambulation, mean time to discharge, and mean overall narcotic usage will be measured between the control and study populations. Data analysis will be performed with the assistance of the biostatistician listed as a member of the study team, Qian Ye, from the Albert Einstein College of Medicine, Division of Biostatistics. Thus, a sample of 60 completed methadone patients will be evaluated against 60 randomized, standard narcotic regimen controls. The mean data for control patients' pain ratings, narcotic usage, time to ambulation, and time to discharge will be obtained, the statistical deviation of this data will be measured and compared to subject data in all facets.

- **Take into account anticipated drop-out or loss-to-follow up rate.**

We intend to screen 200 patients to have 60 in each arm ultimately included in the study. Since the intervention is a single intra-operative occurrence, that when completed patients cannot reverse, we do not anticipate any drop-out. A two week follow-up visit is a required standard of care for all post-operative patients, without patient loss to follow-up historically. The study is completed at this point.

- **Pilot and exploratory studies do not need formal sample size calculations but a data analysis plan should still be included (see above)**

Please see the section above and the Data Analysis section below to address these issues.

- **State inclusion/exclusion criteria.**

See above

- **Provide appropriate justification for the exclusion of any population group (e.g. Minors, Women, Ethnic groups, Non-English Speaking people, etc.)**

  [N.B. federal regulations require inclusion of women, minors and minority group members in research unless adequate justification is provided. Acceptable justifications for exclusion of minors are listed below in Appendix 1].

We are excluding minors from our study according to Appendix 1 item 2 which states: there are laws or regulations barring the inclusion of children in the research. For example, the regulations for protection of human subjects allow consenting adults to accept a higher level of risk than is permitted for children

- **State whether subjects who do not have the capacity to consent will be enrolled.**

No subjects without the capacity to consent will be enrolled in this study; this has been made part of exclusion criteria.

- **Identify the sources of research material.**
  - **State whether materials will be obtained from individually identifiable living human subjects.**
  - **Indicate the type of material (*e.g.* blood samples, tissue specimens, records, data, etc.)**
  - **Indicate whether the material will be obtained as part of routine clinical care or for the specific purpose of research.**

The research material will be obtained from the medical record as obtained as part of the standard care of these post-operative patients. No physical specimens will be collected and all data needed for the study will be encompassed in the medical records, therefore information will not needed to be specially obtained for the purposes of this study.

4) Participant Recruitment

- **Describe the plan for participant recruitment.**

Subjects will be recruited in the office by the principal investigator at the time of consent for surgery if they have met the inclusion criteria, as addressed in part 2.2. They will be contacted prior to their operative date to discuss the study protocol again and confirm that they are still in fact interested in participating.

- **Describe sources and method(s) for recruitment of both subjects and controls.**

The sources of recruitment will be patients presenting to the principal investigator's office for surgical evaluation and the methods as described above. Only patients who are already deemed surgical candidates beyond the scope of this study will be considered for inclusion into this study.

- **Describe the method(s) for ensuring voluntariness of participation.**

Patients will be free to refuse to enroll in the study and will be ensured that in no way will their care be altered due to their enrollment or refusal to participate in this study. All subjects will sign an informed consent form prior to enrollment in the study and reminded that they can reverse their consent and participation at any time.

- **Describe the plan for Patient Privacy protection.**

Patient health data and records will be handled with compliance of HIPAA regulations and will only be accessed on Montefiore computers by members of the study as outlined by the IRB form. All information will be taken from chart to a separate database and will be used in de-identified form only. **De-identifed data will be used for database purposes but a password protected master list matching subject number to MRN and name will be kept by the principal investigator, allowing identification of patients, if required.** We will use secure databases on encrypted Montefiore drives as our repository. They are safe, protected, and HIPAA compliant. All correspondence regarding this study will be through Montefiore secure email servers.

5) Informed Consent

- **Provide an Informed Consent Form containing all of the necessary elements (see below).**

An informed consent document is attached to this application, will use non-medical terminology, and will outline all aspects of this study to the patients, including a clear descriptions of all risks and benefits. Control and methadone intervention patients will be consented in the same manner and patients will be informed that they may not be administered methadone intra-operatively as part of the randomization process.

- **Describe the informed consent process.**

A prospective patient will be called before a planned surgical procedure and the outline of the study will be presented to them. If they are interested in participating, a further discussion will be undertaken immediately before their surgery in person and they will be asked to sign a consent form at that time. They will be reminded of their ability to rescind consent at any time and of the randomization process. For those patients screened in the outpatient clinic, information regarding the study will be presented to them upon agreeing to undergo surgery, however since they will need to pass pre-operative testing before they will be cleared to undergo surgery, only on the morning before surgery will they be asked to officially sign the study consent form.

- **Who will obtain consent?**

Consent will be obtained but the key personnel listed in this study proposal.

- **Where will consent be obtained?**

Consent will be obtained in the office at the time of consent for surgery verbally, confirmed over the phone on the day before surgery, and formally signed in the ambulatory surgery area prior to surgery. This redundant process will further ensure that patients understand the purposes of the surgery and have enough time to make an informed decision regarding their participation.

- **Provide clear justification if a waiver or alteration of the informed consent process is requested.**

Not applicable.

- **If minors are included, describe the plan for parental approval and child assent.**

Not applicable

- **Describe any costs or remuneration:**
    - **State any reimbursement or remuneration, including the pro-rating scale if multiple visits are required.**

- **Clearly identify tests and procedures as for Research Purposes or Standard Clinical Care.**
- **Include a listing of any costs (tests/procedures/supplies which are the responsibility of the subject).**

There will be no costs or remuneration for the study, as the key personnel involved will not be financially compensated in any way and the intervention as well as all data collected is considered part of routine post-op surgical care. The patients will not be reimbursed for participation in any part of the study and they will be reminded that their care will otherwise not be altered as a result of participation. They will be responsible for all the costs of the surgical procedure, either directly, through insurance, or through Montefiore, as would any individual undergoing surgery.

- **For studies with complicated schedules, provide a 1-page table or flow diagram.**

N/a

- **State the plan for obtaining HIPAA authorization (or waiver as appropriate).**

HIPAA authorization and wording will be included in the consent form and will completed during the consent process prior to surgery.

6) Risk/Benefit

- **Identify all anticipated risks (*e.g.* medical, social, psychological, and/or legal).**

  Medical risks of methadone include the risks of using any opioid narcotic, which include overdose leading to respiratory depression, dependence and QTc prolongation. Psychological risks include obtunded, lethargic state or altered mental status due to long half-life and opioid effects post-operatively and any resultant mental distress, especially in opioid-naïve patients

- **Describe how anticipated risks will be minimized.**

The risk of overdose will be minimized as the trained anesthesiologist during the procedure will carefully calculate dose according to their protocol as specified, normally carried out for their routinely administered opioids, and will have naloxone readily available should a patient show signs of overdose. Patient will be closely monitored by nursing staff post-extubation for signs of respiratory depression, as with any other post-operative patient who received intra-op opioids.
The risk of opioid dependence – highly unlikely given one dose of the drug
The risk QTc prolongation has been proven to be negligible except in chronic methadone use, nevertheless – patients with prolonged QT intervals are at increased risk for Torsades de pointes and excluded from this study when identified on pre-operative testing.
The psychological risks will be minimized by warning patients of the possibility of mental lethargy post operatively during initial recruitment and consent. However, given that these risks are shared with other anesthetic agents being used during the procedure and the quality and degree of post-operative monitoring, it is likely that this risk is minimal when compared to non-study patients undergoing the same procedure.

- **Document how potential benefits to participants or others justify potential risks.**

Given that patients would be receiving some other opioid narcotic otherwise, such as fentanyl which carries the same medical risks of methadone and the hypothesis that intra-operative methadone will reduce post-operative narcotic usage, the risks are justified and considered standard practice for patients undergoing these surgical procedures, given the degree of post-operative pain expected from tissue manipulation necessary to obtain access to the operative site.

- **Describe the plan for data storage and for maintenance of subjects' confidentiality.**

Patient health data and records will be handled with compliance of HIPAA regulations and will only be accessed on Montefiore computers by members of the study as outlined by the IRB form. All information will be taken from chart to a separate database and will be used in de-identified form only. **De-identifed data will be used for database purposes but a password protected master list matching subject number to MRN and name will be kept by the principal investigator, allowing identification of patients, if required.** We will use secure databases on encrypted Montefiore drives as our repository. They are safe, protected, and HIPAA compliant.

- **If subjects will be video or audio-taped, address the following: What will be taped, how the tapes will be used, when the tapes will be destroyed, and whether taped subjects will be compensated.**

Not applicable

7) Data Analysis

a) Clearly state statistical methods to be used to evaluate study objectives. For greater than minimal risk (full board) studies the following must also be described in the protocol:

Two sample T-tests will be performed to evaluate continuous variables such a total morphine dose, pain level per VAS, time to first morphine dose, time to ambulation, and time to discharge. The assistance of a statistician, Kenny Ye, from the Albert Einstein College of Medicine, Division of Biostatistics will be used for statistical analyses performed in this study. Wilcoxon Rank Sum Test will be used if outliers are noted in the study population, detected as more than 5 MAD from the median, and a concern presents that single patients may skew the data. Additionally, review of these patients who are outliers may also necessitate their exclusion from this work if they provide data that will significantly modify the mean of the remaining patients. This can be accounted for in the goal of 60 patients to be accrued in each arm of the study. A thorough explanation and review will performed on any such patients in any form of write up of this work.

- **At least one study hypothesis (or a statement that the study is hypothesis-generating or a feasibility study):**

The use of single dose intraoperative methadone will decrease total narcotic usage, time to ambulation, mean pain rating at 24 and 48 hours and will decrease number of days of hospitalization compared to sufentanil (current standard of care) controls.

- **A statement regarding specifically what data are to be used to test the hypothesis (or to generate the hypotheses)**

We will obtain data of total narcotic usage, days until patients ambulate with physical therapy, pain ratings at 24 and 48 hours, and days to discharge, all obtained from the patient's medical record.

- **The statistical method(s) to be used to test the hypothesis with that data**

Two-sample T-test will be used with the assistance of an Albert Einstein statistician, Qian Ye, to analyze the above data and determine if there is statistical significance between the two groups, in addition to the stipulations outlined above to address outlier patients.

- **A power analysis to determine the sample size (even for pilot studies)**

We proposed to recruit 60 patients to undergo the new treatment and another 60 as controls. This gives us greater than 80% (95%) power to detect an improvement of 0.56 (0.74) within-group standard deviation at statistical significance level 0.05 as had been calculated to be 51 patients per group. Using 60 patients will ensure the usability of our data to detect differences of this effect sizes between groups. From our preliminary data, the standard deviation of time to discharge is 6.7 days, therefore, our sample size is able to detect an average reduction of 3.8 days (5.0 days) in time to discharge with 80% (95%) power.

Describe methods for interim analyses or early stopping, if applicable

A data safety monitoring committee will be organized for the purposes of data evaluation in this study. The members of the committee will include Dr. David Altschul, neurosurgeon in the Department of Neurosurgery who performs spinal surgeries yet is not involved in the implementation of this project, and Dr. Mimi Kim, statistician in the Department of Epidemiology and Population Health who is not involved in this protocol. After 20 patients complete the study (approximately 10 patients in each arm), interim analyses will be performed to compare pain ratings, narcotic usage, time to ambulation, and time to discharge to control patients, and the data safety monitoring committee will be asked to review all results and advise the study personnel as well as the IRB about study continuation. If there a significant increase in any of these measured values beyond a single standard deviation of the mean, the data safety monitoring committee and the IRB will come to a decision regarding continuation of the study. Assuming the outcome follows a normal distribution, with 10 patients in each arm, and under the null hypothesis that there is no difference between two groups, the chance of observing a difference greater than or equal to one standard deviation between two groups is about 1/100000. With four measures considered here, the overall Type I error will be no greater than 5/100000. Therefore, the loss of power from the

interim analysis is negligible. If the methadone intervention contributes greater than normal adverse events (>2 patients) the study will be held from further recruitment. The study medication will not be administered further, no dosing changes will be made, and the IRB will be informed. A decision at this point will be reached regarding further accrual. If a patient should die prior to discharge, a thorough cause analysis will be implemented by the DSMB, the IRB, in addition to the analysis that will already be performed by the hospital. If it is due to the surgery outside of the trial mediation, the data for this patient will not be used and the information will be explicitly reported in any publication yet kept separated from the other patient's data, as it would not be feasible or make sense to include this patient in the analysis. If this adverse event is found to be caused by the methadone administration, the trial will be stopped. This is however an extremely unlikely scenario as methadone is used daily by millions of individuals, has already been approved by the FDA, and our study patients will undergo a rigorous screening, namely for QTc prolongation, to remove any potential risk of death as a result of methadone administration. The only wayy to address this possibility is to have a plan to remove this patient's data from the other patient's data, with a clear note made in the report.

Describe how possible confounding and/or effect modification will be addressed

The possible confounders have been addressed via the strict inclusion and exclusion criteria of the study. Other confounding variables including past narcotic usage, and a cutoff of <10mg equivalents of morphine will be considered when selecting patients for participation in this study. Such a low daily morphine dose is unlikely to significantly impact methadone effect or post-operative narcotic use in patients with this low level of narcotic usage compared to narcotic-naïve patients. Patient time to ambulation will be confounded by baseline neurological status and therefore we will randomly assigning patients to each arm of the study as described above. Confounding in regards to time of operative procedure and complexity of surgery will be controlled properly with appropriate randomization.

Describe how loss to follow up will be addressed

As described in previous sections, given that the intervention is a single intra-operative event, we do not anticipate any loss to follow-up within the standard post-operative care protocol. In the unlikely event any patient is lost to follow-up, we will attempt to contact the patients as is normal office procedure for post-surgical follow up. Portions of their data, especially those immediately relevant to the primary endpoints which pertain to their immediate post-operative hospitalization and experience may still be used, if complete up to patients discharge.

8) Data quality control and database management.

a) Describe methods for data entry and data management.
b) Describe the mechanism for checking and editing the data.
c) Describe computer data security and subject confidentiality. This is particularly important for multicenter studies.

Patient health data and records will be handled with compliance of HIPAA regulations and will only be accessed on Montefiore computers by members of the study as outlined by the IRB form. Patients identified from recruitment will kept in a list of enrolled patients in the study on a secure Montefiore drive. From there, all information will be taken from an enrolled patient's chart to a separate database and will be used in de-identified form only, with numbers assigned to each patient that are not related to patient MRN, and there will be no use of names or other personal identifiers. De-identifed data will be used for database purposes but a password protected master list matching subject number to MRN and name will be kept by the principal investigator, allowing identification of patients, if requiredWe will use secure databases on encrypted Montefiore drives as our repository. They are safe, protected, and HIPAA compliant. Data will be checked by study personnel and edited in real-time on only Montefiore secured servers.

9) References: Include a bibliography of all references in the protocol.

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Appendix 1: Criteria for Exclusion of Minors from Research protocols

1. The research topic to be studied is irrelevant to children;
2. There are laws or regulations barring the inclusion of children in the research. For example, the regulations for protection of human subjects allow consenting adults to accept a higher level of risk than is permitted for children;
3. The knowledge being sought in the research is already available for children or will be obtained from another ongoing study, and an additional study will be redundant. NIH program staff can be contacted for guidance on this issue if the information is not readily available;
4. A separate, age-specific study in children is warranted and preferable (consult NIH Policy for specific example of such studies).
5. Insufficient data are available in adults to judge potential risk in children (in which case one of the research objectives could be to obtain sufficient adult data to make this judgment). While children usually should not be the initial group to be involved in research studies, in some instances, the nature and seriousness of the illness may warrant their participation earlier based on careful risk and benefit analysis.
6. Study designs aimed at collecting additional data on pre-enrolled adult study participants (e.g., longitudinal follow-up studies that did not include data on children).
7. Other special cases justified by the investigator and found acceptable to the review group and the Institute Director.